ABC OF AIDS

Fifth edition

Edited by
Michael W Adler

BMJ Books

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ЗНАНИЕ

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Preface

By December 2000 there were 17 538 adult and paediatric patients with AIDS in the UK and 43 774 screened and infected with HIV. Many of those with the virus are well, asymptomatic, and even unaware that they are infected, but others, although they have not yet developed AIDS, have physical, psychological, social, and occupational problems and require as much care as those with AIDS. We therefore need to be concerned not with "a few cases" but with a large number of people infected with the virus, who will be making demands on every part of the health and social services. New infections will occur, and the public health education campaign will need to continue. None of us should feel that the problem of HIV infection and AIDS is unimportant and that it will go away because of the campaign and the possible magic bullet of a cure or vaccine.

We can all hope for these things but it would be a mistake to be lulled into a state of inertia and complacency. All of us will be concerned with AIDS for the rest of our professional lives. This book, originally written as weekly articles for the *BMJ*, attempts to give those doctors and other health care workers, who currently have had little experience of AIDS and HIV, some idea of the clinical, psychological, social and health education problems that they will become increasingly concerned with.

Patients with HIV infection and AIDS spend most of their time out of hospital in the community. Admission is required only when an acute clinical illness supervenes. General practitioners and domiciliary and social services do not always feel skilled and knowledgeable enough to look after them. With the increase in the number of cases, the community services will have to be able and willing to cope. Again, I hope that this book will help to make people feel more skilled and comfortable about caring for patients with HIV and AIDS.

This is the fifth edition of the *ABC of AIDS*; each chapter has been updated or rewritten.

Michael W Adler

1 Development of the epidemic

Michael W Adler

Box 1.1 Early history of the epidemic

1981	Cases of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma in the USA
1983	Discovery of the virus. First cases of AIDS in the UK
1984	Development of antibody test

The first recognised cases of the acquired immune deficiency syndrome (AIDS) occurred in the summer of 1981 in America. Reports began to appear of *Pneumocystis carinii* pneumonia and Kaposi's sarcoma in young men, who it was subsequently realised were both homosexual and immunocompromised. Even though the condition became known early on as AIDS, its cause and modes of transmission were not immediately obvious. The virus now known to cause AIDS in a proportion of those infected was discovered in 1983 and given various names. The internationally accepted term is now the human immunodeficiency virus (HIV). Subsequently a new variant has been isolated in patients with West African connections – HIV-2.

The definition of AIDS has changed over the years as a result of an increasing appreciation of the wide spectrum of clinical manifestations of infection with HIV. Currently, AIDS is defined as an illness characterised by one or more indicator diseases. In the absence of another cause of immune deficiency and without laboratory evidence of HIV infection (if the patient has not been tested or the results are inconclusive), certain diseases when definitively diagnosed are indicative of AIDS. Also, regardless of the presence of other causes of immune deficiency, if there is laboratory evidence of HIV infection, other indicator diseases that require a definitive, or in some cases only a presumptive, diagnosis also constitute a diagnosis of AIDS.

In 1993 the Centers for Disease Control (CDC) in the USA extended the definition of AIDS to include all persons who are severely immunosuppressed (a CD4 count $<200 \times 10^6/1$) irrespective of the presence or absence of an indicator disease. For surveillance purposes this definition has not been accepted within the UK and Europe. In these countries AIDS continues to be a clinical diagnosis defined by one or more of the indicator diseases mentioned. The World Health Organisation (WHO) also uses this clinically based definition for surveillance within developed countries. WHO, however, has developed an alternative case definition for use in sub-Saharan Africa (see chapter 10). This is based on clinical signs and does not require laboratory confirmation of infection. Subsequently this definition has been modified to include a positive test for HIV antibody.

Box 1.2 AIDS-defining conditions without laboratory evidence of HIV

- Diseases diagnosed definitively
  - Candidiasis: oesophagus, trachea, bronchi or lungs
  - Cryptococcosis: extrapulmonary
  - Cryptosporidiosis with diarrhoea persisting >1 month
  - Cytomegalovirus disease other than in liver, spleen, nodes
  - Herpes simplex virus (HSV) infection
    - mucocutaneous ulceration lasting >1 month
    - pulmonary, oesophageal involvement
  - Kaposi's sarcoma in patient <60 years of age
  - Primary cerebral lymphoma in patient <60 years of age
  - Lymphoid interstitial pneumonia in child <13 years of age
  - *Mycobacterium avium*: disseminated
  - *Mycobacterium kansasii*: disseminated
  - *Pneumocystis carinii* pneumonia
  - Progressive multifocal leukoencephalopathy
  - Cerebral toxoplasmosis

Box 1.3 AIDS-defining conditions with laboratory evidence of HIV

- Diseases diagnosed definitively
  - Recurrent/multiple bacterial infections in child <13 years of age
  - Coccidiomycosis – disseminated
  - HIV encephalopathy
  - Histoplasmosis – disseminated
  - Isosporiasis with diarrhoea persisting >1 month
  - Kaposi's sarcoma at any age
  - Primary cerebral lymphoma at any age
  - Non-Hodgkin's lymphoma: diffuse, undifferentiated B cell type, or unknown phenotype
  - Any disseminated mycobacterial disease other than *M. tuberculosis*
  - Mycobacterial tuberculosis at any site
  - Salmonella septicaemia: recurrent
  - HIV wasting syndrome
  - Recurrent pneumonia within 1 year
  - Invasive cervical cancer
- Diseases diagnosed presumptively
  - Candidiasis: oesophagus
  - Cytomegalovirus retinitis with visual loss
  - Kaposi's sarcoma
  - Mycobacterial disease (acid-fast bacilli; species not identified by culture): disseminated
  - *Pneumocystis carinii* pneumonia
  - Cerebral toxoplasmosis

These case definitions are complex and any clinician who is unfamiliar with diagnosing AIDS should study the documents describing them in detail.

CDC Definition of AIDS

Effective 1 January 1993:
All those with confirmed HIV infection with CD4 T lymphocyte count $<0{\cdot}2 \times 10^6/1 \pm$ indicator disease

Transmission of the virus

HIV has been isolated from semen, cervical secretions, lymphocytes, cell-free plasma, cerebrospinal fluid, tears, saliva, urine, and breast milk. This does not mean, however, that these fluids all transmit infection since the concentration of virus in them varies considerably. Particularly infectious are semen, blood, and possibly cervical secretions. The commonest mode of transmission of the virus throughout the world is by sexual intercourse. Whether this is anal or vaginal is unimportant. Other methods of transmission are through the receipt of infected blood or blood products, donated organs, and semen. Transmission also occurs through the sharing or reuse of contaminated needles by injecting drug users or for therapeutic procedures, and from mother to child. Transmission from mother to child occurs *in utero* and also possibly at birth. Finally, the virus is transmitted through breast milk.

Box 1.4 Transmission of the Virus

- Sexual intercourse
  - anal and vaginal
- Contaminated needles
  - intravenous drug users
  - needlestick injuries
  - injections
- Mother → child
  - *in utero*
  - at birth
  - breast milk
- Organ/tissue donation
  - semen
  - kidneys
  - skin, bone marrow, corneas, heart valves, tendons etc.

The virus is not spread by casual or social contact. Health care workers can, however, be infected through needlestick injuries, and skin and mucosal exposure to infected blood or body fluids. Prospective studies in health care workers suffering percutaneous exposure to a known HIV seropositive patient indicate a transmission rate of 0.32%. As of December 1999 there have been 96 reported cases of documented seroconversion after occupational exposure in such workers.

Table 1.1 HIV Transmission: Global Summary

Type of exposure	Percentage of global total
Blood transfusion	3–5
Perinatal	5–10
Sexual intercourse	70–80
(vaginal)	(60–70)
(anal)	(5–10)
Injecting drug use (sharing needles, etc.)	5–10
Health care (needlestick injury, etc.)	<0.01

The precautions and risks for such groups are covered in detail in chapter 15. Finally, there is no evidence that the virus is spread by mosquitoes, lice, bed bugs, in swimming pools, or by sharing cups, eating and cooking utensils, toilets, and air space with an infected individual. Hence, HIV infection and AIDS are not contagious.

Growth and size of the epidemic

Even though North America and Europe experienced the first impact of the epidemic, infections with HIV are now seen throughout the world, and the major focus of the epidemic is in developing/resource-poor countries.

Table 1.2 End-2000 global estimates: children and adults

Categories	Estimate ($\times 10^6$)
People living with HIV/AIDS	36.1
New HIV infections in 2000	5.3
Deaths due to HIV/AIDS in 2000	3.0
Cumulative number of deaths due to HIV/AIDS	21.8

Worldwide
The joint United Nations programme on AIDS (UNAIDS) has estimated that by the end of 2000 there were 36.1 million people living with HIV/AIDS (34.7 million adults and 1.4 million children <15 years). The new infections during that year were 5.3 million, approximately 16,000 new infections per day.

Table 1.3 Regional HIV/AIDS statistics and features, end of 2000

Region	Epidemic started	Adults and children living with HIV/AIDS	Adults and children newly infected with HIV	Adult prevalence rate(*)	% of HIV-positive adults who are women	Main mode(s) of transmission (†) for adults living with HIV/AIDS
Sub-Saharan Africa	late 1970s to early 1980s	25.3 million	3.8 million	8.8%	55%	Hetero
North Africa and Middle East	late 1980s	400 000	80 000	0.2%	40%	Hetero, IDU
South and South-East Asia	late 1980s	5.8 million	780 000	0.56%	35%	Hetero, IDU
East Asia and Pacific	late 1980s	640 000	130 000	0.07%	13%	IDU, hetero, MSM
Latin America	late 1970s to early 1980s	1.4 million	150 000	0.5%	25%	MSM, IDU, hetero
Caribbean	late 1970s to early 1980s	390 000	60 000	2.3%	35%	Hetero, MSM
Eastern Europe and Central Asia	early 1990s	700 000	250 000	0.35%	25%	IDU
Western Europe	late 1970s to early 1980s	540 000	30 000	0.24%	25%	MSM, IDU
North America	late 1970s to early 1980s	920 000	45 000	0.6%	20%	MSM, IDU, hetero
Australia and New Zealand	late 1970s to early 1980s	15 000	500	0.13%	10%	MSM
Total		**36.1 million**	**5.3 million**	**1.1%**	**47%**	

* The proportion of adults (15–49 years of age) living with HIV/AIDS in 2000, using 2000 population numbers.
† Hetero, heterosexual transmission; IDU, transmission through injecting drug use; MSM, sexual transmission among men who have sex with men.

Currently, 95% of all infections occur in developing countries and continents, the major brunt of the epidemic being seen in sub-Saharan Africa and south-east Asia. It is now recognised that cases of AIDS were first seen in Central Africa in the 1970s even though at that time it was not recognised as such. Current surveys from some African countries show that the prevalence of infection is high amongst certain groups – 50–90% of prostitutes, up to 60–70% of those attending departments for sexually transmitted diseases and antenatal clinics. In the developing world, HIV is spread mainly by heterosexual intercourse.

At a family level, UNAIDS estimated that by the end of 1999 the epidemic had left behind a cumulative total of 13.2 million AIDS orphans (defined as those having lost their mother or both parents to AIDS before reaching the age of 15 years). Many of these maternal orphans have also lost their father. Orphans in Zimbabwe are expected to total 1 million by 2005 and 2 million in South Africa by 2010. Traditional family structures and extended families are breaking down under the strain of HIV. Population growth and death rates are increasingly affected. Life expectancy in countries with adult prevalences of over 10% (for example Botswana, Kenya, Zimbabwe, South Africa, Zambia, Rwanda) are expected to see an average reduction in life expectancy of 17 years by 2010–2015. Young, highly productive adults die at the peak of their output, which has a considerable impact on a country's economy.

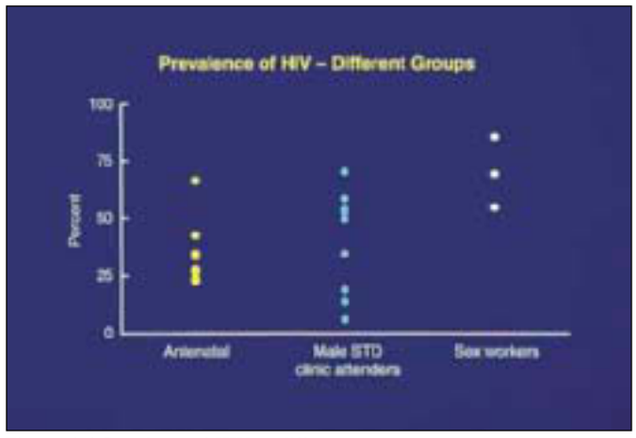


Figure 1.1 Prevalence of HIV — different groups

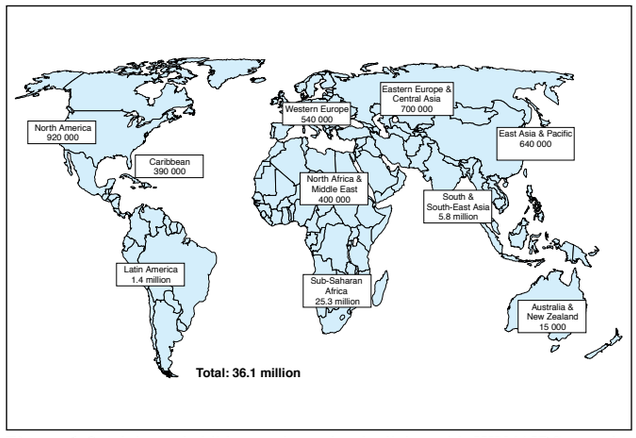


Figure 1.2 Adults and children estimated to be living with HIV/AIDS at end of 2000

USA, UK and Europe

By June 1999, 702 748 adult cases of AIDS had been reported in the USA. In addition there were 8596 paediatric cases (<13 years old). Most of the cases in children (91%) occur because a patient suffered from HIV or belonged to a group at increased risk of HIV; 4% occurred through blood transfusion; 3% in children with haemophilia. Information on risk factors for the remaining 2% of the parents of these children is not complete.

Adult cases in Europe totalled 234 406 by June 2000, and those in the UK 17 151 (December 2000). There are five times more people infected with HIV at any one time than have AIDS. The rate for AIDS cases varies throughout Europe, with particularly high rates in Italy, Portugal, Spain, France and Switzerland, where the commonest mode of infection is through intravenous drug use and the sharing of needles and equipment.

In North America and the UK the first wave of the epidemic occurred in homosexual men. In the UK, proportionally more homosexual men have been notified than in America: 67% of cases compared with 48% respectively. Even though infections amongst men who have sex with men still arise, an increasing proportion of new infections in the USA is occurring amongst intravenous drug users sharing needles and equipment. There is also an increase amongst heterosexuals in both the USA and the UK. Currently in the USA, 16% of cases of AIDS have occurred amongst women, and although the commonest risk factor amongst such women is injecting drug use (42%), the next most common mode of transmission is heterosexual contact (40%).

The nature of the epidemic within the UK is changing with more heterosexual transmission. In the UK 12% of adult cases of AIDS have occurred in women, 70% of which have resulted from heterosexual intercourse. In 2000 there were more new annual infections of HIV than ever before and for the first time more occurring as a result of heterosexual sex than men having sex with men. Most heterosexually acquired infections are seen in men and women who have come from or have spent time in Sub-Saharan Africa.

The advent of an effective antibody test in 1984 has allowed for a clearer understanding of the changing prevalence and natural history of HIV infection. Surveys show that the proportion of individuals infected needs to be high before cases of AIDS start to become apparent. It also underlines the importance of health education campaigns early in the epidemic, when the seroprevalence of HIV is low. Once cases of AIDS start to appear the epidemic drives itself and a much greater effort is required in terms of control and medical care.

Within countries one finds considerable variation in seroprevalence levels for HIV. Over 70% of cases of AIDS and HIV infection within the UK occur and are seen in the Thames regions (London and the surrounding area). Among different groups one also finds geographical differences. For example, the rates among drug users is higher in Edinburgh than London, and for gay men higher in London than anywhere else in the UK. This is also found in the developing world; for example, in Tanzania and Uganda, the urban level of HIV infection in men and women can be five times higher than rural rates.

The use of highly active antiretroviral therapy (HAART) in resource-rich countries has resulted in an increase in life expectancy. This, in combination with the increase in new HIV infections, means that the prevalent pool of those infected, and potentially infectious, is increasing. This presents a continuing challenge for health promotion and a re-statement of the importance of safe sex techniques, particularly condom use (see chapter 16).

Table 1.4 AIDS: adult patient groups in the USA and UK

Patient groups	USA (June 99) n	%	UK (Dec. 00) n	%
Men who have sex with men	334 073	48	11 345	66
Intravenous drug user	179 228	26	1095	6
Men who have sex with men and IV drug user	45 266	6	307	2
Received blood/haemophilia	13 440	2	828	5
Heterosexual contact	70 582	10	3391	20
Other/undetermined	60 159	8	185	1
Total	**702 748**	**100**	**17 151**	**100**

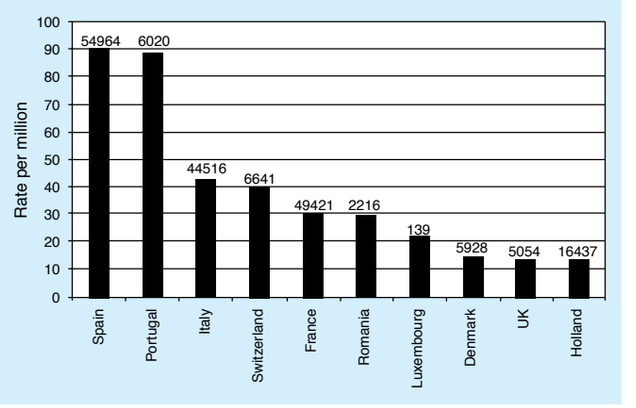


Figure 1.3 AIDS in Europe — top ten countries 1999

Table 1.5 Three main exposure categories (AIDS): % total for various countries in Europe, 1999

	Homosexual/bisexual men	Injecting drug users	Heterosexual exposure
Spain	14.0	65.0	13.0
Italy	14.0	61.0	15.0
Portugal	20.0	47.0	26.0
France	45.0	24.0	20.0
UK	68.0	6.5	18.0
Denmark	67.0	8.0	17.0

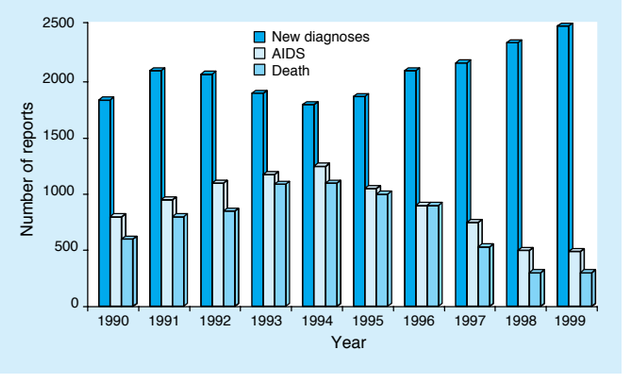


Figure 1.4 New diagnoses, AIDS cases and deaths reported in the year in which they occurred — United Kingdom

AIDS results in a considerable cost not only in human suffering also to health services. Other costs include time off work and the effect of the deaths of young people on national productivity. AIDS represents a major public health problem in the world. A clear understanding of the epidemiology forms the basis of developing a strategy of control ranging from health education to research.

The data on AIDS/HIV in the UK is reproduced with permission from the Communicable Disease Surveillance Centre (CDSC) and the United Nations AIDS Programme.

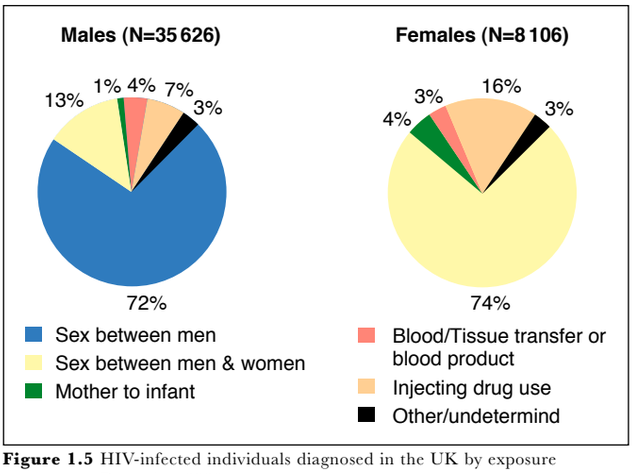


Figure 1.5 HIV-infected individuals diagnosed in the UK by exposure category: to December 2000

2 The virus and the tests

PP Mortimer, C Loveday

Introduction

Although it is clear that HIV is the underlying cause of AIDS and AIDS-related disease, its origin remains obscure. There is firm serological evidence of infection on the east and west coasts of the USA from the mid 1970s, and HIV infection in central Africa may have antedated infection in North America. Phylogenetic analysis of the HIV-1 genome has suggested an origin in chimpanzees while, in the case of HIV-2, similarity to the simian immunodeficiency virus (SIV) genome may point to an origin in sooty mangabey monkeys. In both cases the butchery and consumption of these "bush meats" has been incriminated in transmissions to the human host. Like some other RNA viruses, HIV appears to have mutated and shifted its host range and virulence, explaining how a new pathogenic retrovirus could arise in man. Its virulence may since have been amplified as a result of travel, population dislocation and promiscuous sexual contact, with rapid passage of the virus.

Retroviruses are so named because their genomes encode an unusual enzyme, reverse transcriptase, which allows DNA to be transcribed from RNA. Thus, HIV can make copies of its own genome, as DNA, in host cells such as the human CD4 "helper" lymphocyte. The viral DNA becomes integrated in the lymphocyte genome, and this is the basis for chronic HIV infection. Integration of the HIV genome into host cells is a formidable obstacle to any antiviral treatment that would not just suppress but also eradicate the infection. Nevertheless, modern treatment with combinations of nucleoside analogues and protease inhibitors has transformed the prognosis for carriers of HIV, usually achieving a sustained fall in virus concentration in blood and restoration of the main target cell (CD4 lymphocyte) to near normal levels.

By contrast, the inherent variability of the HIV genome and the failure of the human host to produce neutralising antibodies to the virus, as well as technical difficulties and concerns about safety, have continued to frustrate attempts to make an effective vaccine. This must not, however, allow efforts to develop and evaluate candidate vaccines to slacken. A particular concern is that a useful candidate vaccine (probably a recombinant envelope vaccine developed in North America or Europe against the locally prevalent HIV-1 B subtype) would be ineffective in those parts of the world where other subtypes predominate.

WHO estimates that in the year 2000 there are 36 million carriers of HIV worldwide, and only a small fraction of them have access to suppressive treatment. Both their contacts, their dependants and possibly they themselves would have their life prospects transformed by an effective, or even partially effective, vaccine, and successful application of antiviral treatment in developed countries should in no way be allowed to deflect attention from the necessity of developing and delivering an effective vaccine and of promoting "safe sex" behaviour.

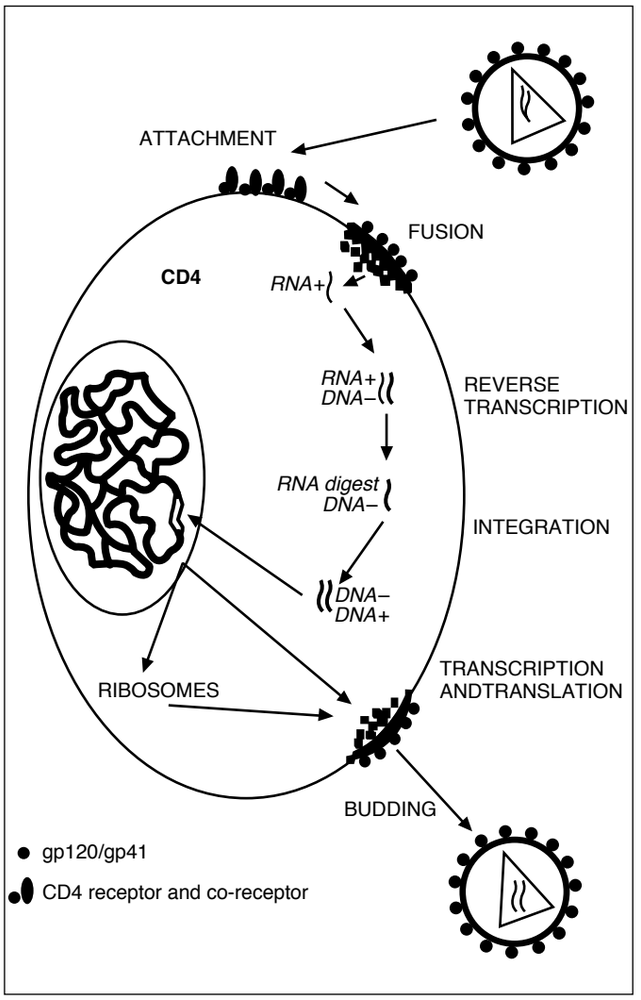


Figure 2.1 HIV replication

HIV and related viruses

HIV was discovered by Barré-Sinoussi, Montagnier, and colleagues at the Institut Pasteur, Paris, in 1983 and given the name lymphadenopathy associated virus (LAV). In 1984 Popovic, Gallo, and co-workers described the development of cell lines permanently and productively infected with the virus. In line with two previously described retroviruses, HTLV-I and HTLV-II, they designated this virus HTLV-III. Other virus isolates from patients with AIDS and AIDS-related disease in America, Europe and Central Africa have proved to be all the same virus, now referred to as HIV-1. Eight subtypes of HIV-1, alphabetically designated, have so far been described.

Around 1985 another human retrovirus, different from HIV-1, was recognised in patients from West Africa. This virus, referred to by the Paris investigators as LAV-2 and more recently as HIV-2, is also associated with human AIDS and AIDS-related disease. It is closely related to the simian retrovirus, SIV, carried by healthy African green monkeys, and the cause of an AIDS-like disease in captive rhesus monkeys. Though potentially important worldwide, HIV-2 infections remain uncommon outside West Africa and they have proved far less virulent than HIV-1 infections.

Transmission of HIV infection

HIV-1 and HIV-2, the major and minor human AIDS viruses, are transmitted in ways that are typical for all retroviruses – "vertically" – that is from mother to infant, and "horizontally" through sexual intercourse and through infected blood. The lymphocytes of a healthy carrier of HIV replicate, and eliminate, over one billion virions each day and the circulating virus "load" may exceed ten million virions per millilitre. At these times viraemia can be recognised by measuring the p24 antigen of HIV in blood and quantifying viral DNA or RNA (see below). Transmission also depends on other factors, including the concentration of HIV secreted into body fluids such as semen, secondary infection of the genital tract, the efficiency of epithelial barriers, the presence or absence of cells with receptors for HIV, and perhaps the immune competence of the exposed person. All infections with HIV appear to become chronic and many are continuously productive of virus. The ultimate risk of spread to those repeatedly exposed is therefore high.

The stage of infection is an important determinant of infectivity. High titres of virus are reached early in infection, though this phase is difficult to study because symptoms may be mild or absent and any anti-HIV response undetectable; it is nevertheless a time when an individual is likely to infect contacts. When, much later, the cellular immune response to HIV begins to fail and AIDS supervenes the individual may again become highly infectious. In the interval between, there may be periods when except through massive exposures – for example blood donation – infected individuals are much less infectious. Nevertheless, in the absence of reliable markers of infectivity, all seropositive individuals must be seen as potentially infectious, even those under successful treatment. Effective ways are constantly being sought to protect their contacts and this has led to the development of the concept of "safe sex". Ideally, this should inform sexual contact between all individuals regardless of whether they are known to be infected with HIV.

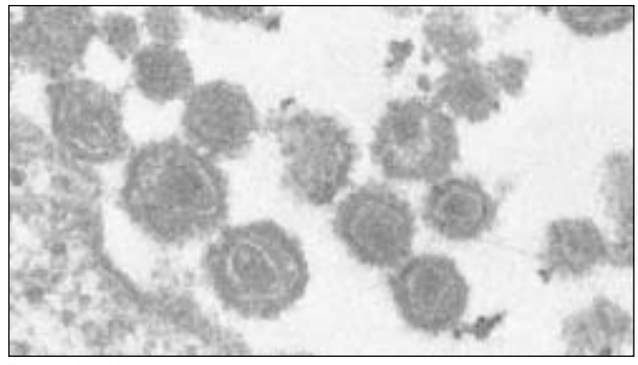


Figure 2.2 HIV particles, many showing typical lentivirus morphology (×118 000)

Box 2.1 Nomenclature of human retroviruses

(a) Two lentiviruses causing AIDS, HIV-1 (previously LAV, HTLV-III) with subtypes A–K, and outliers, HIV-10 and HIV-2
(b) Two oncoviruses causing lymphoma and leukaemia
HTLV-I
HTLV-II

Box 2.2 Transmission factors

- Phase of infection and virus titre
- Local trauma and epithelial damage
- Concurrent sexually transmitted infection
- Intensity of exposure
- Absence of antiretroviral treatment

Figure 2.3 Latex condoms emerging from a dripping tank in the factory
Source: Seohung Industrial Company

Tests for anti-HIV-1 and HIV-2

Anti-HIV tests have transformed our understanding of the epidemiology of AIDS in the years since they were introduced in 1984, and they are still the bedrock of clinical diagnosis and much epidemiological research. Anti-HIV appears three weeks to three months after exposure to HIV and thereafter is invariably detectable in spite of any detrimental effect the virus may have on lymphocyte function and therefore antibody production. Neutralising antibodies to HIV are also measurable, but their titres are low. An inability to mount a neutralising response to HIV antigens together with the mutability of the virus are the most likely reasons why conventional approaches to preparing a vaccine have so far failed.

At first HIV antigen was prepared from infected cell lines. However, antigens can now be made by DNA cloning and expression or by synthesis of viral polypeptides. Several types of anti-HIV test exist, but most use a similar enzyme conjugate and give a colour signal due to the reaction between an enzyme specifically bound onto a polystyrene surface, membrane or inert particles and a substrate that then changes colour. Other tests depend on the binding of a fluorescein or chemiluminescent conjugate, or the visible agglutination of HIV-coated gelatin or latex particles.

Since anti-HIV tests became commercially available in 1985 they have been widely used in diagnostic and transfusion laboratories in the developed world. The accuracy – both sensitivity and specificity – of the antibody assays is continually being improved, and in competent hands the occurrence of false positive and false negative results is less and less frequent. The proportion of true to false positive results depends on the population studied, but even in low risk groups such as volunteer blood donors it is now very high in well conducted laboratories. Human, not test, errors cause most false results, and the key to avoiding these mistakes is continuous review with repeat testing where necessary. All positive reactions should both be confirmed by additional assays and succeeded by a test on a follow-up specimen (see below). The use of several screening tests in parallel on proven positive specimens also acts as a check on the possibility of false negativity in these assays (which it is otherwise difficult to guard against).

More discriminating tests can recognise the components of the antibody response. The serological response to individual HIV proteins can be studied by Western blot, and the immunoglobulin class response to HIV in blood and other fluids can also be investigated. The IgM response slightly proceeds the IgG response early in infection and is indicative of recent infection. Other test procedures, which employ both a highly sensitive and a "detuned" assay for anti-HIV are designed to detect infection within the previous few months and may therefore be used epidemiologically to measure incidence. The IgA anti-HIV response is a feature of infection in infancy.

Simple and non-invasive tests, confirmatory tests, follow-up tests

Simple anti-HIV screening tests have been developed for use in clinics, in unfavourable laboratory conditions and close to the patient. When results are needed urgently, for instance before transplantation procedures and to select a blood donor in the field, they are quick and practical. Saliva (oral fluid) and urine can conveniently be used as specimens to investigate for anti-HIV when venepuncture is difficult, hazardous or unacceptable to the patient. These simple rapid and non-invasive tests are attractive options and may lead to developments such as home

Box 2.3 Anti-HIV

- Appears 3 weeks to 3 months after exposure
- Indicative of infection, except in infants of HIV-positive mothers
- Has weak neutralising capacity
- Persists throughout HIV infection

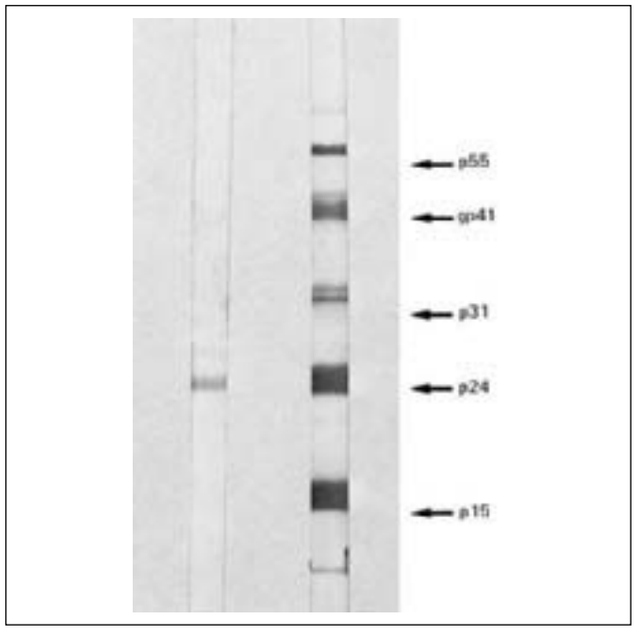


Figure 2.4 The left strip, a Western blot result from a serum specimen collected soon after HIV infection, shows antibody to p24 without other bands being clearly visible. The right strip, a result on a serum sample collected from the same patient 3 months later, shows antibody to many viral proteins, including p15, p24, p31, gp41, and p55

Modern screening kits detect antibody to both HIV-1 and HIV-2. Anti-HIV-2, which is mostly encountered in West Africans and in Europeans who have lived in West Africa, has also been reported in the Indian subcontinent, but it is rare in the Americas. In the UK blood donations and clinical specimens are routinely tested for both infections.

testing. However, few of these tests are quite as accurate as the conventional assays on serum, and follow-up confirmatory tests are essential before a positive diagnosis is made by these means.

In many countries, including the UK, formal procedures have been put in place to secure accurate testing. The most important is that when there is a positive anti-HIV finding the test is repeated and the implicated specimen is tested by other, methodologically independent, anti-HIV assays. Another specimen should then be sought. Although this may cause some delay in confirming a positive finding, anti-HIV testing is as a consequence more precise. A few infected individuals may have little or no detectable anti-HIV when first tested or there may have been technical or clerical mistakes, including specimen misidentifications and transcription errors. Follow-up at an interval of one to four weeks greatly diminishes the chance of either a false negative or a false positive anti-HIV result, and follow-up specimens are the most important element in the accurate laboratory diagnosis of HIV infection. When newly infected individuals are followed up, they show an increase in the titre and range of HIV antibodies. By contrast, persistently weak anti-HIV reactions are usually non-specific. Sometimes PCR (see below) will resolve a difficult-to-confirm antibody reaction. Follow-up procedures also guard against specimen misidentification and transcription errors.

If specimen is anti HIV-positive repeat test using other assay. If HIV-positive take 2nd specimen to confirm.

Test for the virus: antigen, viral DNA and RNA, subtypes, mutants

Viral antigens are present in serum, in particular the HIV core antigen, p24. This is only detectable for as long as it is in excess of antibody to p24, typically at the outset of infection. Tests for this HIV antigen are commercially available, and they assist in the diagnosis of early infection and the recognition of infection in infants. In practice, however, tests for HIV antigen have proved of limited value due to lack of sensitivity, although this may be enhanced by preliminary acid or alkali dissociation of immune complexes in the specimen. Viraemia may also be recognised by isolation of HIV from plasma in cultured lymphocytes, but this is time consuming and not especially sensitive. Essentially it has become a research tool.

HIV can also be detected in specimens in the form of genome sequences. Though only rare lymphocytes carry the HIV genome, the polymerase chain reaction (PCR) can be used greatly to amplify chosen HIV genome sequences in those clinical specimens that contain these small numbers of infected lymphocytes. To a large extent, therefore, viral culture has been superseded by PCR amplification of HIV DNA extracted from mononuclear cells in the circulation. Even more commonly, reverse transcription and amplification of HIV RNA is now being used to detect and quantify virus present in blood. While these procedures are no more accurate than anti-HIV assays and much more expensive, they may be useful in diagnosis, for example in infancy when any anti-HIV detected may be of maternal origin. PCR amplification also provides rapid access to the HIV genome and can lead to characterisation of an HIV isolate to strain level. The (semi) quantification of viraemia (i.e. to within about 0.5 $\log^{10}$) is an important determinant of the need for, and the effect of treatment. It is especially useful as the choice of antiviral combinations widens. Targets for genome amplification include the genes coding for the main envelope, core and transcriptase proteins. On the basis, particularly, of analysis of the sequences of amplified sections of the envelope gene, HIV-1 has been subtyped – so far from A to K. In some cases the sequences found in the various HIV genes are not concordant, showing that recombination occurs in HIV.

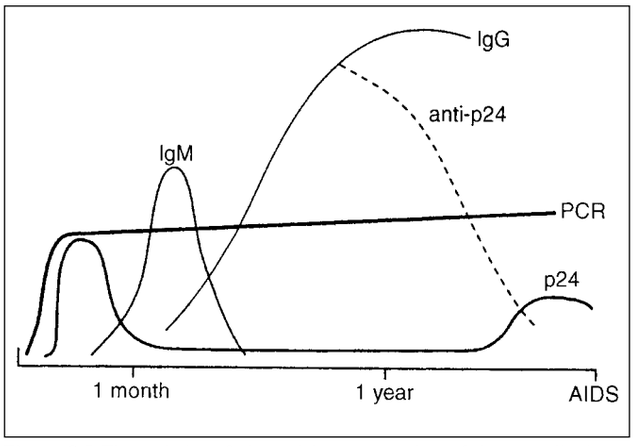


Figure 2.5 The evolution of plasma laboratory markers of the naturalisation of HIV infection ('x' axis not to scale). The course of HIV may now be modified by combined antiviral treatment which will suppress HIV PCR reactivity but not usually modify the anti-HIV response

Sequencing of PCR "amplicons" is also the basis for proving HIV transmission events in special settings, for example, health care.

The growing use of antiretroviral drugs, especially singly, has encouraged the emergence of resistance. This is usually associated with point mutations in the HIV genome. As the common resistance mutations have become better known, testing for them has begun to be used to guide changes in therapy. There is also growing interest in the epidemiology of those mutations that confer resistance for the obvious reason that a highly transmissible resistant mutant might be untreatable and assume an epidemic character.

Testing of patients and blood donors

Tests for anti-HIV-1 and -2, HIV-1 antigen and HIV-1 genome are widely available in the UK. Anti-HIV tests are carried out daily in most public health laboratories and in blood transfusion centres. The facilities in transfusion centres emphatically do not exist to provide testing for those at risk, however. The primary means by which the blood supply is protected from contamination with HIV is through those individuals at increased risk of HIV infection refraining from volunteering to give blood (see chapter 16). Those who wish to be tested for anti-HIV should instead consult their general practitioner or attend a sexually transmitted diseases (genitourinary medicine) clinic, where the advisability of HIV testing can be discussed. If a decision to test is made the necessary investigations are readily and freely available. In some localities "open access" facilities exist to encourage self-referral for counselling and testing. Other innovations, such as home testing on the patient's own initiative, are being considered in the USA and might be introduced into the UK.

As testing becomes more common, and as kits with which people can test themselves are now technically feasible and might be introduced in the future, it is important to be aware of the psychological impact of test findings on those who are tested. While the emergence of effective drug treatment for HIV carriers makes testing for anti-HIV desirable for those who think they may have been put at risk, there should remain an element of medical supervision to respond to patients' questions and anxieties. Telephone helplines have been proposed to provide this support.

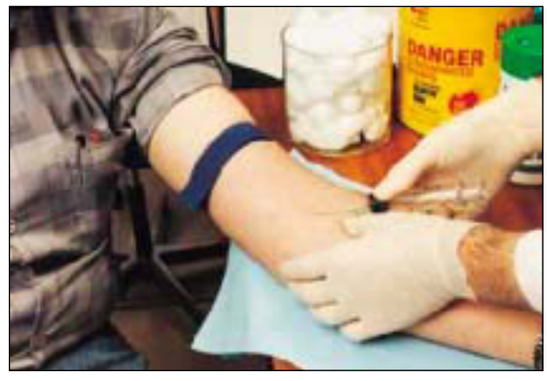


Figure 2.6 Venepuncture to collect a diagnostic specimen. Note the gloved hands and the yellow needleproof container for safe disposal of the needle and syringe.

Important precautions

The desirability of discussing investigations for HIV infection with patients beforehand and of interpreting the results to them afterwards is discussed in Chapter 13. When patients are tested for anti-HIV in a healthcare setting, permission to collect a sample should always have been sought by the doctor and given by the patient. An exception to this is when serum residues, already irreversibly anonymised, are tested for anti-HIV as part of an epidemiological study. Such studies have become a basis for monitoring the epidemic and predicting future trends and resource needs. They have shown, for instance, that in the UK approximately a third of the HIV-infected population (total about 30 000 in year 2000) are unaware of their infection or have not disclosed it at the time of the medical contact.

Clotted blood for testing should be obtained by careful venepuncture without spillage or risk of inoculation accident. The needle and syringe should be disposed of safely and the blood placed in a leakproof container, properly identified, and sent by a secure route to the laboratory. PCR testing requires a fresh EDTA specimen such as commonly used for

Box 2.4 Prevalent HIV infection diagnosed/undiagnosed

30 000 people living with HIV and AIDS in the UK
34% undiagnosed:

Homosexual men	28%
Heterosexual men/women	49%
Injecting drug users	6%

haematological investigations. Oral fluid can be collected from the gum/tooth margin and anti-HIV detected in this fluid. Anti-HIV can also be detected in urine.

The patient's identity and the suspected diagnosis should not be exposed to public gaze, and use of numbers or codes rather than names may be preferred. However, the risk of misidentification may thereby be increased. Patient information should only be shared over the telephone between individuals who know each other, and written reports should be sent to named members of staff, under confidential cover. Positive results should be checked on a fresh newly-drawn specimen. The consequences of breaches of these well-tried procedures may be very serious for patients and damaging to the reputation of doctors. Because of the implications of positive laboratory findings for the health of the patient and his or her family and contacts, and for the patient's social and professional life, a high level of competence and sensitivity is to be expected from all who are concerned in instigating investigation for HIV infection. Testing patients without their informed consent is unacceptable.

Laboratory tests for HIV have increased understanding of AIDS and greatly facilitated diagnosis, management, treatment and control measures. However, to derive most benefit from them and do least harm, tests must be used wisely, with proper regard to all the possible consequences for those who are being tested. Any changes to what are now well-established procedures must be carefully considered, piloted, evaluated for cost-effectiveness, and, if introduced, periodically audited to ensure that they are yielding the benefits promised.

Figure 2.2 was provided by the late JE Richmond and Figure 2.4 by JP Clewley.

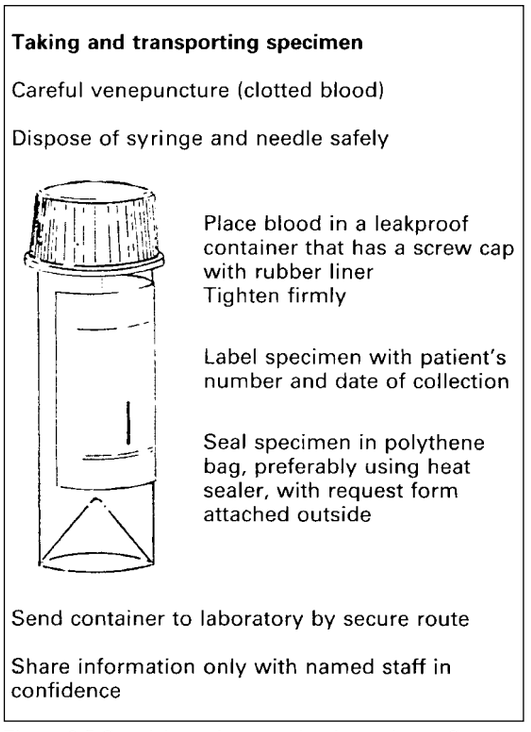


Figure 2.7 Containing and transporting the specimens. Consult the laboratory about appropriate specimens usually clotted blood or blood collected in EDTA

3 Immunology of AIDS

Peter Beverley, Matthew Helbert

Infection with HIV

Many of the clinical features of HIV infection can be ascribed to the profound immune deficit that develops in infected individuals. HIV is immunosuppressive because it infects cells of the immune system and ultimately destroys them. An understanding of this process is helpful in interpreting tests used in monitoring the disease and may explain the failure of immunotherapy and the difficulties in developing vaccines for HIV.

The most obvious target of the virus is a subset of thymus-derived (T) lymphocytes carrying the surface molecule CD4, which has been shown to bind the envelope glycoprotein of HIV (gp120). CD4 is also present on a large proportion of monocytes and macrophages, Langerhans' cells of the skin and dendritic cells of all tissues. More recently it has also become clear that virus entry also requires co-receptors, most of which are members of the seven transmembrane-spanning G protein-coupled receptor family. In the immune system these principally function as receptors for chemokines that orchestrate the migration, differentiation and function of leucocytes during immune responses. Two receptors, CCR5 and CXCR4, are particularly important. CCR5 (R5) is widely expressed on lymphocytes, macrophages, dendritic cells and cells of the rectal, vaginal and cervical mucosae. Virus strains able to infect primary macrophages (macrophage (M) or R5 tropic viruses) use CCR5 as a co-receptor. Only R5 strains are detected early after infection, while both R5 viruses and strains that infect T cells and use CXCR4 (T or X4 tropic viruses) are found late in infection. These data suggest that R5 strains are important for transmission of HIV while X4 variants arise during the course of infection and may be responsible for T-cell loss and disease progression. Even stronger evidence that CCR5-using M tropic viruses transmit infection, comes from the observation that individuals homozygous for a 32 base pair deletion of CCR5 show greatly increased resistance to HIV infection. Several other chemokine receptors have been shown capable of acting as co-receptors *in vitro* and polymorphisms in CCR2 as well as CCR5 and SDF1 (the ligand for CXCR4), are associated with different rates of progression to AIDS.

Table 3.1 Co-receptors and their ligands. A large number of seven transmembrane-spanning receptors which can act as co-receptors have been identified. In most cases their importance *in vivo* remains to be determined. Many are present on some CD4 cells or macrophages

	Type	Ligand
Chemokine receptor		
CXCR4	CXC	SDF-1
CCR2	CC	MCP-1, MCP-2, MCP-3
CCR3	CC	Eotaxin, RANTES, MIP-1α, MCP-3, MCP-4
CCR5	CC	MIP-1α, RANTES, MIP-1β
CCR8	CC	I-309
CCR9	CC	CC chemokines
CX_3CR1	CX_3C	Fractalkine
Orphan receptors		
AJP	?	?
ChemR23	?	?
GPR15/BOB	?	?
STRL33/Bonzo	?	?
Other receptors		
BLTR		Leukotriene B_4
US28	Viral (CMV)	RANTES, MIP-1α, MIP-1β, MCP-1

Immunopathology

CD4 lymphocytes (T helper cells) have been termed "the leader of the immunological orchestra" because of their central role in the immune response, and their destruction accounts at least in part for the immunosuppressive effect of the virus. When these cells are stimulated by contact with an antigen they respond by cell division and the production of lymphokines, such as interferons, interleukins, tumour necrosis factor and the chemoattractant chemokines. Lymphokines act as local hormones controlling the growth, maturation and behaviour of other lymphocytes, particularly the cytotoxic/suppressor (CD8) T-cells and antibody-producing B lymphocytes. Lymphokines also affect the maturation and function of monocytes, tissue macrophages and dendritic cells.

Macrophages and particularly dendritic cells are important antigen-presenting cells for initiating immune responses of lymphocytes. Not only do they act as a reservoir for the virus

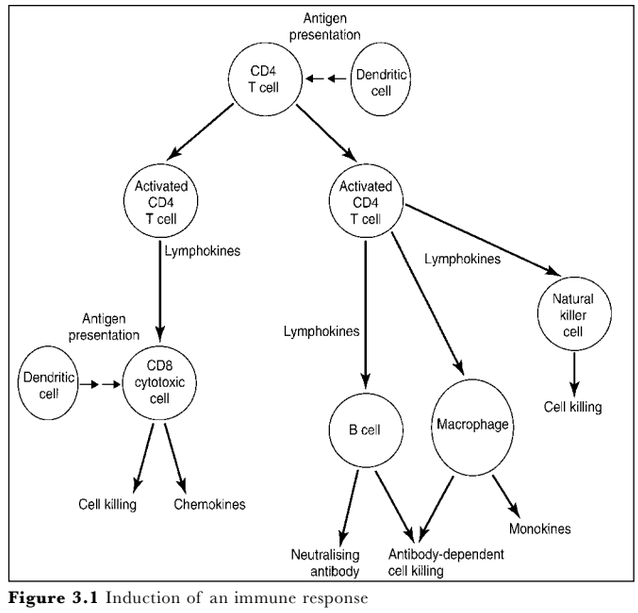


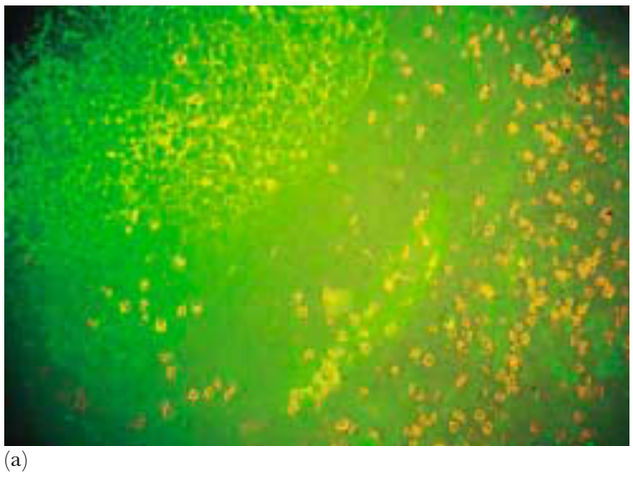
Figure 3.1 Induction of an immune response

but their antigen-presenting function is impaired, with secondary effects on lymphocytes. Monocytes are the precursors to some glial cells and abnormal lymphokine production after HIV infection may have harmful effects on neural tissue and result in HIV encephalopathy.

Early after HIV infection antibody responses are not impaired; indeed, development of antibodies to the virus envelope and core proteins is the principal evidence for HIV infection and persists until death. In adults, massive activation of B lymphocytes is manifested by a rise in serum immunoglobulin concentration, perhaps due to direct activation of B cells by HIV. This polyclonal activation explains why a variety of false positive serological tests are seen in HIV infection. In young children, the reverse pattern may be seen, with extremely low levels of immunoglobulin sometimes requiring intravenous replacement therapy.

Within days or weeks after infection there may be a transient fall in CD4 lymphocyte numbers and a more sustained rise in the number of CD8 cytotoxic/suppressor cells. Among the CD8 cells, expanded oligoclonal populations are frequently seen and as in other acute virus infections, some of these represent a specific response to HIV. Following this acute reaction, healthy seropositive individuals may have normal numbers of lymphocytes, although the numbers of CD8 cells frequently remain high. Even at this stage, however, *in vitro* testing may show a lowered response to previously encountered (recall) antigens (tetanus toxoid or purified protein derivative, for example). This seems to be due to poor production of the lymphokine interleukin 2. Individuals may remain healthy for long periods, but a hallmark of disease progression, often prior to the development of new clinical symptoms, is a fall in the number of CD4 lymphocytes. In AIDS the number of CD8 lymphocytes also falls.

Biopsy of the lymph nodes in patients with persistant generalised lymphadenopathy shows many enlarged follicles, often infiltrated by CD8 lymphocytes, with depletion of CD4 cells. Even in clinically silent HIV infection, lymph nodes are the site of remarkably active HIV replication. Uninfected cells may also die by apoptosis, initiated by unexplained mechanisms. In the later stages lymph nodes return to normal size and follicles become "burnt out", with loss of normal architecture and progressive cellular depletion.



(a)

Figure 3.3 (a): Normal lymph node in which B lymphocytes and follicular dendritic cells (green) form a regular network and suppressor/cytotoxic CD8 T-cells (red) populate the paracortical areas. (b): Node from HIV-positive patient with persistent generalised lymphadenopathy which has been infiltrated by many CD8 cells and in which the regular structure has been destroyed. (c): Same section as middle picture showing complexes of HIV core antigen (orange) and immunoglobulin (red) deposited in germinal centre

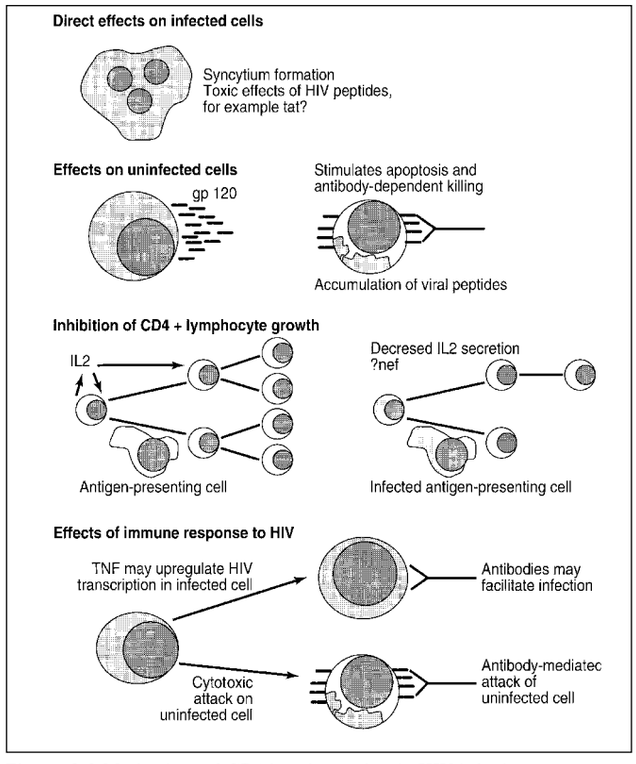
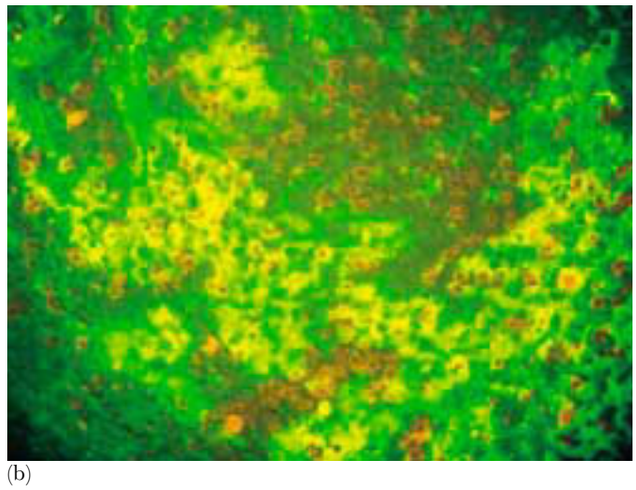
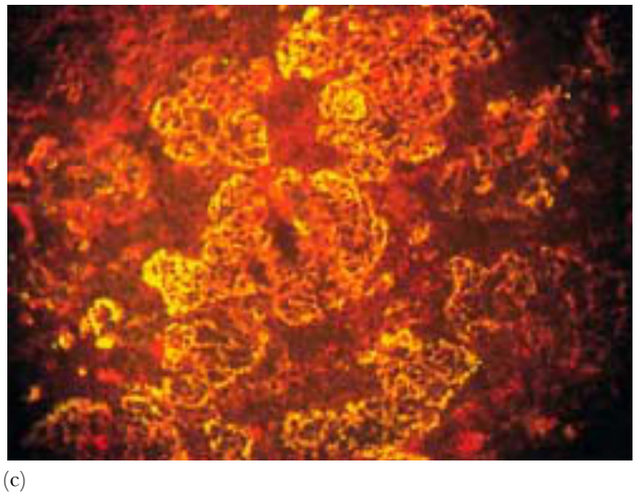


Figure 3.2 Mechanisms of CD4 lymphocyte loss in HIV infection



(b)



(c)

Specific immune responses to HIV

In spite of the fact that HIV-infected individuals show the gross abnormalities of immune function described above, they are able to mount a specific immune response to HIV itself. Although serum reactivity to all the viral proteins is detectable, virus neutralising titres are generally low and directed against the immunising virus strain (type specific immunity). Passive transfer of antibody from asymptomatic to symptomatic patients is claimed to be beneficial, but this requires confirmation. Antibodies to HIV may even facilitate infection of cells bearing immunoglobulin (Fc) receptors, such as monocytes. In AIDS a fall in the titre of antibodies to core protein (p24) is often associated with disease progression. p24 antigen, which is detectable in the serum of some patients, may show a rise at the same time and has been used as a marker of disease progression.

CD8 cytotoxic lymphocytes (CTL) capable of killing HIV-infected targets are detected in most HIV-infected individuals and may be beneficial. This is suggested by the observation that viraemia declines at the time that CTL are first detected following infection, and in patients with stable disease, a high frequency of CTL is detectable in the peripheral blood. In addition, in individuals who have been regularly exposed to HIV while remaining seronegative and without detectable virus, HIV-specific CTL have been detected. As well as killing infected cells directly, CD8 lymphocytes may contribute to protection by producing several chemokines and CAF (CD8 T-cell antiviral factor), which strongly inhibit viral replication in CD4 cells. All this has led to the suggestion that CTL are an effective protective mechanism. However, because reverse transcription is an error-prone process, virus mutants arise, which evade the CTL response (escape mutants). These mutants may not only evade recognition themselves but also inhibit recognition of un-mutated virus.

There is some evidence to suggest that a minority of patients mount a specific CD4 T-cell response to HIV and that this is associated with effective control of virus replication. In animal experiments CD4 cells have been shown to be important for the maintenance of an effective CTL response, which may explain this association.

Box 3.1 Positive and negative effects of immune responses

Antibody

Beneficial effects

- Neutralising antibody (demonstrated *in vitro* only) might prevent primary infection and destroy some infectious particles
- Evidence for beneficial effect of passive transfer of antibody in man requires confirmation

Harmful effects

- Antibody may also help the virus to enter cells with Fc receptors
- Immune complexes may cause tissue damage, anemia and neutropenia

Cellular immune responses

Beneficial effects

- A strong CD8 response is correlated with primary resistance in some individuals and with long-term survival
- Cytotoxic T-cells may delay the progress of disease by killing infected cells.
- They produce CD8 T-cell anti-viral factor (CAF) which inhibits viral replication and may be important in slowing disease progression

Harmful effects

- They may kill uninfected cells which take up shed gp120
- Abnormal cytokine secretion may cause immunopathology (perhaps including encephalopathy)

Table 3.2 Protective mechanisms of CD8 T-cells

	Cytotoxic	Non-cytotoxic
Property or mechanism	Death of infected cells	Inhibition of viral replication
Antigen specificity	Specific for epitopes of viral proteins	Non-specific
Cell contact needed?	Yes	No
Mechanism or CAF	Perforin or fas/fas L	CC chemokines
Induction by vaccination?	Yes	Not known

Monitoring HIV infection

Counting CD4 lymphocyte numbers (the "CD4 count") is an important part of monitoring HIV infection. A progressive downward trend in CD4 cells reflects disease progression and decreased life expectancy, even in the absence of symptoms. Epidemiological studies have firmly correlated distinct ranges of CD4 cell counts with risk of particular opportunist infections. Recent data show that monitoring either the absolute CD4 lymphocyte count or the ratio of CD4 to CD8 cells, the 4:8 ratio, are both equally good at monitoring progression in HIV infection. β_2 microglobulin and neopterin are molecules shed from activated lymphocytes; serum levels increase with progressive HIV infection and can be a useful adjunct to CD4 counts in monitoring.

CD4 lymphocyte numbers have a diurnal variation and delays in the sample reaching the immunological laboratory (for example, when a sample is held overnight) also cause profound changes. Because CD4 lymphocyte counting is a lengthy process, most consistent results are obtained when samples are taken at a set time in the morning and sent straight to the lab. In case of unavoidable hold ups, samples should not be refrigerated.

Box 3.2 Causes of CD4 lymphopenia

- HIV infection: seroconversion illness and during disease progression
- Acute viral infections*
- Tuberculosis*
- Sarcoidosis*
- Corticosteroid therapy
- Purine metabolism defects; ADA and PNP deficiency
- SLE

* Reduce CD4 counts when not associated with HIV and can further reduce levels in HIV infection. ADA, Adenosine deaminase; PNP, Putine nucleoside phosphorylase

CD4 counts should never be used as a substitute for an HIV test because low peripheral blood counts are seen in other conditions. The classic examples are sarcoidosis and tuberculosis (without HIV). Used inappropriately in these settings, a CD4 lymphocyte count may incorrectly suggest a diagnosis of HIV infection. CD4 counts may be low during seroconversion illness but usually recover initially during the asymptomatic phase. Hence there is a need to carry out several baseline CD4 counts if subsequent monitoring is to be useful.

Vaccine development

Immunisation against an organism whose target is an important component of the immune system presents particular difficulties. In addition, HIV has already been shown to be perhaps the most variable virus yet discovered, and HIV-2 differs greatly from all HIV-1 isolates. So far, efforts to immunise against the virus have concentrated on the use of cloned gp120 because all strains of virus so far tested use gp120 to bind to the CD4 molecule, implying that a part of the envelope is similar in all strains. In experimental animals gp120 does induce a neutralising antibody response to the virus but restricted to the immunising strain of virus (type specific immunity) and these neutralising sera do not provide reliable protection against virus challenge *in vivo* in animal experiments. More recently it has been shown that gp120 and its anchor gp41 exist in the viral envelope as a trimer of heterodimers. Because of this and because gp120 is heavily glycosylated, much of the antibody response is to the variable V2 and V3 loops. Furthermore, primary isolates have been shown to be less susceptible to neutralisation than the tissue culture-adapted strains, from which the recombinant gp120 used as immunogen in most experiments derives. Thus new immunogens are needed to raise broadly reactive neutralising antibody and a variety of oligomeric and deglycosylated forms of gp120, lacking the V2 and V3 loops, are being tried.

High levels of CTL are seen in the early stages of HIV infection and the demonstration of CTL escape mutants suggests that they play a role in controlling the virus. That individuals exposed to HIV but with no evidence of infection exhibit CTL responses, reinforces the view that this type of response is important in protection. An effective vaccine might therefore contain components able to stimulate both neutralising antibody, CD4 T-cells and strong CTL responses.

A key factor in generating immune responses is the way in which the antigens are presented to the immune system. For the generation of effective CTL responses attenuated live viruses are effective and attenuated (nef deleted) simian immunodeficiency virus (SIV) has been shown able to protect monkeys against challenge with virulent virus. While such a strategy is unlikely to be used in humans because of worries about the safety of such a virus, it suggests that live viral vectors may be an effective means of immunising against HIV. HIV genes have been inserted into several possible vectors (vaccinia, canary pox, adenovirus) and a number of phase 1 trials are in progress. Alternate means of delivery capable of inducing both antibody and cellular immunity, such as peptides or proteins in novel adjuvants, naked DNA, or the use of different methods of antigen administration in sequence (prime/boost regimes) are under active investigation.

Clearly neither antibody- nor cell-mediated responses prevent the progression of disease in most patients, but they may delay it. However, strong pre-existing humoral and cellular immunity induced by a vaccine might still be protective. Results of vaccination experiments in monkeys and the existence of individuals who appear to be resistant to HIV infection, provide grounds for cautious optimism with regard to the feasibility of

Box 3.3 Strategies for vaccine development

- A good vaccine should induce neutralising antibody, helper T-cells and cytotoxic T-cells.
- Since antibodies bind to three dimensional structures, induction of neutralising antibody requires native envelope.
  Problem: Native envelope is trimeric.
- T-cells recognise 8–15 amino acid-long peptides bound to Major Histocompatibility Complex (MHC) class I and II molecules.
  Problem: Antigen needs to enter antigen presenting cells, usually dendritic cells, to be broken down to peptides.
- Peptides with novel adjuvants can generate good T-cell responses.
  Problem: Different peptides bind to each MHC allele so a large cocktail of different peptides may be needed.
- Adjuvants are needed to induce large responses.
  Problem: There are very few adjuvants available for unrestricted use in humans. Alum is mainly good for induction of antibody responses.
- DNA immunisation can generate antibody, helper and cytotoxic responses and allows incorporation of adjuvant molecules into the vaccine.
  Problem: So far DNA vaccination has not proved as effective in man as in experimental animals.
- HIV is very variable and escape variants arise rapidly in infected individuals. Prophylactic immunisation may tip the balance in favour of the host and prevent escape. Some parts of the virus sequence are relatively invariant, these should be targeted if possible.
- In experimental animals immunisation with different immunogens appears promising. DNA vaccination followed by immunisation with antigen in a recombinant viral vector seems particularly effective. This is now under trial in man.

Table 3.3 Immunotherapy for AIDS

Treatment	Outcome
α and γ interferons	Inconclusive
Interleukin-2	Inconclusive
Cyclosporin A	Not beneficial
Anti-HIV antiserum	Possible transient improvement
Bone marrow transplantation	Transient improvement in lymphocyte count and skin anergy
Anti-CD3 or IL-2 after HAART	Under investigation

producing HIV vaccines. Adequate testing of an HIV vaccine will be difficult in man, although the SIV model provides a model for vaccine development.

Possibilities for immunotherapy

Attempts at immune reconstitution have been made using interleukin 2, interferons, thymic factors or bone marrow transplantation. These have not been notably successful and remain potentially harmful, since the very factors which activate T-cells will also activate HIV replication. *In vivo*, activation of CD4 cells is caused by stimulation with antigens in the form of micro-organisms or vaccines. This suggests that it is sensible to treat intercurrent infections promptly and provides a rationale for prophylactic chemotherapy for pneumocystis. In some studies, vaccination (for example with influenza vaccine) has been shown to be enough of an antigenic stimulus to increase HIV replication.

The advent of highly activated antiretroviral therapy (HAART) has enabled the viral load to be enormously reduced, but the difficulty of maintaining this type of therapy over long periods has led to a search for strategies to complement drug treatment. Two observations are pertinent, the first is that even after 2–3 years of HAART treatment, latent virus can still be detected and the second is that antiviral immune responses decline during treatment. It has therefore been suggested first that latent virus should be "flushed out" by activation of the immune system with anti-CD3 antibody or interleukin 2 while still continuing drug treatment. Secondly vaccination against HIV should be instituted to prevent recrudescence of low level infection. Both strategies are being actively investigated.

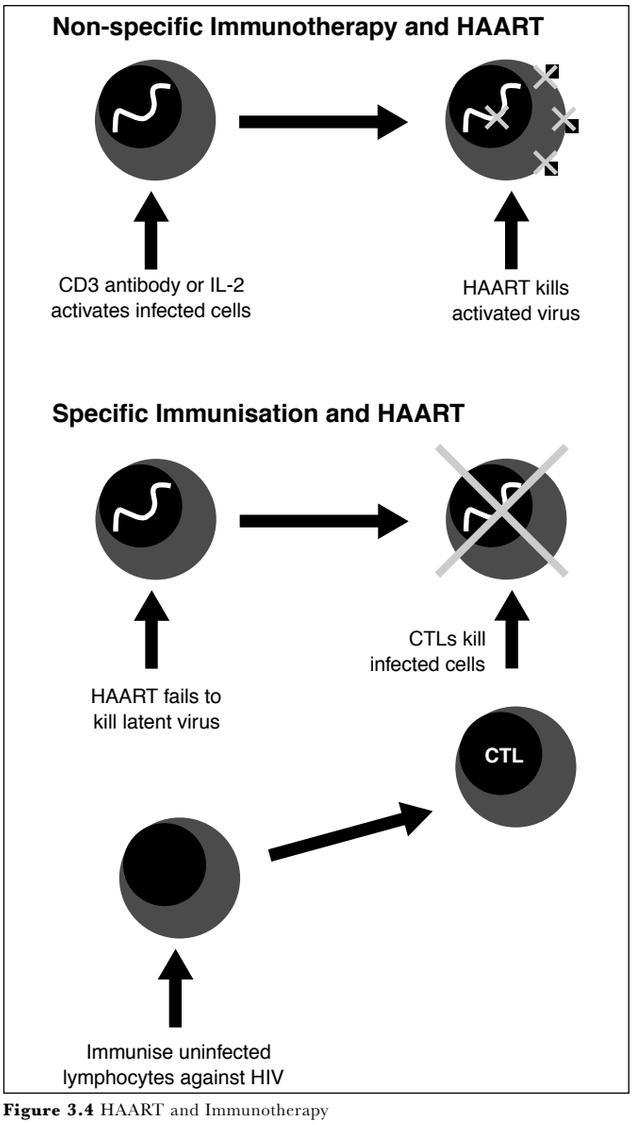


Figure 3.4 HAART and Immunotherapy

4 Natural history and management of early HIV infection

Adrian Mindel, Melinda Tenant-Flowers

Introduction

Infection with HIV causes a spectrum of clinical problems beginning at the time of seroconversion (primary HIV) and terminating with AIDS and death. It is now recognised that it may take 10 years or more for AIDS to develop after seroconversion. The Centers for Disease Control (CDC) in the USA developed the most widely used classification for HIV disease based on the presence of clinical symptoms and signs, the presence of certain conditions and investigative findings, the availability of HIV screening and the degree of immunosuppression as measured by the CD4 lymphocyte count. The infection is divided into four groups (Box 4.1):

Group I Primary HIV infection
Group II Asymptomatic phase
Group III Persistent generalised lymphadenopathy
Group IV Symptomatic infection

Group IV is subdivided into several subgroups and some of these (groups IVA, B, C1 and D) are AIDS-defining conditions (Box 4.1).

In 1993 the CDC included all HIV-infected persons with CD4 lymphocyte counts of <200 cells/mm^3 as fulfilling an AIDS defining diagnosis. However, this additional classification is not widely used outside the USA.

A second classification also combines clinical and CD4 count information. Symptoms and clinical findings are graded in severity from A to C_0 and CD4 counts as they fall from 1 to 3 (Table 4.1).

Group I Primary HIV infection

Primary HIV infection (PHI) is also called the seroconversion illness or acute HIV infection. It represents the stage of infection after the acquisition of the virus when antibodies are developing as shown in Figure 4.1. Between 25% and 65% of people have been found to present with symptoms at the time of seroconversion. These can range from a mild, glandular fever-like illness to an encephalopathy. Common symptoms and signs are shown in Box 4.2. The severe symptoms are rare. The differential diagnosis of the mild seroconversion illness is protean and, without a high index of suspicion and a history indicating relevant risk behaviours or factors, the diagnosis may be missed. Investigations that may be useful in reaching a diagnosis are set out in Table 4.2.

The appropriate diagnostic tests for PHI, which should be carried out on serial blood samples, include tests for HIV antibodies and antigen. If these are negative and PHI is suspected, the definitive test is an HIV RNA PCR, which is the most sensitive test for the detection and quantification of the virus. Some of these assays are not routine and the interpretation of investigation results during PHI is difficult, therefore close consultation with colleagues in virology is strongly advised.

At the time of PHI there is sometimes a high rate of viral replication, leading to a transient rise in HIV viral load and concomitant immunosuppression due to a short-lived fall in the CD4 count. This may result in manifestations of HIV disease

Box 4.1 Summary of CDC 1992 classification system for HIV disease

Group I	Primary HIV
Group II	Asymptomatic infection
Group III	Persistent generalised lymphadenopathy
Group IV	Symptomatic infection
Group IVA	HIV wasting syndrome (AIDS) and constitutional disease
Group IVB	HIV encephalopathy (AIDS) and neurological disease
Group IVC1	Major opportunistic infections specified as AIDS-defining
Group IVC2	Minor opportunistic infections
Group IVD	Cancers specified as AIDS-defining
Group IVE	Other conditions

Table 4.1 Summary of CDC 1993 classification system for HIV disease

	CD4 lymphocyte count $\times 10^6$/l		
	(1)	(2)	(3)
	>500	200–499	<199
(A) Asymptomatic including Groups I, II and III	A1	A2	A3
(B) Symptomatic not A or C	B1	B2	B3
(C) AIDS-defining conditions	C1	C2	C3

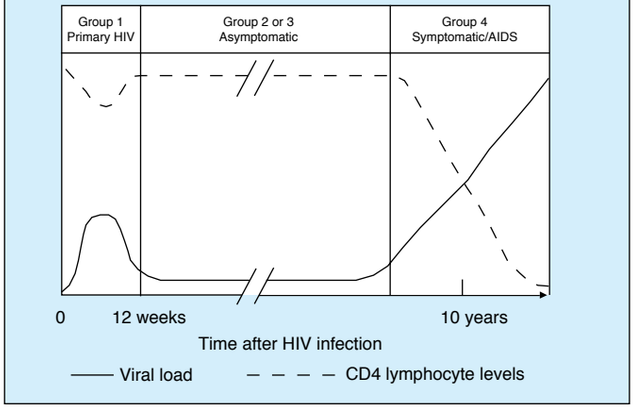


Figure 4.1 Association between virological, immunological and clinical events and time course of HIV infection

Box 4.2 Clinical manifestations of primary HIV infection

- Glandular fever-like illness
- Fever, malaise, diarrhoea, neuralgia
- Arthralgia, sore throat, headaches
- Lymphadenopathy
- Macular papular rash
- Ulceration
  - Oropharynx
  - Anogenital area
- Neurological symptoms
  - Meningitis
  - Neuropathy
  - Myelopathy
  - Encephalopathy

which are normally seen later in the infection, for example oral candida. Diagnostic confusion as to the stage of HIV infection may arise, which can only be resolved by following up the patient for long enough to see the symptoms and signs resolve, HIV antibodies appear, the viral load fall and the CD4 count rise. Treatment should be directed at alleviating any symptoms, and there is considerable interest in the possible use of antiretroviral agents at this time because the virus may be more susceptible due to the relatively low numbers of virus particles which can replicate, the reduced ability of the predominantly non-syncytium-inducing strains of virus to infect a wide variety of cell types and the enhanced immune response seen in PHI.

Such treatment may decrease long-term damage to the immune system and delay or even prevent the development of AIDS. However, if not started within 12–18 months of PHI the theoretical advantage may be lost and, in any case, has to be balanced against the uncertain outcome, drug toxicity, adherence difficulties and the possibility of developing resistant virus, limiting future treatment options.

Group II Asymptomatic infection

After PHI, HIV antibodies continue to be detectable in the blood. The amount of virus in blood and lymphoid tissues falls to very low levels and the rate of HIV replication is slow although it does not cease. CD4 lymphocyte counts are within normal limits or generally above 350 cells/mm^3. This phase may persist for 10 years or more (Figure 4.1). The role of antiretroviral therapy during asymptomatic infections is discussed in chapter 9. The decision to treat is made on the basis of the CD4 count and the viral load. The aim of therapy is to maintain immune function by suppressing viral replication to prevent further damage to the immune system. As for PHI treatment, the potential gain of therapy must be weighed against the potential risks and uncertainties.

Group III Persistent generalised lymphadenopathy

Persistent generalised lymphadenopathy may be a presenting feature of HIV infection in a person who is otherwise well. HIV-related lymphadenopathy persists for at least three months, in at least two extra-inguinal sites and is not due to any other cause. The differential diagnosis of this lymphadenopathy is shown in Table 4.3.

A lymph node biopsy in HIV disease is not recommended as a routine procedure as the findings are non-specific and the presence of lymphadenopathy due to HIV alone does not worsen the prognosis. The indications for a biopsy are the same in HIV and non-HIV-related conditions (Box 4.3).

Group IV Symptomatic HIV infection before the development of AIDS

The progression of HIV infection is a result of a decline in immune competence that occurs due to increased replication of HIV from sites where it has been latent. The exact triggers for this reactivation are poorly understood. As the disease progresses, infected persons may suffer from constitutional symptoms, skin and mouth problems and haematological disorders, many of which are easy to treat or alleviate. A decrease in viral load in response to the introduction of antiretroviral therapy often corresponds to a complete or partial resolution of these symptoms.

Table 4.2 Differential diagnosis of glandular fever-like illness

Condition	Test
Viral	
Infectious mononucleosis	Paul-Bunnell
Cytomegalovirus	Serology/culture
Rubella	Serology
Herpes simplex	HSV culture
Adenovirus	Serology
Hepatitis B/C	Serology
HIV	HIV, Ab, Ag, PCR
Protozoal	
Toxoplasmosis	Serology
Bacterial	
Syphilis	Serology
Streptococcal pharyngitis	Bacterial culture
Brucellosis	Serology
Neoplastic	
Lymphoma or leukaemia	Full blood count/diff Lymph node biopsy Bone marrow

Table 4.3 Common causes of generalised lymphadenopathy

Condition	Test
Infections	
Bacterial	
Syphilis	Serological tests (Venereal Diseases Research Laboratory), *Treponema pallidum* haemagglutination and Fluorescent Antibody tests
Brucellosis	Serological tests
Viral	
Infectious mononucleosis (Epstein–Barr virus)	Paul–Bunnell
Cytomegalovirus	CMV cultures or antibodies
Hepatitis A	Serology
Hepatitis B	Serology
Rubella	Serology
Parasites	
Toxoplasmosis	Toxoplasma serology
Tumours	
Lymphomas, leukaemia's or other tumours	Full blood count, lymph node biopsy, CT or MRI scans etc.
Miscellaneous	
Sarcoidosis	Clinical features, Kviem test

Box 4.3 Indications for lymph node biopsy

- Constitutional symptoms
- Painful nodes
- Asymmetrical enlargement
- Sudden increase in size
- Hilar lymphadenopathy

Constitutional symptoms

Common constitutional symptoms associated with Group IVA HIV infection include malaise, fevers, night sweats, weight loss and diarrhoea. Serious constitutional symptoms are set out in Box 4.4. The exact criteria for diagnosing the AIDS-defining HIV wasting syndrome are, the combination of 10% weight loss from baseline and one of the other serious symptoms set out in Box 4.4. Many patients find these symptoms worrying and debilitating and they should be investigated to diagnose treatable causes other than HIV. Once other causes have been excluded, symptomatic treatment can include antipyretics, antidiarrhoeal agents and, if all else fails, steroids.

Box 4.4 Constitutional symptoms in HIV infection

- Weight loss >10% baseline
- Fever lasting at least 1 month
- Diarrhoea lasting at least 1 month

Skin and mouth problems

Many skin problems occur in patients with HIV infection (Box 4.5). These may represent exacerbations of previous skin disease, or a new problem. Identical skin conditions occur in HIV-negative persons. However, in the immunocompromised, these common conditions may be more severe, persistent and difficult to treat. Many minor opportunistic infections (Group IVC2) manifest themselves on the skin and in the mouth. Seborrhoeic dermatitis is frequently seen and usually presents as a red scaly rash affecting the face, scalp and sometimes the whole body. This condition often responds well to 1% hydrocortisone and antifungal cream.

Box 4.5 Skin and mouth problems associated with HIV

Skin problems

Miscellaneous
Seborrhoeic dermatitis
Fungal
Tinea
  Cruris
  Pedis
  Other
Candida
  Genital
  Perianal
  Other
Pityriasis versicolor
Bacterial
Staphylococcal infection (impetigo)
Acneform folliculitis
Viral
Herpes simplex (types 1 and 2)
  Oral
  Genital
  Perianal
  Other
Varicella zoster
Human papilloma virus
Molluscum contagiosum
Neoplastic
Cervical dysplasia

Mouth problems

Hairy oral leukoplakia
Dental abscesses/caries
Gingivitis
Candidiasis
Ulceration
  Bacterial
  Herpetic
  Aphthous

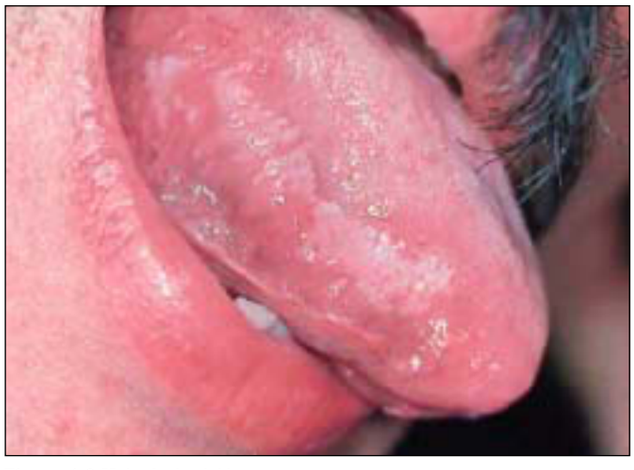


Figure 4.2 Hairy leukoplakia

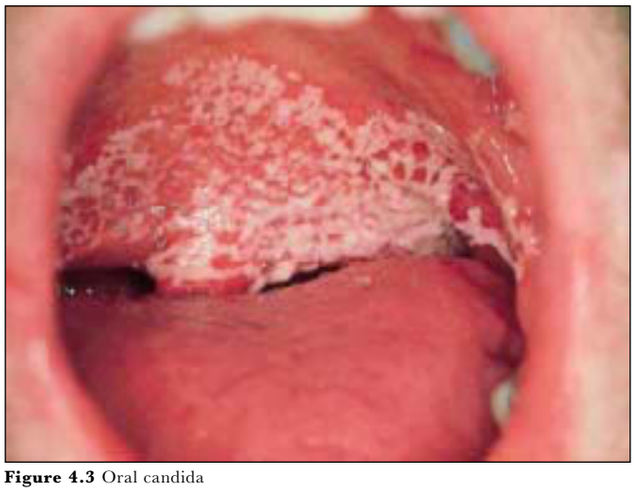


Figure 4.3 Oral candida

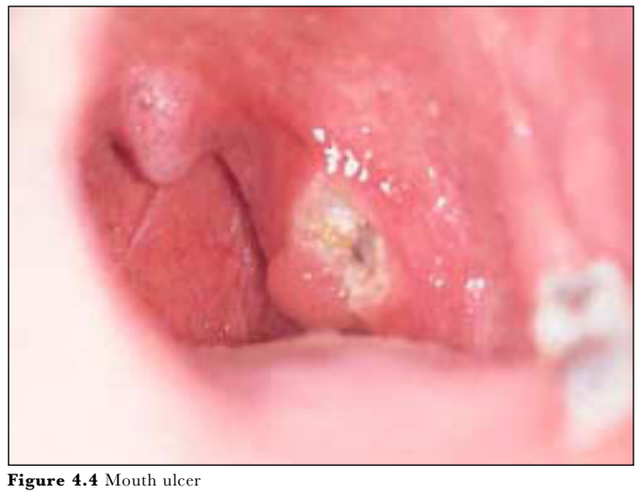


Figure 4.4 Mouth ulcer

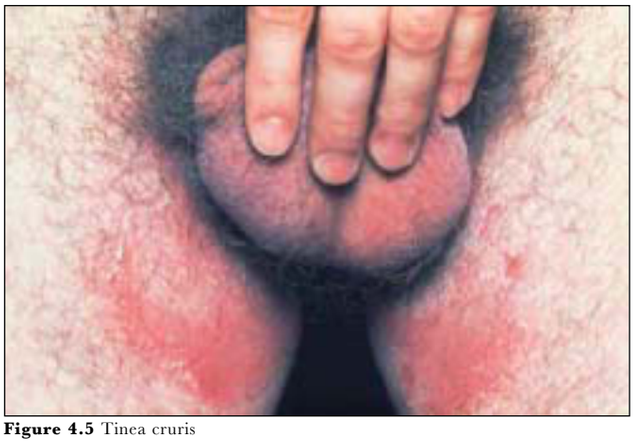


Figure 4.5 Tinea cruris

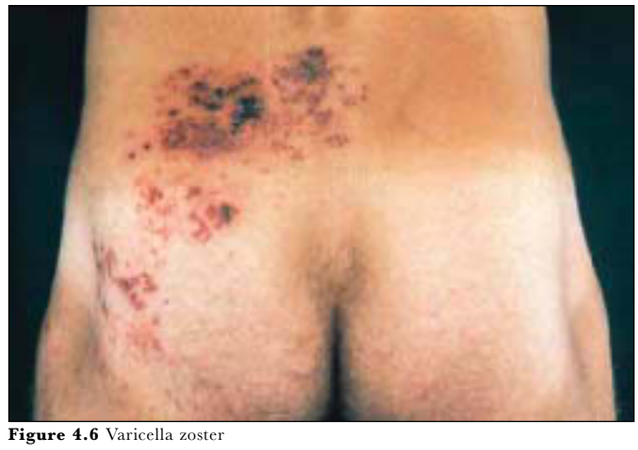


Figure 4.6 Varicella zoster

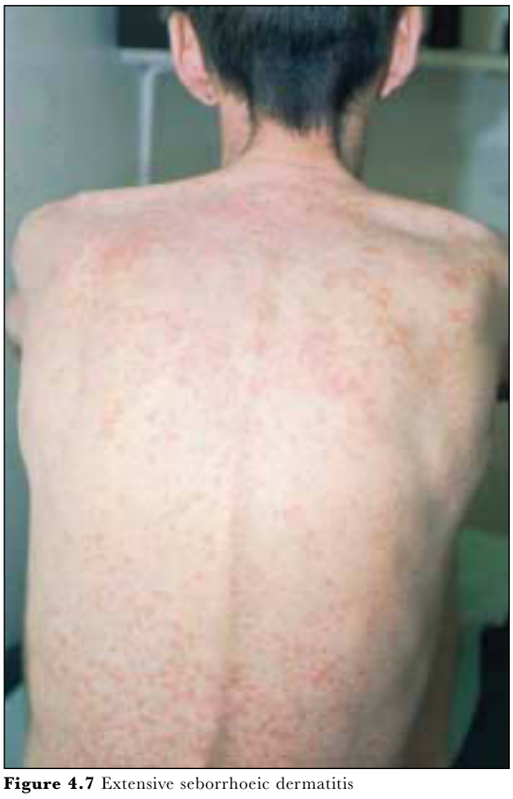


Figure 4.7 Extensive seborrhoeic dermatitis

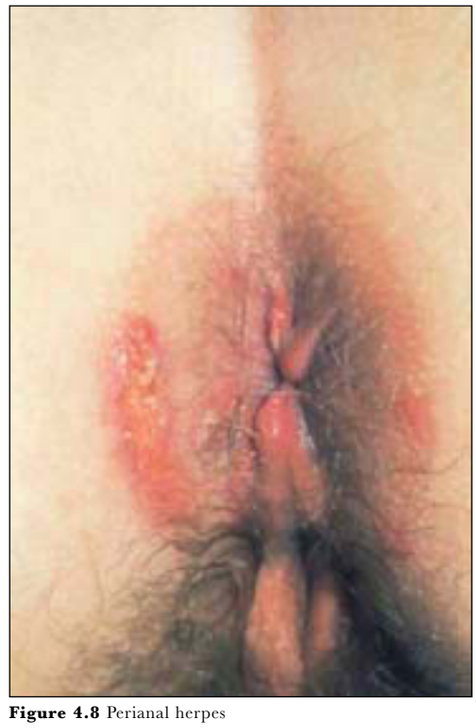


Figure 4.8 Perianal herpes

Other common dermatoses that respond to antifungal creams (for example Clotrimazole) include tinea cruris and pedis and candidiasis. Folliculitis often responds to 1% hydrocortisone and antifungal cream, impetigo to antibiotics and shingles to aciclovir, valaciclovir or famciclovir. Recurrent perianal or genital herpes may become more troublesome, with recurrences lasting longer and occurring more frequently; if this persists for more than 3 months it is considered an AIDS-defining opportunistic infection (Group IVC1). Treatment with long-term acyclovir, valaciclovir or famciclovir suppression is often required. Genital and perianal warts are common, difficult to treat and frequently recurrent, and high-grade cervical dysplasia is seen more often in HIV-infected women.

Mouth problems are also common, cause considerable distress and when severe may result in difficulty with eating and drinking. Oral candida can be managed with topical or systemic antifungals (eg, nystatin, ketoconazole or fluconazole). If dysphagia develops, oesophageal candidiasis should be suspected and investigated. Oral hairy leukoplakia can be differentiated from oral candida by its characteristic distribution along the lateral borders of the tongue and the fact that it cannot be scraped off. Although unsightly, this condition which is due to Epstein–Barr virus reactivation is painless and temporary remission can be obtained with acyclovir, valaciclovir or famciclovir. Other oral conditions including dental abscesses, caries, gingivitis and oral ulceration (herpetic or bacterial) may occur. Mouth ulcers may be particularly difficult to treat and expert specialist assessment is recommended. Metronidazole, acyclovir, 0.2% chlorhexidine mouthwashes and analgesic sprays may all be effective depending on the cause and, in extreme cases, thalidomide has been used. Maintenance of good oral hygiene and dental care are important.

HIV and haematological problems

Lymphopenia with depression of the CD4 cell subset is a marker for HIV disease. Mild to moderate neutropenia and a

normochromic, normocytic anaemia of unknown origin are often seen but usually have no adverse effect on HIV-infected individuals. Severe anaemia or neutropenia should be investigated for other underlying causes. Thrombocytopenia is common in HIV disease and, only if persistent, causing bleeding and less than 20×10^9/litre warrants treatment with antiretrovirals which is usually effective. Many therapies used to treat HIV may be toxic to bone marrow.

Risk of progression and the value of surrogate markers

One of the hardest problems confronting the physician dealing with an asymptomatic patient with HIV infection is predicting how soon that patient will progress to symptomatic disease or AIDS. This issue is important, firstly in terms of counselling and secondly, to decide which patients may benefit from antiretroviral treatment or prophylaxis to prevent opportunistic infections.

Variables associated with rapid disease progression include a symptomatic PHI, older age at diagnosis and receiving a large inoculum of virus, for example via a contaminated transfusion from a donor with a high viral load. The effect of prophylaxis against opportunistic infections (for example cotrimoxazole for pneumocystis and toxoplasmosis) has been to delay the onset of AIDS and to change the pattern of disease represented by the first AIDS-defining illness. Antiretroviral treatment has independently been shown to increase survival before and after AIDS. Some infected individuals do not progress for many years and work is in progress to determine whether this is due to their genetic makeup, amount of viral inoculum, characteristics of the infective virus or their immune system.

Many laboratory indices have been used as prognostic indicators, both to evaluate disease progression and treatment efficacy. The most widely used are the CD4 absolute lymphocyte count or percentage and the viral load. At least two CD4 measurements should be obtained before initiating prophylaxis for opportunistic infections or antiretroviral therapy, as the CD4 count is subject to diurnal and seasonal variation and reduced by intercurrent infection. A fall in CD4 cells is associated with disease progression, particularly if the rate of decline is rapid. Likewise, at least two viral loads, from the same laboratory using the same assay, should be obtained to avoid interassay variation. Some HIV clades are more difficult to monitor with certain assays and the laboratory should be informed of the country of origin of the patient.

Patients who may need close monitoring include individuals whose CD4 count falls below 350 cells/mm^3, those with a rapidly declining CD4 count, those with a rising viral load and patients who are symptomatic as they may all be candidates for antiretroviral therapy. Patients who present with persistent constitutional symptoms, mouth or skin problems should be considered for antiretroviral therapy irrespective of CD4 count and viral load. These issues are discussed further in the chapters on treatment of infections and antiretroviral agents.

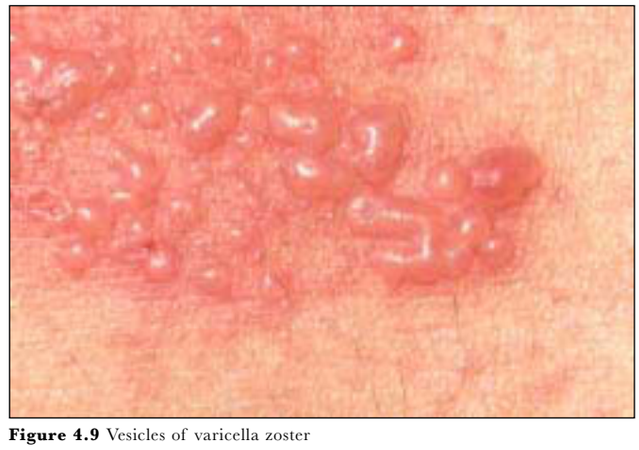


Figure 4.9 Vesicles of varicella zoster

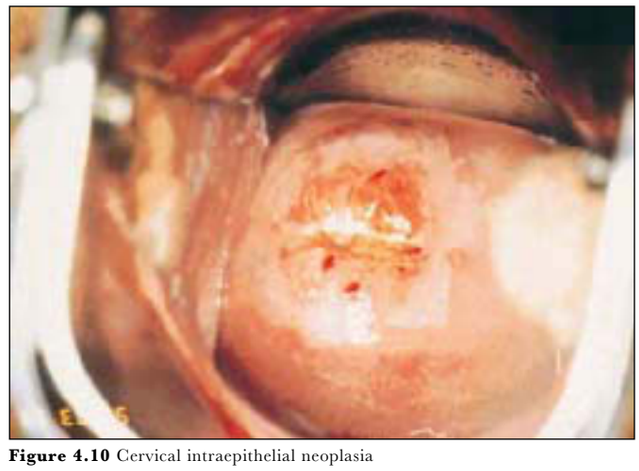


Figure 4.10 Cervical intraepithelial neoplasia

General management of HIV-infected people

One of the most important aspects of dealing with any HIV-infected person is confidentiality (Box 4.6). Maintaining confidentiality might be complicated: for example the patient's family or friends may not know his or her diagnosis or sexual orientation; people at work (or school) may seek medical information (especially if the individual is having time off

Box 4.6 General management of the HIV-infected person

- Protect confidentiality
- Medical issues
- Psychological support (patient, family and friends)
- Avoidance of transmission
- Other issues (dental treatment, insurance, work, or school, etc.)

work); or the person may fear that information may inadvertently be given to third parties. Special precautions may be required, firstly to reassure the patient that confidentiality is protected and, secondly, to limit any unwarranted dissemination of confidential information. Issues related to partner notification are discussed in chapter 13.

The routine medical management of these individuals is usually straightforward. They should be seen regularly, for example every three to six months. At each visit the patient's weight should be recorded and special attention given to mouth or skin problems and, if necessary, they should be referred to the appropriate specialist. Screening for STDs and hepatitis viruses should be offered if the individual is at risk and hepatitis A and B vaccines can be safely given. Repeating a full blood count and measuring the CD4 count and viral load every three to six months allows early detection of actual or imminent immune dysfunction. Patients should be advised to reattend if they develop any symptom, especially those suggestive of opportunistic infections or cancers, for example shortness of breath, cough, haemoptysis, pain or difficulty in swallowing, diarrhoea, weight loss, fevers, headaches, fitting, altered consciousness or purple spots on their skin. Other symptoms may indicate increased viral replication and the need to consider treatment.

Psychological and emotional support of the infected individual, the family and friends are a vital aspect of management (see chapter 13). HIV antibody positive persons should also be advised about reducing the risk of transmitting HIV to others and reducing their own risk of receiving different, possibly drug resistant, strains of HIV. Advice concerning safer sex, safer needle use, pregnancy, breastfeeding and children should also be provided (see chapter 16). Patients should be advised to tell their dentists about their infection, and it may sometimes be necessary to refer them to a dental unit with an interest in HIV-related problems.

The physician may also be asked to advise about insurance, work, immigration, travel passes, housing and disability benefit. Patients should be referred to the relevant legal or benefit agency as soon as possible. Infected individuals will often have considerable difficulty in obtaining life insurance as most insurance companies ask specific questions about the infection and either refuse insurance or charge very high premiums. Finally, patients should be told that being positive is no barrier to employment provided there is no chance of their body fluids entering another person or of them transmitting an opportunistic infection, such as tuberculosis, by coughing. It is worth noting that for notifiable diseases such as TB, standard, confidential public health notification procedures still apply. Because of widespread misconceptions about infectivity which are still prevalent, information about the individual's HIV status should never be divulged to employers without their written consent.

5 Tumours in HIV

Caroline H Bridgewater, Margaret F Spittle

The United States Center for Disease Control recognises three malignancies as AIDS-defining conditions. These are Kaposi's sarcoma, intermediate or high grade B-cell non-Hodgkin's lymphoma (NHL) and cervical carcinoma. Primary central nervous system lymphoma is a rare B-cell NHL that is often considered separately from the other NHLs. Other malignancies are known to have an increased incidence in HIV whilst not being AIDS-defining, for example Hodgkin's disease. All malignancies are more aggressive in HIV positive patients than in the general population and usually present at advanced stages.

The investigation and treatment of suspected malignancy is complicated by unusual presentations and sites of disease, concomitant infections and immunosuppression. Malignancies may occur at different points in the disease process for different individuals and management must be tailored to the patient's overall maximum benefit.

There are many new developments in the understanding of the pathogenesis of AIDS-related malignancies and in the future these will inform new therapies. In the last few years alone highly active antiretroviral therapy (HAART) has had a great impact on the incidence and natural history of some of these malignancies. As opportunistic infections are more easily treated and patients live longer the malignancies are likely to become relatively more common. The incidence of AIDS-related malignancies varies within the different population groups with HIV and as affected groups evolve there will doubtless be a change in the incidence of malignancies seen in the UK. With these rapid changes optimal treatment strategies are controversial and patients should be entered into clinical trials.

Table 5.1 Risk of malignancies in HIV-positive patients

Malignancy	Relative risk compared to HIV-negative population	Viral co-factor
Kaposi's sarcoma	716–972	KSHV (HHV8)
NHL	71–141	EBV
Primary CNS lymphoma (PCNSL)	~100	EBV
Cervical cancer	?	HPV
Hodgkin's disease	5–9	EBV
Anal cancer	3.5–5	HPV
Testicular germ cell tumours	3	?

Box 5.1 Clinical groups of patients with Kaposi's sarcoma (KS)

- "Classic" KS: elderly, predominantly male, Jewish or Eastern European
- "Endemic" or African KS (various types)
- Immunosuppression-related KS (patients with transplants)
- "Epidemic" or AIDS-related KS

Kaposi's sarcoma

Among the first reported illnesses amongst homosexual men in the USA in 1981 was Kaposi's sarcoma (KS), with 20–40% of HIV-infected homosexual men suffering KS. Hitherto KS had been known in three forms. In elderly Jewish or Eastern European patients as "classic" KS, in sub-Saharan Africa as "endemic" KS, and more recently in transplant and other immunosuppressed patients. KS currently remains the most frequent neoplastic condition in AIDS.

Aetiology

The uneven geographical distribution of KS had long suggested that environmental factors were aetiologically important. Epidemiological observations that KS initially occurred in clusters in the HIV population and that it was 20 times more likely in homosexual men than other risk groups suggested a sexually transmitted cofactor. Work in the biological and statistical fields has gone on to establish causality. Whilst no biological pathway has yet been identified, there is now sufficient evidence to state that a DNA virus, Kaposi's sarcoma-associated herpes virus (KSHV) also known as human herpes virus 8 (HHV8), is an essential, although not necessarily a sufficient, cause of KS.

This evidence has primarily come from longitudinal studies showing that KSHV infection precedes KS. This is consistent with analogous evidence of other herpes viruses, for example Epstein–Barr virus (EBV) being oncogenic. KSHV has been

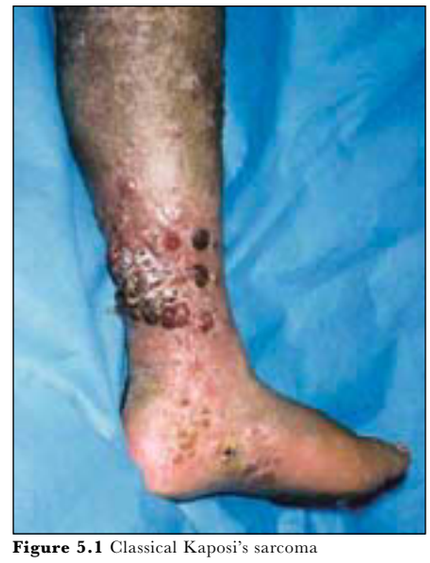


Figure 5.1 Classical Kaposi's sarcoma

detected in tissue biopsies taken from patients with African and classical KS as well as AIDS-related cases.

KSHV can be sexually transmitted and seroconversion has been noted following renal transplantation. In endemic areas non-sexual horizontal and vertical spread are the proposed dominant modes of transmission. The evidence for this is the age-dependent increase in KSHV seroprevalence in prepubescent children in studies from Gambia and Uganda and the greater (29% compared to 0%) seropositivity rate in children born to KSHV seropositive women in South Africa.

Histopathology

The tumours have a characteristic appearance, consisting of groups of spindle cells separated by slits giving a sieve pattern. These spindle cells derive from primitive mesenchymal cells. Red cells are often seen in the slits and early lesions may consist almost entirely of bizarre endothelium-lined vascular spaces in the dermis with few spindle cells.

The tumour stains positive for factor VIII and smooth muscle-specific α-actin on immunocytochemistry staining.

The following cytokines have been shown to promote the growth of KS cells *in vitro*: interleukin 6 (IL-6), tumour necrosis factor (TNF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), Oncostatin M and granulocyte colony-stimulating factor (GCSF). It may be possible to exploit this therapeutically by inhibiting these cytokines.

Kaposi's sarcoma is a multifocal process rather than a metastatic one.

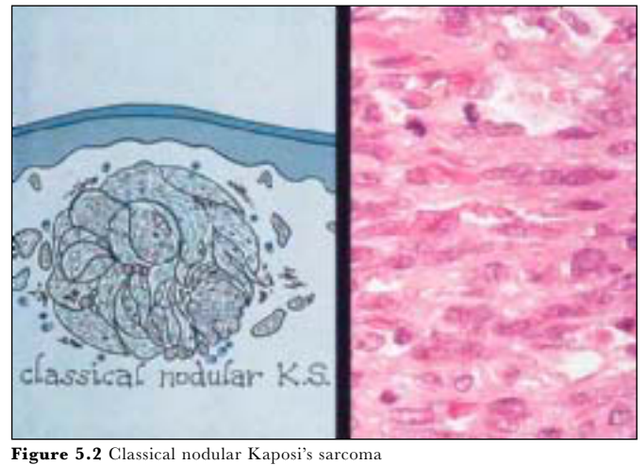


Figure 5.2 Classical nodular Kaposi's sarcoma

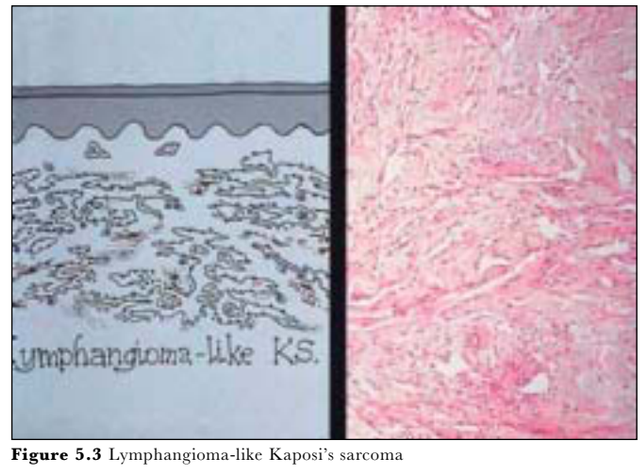


Figure 5.3 Lymphangioma-like Kaposi's sarcoma

Clinical presentation

The classic form tends to follow a very indolent course producing large ulcerated plaques on the lower legs. It shows a strong male preponderance and as most affected individuals are elderly their KS causes significant morbidity but not mortality.

Endemic KS follows a more aggressive course in younger adults with more florid skin lesions and lymph node involvement. Death occurs due to widespread systemic involvement. In young children the lymphadenopathic variant is most commonly seen.

In the non-HIV immunosuppressed patient the lesions of KS may improve with reduction or cessation of the immunosuppression.

In the UK these forms are all rare and most cases of KS are AIDS related.

The presentation of KS in AIDS is variable but the disease tends to become increasingly aggressive and may be lethal. Mucocutaneous lesions begin as flat dusky red papules progressing over weeks or months to vary from a few scattered nodular lesions to large plaques. The legs, trunk, arms, face, hard palate and penis are common sites with associated "woody" oedema and ulceration predominantly affecting the lower limbs. KS on the feet make walking difficult and painful. Other mucocutaneous lesions often cause distress because of their disfiguring appearance.

All organs other than the central nervous system may be affected and the presence of visceral disease is predicted by mucocutaneous disease; one third of respiratory "episodes" in patients with cutaneous KS are due to pulmonary KS. The most common visceral lesions are pulmonary and gastrointestinal. Lymph node disease is also common and may cause venous compression resulting in gross peripheral oedema. Presentation of pulmonary KS is usually with exertional dyspnoea but may be with cough or haemoptysis. Chest radiograph changes are often non-specific with interstitial infiltrates, pleural effusions and mediastinal lymphadenopathy. Further information is

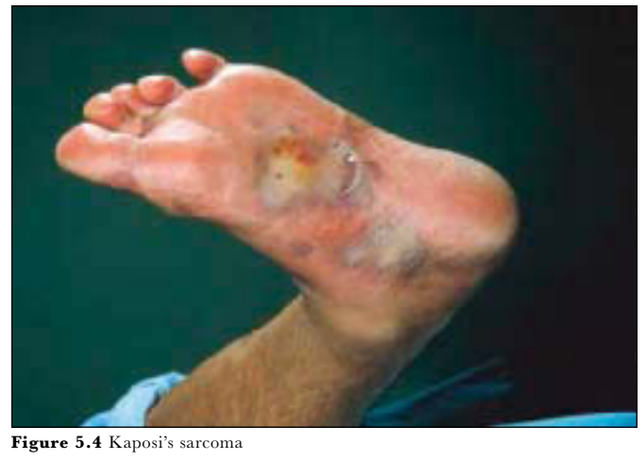


Figure 5.4 Kaposi's sarcoma

gained by bronchoscopy and CT; if possible bronchial biopsy should be avoided as bleeding may be heavy (see chapter 6).

Lesions may occur along the length of the gastrointestinal tract from the palate to the anus and diagnosis is by endoscopy. KS in the oral cavity and oesophagus may cause pain but is usually asymptomatic. Bleeding may occur from lesions throughout the gastrointestinal tract and patients may also suffer protein-losing enteropathy and diarrhoea.

KSHV is also found in two rarer malignancies, primary effusional lymphoma (a subset of B-cell non-Hodgkin's lymphoma) and multicentric Castleman's disease, a lymphoid malignancy which also has an increased incidence in AIDS.

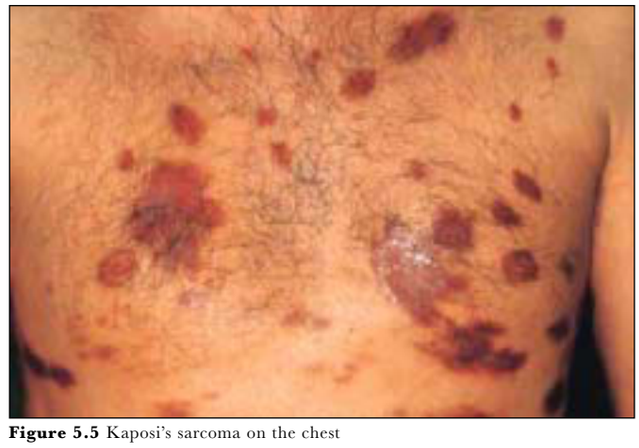


Figure 5.5 Kaposi's sarcoma on the chest

Incidence

KS was the AIDS-defining diagnosis in 30% of patients in the 1980s but this has now fallen. The reduction may be attributed to changes in sexual practices as well as the advent of antiretroviral therapy. KS commonly precedes opportunistic infections and with improvements in treating such infections KS is increasingly common as the cause of death for AIDS patients. Hence whilst the incidence of KS is falling the prevalence is increasing. The deaths of almost 30% of AIDS sufferers are now accounted for by visceral and particularly pulmonary KS.

Treatment

Treatment must be tailored to the site and extent of KS and to the patient's underlying clinical condition. The aim of treatment is resolution of symptoms and prolongation of life. Cure is currently impossible due to the disseminated nature of the condition and its poorly understood pathogenesis as well as the underlying AIDS. HAART has reduced the need for second-line therapies by increasing median time to treatment failure as well as reducing the incidence of KS. There are reports of KS regression with HAART and no other treatment.

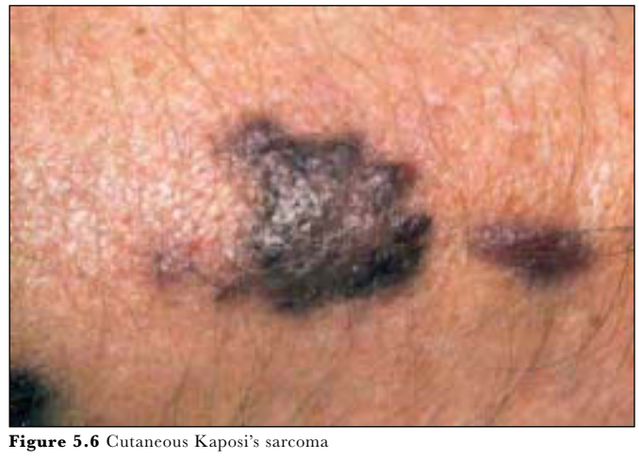


Figure 5.6 Cutaneous Kaposi's sarcoma

Local treatment is important for cosmesis of cutaneous lesions. Superficial radiotherapy is given using 100 kV X-rays applied directly to the skin or palate. A dose of 8 Gy in a single fraction achieves good palliation in 70% of lesions, particularly in early KS with little haemosiderin staining. The area of the lesion is treated with a margin using a lead cutout to protect surrounding tissues. The dose should be given in divided doses on consecutive days (fractionation) to sensitive areas such as the soles or face. Radiotherapy can be repeated if further regression is required or relapse occurs. Alternative treatments include camouflaging with cosmetics and intralesional injection with vinblastine or interferon.

Palatal, bronchial and oesophageal KS can also be treated with radiotherapy. It is particularly useful to stop bleeding.

For extensive mucocutaneous disease or visceral involvement chemotherapy is the preferred option. Several regimens are available and choice of regimen depends on coexistent pathologies and, in some countries, availability and price. Sadly many of the newer treatments with better side-effect profiles are prohibitively expensive for the developing nations where KS is prevalent. In patients with relatively well preserved immune function interferon-α is a useful treatment.

Bleomycin and vincristine in combination was initially the commonest regimen giving a response rate of 50–60% with acceptable side-effects. This has now largely been superseded by the liposomal preparations of doxorubicin and daunorubicin (anthracycline antibiotics) following trials which showed comparable efficacy and reduced toxicity. A liposome is a sphere made of phospholipid bilayers which can be selectively distributed to tumours allowing local drug deposition when the liposome breaks down. Liposomal packaging allows higher doses of these drugs to be delivered with fewer side-effects.

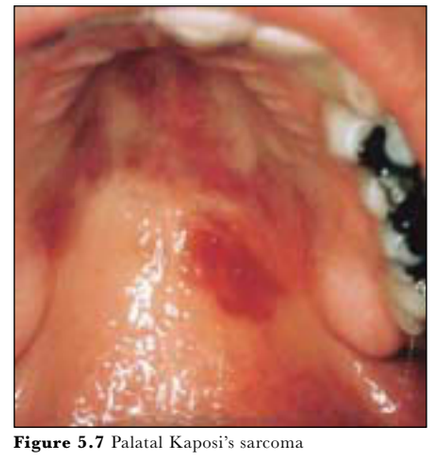


Figure 5.7 Palatal Kaposi's sarcoma

Cumulative doses of non-liposomal anthracyclines are limited at 450–550 mg/m^2 by cardiotoxicity and in a chronic condition like KS long or repeated courses of chemotherapy may be required.

More recently there has been increased interest in the use of antiangiogenics and trials are currently underway on the tyrosine kinase receptor inhibitor SU5416 and thalidomide. This has been fired by studies showing the presence of vascular endothelial growth factor and basic fibroblast growth factor in KS tissues. Paclitaxel, a newer cytotoxic, is also undergoing trials. Common side-effects are those shared with many other cytotoxics including nausea, vomiting, myelosuppression and mucositis. In the AIDS patient, with concomitant diseases and multidrug therapy including HAART, it can be difficult to find the root cause of such symptoms.

Box 5.2 Summary of malignancies

AIDS-defining malignancies
- Kaposi's sarcoma
- High/intermediate grade non-Hodgkin's lymphoma including primary CNS lymphoma
- Cervical carcinoma

Other malignancies with increased incidence
- Hodgkin's disease
- Ano-genital squamous cell carcinoma
- Testicular germ cell tumours

Non-Hodgkin's Lymphoma

The occurrence of non-Hodgkin's lymphoma (NHL) was known to complicate immunodeficiency states before the advent of HIV. Up to 20% of HIV positive people may ultimately develop NHLs and it is the presenting diagnosis in 3% of patients. In immunodeficiency NHLs are commonly extranodal.

Aetiology

Both HIV itself and its related opportunistic infections may cause polyclonal B-cell expansion which is probably cytokine and antigen driven. Patients with AIDS have impaired immunity to EBV when compared to HIV negative EBV-infected individuals and EBV is itself likely to cause polyclonal B-cell proliferation. AIDS lymphomas have modified immunoglobulin variable regions which are consistent with antigen drive as an important factor in lymphomagenesis. Macrophages, acting as antigen-presenting cells, also appear to be clonally expanded. When CD4+ T-cell levels fall, antigen levels rise and the risk of lymphomagenesis increases. Such proliferation allows for sequential genetic errors leading to a monoclonal and hence malignant transformation.

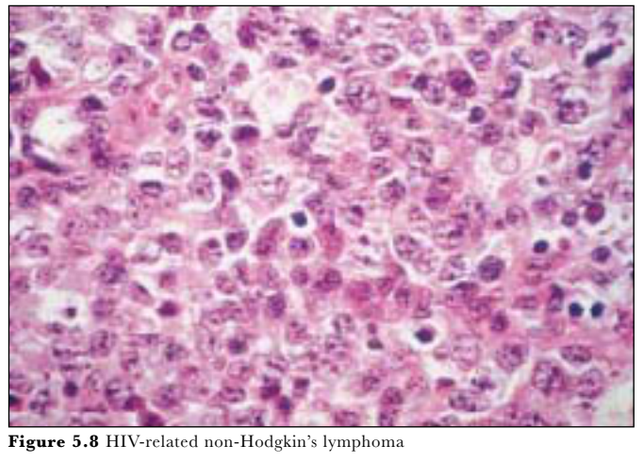


Figure 5.8 HIV-related non-Hodgkin's lymphoma

Pathology

Systemic lymphomas in AIDS are pathologically diverse. A diffuse small non-cleaved subset is unique to HIV patients and is associated with elevated IL-6 and soluble CD23 levels. It is less frequently associated with EBV than the diffuse immunoblastic or diffuse large cleaved cell subtypes. Histological type does not currently affect prognosis although the different subtypes are clinically separate. All these subtypes are high grade.

Immunohistochemistry reveals positive staining for CD20 in 90% of B-cell lymphomas.

Clinical presentation

NHL can occur at any stage of immunodeficiency with approximately one-third of patients with AIDS-related NHL having a previous AIDS diagnosis. Stage III or IV disease accounts for 70%–80% of cases (see Box 5.3) with a majority of patients presenting with extranodal disease. Common sites are the gastrointestinal tract, liver and bone marrow. Bone marrow involvement occurs in 20%–30% of cases and exacerbates chemotherapy-induced bone marrow toxicity.

NHL is associated with B symptoms of sustained fever greater than 38°C, weight loss (greater than 10% of body weight) and night sweats. All of these symptoms may occur in an HIV positive patient without NHL and so are of limited diagnostic and prognostic use in this clinical setting.

Box 5.3 Ann Arbor: classification of lymphoma

Stage I	Single lymph node region +/– local spread to extralymphatic tissue (E)
Stage II	Two or more node regions on same side of diaphragm +/– local spread to extralymphatic tissue (E)
Stage III	Involved nodes both sides of the diaphragm
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs

Prognosis is poor with a median survival of 4–6 months in spite of an often good early response to treatment. A previous AIDS-defining illness, a CD4 count $<100 \times 10^6$, bone marrow involvement and poor performance status are all poor prognostic factors. In good prognosis patients the median survival is still only 11–14 months.

Treatment

Treatment of any lymphoma is based on its stage and grade and the patient's ability to withstand the rigors of treatment. For AIDS patients with their high-stage, high-grade disease this means chemotherapy. When faced with patients who are immunosuppressed and have poor bone marrow reserve before treatment the oncologist must make a balanced choice between reduced doses, which may compromise benefit, and quality of life. CHOP combination chemotherapy giving cyclophosphamide, vincristine and doxorubicin with oral prednisolone is delivered three weekly. Alternatively m-BACOD (methotrexate, Bleomycin, Adrianycin, Cyclophosphamide, Vincristine, Dexamethasone), another combination regimen, can be given. These regimens are toxic to bone marrow and in order to allow second and subsequent courses to be given on time patients may require GCSF. Prophylaxis against *Pneumocystis carinii* pneumonia should be considered. Allopurinol should be given to patients with bulky disease to prevent gout occurring when uric acid levels rise as the tumour breaks down. Patients with positive cytology or EBV DNA detected in their cerebrospinal fluid and those with meningeal or extensive sinus or base of skull disease require concomitant intrathecal methotrexate and cytosine arabinoside. Alternative chemotherapy regimens are undergoing trials but few have proved superior to CHOP and often result in worse immunosuppression and opportunistic infections.

For patients who have poor performance status, low CD4 counts and other AIDS diseases, palliative chemotherapy of vincristine plus prednisolone can be given. Radiotherapy is also useful for the palliation of symptoms caused by bulky disease. In the rare cases where NHL in AIDS presents as Stage I or II disease radiotherapy can be used as first-line treatment, avoiding the toxicity of chemotherapy.

Median survival is better in patients obtaining a complete response initially. In most studies half the patient deaths have been due to the lymphoma with remaining deaths being due to opportunistic infections.

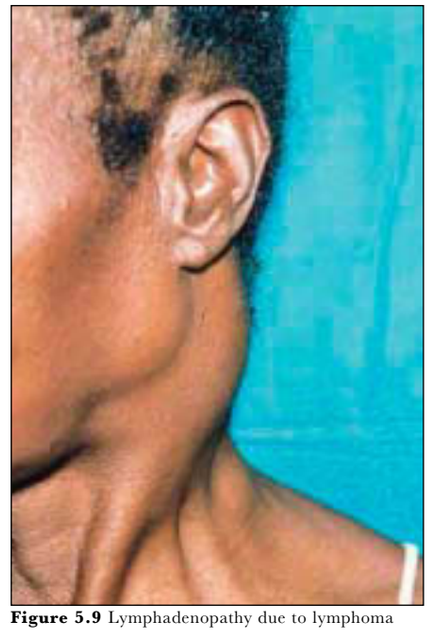


Figure 5.9 Lymphadenopathy due to lymphoma

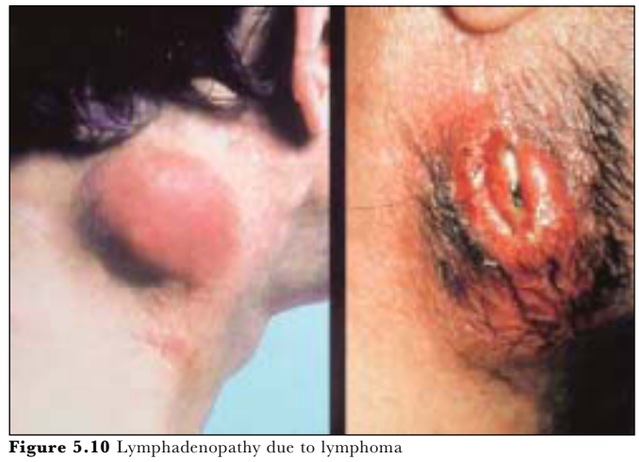


Figure 5.10 Lymphadenopathy due to lymphoma

Primary cerebral lymphoma

This is a strongly EBV-related process which occurs late in the clinical spectrum and accounts for around 15% of AIDS-related lymphomas. It is pathologically very similar to the post-transplant lymphoproliferative syndromes with EBV-latent gene expression. The presence of EBV DNA in the cerebrospinal fluid is highly predictive for primary central nervous system lymphoma (PCNSL). In the general population it is vary rare accounting for only 0.5–1.2% of all intracranial neoplasms which in themselves are rare. The incidence of PCNSL is also increased in other immunosuppressed conditions. PCNSL affected 2–6% of HIV positive individuals in the pre-HAART era. Typically patients have CD4 <50 cells/mm3 and a history of prior opportunistic infections. These lymphomas are always of the diffuse immunoblastic or diffuse large cleaved cell types. Prognosis is even worse than that for systemic lymphoma with median survival being only 1–2 months.

Cerebral lymphoma may be difficult to differentiate from cerebral toxoplasmosis, as both have a variable presentation ranging from subtle personality changes to seizures. Both

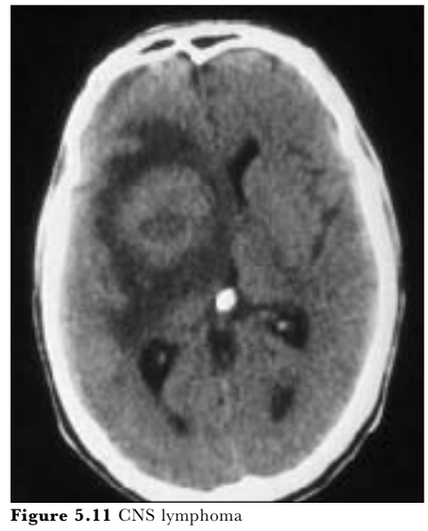


Figure 5.11 CNS lymphoma

commonly appear as multiple enhancing lesions on CT or MRI scanning. Initial treatment is usually empirically directed against toxoplasmosis. If this fails PCNSL can only reliably be confirmed by biopsy and many patients are reluctant to undergo such a procedure when life expectancy is limited. Once a definite diagnosis is made treatment is with high dose steroids and radiotherapy. Patients who respond tend to die of opportunistic infections reminding us that the underlying condition is advanced by the time PCNSL occurs.

Cervical carcinoma

For other malignancies in HIV the main predisposing factor is immune deficiency; however, the relationship between squamous cell neoplasia of the cervix and HIV is unique because of common sexual behaviour risk factors.

Viral DNA from high-risk types of the human papilloma virus (HPV16, 18, 31, 33, and 45) is found in 90% of all cervical cancers irrespective of HIV status. Not every woman with HPV infection develops cervical carcinoma and HPV infection alone is not sufficient for tumour development. Persistence of infection is probably important and other risk factors include smoking, oral contraceptive use and early pregnancy. HPV infection in HIV-infected women may represent reactivation of HPV types acquired in the past rather than recent acquisition of new types.

HIV positive women have a high rate of vulvo-vaginal infection which may make screening unreliable, regular Pap smears are therefore critical. Cervical intraepithelial neoplasia (CIN) is more commonly of a higher grade in HIV positive women and if invasive carcinoma ensues it is also more aggressive. A low threshold for referral for colposcopy is essential. Standard treatment strategies of ablation and excision have yielded disappointing levels of recurrence and patients need to be followed up very closely. If invasive disease ensues treatment is as for immunocompetent patients with surgery, radiotherapy and chemotherapy. Unfortunately treatment reactions are often severe with patients suffering severe vaginal mucositis.

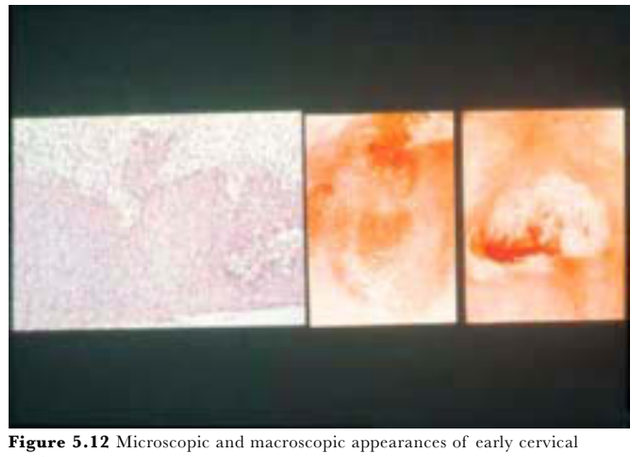


Figure 5.12 Microscopic and macroscopic appearances of early cervical carcinoma

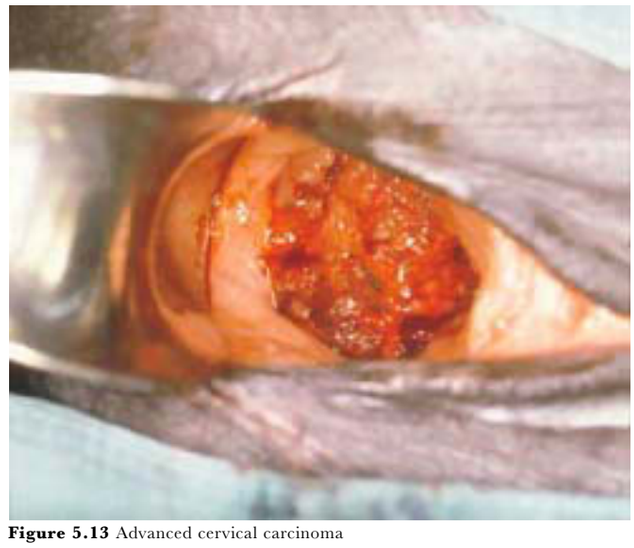


Figure 5.13 Advanced cervical carcinoma

Other associated malignancies

Hodgkin's disease

Hodgkin's disease is three to nine times more common in HIV patients compared with the general population. In Spain and Italy there is a high incidence of HIV amongst intravenous drug abusers who suffer more Hodgkin's disease than HIV sufferers in the UK. Research is needed here as in so many areas to discover the relevance of this observation. Hodgkin's disease tends to occur relatively early in HIV infection with a median CD4 cell count of 300/mm^3.

As with the non-Hodgkin's lymphomas, presentation is usually with bulky or advanced stage disease and 50% have bone marrow involvement. Most patients have B symptoms. In the HIV negative population Hodgkin's disease is typified by contiguous spread, this is not the case in HIV patients. Histologically tumours are usually high-grade mixed cellularity (41-100%) and lymphocyte-depleted subtypes (20%) and behave aggressively. Between 80% and 100% of Hodgkin's disease tissue from HIV-infected individuals is associated with EBV infection and this is probably relevant in pathogenesis. Treatment is with combination chemotherapy using standard regimens such as ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and antiretrovirals. Bone marrow toxicity makes GCSF and dose reductions frequent necessities. If patients can continue their antiretroviral therapy throughout

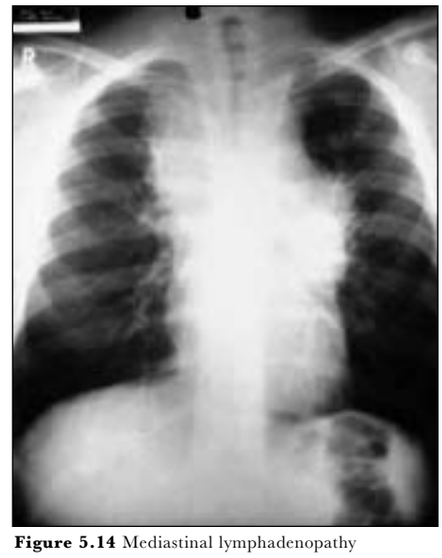


Figure 5.14 Mediastinal lymphadenopathy

chemotherapy they suffer less immunosuppression. Complete responses following chemotherapy are seen in 45–70%. Median survivals are 12–18 months and whilst not being an AIDS-defining condition 94% of patients progress to AIDS by 2 years. Good prognosis is associated with no prior AIDS diagnosis, CD4 $>250 \times 10^6$/l and complete response to treatment.

Ano-genital squamous cell carcinoma

Anal cancer like cervical cancer is related to human papillomavirus. HIV positive patients are two to six times more likely than HIV negative persons to have anal human papillomavirus infection. Persistence of infection is inversely related to CD4 count. Low-grade anal intraepithelial neoplasia is more likely to progress to high grade anal intraepithelial neoplasia in HIV positive patients. However it remains unclear whether HIV directly affects the development of anal carcinoma.

There is a threefold increase in incidence in testicular germ cell tumours in homosexual HIV positive men. Seminoma is much more common than teratoma. Lung cancer of all histological types, non-melanomatous skin cancers, angiosarcomas and paediatric leiomyosarcomas may all be increased in HIV infection. Lung cancers occur at an earlier age and have a poorer prognosis in the HIV positive population.

The effect of HAART

With the improved control of HIV replication brought about by combination antiretroviral therapy, the frequency of AIDS-related malignancy is falling. The incidence of KS has dropped by approximately 75%. Sadly there has been a smaller decline in the incidence of NHL, although primary CNS lymphoma has also markedly declined. The lack of change in the incidence of systemic lymphoma reflects a heterogeneous and complex pathophysiology, not as susceptible to the influence of HAART as KS.

The effect on HPV-associated anogenital squamous cell carcinoma has also been disappointing.

This varied response highlights the continued need for innovative treatments, both in terms of chemotherapy and the manipulation of the immune response.

Current research and the future

The rapidly increasing evidence on viral involvement in AIDS-associated malignancies suggests novel molecular targets for drug discovery using drug screening and molecular modelling. Vaccines for cancers occurring in patients with human papilloma viruses associated with cervical and ano-genital carcinoma and EBV in haematological malignancies are currently being researched. Other therapeutic approaches include biological therapy (for example IL-2, IL-12, IFN-α), immune-based therapy (for example antigen-presenting cells and monoclonal antibodies against B-cell targets) and angiogenesis inhibitors.

New assays to detect KSHV are now in use. Further work is needed on the cofactors influencing the progression of KSHV seropositive individuals to the development of KS. The anti-herpes drug cidofovir has activity against KSHV but it remains to be seen as to whether it is an effective treatment for KS.

To improve existing treatments the effects on the underlying HIV infection and the impact on the immune system of anti-tumour therapy need to be identified. As anti-HIV therapies have a clinical effect on tumour incidence, complex issues of drug–drug interactions and overlapping toxicities must be considered.

In the HAART era NHL is likely to become the most common malignancy associated with AIDS — new treatment strategies are urgently needed as treatment is currently extremely disappointing. Possibilities include the exploitation of cytokine networks, as we already know that these patients have low levels of IL-2 and IFN-γ but elevated IL-6. Treatment with low-dose IL-2 is already undergoing trials.

6 AIDS and the lung

Rob Miller

The lungs are commonly affected in patients infected with HIV, with over 60% of patients having at least one respiratory episode during the course of their disease. When immune responses are relatively well preserved in early HIV infection the pattern of respiratory infections is similar to that found in the general population, although they occur with greater frequency. The risk of opportunistic infections and tumours increases as progressive HIV-induced immunosuppression occurs. Over recent years there have been several changes in the pattern of lung disease seen in those infected with HIV. These changes may be accounted for by the widespread availability and uptake of prophylaxis for *Pneumocystis carinii* pneumonia and combination antiretroviral therapy (also known as highly active antiretroviral therapy or HAART).

Box 6.1 HIV-associated respiratory disease

Infections
Bacterial bronchitis/sinusitis
Bacterial pneumonia
Tuberculosis
P. carinii pneumonia
Fungal pneumonia
Cytomegalovirus pneumonitis

Malignancy
Kaposi's sarcoma
Lymphoma
Lung cancer

Non-malignant conditions
Lymphoid interstitial pneumonitis
Non-specific pneumonitis

Investigations

Symptoms of cough and dyspnoea with or without fever and sweats identify the presence of respiratory disease in HIV positive patients, but these are non-specific and symptomatic patients should be investigated.

Box 6.2 Investigation of respiratory disease

Non-invasive tests
Chest radiograph
Arterial blood gases or oximetry
Pulmonary function tests

Invasive tests
Induced sputum
Fibreoptic bronchoscopy and bronchoalveolar lavage with or without transbronchial biopsy
Open lung biopsy

Non-invasive investigations

These tests should ideally allow a specific diagnosis to be made and a therapeutic response monitored by a quick, cheap and universally available method. Unfortunately, none of these tests fulfils the criteria but they do help to:

- Determine the presence or absence of pulmonary disease.
- Assess disease severity.
- Determine if an invasive test is indicted to make an aetiological diagnosis.

Chest radiology

The chest radiograph may be normal in HIV positive patients with respiratory disease caused by *P. carinii* pneumonia. The most common abnormality seen in patients with pneumocystis pneumonia is bilateral perihilar haze which may be very subtle and easy to miss. More severely unwell patients may have more diffuse interstitial shadowing which may progress to severe consolidation with "white out" throughout both lung fields, with sparing of the apices and costophrenic angles. These radiographic appearances are non-specific and may also be seen in pyogenic bacterial, mycobacterial and fungal infection, and also in Kaposi's sarcoma and lymphoid interstitial pneumonitis. Between 5% and 10% of patients with pneumocystis pneumonia have atypical chest radiographs showing cystic changes, upper lobe infiltrates mimicking tuberculosis, hilar or mediastinal lymphadenopathy or focal consolidation. The chest radiograph in pneumocystis pneumonia may deteriorate very rapidly from being normal to showing severe abnormality in just a few days. By contrast, radiographic recovery can be slow. Nodular shadowing, adenopathy and pleural effusions on the chest radiograph suggest *Mycobacterium tuberculosis*, Kaposi's sarcoma or lymphoma.

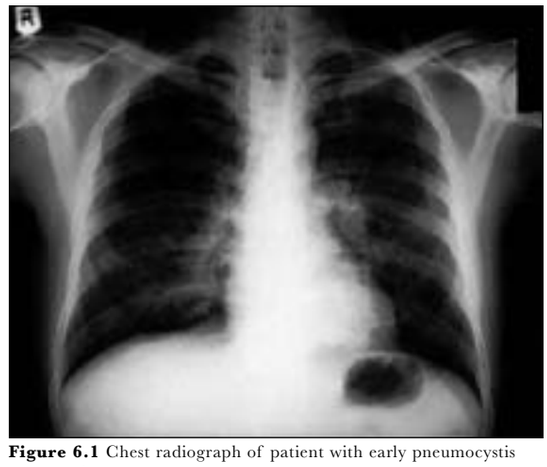


Figure 6.1 Chest radiograph of patient with early pneumocystis pneumonia

Arterial blood gases and oximetry
Hypoxaemia and a widened alveola–arterial oxygen gradient are very sensitive for the diagnosis of pneumocystis pneumonia but may also occur in other conditions. Exercise-induced arterial desaturation detected by oximetry is also sensitive for the diagnosis of pneumocystis pneumonia; desaturation may persist for several months following recovery from *P. carinii* pneumonia and occur also rarely in cytomegalovirus pneumonitis but is unusual in other respiratory conditions.

Pulmonary function tests
The single breath carbon monoxide transfer factor (TLCO), transfer coefficient (KCO), total lung capacity (TLC) and vital capacity (VC) may all be reduced in patients with pneumocystis pneumonia. Reductions in TLCO to 70% of predicted normal occur in HIV positive patients with pneumocystis and other respiratory disease, including Kaposi's sarcoma and bacterial infections, so this finding is not specific.

Invasive tests
These allow an aetiological diagnosis to be made.

Sputum induced by hypertonic saline
This procedure must be carried out away from other patients and staff in a separate room, ideally with "negative pressure" facilities in order to reduce the risk of nosocomial transmission of infection including tuberculosis. The patient inhales 20–30 ml of 2.7% (3 N) saline through an ultrasonic nebuliser. Saline deposits in the peripheral airways and alveoli, causing irritation and inducing bronchial secretion. Fluid is also drawn into the airways from the interstitium, loosening inflammatory exudate and casts from alveoli. These are mobilised by the mucociliary escalator and move centrally where they are coughed out by the patient. Careful preparation of the patient is needed, including starving for several hours before the procedure and rigorous cleansing of the mouth to remove oral debris so that the sputum sample is not contaminated (food debris and squames take up stain and make analysis difficult). Purulent samples of sputum suggest a bacterial cause. *P. carinii* infection is usually found in clear "saliva-like" samples that become viscid on cooling to room temperature. Fungal infection and mycobacterial infection may also be diagnosed by this technique. Many centres do not carry out sputum induction because of the need for special equipment and the low yield when the technique is compared with fibreoptic bronchoscopy, both for the diagnosis of pneumocystis pneumonia and other pathogens. Some patients find sputum induction unpleasant and become nauseated or dyspnoeic. Arterial desaturation may also occur during the procedure.

Fibreoptic bronchoscopy
Bronchoscopy allows inspection of the bronchi to be carried out and lesions of Kaposi's sarcoma may be identified. Bronchoalveolar lavage is routinely carried out from the middle lobe or from the area of maximum abnormality seen on the chest radiograph. Transbronchial biopsies are now rarely done as they add little to the diagnostic yield for *P. carinii* and other diagnoses, and the technique is associated with adverse effects including haemorrhage and pneumothorax. If transbronchial biopsy is not performed a diagnosis of non-specific or lymphocytic interstitial pneumonitis might be missed.

Open lung biopsy
It is rarely necessary to carry out open lung biopsy because of the high yield from bronchoalveolar lavage. This investigation may be necessary if fibreoptic bronchoscopy and lavage fail to

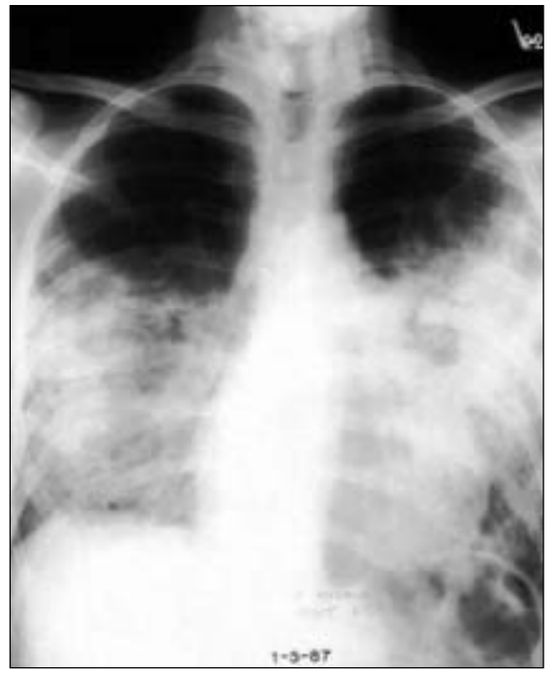


Figure 6.2 Chest radiograph of patient with severe pneumocystis pneumonia

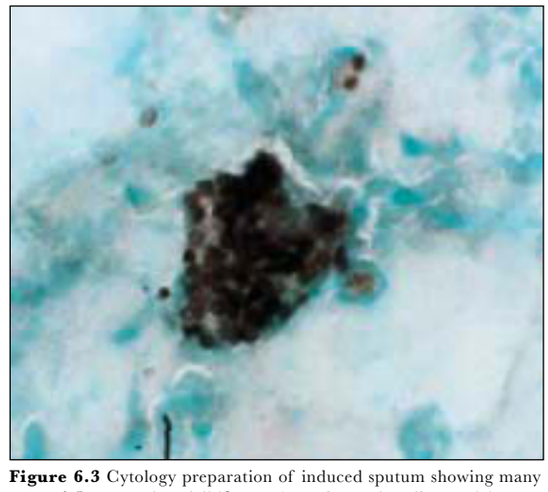


Figure 6.3 Cytology preparation of induced sputum showing many cysts of *Pneumocystis carinii* (Grocott's methenamine silver stain)

Box 6.3 Open lung biopsy
If fibreoptic bronchoscopy and lavage fail to identify diagnosis
or
where patient with bronchoscopic diagnosis deteriorates despite specific treatment

identify a diagnosis or in cases where a patient with a bronchoscopic diagnosis, deteriorates despite specific treatment.

The presenting clinical features and treatment of the common pulmonary manifestations of HIV disease are described below.

Pneumocystis carinii pneumonia

Despite widespread use of anti-pneumocystis prophy!axis and HAART, *P. carinii* pneumonia remains a common AIDS-defining diagnosis in patients who at presentation with pneumonia are unaware of their HIV serostatus or who, despite knowing they have HIV infection, are non-compliant with or intolerant of their prophylaxis and/or HAART.

Patients complain of a non-productive cough and increasing dyspnoea (over two to three weeks or more); they may also have fever and sweats. The chest radiograph may be normal or show interstitial infiltrates: in severe pneumonia there may be widespread alveolar consolidation.

Table 6.1 Grading of severity of *P. carinii* pneumonia

	Mild	Moderate	Severe
Symptoms and signs	Increasing exertional dyspnoea, with or without cough and sweats	Dyspnoea on minimal exertion, occasional dyspnoea at rest, fever with or without sweats	Dyspnoea at rest tachypnoea at rest, persistent fever, cough
Blood gas tensions (room air)	PaO_2 >11.0 kPa	PaO_2 8.0–11·0 kPa	PaO_2 <8.0 kPa
SaO_2 (at rest)	>96%	91–96%	<91%
Chest radiograph	Normal or minor perihilar interstitial infiltrates	Diffuse interstitial shadowing	Extensive interstitial shadowing with or without diffuse alveolar shadowing

PaO_2 = partial pressure of oxygen; SaO_2 = arterial oxygen saturation, measured with a transcutaneous pulse oximeter.

Treatment

It is important to assess the severity of the pneumonia in order to choose appropriate treatment, as some drugs are ineffective in severe disease. High-dose co-trimoxazole remains the "gold standard" treatment. Treatment is for 21 days, given intravenously for the first 10–14 days, diluted in 1 in 25 of 0.9% saline, subsequently, orally. Patients with mild disease may be treated with oral co-trimoxazole from the outset. The principal side-effects are nausea and vomiting, leucopenia and rash. Routine use of folic or folinic acid does not prevent leucopenia and may be associated with increased therapeutic failure. HAART is usually stopped while co-trimoxazole is being given to avoid profound myelosuppression. Conventionally used doses of co-trimoxazole (20 mg/kg day of the trimethoprim component) may be excessive: dose reduction to 75% of this dose (to maintain serum trimethoprim concentrations at 5–8 µg/ml) has equivalent efficacy and reduced toxicity.

Table 6.2 Treatment of *P. carinii* pneumonia

Choice	Mild	Moderate	Severe
First	Co-trimoxazole	Co-trimoxazole	Co-trimoxazole
Second	Clindamycin and primaquine or Dapsone and trimethoprim or Atovaquone	Clindamycin and primaquine or Dapsone and trimethoprim or Atovaquone	Clindamycin and primaquine or Trimetrexate and folinic acid or Pentamidine iv
Third	Pentamidine iv	Pentamidine iv or Trimetrexate and folinic acid	
Glucocorticoids	Unproven benefit	Of benefit	Of benefit

Alternative treatment regimens include:

Clindamycin–primaquine combination (clindamycin 600 mg ×4/day iv or orally and primaquine 15 mg/day orally) has been used in patients intolerant of, or failing to respond to, co-trimoxazole. Principal side-effects are rash, nausea and vomiting, and leuco(neutro)penia.

Dapsone–trimethoprim (100 mg/day dapsone and 20 mg/kg/day trimethoprim) given orally for 21 days is as effective as oral co-trimoxazole in mild to moderate disease and is better tolerated by patients. Side-effects include methaemoglobinaemia and hyperkalaemia, nausea and rash.

Atovaquone suspension (750 mg × 2/day) given orally for 21 days is less effective (and less toxic) than either co-trimoxazole or pentamidine for mild to moderate disease. Absorption from the gut is variable but may be increased if taken with food.

Pentamidine is not often used because of significant toxicity and because other regimens have similar efficacy and less toxicity. It is given at a dose of 4 mg/kg/day (of the isethionate salt) given diluted in 250 mg 5% dextrose by slow intravenous infusion (over 2 hours); it should not be given by intramuscular injection. The major side-effects are hypotension and hypoglycaemia; nephrotoxicity with increases in creatinine and urea concentrations may occur. Dose reduction to 3 mg/kg/day is associated with reduced toxicity but may be less effective. Blood pressure and blood glucose concentrations should be closely monitored. Response to pentamidine (defervescence of fever, reduction in dyspnoea and improvement in blood gases) may take longer (4–7 days) than intravenous co-trimoxazole.

Box 6.4 Adjuvant glucocorticoids in moderate/severe pneumonia

- Reduce risk of respiratory failure (by 50%)
- Reduce risk of death (by 33%)
- Should be started at same time as specific anti-pneumocystis treatment

Nebulised pentamidine is now no longer used to treat *P. carinii* pneumonia as there are several other more effective therapies and because this form of treatment does not suppress the development of extrapulmonary pneumocystosis.

Adjuvant glucocorticoids for patients with moderate or severe pneumocystis pneumonia reduces the risk of respiratory failure (by up to 50%) and the risk of death (by up to 33%). Glucocorticoids should be started together with specific anti-pneumocystis treatment in any patient presenting with a PaO_2 of 9.3 kPa breathing air. In some patients this will be on the basis of a presumptive diagnosis; clearly there will be a need to confirm the diagnosis rapidly. Treatment is with intravenous methylprednisolone 1 g/day for three days, followed by 0.5 g for two days, followed by oral prednisolone 40 mg daily tailing off over 10 days. Alternatively, prednisolone 40 mg orally twice daily is given for 5 days and then gradually reduced over 21 days (or intravenous methylprednisolone is given at 75% of these doses).

Figure 6.4 Transfer to the ICU may be necessary if respiratory failure occurs

Intensive care

Over 90% of patients respond to treatment and survive their first episode of pneumocystis pneumonia. In those who fail to respond and who develop respiratory failure, mortality is 50%. Transfer to the intensive care unit for mask CPAP ventilation or intubation and mechanical ventilation should be considered in this situation. When considering the appropriateness of intensive care, assess the patient's wishes and those of their partner and relatives as well as the patient's previous and expected quality of life in relation to their HIV disease.

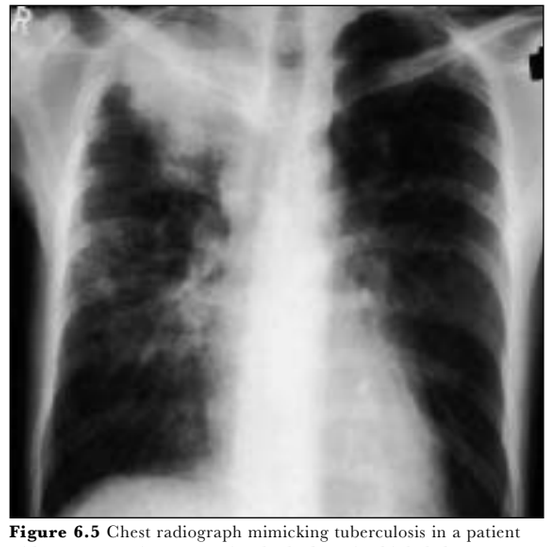


Figure 6.5 Chest radiograph mimicking tuberculosis in a patient with pneumocystis pneumonia who had received inhaled pentamidine prophylaxis

Prophylaxis

HIV positive patients, including those receiving HAART should receive primary prophylaxis against *P. carinii* pneumonia if they have a CD4 count < 200 cells/μl or a history of oral/pharyngeal candidiasis or if they have a CD4 lymphocyte count <14% of total lymphocyte count, or if they have other AIDS-defining diagnoses, for example Kaposi's sarcoma, regardless of CD4 count. If close monitoring of CD4 counts (at least every three months) is not feasible then prophylaxis should be considered for patients with CD4 counts between 200 and 250 cells/μl. Secondary prophylaxis is given to all HIV-infected patients after an episode of *P. carinii* pneumonia, regardless of CD4 count.

The prophylaxis regimen of choice is co-trimoxazole 960 mg once daily. A dose of 480 mg once daily or 960 mg three time a week are also effective and may be better tolerated by the patient. Co-trimoxazole also protects against bacterial infection and reactivation of cerebral toxoplasmosis. In patients who develop mild to moderate adverse reactions to co-trimoxazole, desensitisation may be attempted before changing to alternative therapy. Second-line prophylaxis (for those intolerant of, or unwilling to take, co-trimoxazole) include dapsone, with or without pyrimethamine, atovaquone or monthly nebulised pentamidine (300 mg given using a Respirgard II or similar nebuliser). There is a higher relapse rate of pneumocystis pneumonia with this regimen compared with that using co-trimoxazole. Some patients who relapse while receiving nebulised pentamidine have atypical chest radiographs with upper zone infiltrates which mimic tuberculosis. Atovaquone is as effective as dapsone or nebulised pentamidine but is much more expensive.

Stopping prophylaxis

Primary *P. carinii* prophylaxis can be discontinued in HIV-infected patients responding to HAART with an increase in CD4 count from below 200 cells/μl to above 200 cells/μl and a reduction in HIV-1 viral load, both sustained for 3–6 months. If

Box 6.5 Prophylaxis of *P. carinii* pneumonia

Primary prophylaxis
Any HIV positive patient with a CD4 count of <200 cells/μl
Or a history of oral/pharyngeal candidiasis
Or a CD4 count <14% of total lymphocyte count
Or another AIDS-defining diagnosis, for example Kaposi's sarcoma

Secondary prophylaxis
Any HIV positive patient *after* an episode of *P. carinii* pneumonia

despite HAART, CD4 counts again fall below 200 cells/μl and HIV-1 viral load rises, then the criteria for starting primary prophylaxis should be used. There are insufficient data to support the discontinuation of secondary prophylaxis.

Bacterial infections

Upper respiratory tract infections and pyogenic bacterial infection (sinusitis, bronchitis and pneumonia) occur more often in HIV-infected individuals than in the general population. Bacterial infections are particularly common in HIV positive intravenous drug users. The most commonly isolated organisms are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Severe pneumonia due to *Staphylococcus aureus* or Gram negative bacteria such as *Pseudomonas aeruginosa* also occurs, especially in the later stages of AIDS. Respiratory infection may occur with rapid onset, the patient complaining of a cough with or without sputum and fever with chills; patients are frequently bacteraemic. There is a high rate of complications including intrapulmonary abscess formation and empyema. A rapid response usually occurs to treatment with appropriate antibiotics but relapse may occur. Some groups recommend that all HIV positive patients should be immunised with polyvalent pneumococcal polysaccharide vaccine although not all studies have demonstrated effective antibody responses to this agent, particularly in patients with CD4 counts <200 cells/μl.

Kaposi's sarcoma

Pulmonary Kaposi's sarcoma is the commonest non-infectious pulmonary manifestation of AIDS. Almost all patients with pulmonary Kaposi's sarcoma have mucocutaneous or lymph node Kaposi's sarcoma. Palatal Kaposi's sarcoma (with or without mucocutaneous Kaposi's sarcoma) strongly predicts for the presence of pulmonary Kaposi's sarcoma. Pulmonary Kaposi's sarcoma can affect the pulmonary parenchyma, bonchi, pleura and hilar/mediastinal lymph nodes. Chest radiographs most frequently show non-specific features, with bilateral interstitial (often nodular) or alveolar infiltrates; more than 40% of patients have pleural effusion and 25% have mediastinal lymph node enlargement. Routine respiratory function tests show decreased lung, volumes (FEV_1 and FVC) and decreased TLCO; airflow obstruction may occur with extensive Kaposi's sarcoma in the airways.

At fibreoptic bronchoscopy 45% of patients with pulmonary Kaposi's sarcoma have visible endotracheal and endobronchial lesions consisting of multiple, red or purple, flat or raised lesions. Biopsy is not routinely done as most patients have the diagnosis made by the presence of cutaneous Kaposi's sarcoma, because of the risk of haemorrhage (up to 30% will have a significant bleed) and the low diagnostic yield (<20%) which occurs because of submucous distribution of the tracheobronchial tumour.

Transbronchial biopsy also has a low yield of less than 20% due to the patchy nature of parenchymal disease. Histological diagnosis is difficult to make at bronchial or transbronchial biopsy as crush artefact and reactive fibrous tissue have similar appearances. Open lung biopsy has a diagnostic yield of >75% but this procedure is very invasive and should probably be avoided as patients with pulmonary Kaposi's sarcoma have a poor prognosis.

Treatment

Chemotherapy most often consists of bleomycin 10 000 units/m^2 and vincristine 2 mg once every three weeks. Liposomal formulations of daunorubicin and doxorubicin may

Box 6.6 Bacterial infections

- Increased incidence of sinusitis, bronchitis and pneumonia in HIV infected persons, compared to general population
- Bacterial infection especially common in HIV infected IVDU

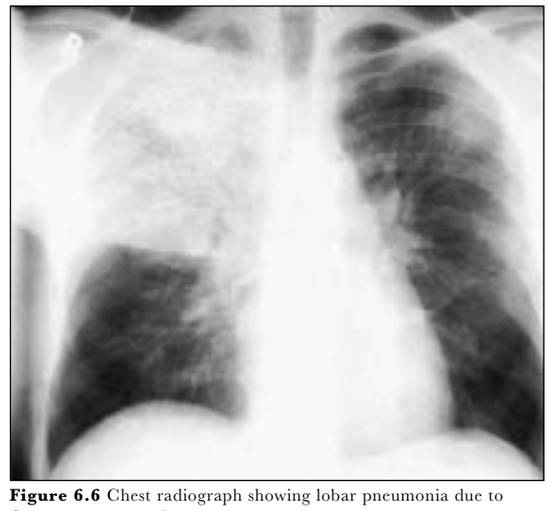


Figure 6.6 Chest radiograph showing lobar pneumonia due to *Streptococcus pneumoniae*

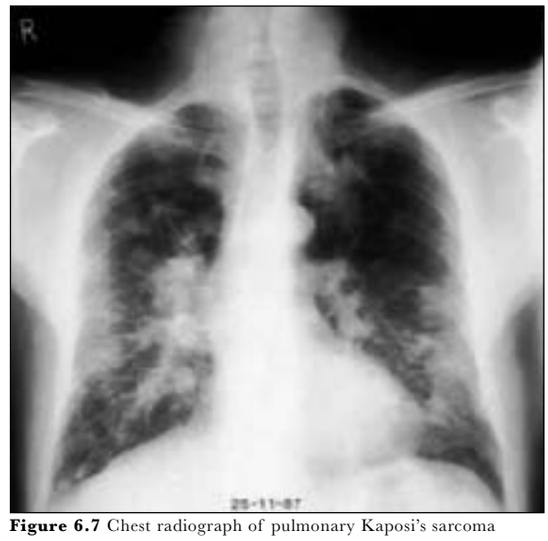


Figure 6.7 Chest radiograph of pulmonary Kaposi's sarcoma showing multiple pulonary nodules

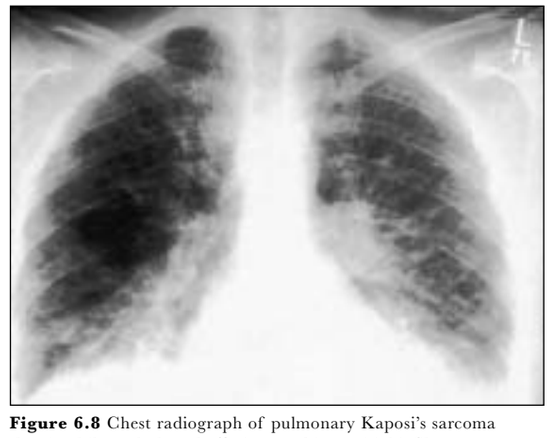


Figure 6.8 Chest radiograph of pulmonary Kaposi's sarcoma showing bilateral pleural effusions and interstitial infiltrates

also be used as single-agent chemotherapy. Treatment of pleural effusions (which occur secondary to Kaposi's sarcoma on the visceral pleura or to mediastinal glands) is problematical. Chemical pleuradesis is rarely successful and radiotherapy has not been shown to be of value.

Tuberculosis

Tuberculosis may speed up the natural history of HIV disease

Unlike opportunistic infections in AIDS tuberculosis is also infectious for healthy individuals. Tuberculosis is a potent stimulator of cell-mediated immunity and so may speed up the natural history of HIV disease. The incidence of tuberculosis is currently increasing in the USA; this is directly attributable to the effects of HIV in certain populations. No increase has occurred yet in Britain but the unpredictable features of the HIV epidemic in heterosexuals, migrants and injecting drug users means careful vigilance is required. Tuberculosis can precede the development of AIDS, be diagnosed at the same time or occur at any time during established AIDS. Tuberculosis in HIV positive patients is AIDS defining and in the USA, the UK and most other European countries is a statutorily notifiable disease.

Over two thirds of cases of tuberculosis in HIV-infected patients present with pulmonary disease. Clinical presentation varies according to the stage of HIV disease. Early on, with relatively well preserved cell-mediated immunity, pulmonary tuberculosis resembles classic adult post-primary disease with upper lobe infiltrates and cavitation; the tuberculin test is usually positive and acid and alcohol fast bacteria (AAFB) are frequently seen when sputum is examined by microscopy. With advanced HIV disease and destroyed cell immunity, presentation is non-specific with fever, weight loss and fatigue, with or without cough. Patients with low CD4 counts $<150 \times 10^6/1$ may also have extrapulmonary disease affecting bone marrow, lymph node, central nervous system or liver. In the chest, the clinical pattern is one of primary infection with hilar and mediastinal adenopathy, diffuse or miliary shadowing; pleural effusions are common. Cavitation occurs rarely and up to 10% of chest radiographs are normal. The tuberculin test is usually negative, sputum (and bronchoalveolar lavage) are often smear negative and culture may also be negative.

As culture and species identification may take up to six weeks, *M. tuberculosis* infection should be assumed if AAFB are found in respiratory sample, an aspirate or biopsy site, or blood, and conventional antituberculous therapy should be started. Treatment can be modified if culture subsequently reveals an atypical mycobacterium and not *M. tuberculosis*.

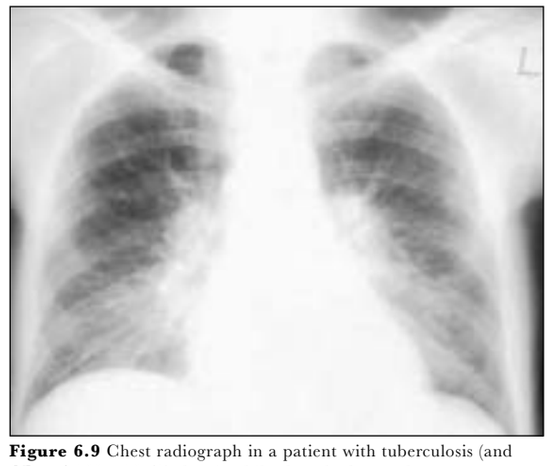


Figure 6.9 Chest radiograph in a patient with tuberculosis (and CD4 of $100 \times 10^6/1$) showing hilar lymphadenopathy

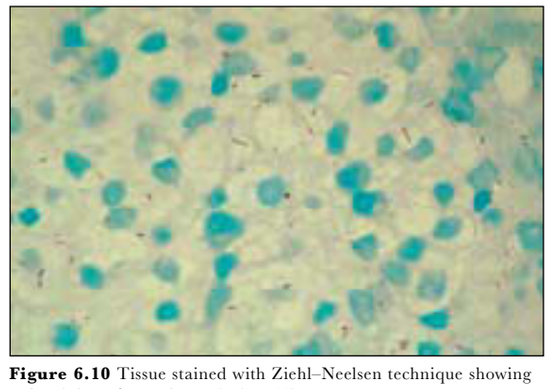


Figure 6.10 Tissue stained with Ziehl–Neelsen technique showing red staining of mycobacteria (× 400)

Treatment

Clinical response to conventional treatment with four-drug regimens is good, but compared with the non-HIV-infected general population, survival is poor. The incidence of adverse reactions to antituberculous drugs, including isoniazid, rifampicin and thiacetazone, is higher in HIV-infected patients than in the general population.

Many of the drugs used to treat tuberculosis share routes of metabolism and elimination or have overlapping toxicities with other medication taken by HIV-infected patients, so there exists the potential for drug–drug interactions. For example, rifampicin renders dapsone, as prophylaxis of *P. carinii* pneumonia, ineffective — by inducing its hepatic metabolism. Clinically important drug–drug interactions occur between rifampicin/rifabutin and antiretroviral therapy particularly protease inhibitors such as ritonavir and non-nucleoside reverse transcriptase inhibitors such as delavirdine.

Compliance with therapy is a problem in some groups and directly observed therapy (DOTS) may be needed.

Box 6.7 Treatment of tuberculosis

- Conventional four-drug regimens are associated with good response
- Adverse reactions to anti-tuberculous therapy occur more frequently in HIV infected patients
- Important drug-drug interactions occur between drugs used to treat tuberculous and drugs used to treat HIV infection

Multi-drug resistant (MDR) tuberculosis
This is tuberculosis resistant to rifampicin and isoniazid with or without resistance to other drugs. Outbreaks of MDR tuberculosis have occurred in the USA, the UK and elsewhere in Europe. Most MDR tuberculosis arises because of inadequate treatment or poor compliance with therapy. Some cases occur in HIV-infected patients who are exogenously re-infected whilst receiving treatment for drug-sensitive disease. Despite treatment, MDR tuberculosis has a poor prognosis in HIV-infected and non-infected patients and healthcare workers who acquire the infection.

Chemoprophylaxis
Some expert groups, for example WHO and International Union Against Tuberculosis and Lung Disease (IUATLD), recommend that HIV-infected patients co-infected with *M. tuberculosis* (but without disease) should receive chemoprophylaxis. There are few data to support this policy. The preferred policy should be close clinical monitoring rather than chemoprophylaxis, because of increasing rates of drug resistance and MDR tuberculosis, difficulties in distinguishing between infection and disease, and concerns that single-drug prophylaxis is associated with the development of resistance.

Once clinical disease is excluded, HIV-infected patients who have had recent contact with a smear-positive index case should receive chemoprophylaxis and life-time follow up should be instituted. Once HIV-infected patients have successfully completed a course of treatment for tuberculosis close clinical monitoring is recommended: such patients do not need to take life-long secondary prophylaxis.

Box 6.8 Chemoprophylaxis of tuberculosis

- Once active tuberculosis excluded, close clinical monitoring, rather than chemoprophylaxis is preferred policy in patients co-infected with HIV and tuberculosis
- HIV-infected patients in close contact with a smear positive index case should receive chemoprophylaxis and careful follow-up.

Fungal pneumonia

Infection with *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Aspergillus fumigatus* and other fungi is well recognised in HIV positive patients in the USA and Africa. Infection with these organisms is relatively uncommon in the UK. Cryptococcal pneumonia often occurs as part of a disseminated infection with fungaemia and meningoencephalitis; respiratory symptoms of cough and dyspnoea are non-specific. The chest radiograph may be normal or show diffuse shadowing which may be nodular. Diagnosis is made by culture of bronchoalveolar lavage or transbronchial biopsy specimen (or blood, bone marrow, or cerebrospinal fluid in disseminated infection). Treatment of cryptococcus infection is with fluconazole 400–600 mg/day or intravenous amphotericin B or itraconazole 400 mg twice a day. Aspergillus pulmonary infection has a very poor prognosis despite treatment with amphotericin. It occurs almost exclusively in patients with advanced HIV disease who are either neutropenic or who have received broad-spectrum antibiotics.

Box 6.9

- Cryptococcal pneumonia often part of disseminated infection
- Respiratory symptoms of cough and dyspnoea non-specific
- Chest radiograph may be normal or show diffuse shadowing

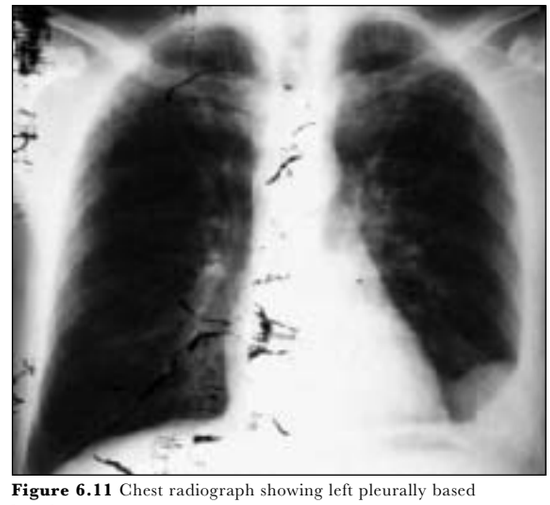


Figure 6.11 Chest radiograph showing left pleurally based lymphoma

Lymphoma

Lymphoma occurs more often in HIV positive patients, particularly in those with advanced HIV disease. Most lymphomas are B cell in origin and are of high grade. Intrathoracic disease most frequently occurs in the context of disseminated disease. Symptoms are non-specific. The chest radiograph may show mediastinal lymphadenopathy, pleural lesions or focal parenchymal abnormalities. The prognosis is poor and there is a high relapse rate after treatment. Median survival is <1 year, reflecting the advanced stage of HIV disease.

Lymphocyte interstitial pneumonitis

This condition occurs more commonly in children; it is unusual in HIV-infected adults. Parotid enlargement and lymphocytic infiltration of the liver and bone marrow may accompany pulmonary involvement. Patients often present with slowly progressive dyspnoea and cough, symptoms that cannot be distinguished from infection. Examination of the chest may be normal or reveal fine end inspiratory crackles. The chest radiograph usually shows bilateral reticulonodular infiltrates but may show diffuse shadowing and thus mimic *P. carinii* pneumonia. Diagnosis is made by transbronchial biopsy or open lung biopsy. Some patients have been shown to respond to HAART and others to treatment with prednisolone 60 mg once a day.

Box 6.10 Lymphocytic interstitial pneumonitis

- Commoner in children
- Parotid enlargement and lymphocytic infiltration of liver/bone marrow may also occur
- Presents with slowly progressive dyspnoea/cough
- Treatment is with HAART or prednisolone

Non-specific pneumonitis

This condition is important as patients present with symptoms and chest radiographic appearances similar to those of *P. carinii* pneumonia. It may also occur when the CD4 count is still normal. The diagnosis can only be made by biopsy. Episodes are usually self limiting but prednisolone may be of benefit.

Cytomegalovirus

Cytomegalovirus (CMV) infection in HIV positive patients with advanced disease and low CD4 counts (<100 cells/μl) is common and is a well-documented cause of retinitis, colitis, adrenalitis and radiculopathy. In patients with renal allografts and bone marrow transplants, CMV may cause pneumonitis on an immunopathogenic basis and this is frequently fatal.

CMV was originally thought to be an important cause of pneumonitis in patients with AIDS but it is now known that CMV pulmonary infection occurs only rarely in the absence of other pathogens and its presence does not adversely affect outcome and survival. Treatment with specific anti-CMV treatment such as foscarnet (phosphonoformate) does not seem to improve outcome (as would be expected if CMV was causing the pneumonitis).

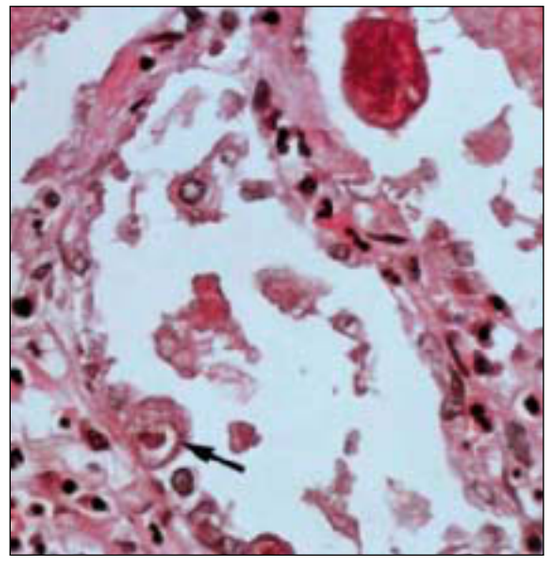


Figure 6.12 A transbronchial biopsy specimen showing a large eosinophilic nuclear inclusion (arrowed) in a pneumocyte infected with cytomegalovirus (haematoxylin and eosin stain)

Lung cancer

Lung cancer in HIV-infected patients presents an earlier age than in the general population and appears to have a poorer outcome, as it is more aggressive. Smoking is strongly associated with the development of lung cancer.

Figure 6.3 is reproduced courtesy of Dr Gabrijela Kocjan; Figures 6.10 and 6.12 are reproduced courtesy of Dr Meryl Griffiths.

7 Gastrointestinal and hepatic manifestations

Ian McGowan, Ian VD Weller

Gastrointestinal symptoms are a common manifestation of HIV infection. Significant clinical problems tend to occur in patients with advanced immunosuppression. The differential diagnosis of gastrointestinal disease is broad and includes opportunistic infection, malignancy, and the effects of medication. Antiviral drugs and antibiotics have gastrointestinal side effects such as nausea, vomiting, and diarrhoea. HIV can be readily detected in mucosal tissue but the direct role of mucosal HIV infection in the cause of clinical disease remains controversial.

This chapter will focus on the differential diagnosis and management of common gastroenterological syndromes associated with HIV infection. Clinical investigation may not always be appropriate in advanced disease. It is important to counsel patients about the risks and benefits of invasive procedures as many "specific" diagnoses may not be treatable.

Box 7.1 Differential diagnosis of HIV-associated gastrointestinal disease

- Infection
- Malignancy
- Medication
- HIV infection

Oral and oesophageal disease

Oral cavity pain or discomfort are caused by candidiasis, herpetic or aphthous ulceration, periodontal disease, and tumours. Often the diagnosis can be made by simple inspection and appropriate treatment initiated without further investigation. Systemic oral therapy of herpes simplex ulceration and candidiasis is preferred for reasons of efficacy and ease of use. Recurrence is common and if frequent, maintenance therapy may be required rather than the short treatment of each occurrence. Maintenance therapy may be more likely to induce resistance.

About one third of patients develop oesophageal disease. The likelihood of candidiasis is so high that a therapeutic trial with a systemic antifungal agent is indicated before considering further investigation. If symptoms fail to respond, or recur despite adequate maintenance therapy, endoscopy is performed to exclude herpes simplex, cytomegalovirus and other causes of oesophageal ulceration including malignant lesions.

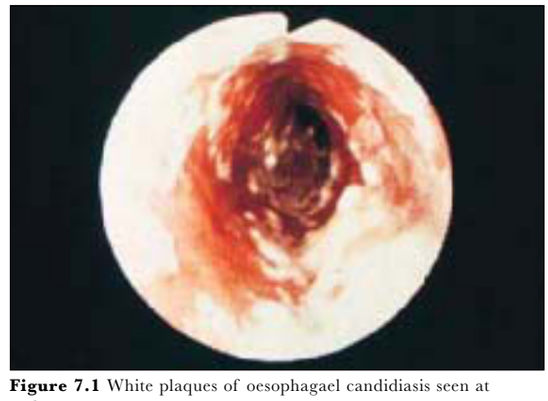


Figure 7.1 White plaques of oesophagael candidiasis seen at endoscopy

Diarrhoea

Patients with diarrhoea lasting more than two weeks should be investigated. The diagnostic yield is likely to be highest in patients with CD4 counts $<200 \times 10^6$/l. Careful microbiological and parasitological examination of multiple stool specimens is the most cost-effective initial investigation. Endoscopy with collection of tissue from the distal duodenum, ascending and descending colon should be performed to exclude cytomegalovirus and occult parasitic infection.

Bacterial infection with *Campylobacter*, *Salmonella* or *Shigella* spp. may present with severe diarrhoeal symptoms and/or bacteraemia. It is important to exclude toxic megacolon with plain abdominal radiography. Organisms are usually sensitive to conventional therapy but drugs may need to be given parenterally. Evidence of atypical mycobacterial infection is found in 60% of patients with advanced HIV disease at necropsy. Gastrointestinal infection may be associated with fever, weight loss, diarrhoea, and malabsorption. Diagnosis can be made by acid fast staining of the stool or biopsy material and by culture. Positive stool culture alone indicates colonisation only. *Mycobacterium tuberculosis* infection of the bowel does occur but is less common. Antibiotic-associated diarrhoea,

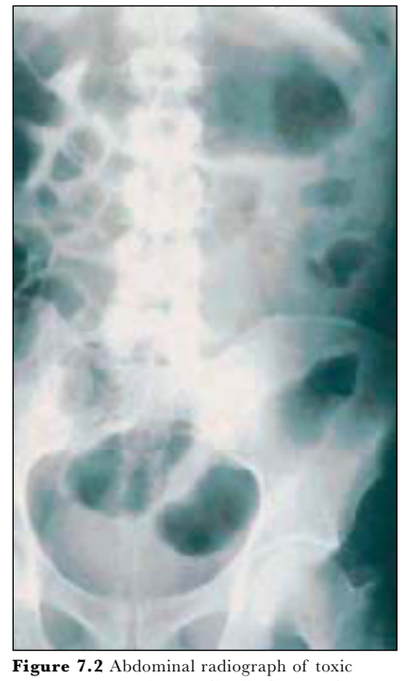


Figure 7.2 Abdominal radiograph of toxic megacolon secondary to *Shigella flexneri infection*

including pseudomembranous colitis due to *Clostridium difficile*, is occasionally seen in patients with HIV infection and is treated with oral metronidazole or vancomycin.

Cryptosporidium spp. is one of the most common pathogens isolated from HIV-infected patients with diarrhoea. The degree of immunosuppression influences patient prognosis and patients with a CD4 count $>200 \times 10^6$/l may recover spontaneously. Treatment is supportive as no agent has shown convincing efficacy. The organism is heat sensitive and immunosuppressed patients are advised to boil water for drinking purposes.

Microsporidia are also an important cause of diarrhoea as well as being associated with hepatitis, peritonitis, sclerosing cholangitis, sinusitis, and renal failure. Diagnosis is difficult as the spores are only 1–5μm in diameter. A number of centres have reported successful identification of spores in stool using trichrome and fluorescent stains but morphology is best determined using electron microscopy. Albendazole has shown promise in AIDS patients with microsporidiosis but may only be active against *Encephalitozoon intestinalis* and not *Enterocytozoon bienusi*.

Isospora belli is an infrequent cause of diarrhoea in AIDS patients in the USA and Europe but accounts for up to 25% cases of chronic diarrhoea in patients in tropical and subtropical countries. Response to trimethoprim–sulphamethoxazole has been described.

Cyclospora sp. is the most recent protozoan to be associated with diarrhoea in AIDS. It appears to be more common in the developing world and in returning travellers and like *Isospora belli* appears to be sensitive to trimethoprim–sulphamethoxazole.

Other protozoa including *Entamoeba histolytica* are frequently identified in stools from HIV-infected homosexual men but appear not to be pathogenic.

Cytomegalovirus colitis occurs in less than 5% of patients with AIDS. Symptoms include bloody diarrhoea, abdominal pain, and fever. Sigmoidoscopy may show diffuse erythema and mucosal ulceration. Diagnosis is histopathological and is made on the basis of characteristic intranuclear "owl's-eye" inclusion bodies or detection of CMV antigen with monoclonal antibodies. Treatment is with ganciclovir or foscarnet.

Adenoviruses have been identified by culture and electron microscopy in HIV-infected homosexual men with diarrhoea. No specific treatment is available.

Weight loss and anorexia

Weight loss is a major problem in AIDS and directly influences survival. The causes of weight loss are complex and several factors may coexist in individual patients. Anorexia may occur secondary to drug therapy, opportunistic infection, taste disturbance, or oral discomfort, resulting in inadequate food intake. Malabsorption of fat, lactose, vitamin B12, and bile salts has been demonstrated.

Simple dietary measures such as encouraging smaller, more frequent, meals may be helpful and a wide variety of nutritional supplements are available. Appetite stimulants such as megestrol acetate may be beneficial but weight gain is usually modest. Recombinant human growth hormone, although expensive, may partially reverse HIV-associated weight loss. In patients unable to tolerate oral feeding, enteral and parenteral feeding are alternative forms of nutrition but their efficacy and place in management are still being evaluated. Enteral nutrition offers a safer and cheaper alternative to total parenteral nutrition which is perhaps most useful in patients with severe diarrhoea, nausea, and vomiting, in whom fluid balance and control of symptoms has been difficult.

Box 7.2 Infective causes of diarrhoea

- Bacteria
  - campylobacter, salmonella, shigella
  - atypical mycobacteria
  - *Clostridium difficile*
- Protozoa
  - cryptosporidium
  - microsporidia
  - *Isospora belli* and cyclospora
- Viruses
  - cytomegalovirus
  - adenovirus
  - (HIV)

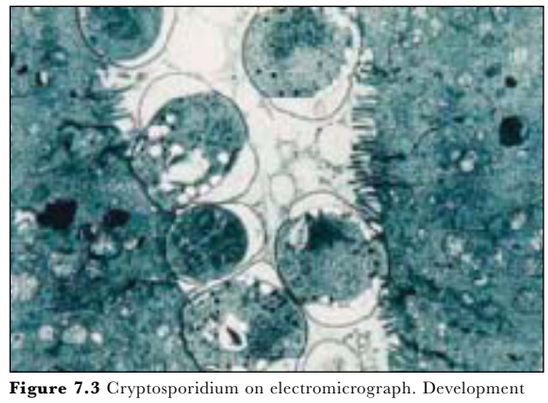


Figure 7.3 Cryptosporidium on electromicrograph. Development stages of cryptosporidium on the surface of enterocytes (note microvilli). The cryptosporidia are surrounded by a parasitophorous vacuole, the outer layers of which are derived from host cell outer membranes

Box 7.3 Treatment of HIV-associated diarrhoea

- Specific
  - antibiotics
  - antivirals
- Fluid replacement
- Antidiarrhoeal agents
  - loperamide
  - diphenoxylate
  - codeine
- Slow release morphine
- Subcutaneous diamorphine

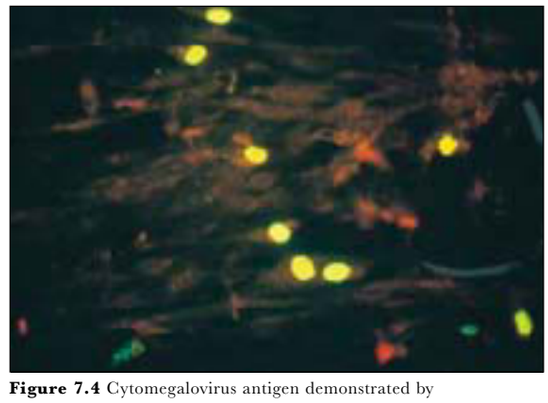


Figure 7.4 Cytomegalovirus antigen demonstrated by immunofluorescence microscopy after culturing human fibroblasts with homogenised intestinal tissue

Hepatitis and cholestasis

Abnormal liver biochemistry and/or hepatomegaly are common clinical problems although frank jaundice is uncommon. With the multiple therapies being used in treatment and prophylaxis, a drug-induced hepatitis must always be considered in a patient with AIDS and abnormal liver function tests. The differential diagnosis is wide and may involve the use of serology, abdominal ultrasound, ERCP, and liver biopsy. These latter two diagnostic procedures are clearly invasive and would not be indicated unless treatment of opportunistic infection, malignancy or biliary strictures was contemplated. In the absence of dilatated bile ducts on ultrasound, liver biopsy usually shows a granulomatous hepatitis caused by atypical mycobacteria.

AIDS sclerosing cholangitis presents with right upper quadrant pain, accompanied by a raised alkaline phosphatase. Abdominal ultrasound is abnormal in the majority of patients with biliary tract dilatation. ERCP may demonstrate papillary stenosis, dilatation of the common bile duct and dilatations and strictures with "beading" of the intrahepatic ducts. The disease is commonly associated with cryptosporidiosis, microsporidiosis, or cytomegalovirus infection. Endoscopic sphincterotomy may give pain relief in a proportion of patients with papillary stenosis. Liver function tests do not usually improve, and as it is a late-stage manifestation, the prognosis is poor, with most patients dying from some other HIV-related complication within six months of diagnosis.

HIV infection may alter the natural history of hepatitis B infection in a number of ways. The response rate to hepatitis B vaccination is lower in HIV-infected recipients. Immunodeficiency may favour the establishment of chronic infection following acute infection and HBV replication is increased with a reduction in the rate of spontaneous loss of HBe antigen. Interferon therapy would appear to be less effective in chronic HBV/HIV dual infection. The immune restoration following the initiation of antiretroviral therapy may lead to a hepatitis "flare" in chronic HBV carriers.

Hepatitis C virus infection is found primarily in intravenous drug users, although it may also be sexually transmitted. HIV can modify the natural history of HCV infection and patients with HIV/HCV dual infection tend to have more aggressive liver disease.

Figure 7.5 ERCP of AIDS sclerosing cholangitis with intrahepatic biliary tract distortion and dilatation of the common bile duct

Box 7.4 Differential diagnosis of liver disease

- Hepatitis or cholestasis
  - *M. avium-intracellulare complex*
  - Drug-induced
  - Viral hepatitis
  - Cytomegalovirus
  - *Mycobacterium tuberculosis*
  - *Cryptococcus*
  - Microsporidia
  - Lymphoma
  - Kaposi's sarcoma
- Biliary disease
  - *Cryptosporidium*
  - Cytomegalovirus
  - Microsporidia
  - Lymphoma
  - Kaposi's sarcoma

Anorectal disease

Perianal discomfort is often caused by recurrent herpes simplex infection. The diagnosis should be confirmed by viral culture. Patient-initiated intermittent aciclovir can give adequate symptom control in some cases but many patients will require long-term maintenance therapy. Resistance to both aciclovir and ganciclovir has been reported. Foscarnet is then the treatment of choice.

Anal warts are common but rarely cause much in the way of symptoms and should be treated on merit given the absence of any effective antiviral therapy. Anal intraepithelial neoplasia has been described in association with human papillomavirus infection but reports of invasive malignancy are still infrequent.

Patients may present with a mucopurulent proctitis, possible causes of which include recently acquired or long-standing *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infection.

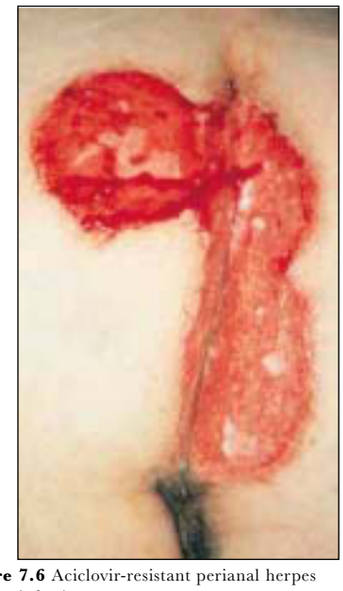


Figure 7.6 Aciclovir-resistant perianal herpes simplex infection

Neoplasia

Kaposi's sarcoma (KS) is commonly seen in the gastrointestinal tract and occurs in homosexual men more frequently than in patients from other risk groups. A new human herpes virus (HHV8) or Kaposi's sarcoma-associated herpes virus (KSHV) has been recently identified as a likely aetiological agent. KS lesions in the gut have the range seen in the skin, from small telangiectatic lesions, not well shown on contrast studies and only seen at endoscopy, to larger nodular or polypoid lesions. Complications from gastrointestinal disease are unusual, but include ulceration, obstruction, haemorrhage, and diarrhoea.

Lymphoma is much less common than KS however, although the incidence of KS has decreased along with the incidence of life-threatening opportunistic infections in association with the introduction of highly active antiretroviral therapy. The incidence of lymphoma has not been affected. HIV-associated lymphomas are usually high grade non-Hodgkin's type, of B-cell origin. Extranodal involvement is typical and the gut is one of the commonest sites involved.

We thank Dr Wilfred Weinstein, UCLA Medical School, Los Angeles for providing the photograph of oesophageal candidiasis and Dr David Casemore, PHLS Glan Clwyd, North Wales for the electronmicrograph of cryptosporidium.

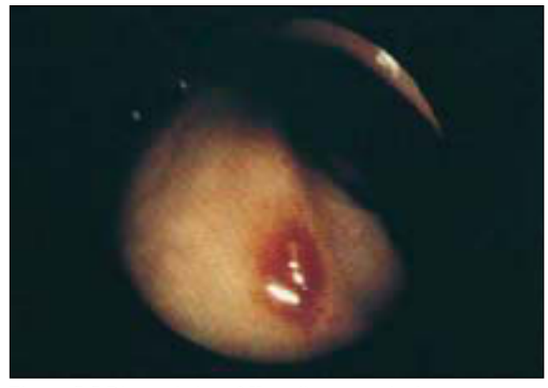


Figure 7.7 Discrete lesion of Kaposi's sarcoma in the rectum

8 Neurological manifestations

Hadi Manji

In patients infected with HIV, the whole neuraxis is vulnerable to damage. Up to 10% of patients may present with a neurological disorder at seroconversion (Box 8.1). The aseptic meningoencephalitis, which is usually self limiting, presents with headache, meningism, cranial nerve palsies and seizures. An acute demyelinating polyradiculoneuropathy (Guillain–Barré syndrome) is identical to that found in non-HIV-infected individuals, clinically and in the response to treatment with intravenous immunoglobulin or plasmapharesis. However, the cerebrospinal fluid shows a pleocytosis of over 20 cells/mm^3 which is unusual in non HIV cases. A high index of suspicion is required and HIV should be considered in all such cases.

During the asymptomatic phase of the illness, which may be of variable duration, headache and cranial nerve palsies (especially VIIth nerve – Bell's palsy) may be the only manifestation of a low-grade chronic meningitis.

The opportunistic infections and tumours as well as the complications ascribed to HIV itself usually develops when the CD4 count drops below 200/mm^3 (Box 8.2). Since the introduction of HAART, there has been a significant reduction in the incidence of infections such as toxoplasmosis and CMV.

Box 8.1 Seroconversion neurological presentations

- Encephalitis
- Aseptic meningitis
- Myelitis
- Cauda equina syndrome
- Acute demyelinating neuropathy (Guillain–Barré syndrome)
- Myositis

Box 8.2 Neurological complications in HIV infection

Opportunistic infections
- *Toxoplasma gondii* – abcesses and encephalitis
- *Cryptococcus neoformans* – meningitis
- JC virus – leucoencephalopathy (PML)
- CMV – retinitis, encephalitis, cauda equina syndrome, mononeuritis multiplex

Tumours
- Primary CNS lymphoma

HIV-related disorders
- HIV-associated dementia complex
- Vacuolar myelopathy
- Peripheral neuropathy (distal sensory polyneuropathy)
- Polymyositis

Clinical approach

The CD4 count is a useful guide to the aetiology of a neurological presentation – toxoplasmosis and cryptococcal meningitis occur at CD4 counts below 200/mm^3 whereas CMV complications occur below 50/mm^3. Since HIV infection itself results in CSF abnormalities such as a raised white cell count and an elevated protein level, more specific tests are required to diagnose encephalitic and meningitic illnesses. These include the measurement of cryptococcal antigen levels in cases of meningitis due to *C. neoformans* and CSF–VDRL and TPHA if syphilis is a differential. The inflammatory response is impaired and patients with meningitis may present with only mild symptoms of headache and no neck stiffness or photophobia. The threshold for investigating with CT/MRI and lumbar puncture is necessarily low. The measurement of serum antibodies to diagnose, for example toxoplasmosis, is unhelpful since the usual rise in levels of IgM does not occur. Infection with more than one organism occurs not infrequently, for example *Cryptococcus neoformans* and *Mycobacterium tuberculosis* and needs to be considered in cases of non-response or deterioration.

Box 8.3 Clinical guidelines

- CD4 useful guide to aetiology
- Persistent CSF abnormalities due to HIV
- Reduced inflammatory response
- Impaired antibody response
- Multiple simultaneous infections
- Maintenance treatment required

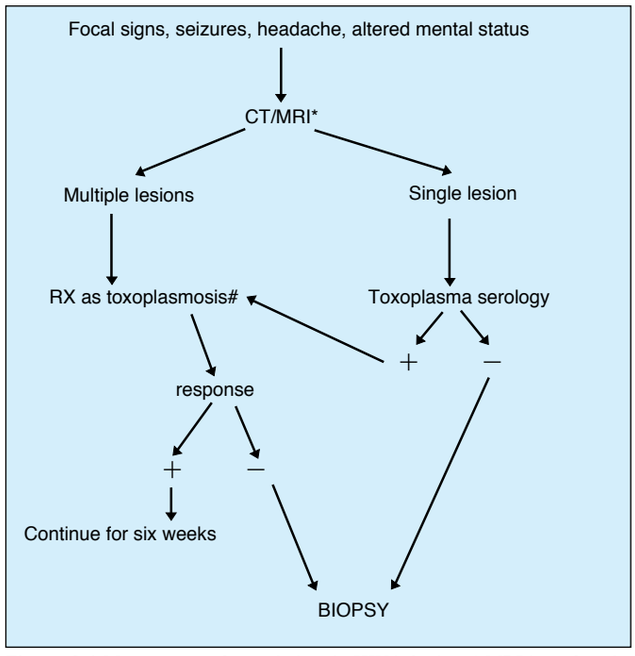


Figure 8.1 Management of mass lesions in HIV infection. * MRI is preferred mode of imaging. # If significant mass effect treat with reducing course of dexamethasone in addition to toxoplasma therapy

Opportunistic infections

Toxoplasma gondii

Toxoplasmsosis in HIV infection is usually a reactivation of latent infection in individuals who have been exposed previously to the organism. The clinical presentation is with headache with rapidly evolving focal neurological deficits over one to two weeks which include hemiparesis, dysphasia, visual field deficits, movement disorders (chorea/athetosis, parkinsonism) and seizures. Rarely, toxoplasmosis may affect the spinal cord and present with a myelopathy or a cauda equina syndrome. Blood serology for *T. gondii* is only helpful if negative since this makes the diagnosis less likely. Patients should have their toxoplasma serology documented at the first diagnosis of HIV infection. The risk of developing toxoplasma encephalitis in IgG seropositive patients is between 12% and 30%. These patients should be offered primary prophylaxis with co-trimoxazole at CD4 counts below 200.

CT/MRI shows multiple enhancing lesions with mass effect in the region of the basal ganglia and at the grey/white interface. A response to treatment is seen in 85% by day 7 and in over 90% by day 14. Repeat imaging should be performed after two weeks even if there is clinical improvement in cases of mixed pathology.

In patients with significant mass effect and cerebral oedema who are in danger of coning, additional treatment with dexamethasone will be necessary. A deterioration after this has been tailed off makes it necessary to consider a biopsy.

Cryptococcus neoformans

C. neoformans is a ubiquitous organism acquired by inhalation. Patients with meningitis may present acutely or insidiously over days or weeks with a headache, general malaise, confusion or seizures. The classical signs of meningism – neck stiffness, photophobia and Kernig's sign – are frequently absent.

Brain imaging is usually normal but MRI may reveal small abcesses – cryptococomas. The CSF cell count and protein may be normal and the diagnosis is confirmed by the presence of cryptococcal antigen in the CSF in 95% of cases. India ink staining is positive in 75%. 85% of cases are culture positive – the gold standard. Measurement of the serum cryptococccal antigen is a useful screening tool in patients presenting with headache or fever but should not be considered definitive.

Intracranial hypertension in the absence of mass lesions or hydrocephalus is an important cause of mortality and visual failure in approximately 20%. This is managed by repeated lumbar punctures or by the insertion of a lumbar or ventricular drain.

JC virus

Progressive multifocal leucoencephalopathy (PML) results from reactivation of the JC virus in immunosuppressed individuals. 80% of the general population will have been exposed to this virus as a banal childhood upper respiratory infection and have positive serology.

The presentation is with slowly evolving focal neurological deficits such as a hemiparesis, visual field and language problems and incoordination due to cerebellar involvement. Occasionally patients develop a dementia in association with these focal abnormalities. Symptoms and signs of raised intracranial pressure are absent although headache may be a feature.

Blood serological testing is unhelpful. Cranial CT shows non-enhancing areas of low attenuation in the white matter. MRI shows characteristic scalloping abnormalities at the grey/white interface with no mass effect or enhancement. The diagnosis may be confirmed by isolating JC virus by polymerase

Box 8.4 Focal lesions in AIDS

- Toxoplasmosis
- Primary CNS lymphoma
- Tuberculoma
- PML

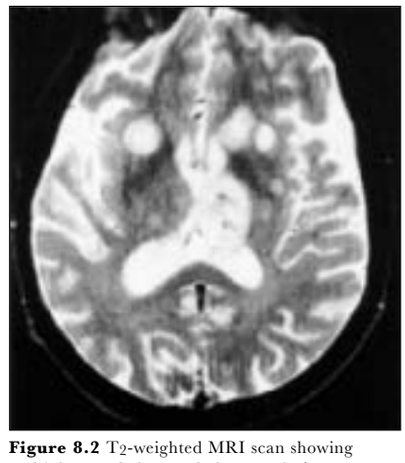


Figure 8.2 T_2-weighted MRI scan showing multiple rounded or oval abscesses before treatment in cerebral toxoplasmosis

Box 8.5 Meningitis in HIV infection

Fungal
- Cryptococcus neoformans

Bacterial
- Mycobacterium tuberculosis
- Listeria monocytogenes
- Streptococcus pneumoniae
- Treponema pallidum

Viral
- HIV
- Herpes simplex, herpes varicella zoster

Box 8.6 Poor prognostic features of AIDS-related cryptococcal meningitis

- Relapse episode
- CSF cryptococcal Ag titre > 1:10 000
- Positive India ink preparation
- Hyponatraemia
- Culture of extrameningeal cryptococcus

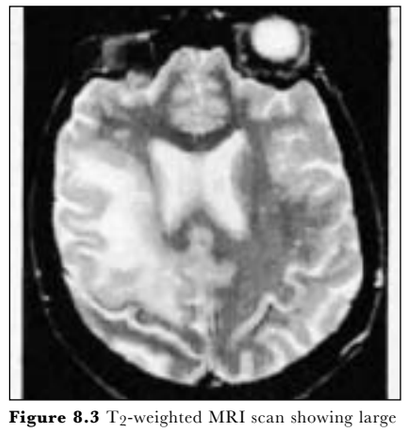


Figure 8.3 T_2-weighted MRI scan showing large area of high signal in one hemispheric white matter with no mass effect. Biopsy proved progressive multifocal leukoencephalopathy

chain reaction (PCR) techniques in the CSF in 75% of cases. If this is negative, a brain biopsy may need to be performed. This typically shows areas of focal demyelination, bizzare enlarged astrocytes and abnormal oligodendrocytes with inclusions which stain for JC viral antigens.

There is at present no specific treatment for PML. Cytosine arabinoside has been shown to be ineffective but trials are underway looking at the efficacy of drugs such as cidofovir (an anti CMV drug) and alpha interferon. Improvement in immune function with HAART has resulted in significantly better survival times.

Box 8.7 Clinical signs and symtoms in PML

- Motor function abnormalities (including hemiparesis)
- Mental status charges
- VIIth cranial nerve palsy
- Cerebellar syndrome
- Language disorders (dysphasia)
- Visual problems (for example hemianopia)
- Seizures

Cytomegalovirus

Over 90% of HIV-infected individuals have serological evidence of CMV infection. The neurological complications, which occur at CD4 counts below 50/mm^3, include retinitis, a cauda equina syndrome, an encephalitis and a mononeuritis multiplex. Apart from retinitis, the other complications occur infrequently.

CMV retinitis

The initial presentation of CMV retinitis depends upon the location – patients may be asymptomatic, complain of floaters, lose peripheral vision or if the lesions are centred around the macula, have poor visual acuity. Patients will often have evidence of CMV disease elsewhere such as colitis and such patients need to be screened for retinitis regularly.

On fundoscopy, there is a perivascular yellow-white infiltrate with retinal haemorrages. The differential diagnosis includes retinal complications of toxoplasmosis, lymphoma, syphilis, herpes zoster and herpes simplex.

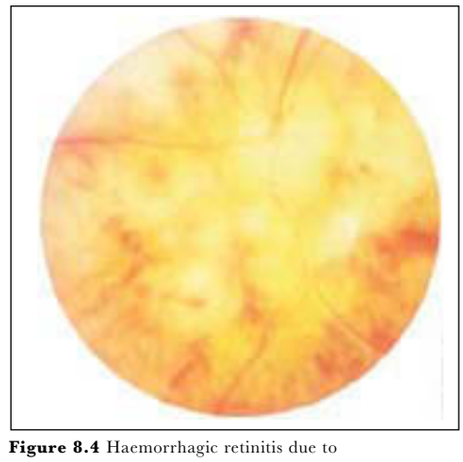


Figure 8.4 Haemorrhagic retinitis due to cytomegalovirus

CMV polyradiculopathy

This well-recognised syndrome presents over a period of days with back pain followed by the development of a progressive flaccid weakness of the legs with sensory loss and sphincter disturbance. Imaging studies which are essential to exclude compressive lesions due to, for example, lymphoma are normal or may show thickened nerve roots. The CSF shows a characteristic neutrophil pleocytosis which is unusual in a viral infection. Without treatment there is a progression of the neurological deficits, with death in 2 or 3 months.

CMV encephalitis

Although evidence of CMV infection is often found in the brains of patients dying from AIDS, the clinical correlates are unclear. A CMV encephalitis needs to be considered in patients presenting with a rapidly progressive encephalitis with cranial nerve palsies and seizures. CMV may be isolated from the CSF using PCR.

Primary CNS lymphoma (PCNSL)

PCNSL is the most common cause of mass lesions in children and the second most common in adults after toxoplasmosis. Histologically, this is a high-grade B cell lymphoma. The Ebstein–Barr virus can be isolated from tissue specimens and is believed to have a causal role in the development of the lymphoma.

The clinical presentation is similar to that of toxoplasmosis with focal neurological deficits such as hemiparesis and seizures. There are usually signs and symptoms of raised intracranial pressure with increasing headache, vomiting and papilloedema.

Although the isolation of EBV by PCR in the CSF is specific, most patients present with mass lesions and raised intracranial pressure. Lumbar puncture is therefore contraindicated. The CT and MRI findings may be

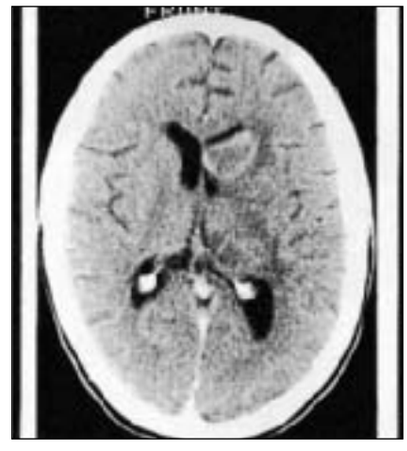


Figure 8.5 Enhancing right frontal mass lesion due to lymphoma

indistinguishable from those due to toxoplasmosis with multiple enhancing lesions with associated cerebral oedema and mass effect. However, a single lesion on MRI especially if the toxoplasma serology is negative, is more likely to be lymphoma, as are lesions which closely adhere to the ventricular walls.

The diagnosis of PCNSL is usually made by biopsy.This may be performed after failure of treatment with antitoxoplasma therapy for at least two weeks. However, since prognosis is poor even with whole brain radiotherapy, it is reasonable not to proceed with a biopsy unless there is a suspicion that other more treatable pathogies may be identified.

HIV-associated dementia complex (AIDS dementia complex) or HIV dementia

This complication occurs in 15% of AIDS patients usually in patients with a CD4 count below 200/mm^3. The early reports of evidence of cognitive abnormalities in HIV positive asymptomatic individuals have been discounted by large cohort studies using clinical, neuropsychological, MRI and neurophysiological methods of assessment. The clinical picture is of a variably progressive dementia with psychomotor slowing and impairment of memory.

The diagnosis is one of exclusion of other infective or neoplastic aetiologies by brain imaging and CSF examination. Although there is a correlation between the CSF HIV RNA viral load and the severity of dementia, there is too much overlap for use as a diagnostic test. A neuropsychological assessment is also helpful. MRI shows cortical atrophy and diffuse or patchy white matter high signal on T2-weighted images.

The underlying pathophysiological mechanisms are unclear but HIV is usually isolated from the microglial cells and astrocytes rather than neuronal cells. Productive infection of the macrophages and microglia with the release of cytokines such as TNF results in neuronal damage.

Since the introduction of zidovudine and subsequently HAART the incidence of HIV-associated dementia has progressively declined. However, more recently there is concern that the CNS may become a sanctuary for HIV, since most of the newer drugs penetrate the CNS poorly.

Peripheral nerve disorders in HIV infection

DSPN is the commonest neurological complication encountered in HIV patients, with 30% of AIDS individuals experiencing symptoms. It is unusual in the asymptomatic stages of HIV infection. Pathologically, this is a length-dependent axonal neuropathy usually sparing the hands. The symptoms and signs are typical of a small fibre neuropathy. Treatment is symptomatic using antidepressant and anticonvulsant drugs.

The neuropathy due to the nucleoside analogue drugs (ddl, ddC and D4T) is similar and therefore difficult to differentiate from DSPN. These drug related neuropathies are dose dependent and reversible. However, patients may continue to deteriorate for 6–8 weeks after stopping the drug – "coasting".

Box 8.10 Symptoms and signs of DSPN

- Numb, burning feet
- Pins and needles
- Contact hypersensitivity
- Little or no weakness
- Impaired pain and temperature sensation
- Depressed or absent ankle jerks

Box 8.8 Symptoms and signs of HIV dementia

Early
- Poor concentration
- Forgetfulness
- Clumsiness
- Unsteady gait
- Apathy
- Impaired eye movements
- Brisk reflexes
- Slowed fine finger movements

Late
- Global dementia
- Incontinent of urine and faeces
- Seizures
- Spastic paraparesis (due to vacuolar myelopathy)
- Myoclonus

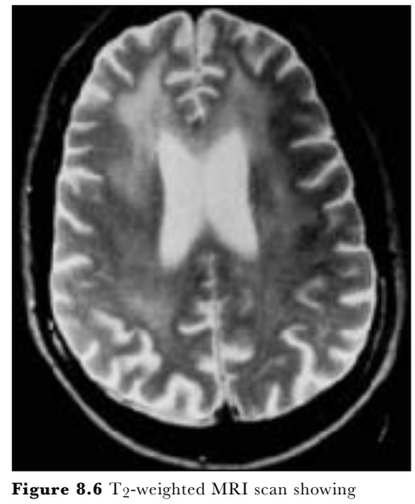


Figure 8.6 T_2-weighted MRI scan showing "milky" hyperintensity of the hemispheric white matter due to HIV dementia

Box 8.9 Peripheral nerve disorders in HIV infection

HIV related
- Axonal neuropathy (distal sensory peripheral neuropathy, DSPN)
- Demyelinating neuropathy – acute (Guillain-Barré syndrome), chronic (CIDP)
- Vasculitic neuropathy (mononeuritis multiplex)
- Diffuse infiltrative lymphocytic syndrome (DILS)

CMV related
- Vasculitis (mononeuritis multiplex)
- Lumbosacral polyradiculopathy

Toxic
- ddl, ddC, D4T
- isoniazid
- thalidomide
- dapsone

Box 8.11 Investigations in HIV neuropathy

- Neurotoxic drugs, including excess vitamin B_6
- Excess alcohol
- Blood tests: vitamin B_{12}, glucose, VDRL, vitamin E (if severe diahorrea)
- Nerve conduction tests – only if marked weakness or unusual presentation
- Nerve biopsy may be indicated to exclude an inflammatory neuropathy (vasculitis or demyelination)

9 Treatment of infections and antiviral therapy

Ian VD Weller, IG Williams

The treatment of HIV infection can be largely divided into: (i) specific antiviral agents that inhibit viral replication, (ii) measures that either treat or prevent (prophylaxis) its complications – namely opportunistic infections and tumours. Major advances in the treatment of HIV infection have occurred in the last few years. This has resulted in marked falls in the reported number of new AIDS cases and deaths in the developed world since 1996. Effective antiretroviral therapy regimens which substantially inhibit HIV replication and allow sustained improvements in the immune system are the main reason for this. There are currently three classes of antiretroviral agents: the nucleoside and non-nucleoside reverse transcriptase inhibitors and the protease inhibitors. Improved formulations and new drugs are continuously being evaluated and there is increasing interest in the possible role of immunotherapy combined with antiretroviral therapy to improve specific immune responses.

However, in those who are severely immunosuppressed the treatment and prophylaxis of opportunistic infections remains important. Though it cannot be overemphasised that the most effective way to prevent first episodes or recurrences of opportunistic infections is treatment with antiretroviral drugs. This chapter will cover both antiretroviral therapy and the treatments of the infections previously described in other parts of this book, in an attempt to bring all of these together in a comprehensive manner.

Box 9.1 Treatment strategies in HIV disease

- Antiretroviral therapy: suppresses viral replication
  results in immune reconstitution
- Prophylaxis of opportunistic infections
- Prevent exposure to opportunistic pathogens

Protozoal infections

***Pneumocystis carinii* pneumonia (PCP)**

Although recently recognised as being more like a fungus, *P. carinii* is considered under protozoa here. Nowadays PCP most commonly occurs in those at risk who fail to take adequate prophylaxis or who are newly diagnosed with HIV infection in advanced disease where it is frequently the presenting illness.

Clinical suspicion is aroused early in patients who are under regular medical supervision, leading to earlier diagnosis. Later diagnosis is asssociated with more severe disease and poorer treatment outcome. Techniques of diagnosis include sputum induction with nebulised saline; this obviates the need for bronchoscopy but the diagnostic sensitivity is lower. The use of lavage alone at bronchoscopy avoids transbronchial biopsy with its complications of haemorrhage and pneumothorax. Exercise oximetry and alternative imaging techniques with radiolabelled compounds are also being used in diagnosis. Monoclonal antibodies to pneumocystis proteins and sensitive DNA probes have been developed but have yet to reach the bedside. In the absence of a confirmatory test, a presumptive diagnosis may be made based on the clinical presentation and chest *x* ray appearances in a patient severely immunosuppressed and at risk.

High-dose intravenous co-trimoxazole for two to three weeks remains a standard first-choice regimen for severe PCP, but once fevers and symptoms have settled and blood gas values have improved the drug can be given by mouth. Side-effects are common, typically after 7–10 days. If co-trimoxazole treatment is not tolerated, alternative treatment regimens include either intravenous pentamidine or a combination of clindamycin and primaquine. Pentamidine is as effective as co-trimoxazole but has side-effects that can be life threatening and should be given

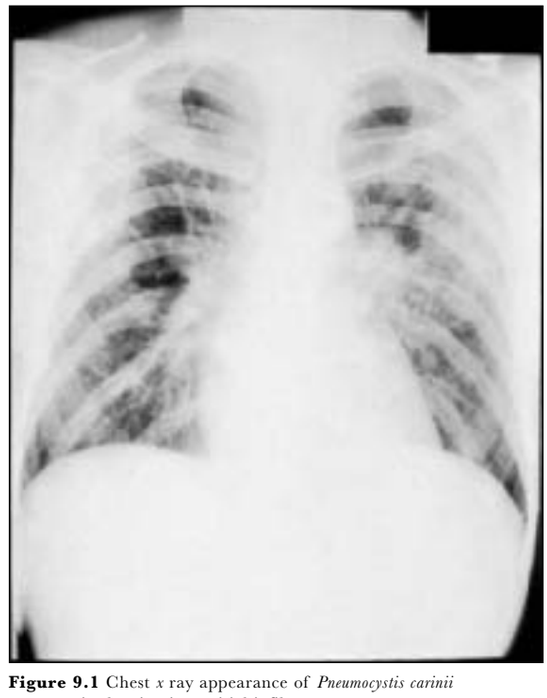


Figure 9.1 Chest *x* ray appearance of *Pneumocystis carinii* pneumonia showing interstitial infiltrates

by slow intravenous infusion with careful monitoring. In patients with moderate or mild PCP a combination of clindamycin and primaquine has proven clinical efficacy and is an alternative first choice for those patients who have a previous history of severe co-trimoxazole hypersensitivity. Side-effects of rash and diarrhoea are frequent.

In patients presenting with severe hypoxaemia high-dose adjunctive corticosteroid therapy is indicated and has been shown in clinical studies to reduce both mortality and morbidity

Alternative second-line therapies include dapsone with trimethoprim, trimetrexate with folinic acid or Atovaquone, a hydroxy-naphthoquinone. The efficacy of atovaquone has only been established in mild to moderate *P. carinii* infection. Like trimetrexate it is probably less effective than co-trimoxazole but it is less toxic. New formulations have improved atovaquone's bioavailability but it still should not be given to patients with malabsorbtion conditions, previous severe diarrhoea or those not taking oral nutrition. Due to acquired resistance, where possible atovaquone should not be given as single-agent therapy. It is commonly combined with intravenous pentamidine as an effective second-line treatment.

Prophylaxis for PCP pneumonia is essential after a first attack (secondary prophylaxis) but is also recommended for all patients once their CD4 cell counts falls below 200×10^6/l (primary prophylaxis). The risk of a first episode PCP below this CD4 count level in patients not on antiretroviral therapy is estimated to be 18% at 12 months for those who are asymptomatic, rising to 44% for those who have early symptomatic disease (for example, oral candida, fever). Co-trimoxazole 960 mg given by mouth daily or three times per week is the most effective agent. In patients who are intolerant, alternative regimens include oral dapsone 100 mg with pyrimethamine 25 mg daily or three times per week, atovaquone 1500 mg daily or nebulised pentamidine. Dose of the latter depends on the nebuliser system: with a Respirgard II nebuliser the recommended regimen is 300 mg every four weeks. In patients with more advanced disease and CD4 counts less than 100×10^6/l, 300 mg given every two weeks should be considered in view of the high failure rate of the monthly regimen.

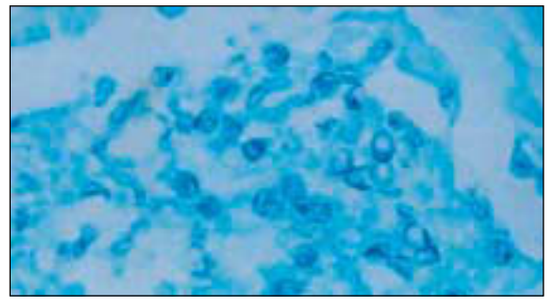


Figure 9.2 Cysts of *Pneumocystis carinii* in broncho lavage specimen

Table 9.1 *Pneumocystis carinii* pneumonia treatment

Drug	Duration	Side-effects	Comments
First choice:			
Co-trimoxazole (trimethoprim component 15–20 mg/kg per day p.o./i.v. in divided doses).	21 days	Nausea, vomiting, fever, rash, marrow suppression, raised transaminases	Intolerance common (25–50% of treated patients)
Alternative regimens:			
1. Severe disease: Pentamidine isethionate 4 mg/kg per day as slow intravenous infusion	21 days	Hypotension, hyper- and hypoglycaemia, renal failure, marrow suppression, nausea, vomiting, cardiac arrest	80% of patients will respond to treatment
Trimetrexate 45 mg/m^2 i.v. and folinic acid 80 mg/m^2	21 days	Marrow suppression, raised transaminases rash, anaphylaxis	Should only be used as third or fourth line treatment
2. Mild to moderate disease: Clindamycin 600 mg 6 hourly p.o./i.v. and primaquine 15 mg daily p.o.	21 days	Diarrhoea, rash, nausea, vomiting, marrow suppression, methaemoglobinaemia, haemolysis	*Clostridium difficile* toxin associated diarrhoea is a frequent complication of clindamycin therapy
Trimethoprim 20 mg per kg/day p.o./i.v. in 2–3 divided doses and dapsone 100 mg daily p.o.	21 days	Rash, nausea, methaemoglobinaemia, marrow suppression	Alternative regimens should be used in patients with G6PD deficiency
Atovaquone suspension 750 mg twice daily	21 days	Rash, raised transaminases and neutropenia	Must be taken with food. Consider combination with i.v. pantamidine as resistance reported with monotherapy
Adjuvant high-dose steroids (for example, prednisolone 40–60 mg daily p.o.)	5 days tapering over 14–21 days		Indicated in severe disease. Optimal dose not determined

Although clinical trials have shown greater efficacy for co-trimoxazole compared to other regimens, there is a high rate of discontinuation due to side-effects. Desensitisation regimens are used with the aim of reducing the rate of intolerance but there is uncertainty about their efficacy and which regimen is best.

In patients responding to antiretroviral therapy, primary or secondary prophylaxis can be safely discontinued once the CD4 count has increased to levels persistently above 200×10^6/l.

Toxoplasmosis

Cerebral toxoplasmosis is the commonest manifestation of toxoplasma infection. As toxoplasmosis is the most common cause of ring-enhancing lesions on contrast CT brain scans a presumptive diagnosis is usually made and treatment started. The condition responds well if treatment is started early, and a combination of sulphadiazine 4–6 g/day and pyrimethamine 50–100 mg a day (both by mouth in divided doses with folinic acid 15 mg daily) is the treatment of choice. Side-effects may prevent continued use of sulphadiazine, and clindamycin 600–1200 mg four times a day has been shown to be an effective alternative in controlled studies.

Corticosteroids are sometimes used in addition to first-line treatment to reduce symptomatic cerebral oedema, but a clinical and radiological response seen after two weeks of treatment may be due solely to the corticosteroid effect rather than the anti-toxoplasma treatment. A presumptive diagnosis of toxoplasma may therefore be made, although the underlying lesion may be due to something else, such as lymphoma or another infection. Relapse is common after treatment is stopped, and maintenance treatment is therefore necessary. In patients responding to antiretroviral therapy with sustained increases in CD4 count, discontinuation of prophylaxis is safe but there is limited current data to make definite recommendations.

Atovaquone 750 mg four times a day with or without pyrimethamine may be considered an alternative and the new macrolides clarithromycin 2 g daily and azithromycin, both given with pyrimethamine 75 mg/day, have also been effective in small uncontrolled studies. The most appropriate regimen for secondary prophylaxis has not been determined but treatment doses of either sulphadiazine and pyrimethamine or clindamycin and pyrimethamine are usually halved.

Of patients with positive toxoplasma serology and a CD4 count of less than 100×10^6/l, approximately 1 in 3 will develop cerebral toxoplasmosis within 12 month without prophylaxis. Primary prophylaxis in patients with positive serology with a CD4 count of less than 100×10^6/l is therefore recommended. Co-trimoxazole or dapsone with pyrimethamine have been shown to reduce the incidence of toxoplasmosis compared to patients taking nebulised pentamidine for prophylaxis against PCP. Atovaquone with or without pryrimethamine may also be considered but this is based on more limited data. The macrolides clarithromycin and azithromycin might be anticipated to provide broad-spectrum prophylaxis for toxoplasmosis, atypical mycobacterial and bacterial infections, but bacterial resistance might limit their use in this situation.

Patients who are toxoplasma serology negative should be given advice to prevent exposure in primary infection with toxoplasmosis. They should be advised not to eat raw or undercooked meat and avoid directly handling cats' faeces.

Cryptosporidiosis and other protozoa

In patients with less advanced HIV disease (CD4 counts >200 $\times 10^6$/l) cryptosporridial infection usually causes a self-limiting gastrointestinal illness and symptomatic treatment with

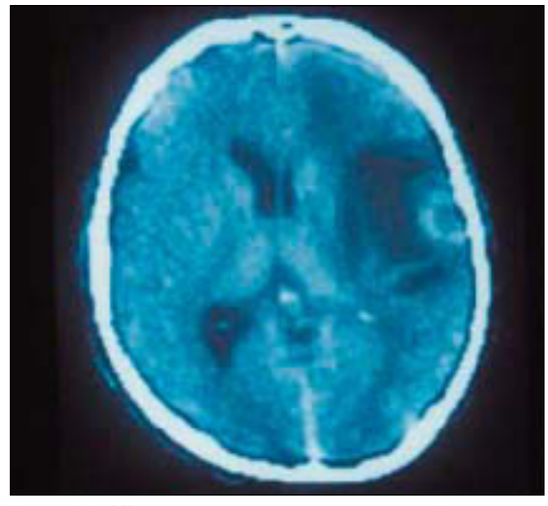


Figure 9.3 CT scan showing ring-enhancing lesions of cerebral toxoplasmosis surrounded by cerebral oedema (dark area)

Box 9.2 Treatment of toxoplasmosis

First line

Sulphadiazine 4–6 g per day or clindamycin 600–1200 mg × 4 per day

+

Pyrimethamine 50–100 mg per day

+

Folinic acid 15 mg per day

Alternatives

- Clarithromycin 2 g per day or
- Atovaquone 750 mgs 4 × per day p.o.
  +
  Pyrimethamine 50–100 mg per day p.o.

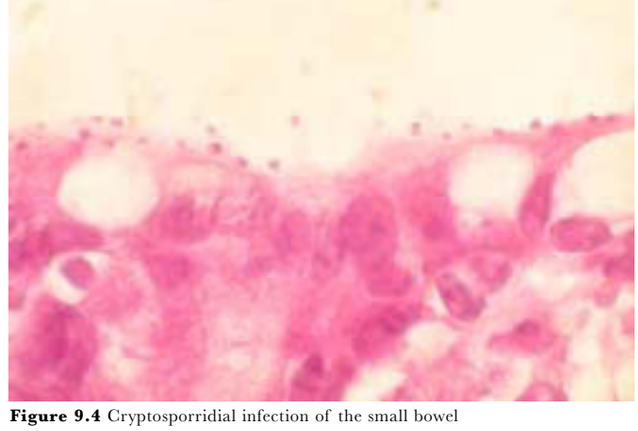


Figure 9.4 Cryptosporridial infection of the small bowel

anti-diarrhoeal agents is all that maybe needed. In those with more severe immunosuppression and persistent symptoms treatment is more difficult and reported successes with a variety of agents are still anecdotal. Symptoms and excretion of cysts may be intermittent. Responses have been described after treatment with a variety of agents, including spiramycin, erythromycin, diclazuril, letrazuril, hyperimmune bovine colostrum, paromamycin, azithromycin and subcutaneous somatostatin.

Symptomatic treatment with antidiarrhoeal and antiemetic agents together with fluid, electrolyte and nutritional support should be provided. Case reports suggest that immune reconstitution is likely to result in improvement and resolution of both symptoms and infection. Thus in the absence of an effective specific treatment against cryptosporidium, infected patients should be started on antiretroviral therapy to increase the CD4 count.

Patients at risk of infection should be advised to avoid possible exposure in water supplies particularly at times of documented outbreaks. Although unproven, measures that may be considered for patients with CD4 counts less than 200×10^6/l include using bottled water, point of use filters or boiling water for more than one minute.

For microsporidiosis there have been anecdotal reports of symptomatic improvement with albendazole 400 mg twice a day or metronidazole 500 mg three times a day.

Isosporiasis is less common and appears to respond to co-trimoxazole 960 mg four times a day, but relapses occur in half of all cases.

Diarrhoea often occurs in the absence of recognised pathogens in the stool, and metronidazole has relieved symptoms in some cases.

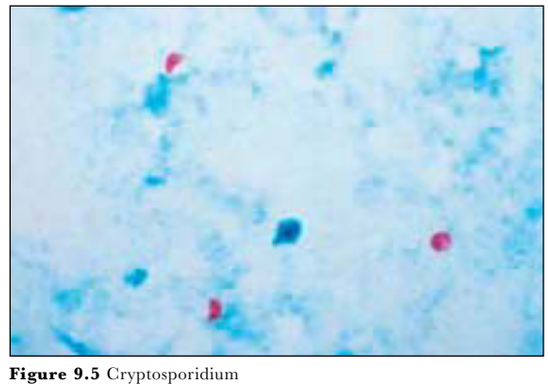


Figure 9.5 Cryptosporidium

Table 9.2 Viral opportunistic infections

Infection	Drug	Duration	Side-effects	Comments
Herpes simplex				
Treatment	Aciclovir 200 mg 5 × a day orally or 10 mg/kg 8 hourly i.v.	5–7 days		Duration may be extended in severe infections
Prophylaxis	Aciclovir 200 mg 4 × a day or 400 mg 2 x day	Indefinite		
Cytomegalovirus				
Treatment	Ganciclovir 5 mg/kg twice a day i.v.	14-21 days	Neutropenia, anaemia	GCSF support may be required
	Cidofovir 5 mg/kg i.v. once a week	2 weeks	Nephrotoxicity: impaired creatine clearance, proteinuria, hypophosphataemia Neutropenia Ocular toxicity	Co-administer with probenecid and adequate hydration to reduce risk of nephrotoxicity
	Foscarnet 180 mg/kg daily i.v.	14–21 days	Nephrotoxicity, hypomagnesaemia, hyper- and hypocalcaemia, hyper- and hypophosphataemia, hypokalaemia, nausea vomiting, genital ulceration	Dose must be adjusted according to renal function
Maintenance ganciclovir	Ganciclovir 3 gr daily orally	Until CD4 count > 100×10^6/l on HAART	As above	May be combined with intraoccular implants Avoid in patients with diarrhoea Increases levels of didanosine
	Cidofovir 5 mg/kg once every 2 weeks	Until CD4 count > 100×10^6/l on HAART	As above	As above
Alternative secondary prophylaxis regimens include daily intravenous foscarnet or ganciclovir, intravitreal injections of ganciclovir or foscarnet and intraoccular ganciclovir implants				

Viral infections

Severe mucocutaneous and systemic infections with herpes simplex virus are best treated with aciclovir. Prophylaxis is used after severe infection and in patients with increasing severity and frequency of recurrences. These recurrences can be a prelude to the chronic persistent mucocutaneous ulceration characteristic of AIDS.

Varicella zoster virus infections are usually treated with high-dose aciclovir given by mouth. However, dissemination of infection from dermatomal zoster is unusual even without treatment.

Valaciclovir is a pro-drug of aciclovir which is used in the treatment of herpes zoster and herpes simplex infections of skin and mucous membranes. Valaciclovir is a L-valine ester of aciclovir that is rapidly converted to aciclovir after oral administration. The antiviral spectrum and mode of action is therefore the same as aciclovir. Aciclovir has, however, a low oral bioavailability (about 15–20%). Valaciclovir has three or four times the oral bioavailability of aciclovir.

Famciclovir is a diacetyl ester of 6-deoxy penciclovir which has been used in the treatment of herpes zoster and genital herpes infections. Famciclovir is metabolised to penciclovir in the intestinal wall and liver. Penciclovir and aciclovir have similar antiviral spectrum.

Aciclovir resistant herpes simplex infections can occur, particularly in patients with advanced disease and severe immunosuppression. Alternative agents to treat resistant infections include foscarnet and cidofovir.

Reactivation of cytomegalovirus with viraemia and end-organ disease tends to occur when CD4 cell counts are persistently below 50×10^6/l. Ganciclovir (an acyclic analogue of deoxyguanosine), foscarnet phosphonoformate (a pyrophosphate analogue, which inhibits polymerase enzymes) and cidofovir (a nucleoside analogue with potent *in vitro* activity against viruses) are used for the treatment of cytomegalovirus retinopathy, gastrointestinal and neurological disease. Treatment arrests progression retinitis in most patients, and maintenance therapy is required in those patients who continue to be severely immunosuppressed to delay the time to further relapse. There is little comparative data to guide initial choice of treatment. A study comparing ganciclovir with foscarnet for treatment of CMV retinitis found no difference between the drugs in their ability to delay progression of disease, but there was a survival advantage in those patients treated with foscarnet. However, foscarnet is not as well tolerated as ganciclovir, as it produces reversible renal failure and electrolyte disturbances. Careful and frequent monitoring is required which complicates outpatient management. The major side-effect of ganciclovir is bone marrow suppression, particularly neuropenia. Support therapy with granulocyte colony simulating factor (GCSF) maybe required.

The detection of mutations in the CMV UL97 gene is associated with an increase in CMV DNA levels in blood and clinical progression of CMV retinitis during ganciclovir therapy. High-level resistance to ganciclovir results in cross-resistance to cidofovir. Resistance to foscarnet can occur but the mechanism is different.

Cidofovir has been shown to be effective however in delaying progression and time to relapse in patients who have experienced therapy failure on ganciclovir and foscarnet. The dosing schedule of cidovofir is convenient and more suitable to outpatient care than with either intravenous ganciclovir or foscarnet. It is given once weekly (5 mg/kg) for two weeks as induction therapy and then at the same dose every two weeks thereafter as maintenance therapy. The main side-effect is

Box 9.3 Management of CMV disease: key points

- Population at highest risk of clinical disease:
  CD4 < 50×10^6/l
  positive CMV viraemia
- Diagnostic criteria: combination or clinical presentation +/− histopathology +/− virus isolation (culture or antigen detection)
- Choice of first line therapy dependent upon renal function, haematological indices and risk of toxicity
- Where possible all patients should be started on an effective HAART regimen to increase the CD4 count to above 100×10^6/l
- Secondary prophylaxis maybe discontinued once the CD4 count has risen and remains above 100×10^6/l

Table 9.3 Opportunistic infections: recommendations for initiation of primary prophylaxis

Opportunistic infection	Recommendations
Pneumocystitis carinii pneumonia	CD4 count <200 × 10^6/l
Cerebral toxoplasmosis	CD4 count <100 × 10^6/l and positive lg G toxoplasma serology
Mycobacterium avium complex	CD4 count <50 × 10^6/l
CMV disease	under evaluation: may consider if CD4 <50 × 10^6/l and positive CMV viraemia
Tuberculosis	If recent close contact of smear positive index patient and no evidence of active clinical disease National Guidelines for use of Tuberculin skin testing for screening varies.

Figure 9.6 Penile ulceration caused by intravenous foscarnet therapy.

nephrotoxicity. The dose needs to be adjusted or treatment delayed or discontinued if there is evidence of renal tubular dysfunction, for example proteinuria, hypophosphataemia and impaired creatinine clearance.

The choice of initial treatment is therefore dependent on the preferred dosing schedule, the risk of drug-associated toxicity and previous anti-CMV treatment history. Alternative treatment strategies include combination regimens of foscarnet and ganciclovir, intravitreal injections of ganciclovir or foscarnet and intraoccular implants of ganciclovir. The latter effectively prevents relapse in the treated eye for up to three months but there is an increased risk of early retinal detachment. There is a risk of CMV disease occurring in the contralateral eye or elsewhere, and thus concomitant oral ganciclovir is indicated.

Following induction therapy, secondary prophylaxis is required but can be safely discontinued without risk of relapse of retinopathy in patients who have responded to highly active antiretroviral therapy (HAART). Improved cytotoxic T-lymphocyte responses to CMV and suppression of CMV viraemia is seen in those patients with advanced disease who sustain a rise in CD4 count on HAART. Effective antiretroviral therapy has resulted in dramatic falls in the incidence of new episodes of CMV disease and of relapse. However, in patients who remain severely immunosuppressed and at risk of CMV disease and relapse, secondary prophylaxis is required. Daily intravenous foscarnet or ganciclovir regimens require an in-dwelling intravenous catheter which is inconvenient and complicated by the risk of bacterial infections. Either daily oral ganciclovir or two-weekly intravenous cidofovir are preferable. Although ganciclovir is poorly absorbed, the oral preparation at a daily dose of 3 g has similar efficacy to intravenous regimens in preventing progression of retinitis. Combinations of ganciclovir with greater oral bioavailability are under evaluation.

Primary prophylaxis against CMV retinitis with oral ganciclovir has been investigated, but the results of two large clinical trials are conflicting, and in view of the high cost has not gained acceptance in routine clinical practice. Immune preservation or reconstitution as a result of HAART is the best prophylaxis (both primary and secondary) against CMV end-organ disease and other major opportunistic infections.

Table 9.4 Fungal opportunistic infections

Infection	Drug	Duration	Side-effects	Comments
Candidiasis				
Local treatment	Nystatin oral suspension or pastilles, miconazole oral gel or amphotercin lozenges all 4–6 times a day	As required		Systemic therapy is commonly required
Systemic treatment	Ketoconazole 200 mg a day (p.o.)	1–2 weeks	Nausea (less if taken with food), abnormal liver function tests, hepatitis thrombocytopenia, rash	In patients who remain severely immunosuppressed, relapse is common and maintenance therapy is required
	Fluconazole 50–200mg a day (p.o.)	1–2 weeks	Nausea, abnormal liver function tests	As above
	Itraconazole capsules or solution 200 mg/day (p.o.)	1–2 weeks	Nausea, abnormal liver function tests	
Cryptococcosis				
Treatment	Amphotericin B 0.7–1.0 mg/kg/day (i.v.) ± flucytosine 75–100mg/kg/day in 3–4 divided doses		Nausea, vomiting, rash, bone marrow suppression, renal impairment, hypocalcaemia	In patients who remain severely immunosuppressed, relapse is common and maintenance therapy is required Liposomal preparations of amphotericin reduces risk of nephrotoxicity
	or Fluconazole 800 mg daily 1–3 days 600 mg daily thereafter (p.o. or i.v.)		As above	

Fungal infections

Dermatophytic fungal infections respond well to imidazole creams. Oral candida is often asymptomatic in its early stages and may not require treatment. In more severe infections local treatment with frequent nystatin suspension, or pastilles, or amphotericin lozenges can be used. Systemic treatment with oral ketoconazole or fluconazole daily is required for more severe oropharyngeal and oesophageal candidiasis. Long-term maintenance treatment may be required to prevent recurrences, and liver function tests should be monitored. Clinical resistance to treatment can occur and in the case of fluconazole may be related to emerging candida species that are less sensitive to fluconazole or to *Candida albicans*-resistant strains. Intermittent therapy rather than maintenance may be a more appropriate strategy to reduce this risk but has yet to be assessed in a large controlled trial. Itraconazole solution has been found to be useful in cases of clinical resistance and this may be related to its topical action, better absorption and greater spectrum of activity.

Vulvovaginal candidiasis can be a recurrent problem in women and should be treated either with topical agents (clotrimazole or miconazole pessaries and cream) or single high dose fluconazole.

Cryptococcal meningitis is treated with either fluconazole or amphotericin B with or without flucytosine. A large comparative study has shown that the overall mortality was similar in both treatment groups. However, there were more early deaths in the fluconazole group, and amphotericin sterilised the cerebrospinal fluid more rapidly but fluconazole was better tolerated. There was a 20% mortality and the factors predictive of death were an abnormal mental state, a cryptococcal antigen titre above 1 024 and a white cell count below 0.02×10^9/l in the cerebrospinal fluid. Physicians will probably therefore prefer to treat patients with these poor prognostic markers with amphotericin rather than fluconazole. With a 20% mortality irrespective of what treatment is used it is clear that improvements in treatment are required.

Maintenance treatment is required in those who remain severely immunosuppressed, as replase is common. Fluconazole (200 mg/day) was more effective than amphotericin B (1 mg/kg/week) in a large randomised study. The comparative efficacy of higher doses of amphotericin maintenance treatment is unknown. Liposomal preparations of amphotericin B may be useful, particularly in patients at risk of renal toxicity. Controlled studies of high doses of fluconazole suggest greater efficacy. As with other severe opportunistic infections, immune reconstitution following HAART will allow safe discontinuation of secondary prophylaxis regimens.

Amphotericin B is still the mainstay of treatment of other systemic fungal infections. Itraconazole has shown to be effective in induction and maintenance treatment of disseminated histoplasmosis.

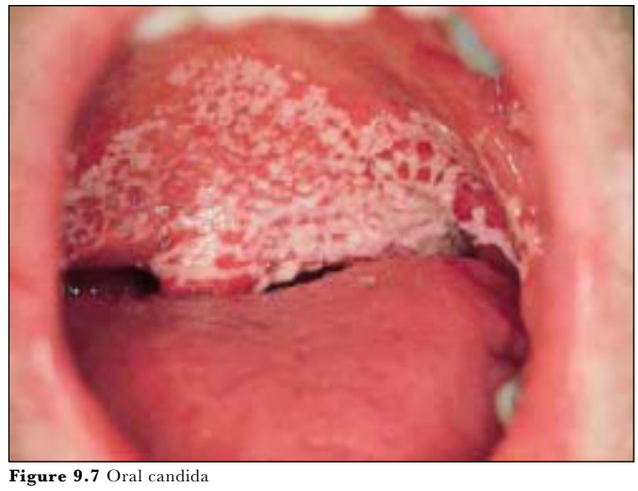


Figure 9.7 Oral candida

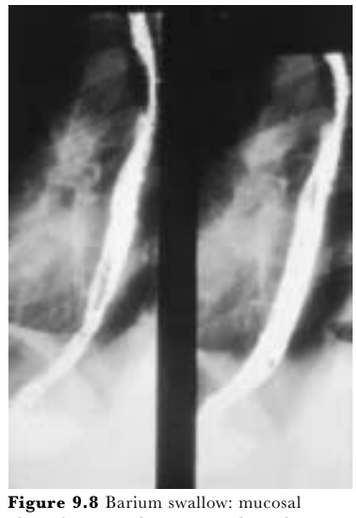


Figure 9.8 Barium swallow: mucosal ulceration secondary to oesophageal candida infection

Bacterial infections

Tuberculosis in HIV infection is treated in the standard way with isoniazid and rifampicin plus either pyrazinamide or ethambutol. Rifampicin is a potent enzyme inducer and increases the metabolism of drugs such as oral contraceptives, dapsone, fluconazole, ketoconazole and anticonvulsants. Clinicians should also be aware of drug interactions between rifamycins (rifampicin and rifabutin) and antiretroviral drugs, particularly the protease inhibitors (PIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs). Certain combinations of each are contraindicated or require dose adjustment to

Box 9.4 Treatment of MAC

Clarithromycin 1 g–2 g daily in divided doses
+
Ethambutol 15 mg/kg/day daily
+
Either Rifabutin 450–600 mg daily
Rifampicin 450–600 mg daily
Ciprofloxacin 500 mg twice daily
Clofazimine 100 mg daily
3 or 4 drug regimens are recommended

maintain therapeutic levels. Knowledge of these potential interactions is essential to avoid loss of clinical efficacy or increased risk of drug toxicity.

Although extrapulmonary disease is more common in HIV seropositive patients than in uninfected controls, the responses to treatment appear similar in the developed world if patients are compliant. Over the last few years there have been several outbreaks of tuberculosis with multiple drug-resistance (MDR) in the USA and Europe including the UK. Transmission of drug-resistant strains has occurred between patients and from patients to family members, healthcare workers and prison guards. Mortality from drug-resistant tuberculosis in this setting is high, around 70–90%. To reduce the risk of MDR TB it is essential to ensure adherence to antituberculosis therapy by patients and for healthcare facilities to have in place procedures and facilities to reduce the risk of nosocomial transmission.

Disseminated infection with *Mycobacterium avium* complex (MAC) causes considerable morbidity and mortality in the later stages of HIV infection (when CD4 counts are persistently below 50×10^6/l). Various combinations of drugs have been shown to decrease mycobacteraemia and improve symptoms in uncontrolled studies. Four, three and two drug regimens have and are being assessed in clinical trials. A commonly used regimen in clinical practice is rifampicin or rifabutin (450–600 mg/day), ethambutol (15 mg/kg, max 1 g/day) and clarithromycin (500 mg twice a day). Other drugs that have been studied and may be considered include: clofazimine (100 mg/day), ciprofloxacillin (500–75 mg twice a day), parental amikacin (7.5–15 mg daily for 2–4 weeks) and another macrolide azithromycin.

Primary prophylaxis has been shown to significantly reduce the incidence of M.avium complex bacteriaemia and should be considered in patients whose CD4 counts are less than 75×10^6/l. A variety of agents have been shown to be effective including rifabutin 300 mg daily, clarithromycin 500 mg twice daily or azithromycin 1200 mg once weekly. Resistant strains on clarithromycin and azithromycin prophylaxis can occur in those who develop breakthrough bacteriaemia, and there is cross-resistance. A combination of once weekly azithromycin and once daily rifabutin is probably the most effective prophylaxis regimen and may also provide additional prophylaxis against PCP.

Salmonella infections are treated with either co-trimoxazole or ciprofloxacin and campylobacter with ciprofloxacin. In salmonella infections relapses of enteritis or bacteraemia are common.

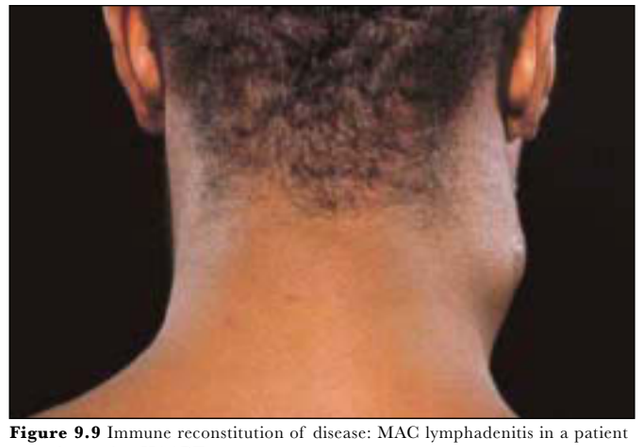


Figure 9.9 Immune reconstitution of disease: MAC lymphadenitis in a patient recently starting HAART

Table 9.5 Targets for antiretroviral therapy

Target	Treatment
Virus receptor and entry	Fusion inhibitors, chemokine receptor blockers
Reverse transcriptase	Inhibitor/DNA chain terminators
RNAase	Inhibitors
Integration	Viral integrase inhibitors
Viral gene expression	Inhibitors of HIV regulatory genes and their products
Viral proteins synthesis	Enzyme inhibitors, for example, protease inhibitors
Viral budding	Interferons (also act at other sites of replication cycle) antibodies and ligands

Antiretroviral drugs

The clinical effectiveness of antiretroviral therapy has improved markedly over the last few years. Since 1996 in the developed world there have been dramatic falls in the incidence of new AIDS cases and AIDS-associated deaths. Published data in the late 1990s estimated the mortality rate in patients with CD4 counts of less than 100×10^6/l had fallen by nearly two-thirds to <8 per patient years. Although the long-term clinical efficacy of the current antiretroviral treatment regimens remains uncertain, the biological rationale for maintaining a clinical response has been established. Sustained inhibition of viral replication results in partial reconstitution of the immune system in most patients, substantially reducing the risk of clinical disease progression and death. Reservoirs of HIV in latently infected resting T-lymphocytes and other long-lived cell populations makes it unlikely that HIV can be eradicated by antiretroviral therapy alone. Strategies to sustain suppression of viral replication in the long-term will be necessary.

Box 9.5 Antiretroviral regimens

1. 2 NRTIs: eg. Zidovudine or Stavudine + Lamivudine or Didanosine
   plus either
   1 NRTI: Nevirapine or Efavirenz
   or
   1 PI: Nelfinavir, Saquinavir soft gel or a low dose Ritonavir boosted PI
   or
   2 PIs: eg. Saquinavir + Ritonavir
2. 3 NRTIs: Zidovudine, Lamivudine + Abacavir

Antiretroviral regimens for the initial treatment of chronic infection in adults (2001). Choice would depend upon efficacy, tolerability, adherence and resistance profile of the regimen. Treatment guidelines are constantly reviewed and updated.

There are several potential targets for antiretroviral drugs in the viral replication cycle. Three classes of antiretroviral drugs are currently used in combination for the treatment of HIV infection, which target the activity of two viral enzymes. New therapeutic agents are constantly being evaluated.

Reverse transcriptase inhibitors

The first drugs made available for clinical use were inhibitors of the HIV reverse transcriptase enzyme. Before the virus can be integrated into the host cell genome DNA, a copy of the viral RNA has to be formed (pro-viral DNA). This is regulated by the specific HIV DNA polymerase: reverse transcriptase (RT). If a DNA copy is not formed, the viral RNA genome becomes susceptable to destruction by cellular enzymes.

The nucleoside reverse transcriptase inhibitors (NRTIs) are both competitive inhibitors of RT and DNA chain terminators. The normal 2' deoxynucleosides which are substrates for DNA synthesis link to form a chain by phosphodiester linkages bridging the 5' and 3' positions on the five carbon sugar molecule. The 2', 3'-dideoxynucleosides analogues are formed by the replacement of the 3'-hydroxy group by an azido (zidovudine), hydrogen or other group. These nucleoside analogues as substrates will bind to the active site of the HIV RT enzyme and will be added to the growing HIV proviral DNA chain. However, once inserted, the normal 5' to 3' links will not occur resulting in HIV proviral DNA chain termination.

Genotypic mutations at various codons in the RT gene result in decreased susceptability of HIV to inhibition by the NRTIs. Several NRTIs are currently licensed for the treatment of HIV infection in combination regimens and newer agents with better tolerability and resistance profiles are under evaluation.

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a group of structually diverse agents which bind to RT at a site distant to the active site resulting in confirmational changes at the active site and inhibition of enzyme activity. These agents show high antiviral activity *in vitro* and have relatively low toxicity. They are also highly specific, inhibiting the reverse transcriptase of HIV-1 but not HIV-2. As monotherapy, rapid emergence of resistant strains associated with single point mutations of the RT gene, high-level phenotype resistance and loss of antiviral effect occurs. The drugs therefore need to be combined with other antiretroviral agents, usually two NRTIs, to achieve and maintain an effective long-term treatment response.

Protease inhibitors

The protease inhibitors bind competitively to the substrate site of the viral protease enzyme. This enzyme is responsible for the post-translational processing and cleavage of a large structural core protein during budding from the infected cell. Inhibition results in the production of immature virus particles. Their potent anti-HIV activity and introduction to clinical use from 1996 was one of the main reasons for the observed substantial falls in morbidity and mortality associated with HIV infection in the developed world. However, tolerability, relatively high pill burden and poor adherence were frequent problems with the initial protease inhibitor containing regimens. Specific genotypic mutations in the protease gene can result in high levels of phenotype resistance to individual protease inhibitors and cross-resistance. New protease inhibitors are under evaluation.

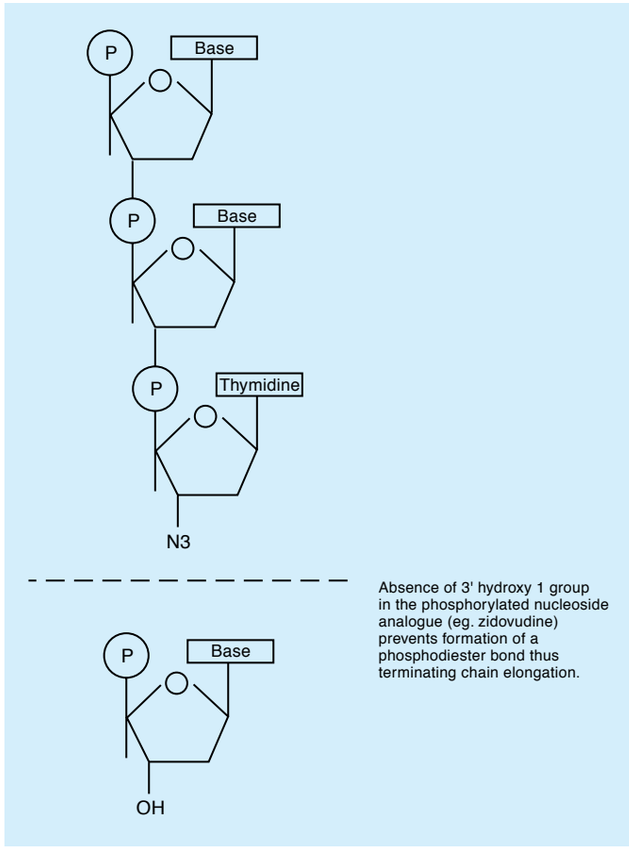


Figure 9.10 Mechanism of action of nucleoside reverse transcriptase inhibitors

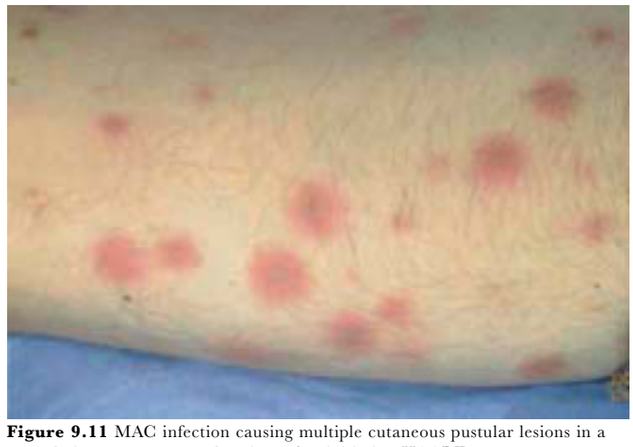


Figure 9.11 MAC infection causing multiple cutaneous pustular lesions in a severely immunosuppressed patient after initiating HAART

Treatment of chronic adult infection

In the mid 1990s, several large clinical endpoint studies demonstrated a strong association between falls in plasma HIV RNA levels (plasma viral load) in the first few weeks on therapy and clinical outcome at one year. It is now accepted that falls in plasma viral load combined with increases in CD4 count are predictive of the clinical treatment response on different combination regimens at 1–2 years, although changes in the markers probably do not fully predict the observed clinical effect.

Studies have also shown an association between the plasma viral load nadir on therapy and both the risk of subsequent viral load rebound, and the emergence of viral genotypic mutations associated with reduced drug susceptibility. Where possible an objective of antiretroviral therapy is to reduce and sustain plasma viral load levels to below the level of detectability of the current ultra-sensistive viral load assays (< 50 copies/ml). If patients are adherent to therapy, the likelihood of a viral load rebound and drug resistance is minimal. Despite inhibition of viral replication in plasma, lymph nodes and at other sites, reservoirs of HIV infection in latently infected resting T-lymphocytes remain. Continued activation of these cells will theoretically result in the reduction of this reservoir, however new cells probably continue to be infected either as a result of localised small bursts of viral replication or loss of the antiretroviral effect of the treatment regimen. Even in patients who have sustained, undetectable levels of plasma viral load (< 50 copies/ml) for three years or more, discontinuation of antiretroviral therapy results in rapid rebound of plasma viral load to pretreatment levels.

Sustained inhibition of viral replication does however result in substantial immune reconstitution, even in those patients with advanced disease who start antiretroviral therapy at very low CD4 counts. Reduction in immune activation markers, increases in both memory and naïve CD4 and CD8 T cells and development of improved lymphoproliferative responses to antigens such as CMV and mycobacteria occur in patients on HAART. Immune responses to HIV are generally not regained, and it remains uncertain what levels of immune reconstitution can be achieved over time. This may depend on any residual thymic function or the ability of extrathymic pathways to facilitate immune reconstitution.

To achieve sustained falls in plasma viral load it is standard of care in patients starting antiretroviral therapy for the first time to use a triple drug regimen containing two NRTIs in combination with either one NNRTI or one or two protease inhibitors. In clinical trials, a combination of two NRTIs and a protease inhibitor has been shown to reduce the risk of progression to AIDS or death compared to treatment with two NRTIs alone. There is no similar clinical endpoint data for NNRTI-containing combinations, however randomised trials have shown that treatment with a combination of two NRTIs and one NNRTI results in similar falls in plasma viral load and increases in CD4 count after one year to treatment with two NRTIs and a protease inhibitor. On the basis of these results, it is recommended to inititate therapy with either a PI or an NNRTI containing triple combination. Large randomised trials are under way to evaluate which starting regimen is better in the long term.

The efficacy of antiretroviral therapy has improved over the last few years, however only approximately 50–70% of patients will have sustained plasma viral loads to <50 copies/ml at one year. An important factor associated with treatment success is adherence. Patients who are able to tolerate and adhere to their treatment regimen are more likely to achieve and sustain

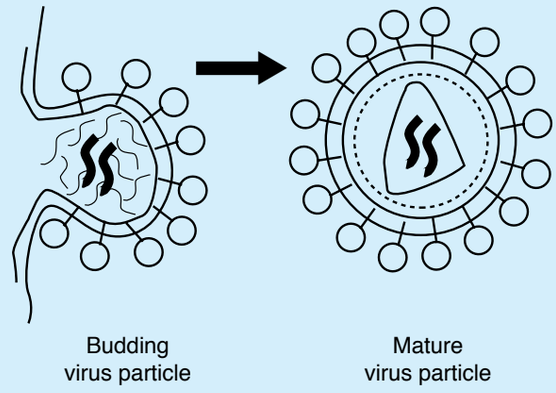


Figure 9.12 Site of Action of Protease Inhibitors

Table 9.6 Recommendations for starting antiretroviral therapy in adults

Disease stage	BHIVA (1)	USDHHS (2)
Symptomatic	Treat	Treat
Asymptomatic: CD4 $<200\times10^6$/l	Treat	Treat
CD4 count $200–350\times10^6$/l	Consider treatment depending upon VL, rate of CD4 count decline, symptoms and patient wishes	Treatment should generally be offered
CD4 $>350\times10^6$/l	Defer	Defer or consider treatment if high VL

(1) BHIVA: British HIV Association Guidelines (March 2001)
(2) USDHHS: United States Department of Health and Human Services (February 2001)

Box 9.6 Factors associated with virological treatment failure

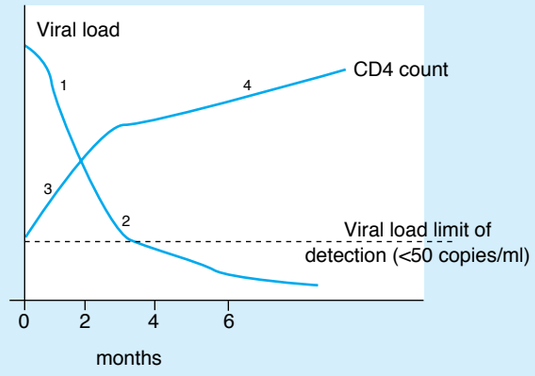
- poor adherence
- drug intolerance and toxicity
- drug–drug interactions resulting in sub-optimal drug levels
- development of genotypic mutations associated with reduced drug susceptibility
- pharmacological resistance resulting in decreased intracellular drug levels

suppression of plasma viral load than those who do not. Few patients experience virological treatment failure as a result of poor antiviral potency. The ability of a patient to adhere to a treatment regimen is important in determining the choice of treatment regimen. The dosing schedule, pill burden, the requirement or not for dietary restrictions, risk of side-effects and patient motivation are important in determining adherence. Other factors which contribute to the initial treatment choice are baseline viral load, resistance profile of the drug, future options for treatment, known efficacy of the treatment regimen, the potential for drug to drug interactions and the presence of drug resistance at baseline.

The optimal time to initiate therapy with the current antiretroviral drugs has not been established in clinical studies. CD4 count and plasma viral load are predictors of the estimated risk of progression to AIDS which is a factor in determining when to start treatment. The motivation of a patient to start and adhere to therapy and the known effectiveness of current regimens are also important. Clinical practice across Europe and North America varies, but most clinicans would consider initiating therapy at some point between a CD4 count of 200–500 $\times$ 10^6/l and in all patients who are symptomatic. Even in patients who initiate therapy with CD4 counts of <100 $\times$ 10^6/l, substantial increases in CD4 count and clinical benefit can be achieved. Patients on therapy should have CD4 count and plasma viral load levels monitored at regular intervals. On effective therapy, plasma viral load falls rapidly as viral replication is inhibited. By four weeks a fall of greater than 1 log and by 3–6 months a fall to < 50 copies/ml should be expected.

Apart from drug intolerance, indications to change therapy have not yet been fully defined and evaluated. Physicians, however will use evidence of clinical progression, a fall in CD4 count and a rise in plasma viral load as markers of therapy failure, and consider changing therapy. When to switch therapy will also depend on available treatment options, patient adherence and the emergence of drug resistance and the potential for cross-resistance to other drugs.

In the antiretroviral experienced patient, the objective of therapy remains similar to that in patients starting treatment for the first time. Therapeutic options, however, are more limited because of previous drug toxicity and the presence of genotypic mutations conferring drug resistance.



1. Initial rapid fall in viral load: as a result of inhibition of viral replication in productively infected lymphocytes
2. Slower second phase decay in viral load, becoming undetectable (<50 copies/ml) at 4–6 months or treatment
3. Initial increase in CD4 count due to redistribution and expansion of CD4 memory cells
4. Subsequent rise due to production and expansion of new naive and memory cells

Figure 9.13 Changes in CD4 count and plasma HIV RNA levels (viral load) in patients treated with HAART

Box 9.7 Factors determining when to start and choice of therapy

- Risk of clinical disease progression (CD4 count, viral load)
- Willingness of patient to start therapy
- Clinical effectiveness of combination regimen
- Ability and motivation of patient to adhere to therapy
- Drug toxicity profile
- Pill burden and dosing schedule
- Transmitted drug resistance
- Future therapy options
- Likelihood of drug resistance
- Drug–drug interactions

Treatment of primary infection

It remains uncertain whether patients who present with acute primary HIV infection should be started on antiretroviral combination therapy. It is likely that the quality and breadth of cytotoxic T lymphocyte-cell (CTL) responses to different HIV antigens at the time of primary infection determines how well the immune system controls HIV replication over time. Studies have also shown that specific T-helper cell responses to HIV antigens are rapidly lost during primary infection, disabling the immune response to HIV. In patients who start antiretroviral therapy within the first few weeks of initial infection, specific T-helper cell responses to HIV are preserved, and CD4 cell counts are higher compared to the levels in patients who do not start therapy. The relevance of this immunological benefit is uncertain, or whether there is any long-term clinical advantage compared to patients who initiate effective antiretroviral therapy at some point during established chronic infection. Even after 2–3 years of sustained reduction in plasma viral load, discontinuation of therapy results in rapid viral rebound. Whether specific immune responses to HIV are more likely to be preserved and the level of viral load on discontinuation of

Box 9.8 Treatment of primary HIV infection

Pros:

- Preserve immune function including specific T helper cell responses to HIV
- Decrease magnitude of virus dissemination and establishment of viral reservoirs
- Potentially alters viral set-point in favour of slower disease progression on discontinuation of HAART

Cons:

- Longterm toxicity associated with drug treatment, potential for therapy failure and emergence of drug resistance
- Uncertainty of improved longterm clinical benefit compared to initiating treatment during established chronic HIV infection
- Probably need to treat within a few weeks of exposure to HIV infection to gain immunological benefit.

therapy is lower than might have occurred in patients who were not treated during primary infection is not known. Antiretroviral therapy should be considered in patients presenting with acute primary HIV infection, however the immunological arguments need to be balanced against the unknown long-term efficacy of such a strategy, the risk of drug toxicity over time and the development of drug resistance.

Drug resistance

Soon after the introduction of zidovudine into clinical practice it was recognised that viral isolates taken from patients six months after therapy were less susceptible to zidovudine than at baseline. The emergence of genotypic mutations in the reverse transcriptase gene was associated with reduced susceptibility. Genotypic and phenotypic resistance can develop against all currently antiretroviral drugs and is a major factor contributing to therapy failure. Multiple mutations in the RT and the protease genes have now been identified to be associated with reduced drug susceptibility. The pattern and number of mutations which emerge and whether they confer cross-resistance within the class differs between each drug and regimen. For certain drugs, for example, lamivudine, nevirapine or efavirenz, the emergence of a single point mutation within the RT gene confers a very high fold decrease in susceptibility. For other drugs the fold decrease in susceptibility is much lower and multiple mutations may be needed to confer high-level drug resistance. Cross-resistance within a class can occur particularly with the NNRTIs and the protease inhibitors. For the NNRTIs this requires single genotypic mutation only, while for the protease inhibitors this usually requires a primary mutation plus four or five other secondary mutations. The emergence of resistance to all drugs does not always occur with a combination in a patient who experiences virological rebound on therapy. Some patients do not develop any genotypic mutations on treatment failure and this may reflect poor adherence and low drug selection pressure. Patients who achieve sustained falls in plasma viral load to less than 400 copies per ml are less likely to develop genotypic mutations associated with drug resistance than those who do not. Drug-resistant viruses can be transmitted and various recent studies have shown that 10–15% of patients presenting with primary HIV infection have genotypic mutations associated with drug resistance particularly in the RT gene. Drug-associated genotypic mutations usually fade on withdrawal of drug therapy but frequently rapidly re-emerge if the same drugs are taken again in combination.

The presence of drug resistance may affect the choice and efficacy of therapy in patients who have previously failed one, two or more combination regimens. Genotypic and phenotypic resistance assays are available in clinical practice and early randomised studies suggest that their utility in helping with the choice of therapy may result in greater falls in viral load in the short term. There are larger randomised studies ongoing and the exact role of these assays in clinical practice is yet to be established. The usefulness of these assays may depend upon the availability of alternative effective antiretroviral agents in a treatment experienced patient.

Drug toxicities

The tolerability and side-effects of a combination regimen is very important in determining the antiviral response. In clinical practice 40–50% of patients will not have sustained falls in plasma viral load by one year of therapy and a major factor contributing to this is poor tolerability. Drug-specific side-effects are listed in Table 9.6.

Table 9.7 Common Primary Genotypic Mutations associated with reduced drug susceptibility in-vivo

NRTIs	**Codon**
Zidovudine	K70N, T215Y
Abacavir	K65R, L74V, M184V
Didanosine	L74V
Lamivudine	M184V
Zalcitabine	K65R, T69D, L74V
Stavudine	T215Y + other TAMS[1]
Multi nucleoside resistance	Q151M, T69S-SS
NNRTIs	
Nevirapine	K103N, V106A, Y181C, G190A, Y188C/L/H
Efavirenz	K103N, G190A, Y188C/L/H
PIs	
Saquinavir	G48V, L90M
Ritonavir	V82A/T/F
Indinavir	M46I/L, V82A/T/F
Nelfinavir	D30N, L90M
Amprenavir	I50V, I54L/M, I84V

1. TAMS: Thymidine analogue mutations
2. Resistance profile of lopinavir/r in-vivo is uncertain

Clinically relevant phenotypic resistance may require only a single primary mutation or 2 or more primary and secondary mutations. Interpretation of a genotypic test is complex and requires expert advice.

Box 9.9 Role of resistance testing

- detection of transmitted resistance in primary infection
- detection of resistance prior to starting treatment for the first time
- guide choice of new treatment regimen in patients experiencing virological treatment failure on first or subsequent regimens
- guide treatment choice in pregnant mothers for prevention of vertical transmission

The utility of genotypic and phenotypic resistance tests are continuing to be evaluated.

In the last two to three years abnormalities of fat redistribution have been observed in patients on combination regimen. Observational cohort studies suggest that lipodystrophy may occur in up to 50–60% of patients after one to two years on therapy. Patients either present with peripheral fat wasting affecting the buttocks, limbs and face or fat accumulation round internal viscera in the abdomen resulting in a distended abdomen and bloating. The exact pathogenosis of these fat distribution syndromes is unknown but age of patient, antiretroviral drug therapy and time on therapy may all be implicated. They have been reported in both protease inhibitor and NRTI-containing combination regimens, and it is likely that it is a mixed syndrome with a multifactorial cause. The occurrence of lipodystrophy can affect the psychological well being of the patient but as yet we do not know how it is best managed.

It has recently been suggested that mitochondrial toxicity may account for some of the toxcities associated with the NRTIs as a result of inhibition of mitochrondirial gamma DNA polymerase. Severe lacticacidosis is a rare complication of NRTI therapy.

Future agents

For the reasons of poor tolerability, suboptimal antiviral potency and long-term drug toxicity, it is important that new antiretroviral agents and therapeutic strategies are developed and evaluated. New formulations of current drugs which improve tolerability and reduce pill burden will help to improve adherence in patients. New protease and reverse transcriptase inhibitors are currently undergoing clinical trials which *in vitro* appear to be effective against viral isolates which are resistant to different drugs. Whether these agents will prove to be clinically effective will be important in treating those patients who have previously failed combination therapies.

New classes of drugs are also being developed. Fusion inhibitors which block the activity of the GP41 viral transmembrane protein are in Phase III clinical trials and are likely to be the first new class of drug to reach the bedside.

As well as specific drugs that inhibit targets in the viral replication cycle, immunotherapeutic approaches are so being assessed. Treatment with cycles of the cytokine interleukin 2 results in substantial increase in CD4 counts but has little effect on plasma viral load levels. Interleukin 2 may also improve immune responses to HIV and a large randomised international trial is underway to assess its efficacy in combination with effective antiretroviral combination regimens. Therapeutic vaccines are also under evaluation which might improve specific immune responses and assist immunological control of HIV replication. Their clinical effectiveness remains uncertain.

Few areas of medicine have seen such dramatic changes in treatment with a resulting reduction in morbidity and mortality as there has been in patients with HIV infection. It is very likely that therapeutic options will continue to improve, although the long-term efficacy of treatment over many years still remains uncertain.

Table 9.8 Drug toxicities

Drug	Toxicity
NRTIs	
Class associated	Lactic acidosis
	Hepatitic steatosis
	Lipodystrophy (peripheral fat wasting)
Drug specific	
Zidovudine	Bone marrow suppression, nausea, vomiting, myopathy
Stavudine	Peripheral neuropathy, hepatitis
Zalcitabine	Peripheral neuropathy, mouth ulcers
Didanosine	Pancreatitis, dry mouth, peripheral neuropathy
Lamivudine	Few side-effects
Abacavir	Hypersensitivity reaction, nausea
NNRTIs	
Nevirapine	Rash, hepatitis, Steven–Johnson syndrome
Efavirenz	Rash, dysphoria, mood changes, vivid dreams, hypercholesterolaemia, hepatitis
PIs	
Class specific	Lipodystrophy (fat wasting or accumulation)
	Hyperlipidaemia, diabetes mellitus
Drug specific	
Nelfinavir	Diarrhoea, rash
Saquinavir	Few side-effects
Indinavir	Hyperbilirubinaemia, nephrolithiasis, nail changes, dry skin
Ritonavir	Perioral dysathesia, flushing, hepatitis, diarrhoea, nausea, vomiting
Amprenavir	Rash, nausea, diarrhoea
Lopinavir	Diarrhoea

10 HIV infection and AIDS in the developing world

Alison D Grant, Kevin M De Cock

Epidemiology of HIV-1 and HIV-2 infections in developing countries

The epidemiology and burden of HIV in the developing world are discussed earlier (see chapter 1). Two distinct viruses, HIV types 1 and 2 (HIV-1/HIV-2), cause AIDS. HIV-1 is responsible for the great majority of infections globally, HIV-2 being very rare outside of West Africa. Individual cases of HIV-2 infection have been described in other parts of Africa, Europe, the Americas and Asia (India), but most people with HIV-2 infection have some epidemiological link to West Africa.

The routes of transmission of HIV-1 and HIV-2 (as described in chapter 1) are the same worldwide, but the relative importance of different modes of transmission differs according to region. In most developing countries, heterosexual transmission is the dominant mode of spread, and mother-to-child transmission of HIV is much more common than in industrialised countries. Homosexual transmission is rare in Africa, but is more common in south-east Asia and central and south America. Transmission associated with injecting drug use is particularly frequent in parts of south and south-east Asia and central and south America. Acquisition of infection from contaminated blood remains a problem, especially in parts of sub-Saharan Africa and south Asia; in some countries commercial blood donation acts to amplify the spread of transfusion-transmitted HIV infection, both to the recipients of blood as well as to donors who may become infected through exposure to unsterile equipment. Women and children are at especially high risk for transfusion-transmitted HIV infection, the former because of the high incidence of anaemia and haemorrhage associated with pregnancy and childbirth, and the latter because of malarial anaemia.

The transmission of HIV-2 infection is less efficient than that of HIV-1; this applies particularly to mother-to-child transmission, with only about 1% of HIV-2 infected mothers passing the infection on to their offspring. By comparison, up to 42% of HIV-1 infected mothers pass the infection to their children by all routes (intrauterine, puerperal and breast milk). Sexual transmission of HIV-2 is also less efficient, especially before the development of end-stage immune deficiency. Postnatal transmission of HIV-1 by breast milk is more important than previously believed and approximately doubles the risk of mother-to-child transmission.

Natural history of HIV-1 and HIV-2 infections in developing countries

There is still relatively little information available about the natural history of HIV-1 and HIV-2 infections in the developing world. Prospective studies from industrialised countries before highly active antiretroviral therapy (HAART) was widely used suggest that after 10 years of infection with HIV-1, approximately 50% of people will have developed AIDS. There has been a widespread belief that HIV-1 disease progresses more rapidly in developing countries, but more recent evidence suggests that the rate of progression from infection to severe immunosuppression may be little different from that documented in industrialised countries in the pre-HAART era.

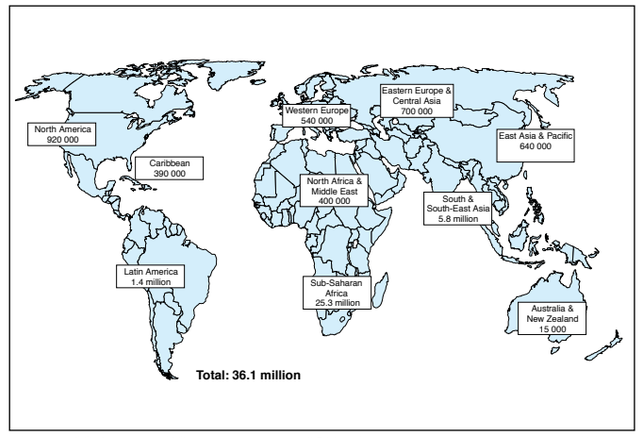


Figure 10.1 UNAIDS estimates that 95% of people living with HIV/AIDS are in developing countries

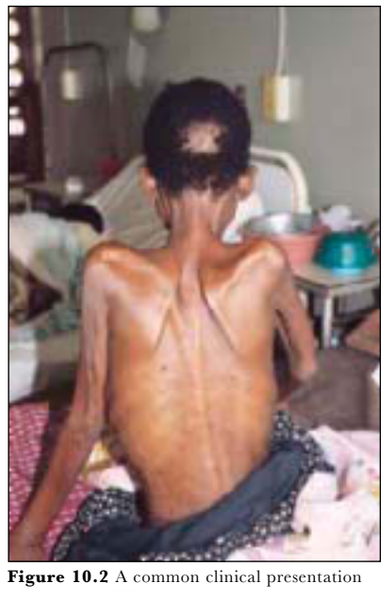


Figure 10.2 A common clinical presentation of advanced HIV disease in African countries is with marked wasting, known in Uganda as "slim" disease (courtesy of Professor Sebastian Lucas)

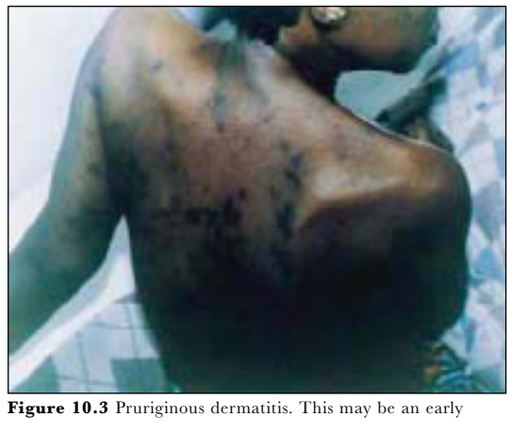


Figure 10.3 Pruriginous dermatitis. This may be an early manifestation of HIV infection

Because bacterial diseases such as pneumococcal disease and tuberculosis are prevalent in developing countries and may occur at relatively high CD4+ lymphocyte (CD4) counts, some HIV-infected persons may appear to become symptomatic earlier. In addition, outcome may be worse in developing countries than in the industrialised world because of lack of access to care: this is almost certainly the main explanation for the reduced survival following the development of an AIDS-defining illness in developing countries, generally around six to nine months.

Progression from infection to disease is substantially slower for HIV-2 infection compared with HIV-1. Evidence for this includes individual reports of long survival with HIV-2 infection, higher levels of CD4 counts in HIV-2- than in HIV-1-infected people in cross-sectional studies, and a lower incidence of CD4 decline and AIDS in cohort studies comparing HIV-1- and HIV-2-infected people. Nonetheless, HIV-2 may eventually cause severe immunosuppression, accompanied by disease which is clinically indistinguishable from that caused by HIV-1.

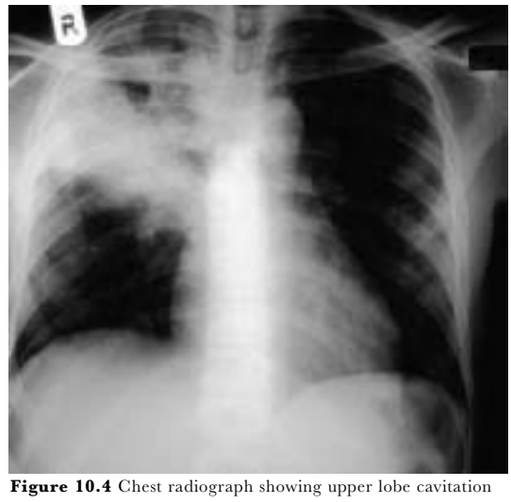


Figure 10.4 Chest radiograph showing upper lobe cavitation typical of pulmonary tuberculosis. Appearances may also be atypical (see chapter 6)

Clinical aspects of HIV disease in developing countries

As in industrialised countries, the spectrum of clinical manifestations associated with HIV infection is wide, ranging, as the CD4 count falls, from an asymptomatic state, through symptomatic disease, to fatal illness characterised by opportunistic infections, malignancies, neurological disease and wasting. Initial acquisition of HIV infection ("acute HIV infection" or "seroconversion illness") may be complicated by a syndrome resembling infectious mononucleosis, or a wide range of other manifestations as described in chapter 4. However, since this syndrome is not specific, it is rarely recognised even when clinically apparent.

Early manifestations of HIV disease

Common early symptoms and signs are weight loss, fever, night sweats and diarrhoea. Skin disorders are frequent early manifestations, especially varicella zoster, fungal infections and pruriginous dermatitis, an itchy rash consisting initially of papules which become shallow ulcers due to scratching, and finally heal, leaving pigmented macules.

Tuberculosis

Tuberculosis is unquestionably the most important opportunistic infection complicating HIV infection in developing countries, and may present at any stage in the course of immunodeficiency. In early HIV disease, pulmonary tuberculosis is similar to that found in HIV-negative people. In advanced immunodeficiency, tuberculosis is often disseminated and multibacillary in nature. Nocardiosis, while much less common, is a differential diagnosis in some areas.

Bacterial septicaemia

An inadequately recognised manifestation of HIV disease in developing countries has been bacterial septicaemia. Gram-negative organisms are the most common pathogens identified, especially non-typhoid *Salmonella* spp. Invasive pneumococcal disease is also frequent, and may occur earlier than Gram-negative infections. In some patients with advanced HIV disease, mycobacteraemia is detectable; this is much more frequently due to *Mycobacterium tuberculosis* than *Mycobacterium avium intracellulare* complex.

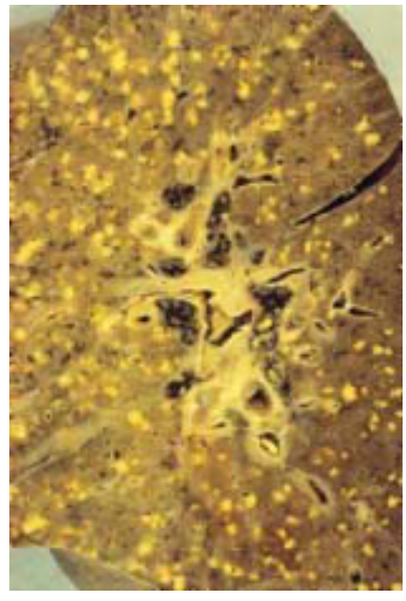


Figure 10.5 Post-mortem lung showing miliary tuberculosis (courtesy of Professor Sebastian Lucas)

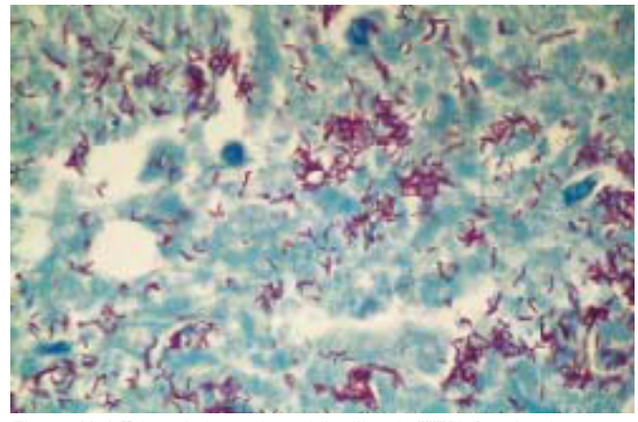


Figure 10.6 Tuberculosis may be multibacillary in HIV-infected patients: non-reactive tuberculous infection of the pericardium, showing abundant acid-fast bacilli (courtesy of Professor Sebastian Lucas)

Diarrhoeal disease and HIV wasting syndrome
The best known clinical picture of AIDS in Africa is "slim", the term given by people in rural Uganda to the HIV wasting syndrome. Profound wasting, chronic diarrhoea and fever are the typical features. About half the time no specific aetiology can be found for the diarrhoea: among identified causes, the most common are cryptosporidiosis, microsporidiosis, isosporiasis and bacterial infections. The commonest autopsy finding in African patients with HIV wasting syndrome is disseminated tuberculosis, and undue emphasis may have been put on searching for a primary gastrointestinal cause of this whole syndrome. As with all medical causes of wasting, an important contributing factor to the HIV wasting syndrome is reduced food intake.

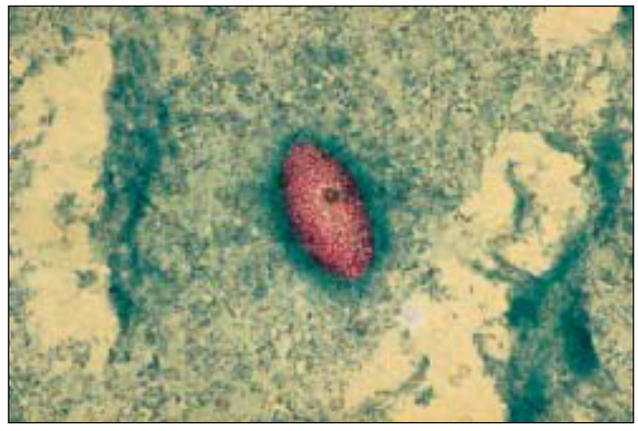


Figure 10.7 *Isospora belli*, a treatable course of diarrhoea in HIV-infected people

Neurological disease
Cerebral toxoplasmosis and cryptococcal meningitis are probably more frequent causes of severe HIV-related disease in developing than industrialised countries, and their prevalence may vary by geographical region. Cerebral toxoplasmosis most often presents as a space-occupying lesion of the brain, and cryptococcosis as a chronic meningitis.

Regional variation in disease spectrum
Tuberculosis and bacterial infections, particularly pneumococcal disease, are common HIV-related diseases in developing countries worldwide. Other HIV-related diseases show regional variation. Pneumocystosis, cytomegalovirus disease and disease due to atypical mycobacteria such as *Mycobacterium avium intracellulare*, common in industrialised countries, are unusual in adults in many African countries (although *Pneumocystis carinii* pneumonia is common in HIV-infected African infants). The reasons for this are uncertain, but may include development of diseases such as tuberculosis at higher levels of CD4 counts, and shorter survival once the stage of profound immunodeficiency has been reached. Endemic Kaposi's sarcoma is more common in Central and East than in West Africa, and this is probably also true for the AIDS-associated form.

Some HIV-related diseases are limited to specific geographic areas, such as disease due to the fungus *Penicillium marneffei*, which is confined to south-east Asia. Penicilliosis causes disseminated disease in patients with advanced immune deficiency, with nodular skin lesions as the most obvious manifestation. Tuberculosis, salmonellosis and cryptococcosis are other frequent AIDS-defining conditions in south and south-east Asia. Tuberculosis is frequent in Latin America, where the spectrum of disease is otherwise similar to that in the industrialised world.

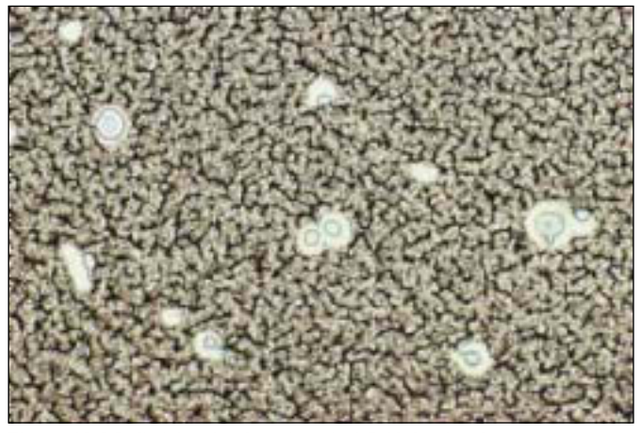


Figure 10.8 India ink stain of cerebrospinal fluid showing *Cryptococcus neoformans*, a common cause of meningitis (courtesy of Professor Sebastian Lucas)

Association with endemic tropical diseases
The association between endemic tropical diseases and HIV infection has only been studied to a limited degree. Theoretically, HIV infection could increase the incidence of tropical diseases, and alter their natural history, clinical expression, or response to treatment. Malaria is indirectly linked to HIV infection by causing anaemia in children, who may then be at risk for HIV infection transmitted through blood transfusion. HIV-infected pregnant women experience greater frequency and severity of malarial parasitaemia, and increased frequency of placental malaria compared with HIV negative women. HIV-infected people with *Schistosoma mansoni* excrete fewer eggs than those who are HIV negative, but it is not known whether the severity of schistosomiasis is affected by HIV infection, and response to treatment seems to be unaffected by HIV status. Amoebiasis and strongyloidiasis might be expected to be more frequent in HIV disease, but are not; on the basis of

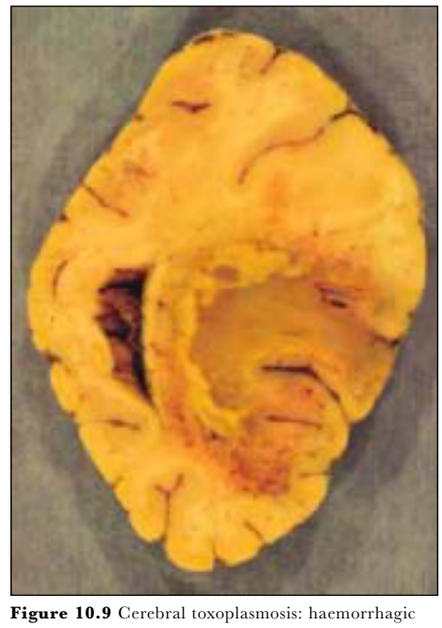


Figure 10.9 Cerebral toxoplasmosis: haemorrhagic and necrotic mass in the occipital lobe (courtesy of Professor Sebastian Lucas)

limited data, the same seems to be true of trypanosomiasis and leprosy. Little information is available concerning the influence of HIV infection on filariasis. Visceral leishmaniasis, often disseminated, appears to be increased in incidence in HIV-infected persons, although most reports have been from southern Europe rather than sub-Saharan Africa or South America. HIV-infected persons with leishmaniasis require maintenance treatment as relapse is otherwise likely.

AIDS case definitions and staging of HIV disease

Case definitions of AIDS for epidemiological surveillance

For epidemiological surveillance, a practical case definition of severe HIV-related disease is needed. The Centers for Disease Control (CDC) AIDS surveillance case definition is used in many industrialised countries (see chapter 1), but cannot be used in most developing countries because it requires access to sophisticated laboratory investigations. For this reason, the World Health Organisation (WHO) introduced a clinical case definition that could be used in settings where laboratory facilities are inaccessible (Box 10.1). In 1994, this definition was expanded to incorporate HIV serology (thus increasing specificity) and to take account of revisions of the CDC case definition (Box 10.2). If serological testing is unavailable or inaccessible, the clinical case definition should be used; if serological testing is available, the expanded case definition should be used.

Diagnosis and clinical staging of HIV disease in resource poor settings

Although advanced HIV disease may be easy to diagnose clinically, it is desirable to have HIV serology on patients with suspected HIV disease, particularly since HIV negative tuberculosis may be clinically indistinguishable from advanced HIV disease.

The case definitions in Boxes 10.1 and 10.2 were developed for epidemiological surveillance, and are not intended to be used for clinical staging of patients, for which they are neither sensitive nor specific. In order to estimate prognosis in individual patients, a clinical staging system is more useful than a case definition. Box 10.3 overleaf outlines the WHO proposed staging system for HIV infection and disease, using clinical and laboratory data, which can be used in developing countries. This system categorises patients into four stages based on clinical features of prognostic significance. The stages are interpreted as:

Stage 1: asymptomatic infection.
Stage 2: early (mild) disease.
Stage 3: intermediate (moderate) disease.
Stage 4: late (severe) disease.

The system can be refined using a laboratory axis: the CD4 count is the most useful laboratory marker for clinical staging, but is rarely available in developing countries. The total lymphocyte count can be used as a surrogate, although this is not ideal. Manifestations of HIV disease are rare at CD4 counts above 500×10^6/l and severe illness and death are rare in patients with counts above 200×10^6/l. Tuberculosis and pneumococcal disease may occur at higher as well as lower CD4 counts. Once patients in developing countries have developed advanced HIV disease, they die with higher CD4 levels than in industrialised countries because of lack of access to high quality medical care; nonetheless, most patients die at the stage of advanced immunodeficiency.

Box 10.1 WHO AIDS case definition for AIDS surveillance

For the purposes of AIDS surveillance an adult or adolescent (>12 years of age) is considered to have AIDS if at least two of the following major signs are present in combination with at least one of the minor signs listed below, and if these signs are not known to be due to a condition unrelated to HIV infection.

Major signs
- Weight loss 10% of body weight
- Chronic diarrhoea for > 1 month
- Prolonged fever for > 1 month (intermittent or constant)

Minor signs
- Persistent cough for > 1 month*
- Generalised pruritic dermatitis
- History of herpes zoster
- Oropharyngeal candidiasis
- Chronic progressive or disseminated herpes simplex infection
- Generalised lymphadenopathy

The presence of either generalised Kaposi's sarcoma or cryptococcal meningitis is sufficient for the diagnosis of AIDS for surveillance purposes.

*For patients with tuberculosis, persistent cough for >1 month should not be considered as a minor sign.

Box 10.2 Expanded WHO case definition for AIDS surveillance

For the purposes of AIDS surveillance an adult or adolescent (>12 years of age) is considered to have AIDS if a test for HIV antibody gives a positive result, and one or more of the following conditions are present:
- 10% body weight loss or cachexia, with diarrhoea or fever, or both, intermittent or constant, for at least 1 month, not known to be due to a condition unrelated to HIV infection
- Cryptococcal meningitis
- Pulmonary or extrapulmonary tuberculosis
- Kaposi's sarcoma
- Neurological impairment that is sufficient to prevent independent daily activities, not known to be due to a condition unrelated to HIV infection (for example, trauma or cerebrovascular accident)
- Candidiasis of the oesophagus (which may be presumptively diagnosed based on the presence of oral candidiasis accompanied by dysphagia)
- Clinically diagnosed life-threatening or recurrent episodes of pneumonia, with or without aetiological confirmation
- Invasive cervical cancer

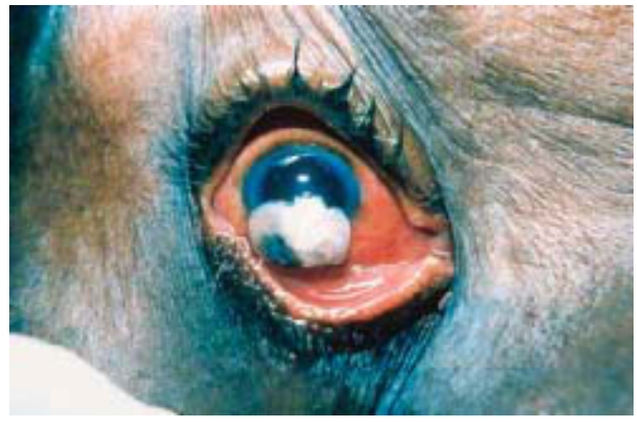


Figure 10.10 Squamous cell carcinoma of the conjunctiva: an unusual cancer, strongly associated with HIV infection. Its incidence has increased markedly in Uganda and Rwanda (courtesy of Dr Keith Waddell)

Box 10.3 Proposed WHO staging system for HIV infection and disease

Clinical staging

Patients with HIV infection who are aged 13 years are clinically staged on the basis of the presence of the clinical condition, or performance score, belonging to the highest level

- Clinical stage 1: asymptomatic or persistent generalised lymphadenopathy; performance scale 1 (asymptomatic, normal activity)
- Clinical stage 2: weight loss <10% body weight; minor mucocutaneous manifestations, varicella zoster within the last five years, recurrent upper respiratory tract infections (bacterial sinusitis); performance scale 2 (symptomatic but normal activity)
- Clinical stage 3: weight loss > 10% body weight, unexplained chronic diarrhoea > 1 month, unexplained chronic fever > 1 month, oral candidiasis, oral hairy leukoplakia, pulmonary tuberculosis within the past year, severe bacterial infections; performance scale 3 (bedridden < 50% of day during the last month)
- Clinical stage 4: most other CDC AIDS-defining diseases (but not pulmonary tuberculosis); performance scale 4 (bedridden > 50% of day during the last month)

Clinical/laboratory classification

Laboratory axis			Clinical axis			
	Lymphocytes or ($\times 10^6$/l)	CD4 ($\times 10^6$/l)	1 Asymptomatic	2 Early	3 Intermediate	4 Late
A	>2000	>500	1A	2A	3A	4A
B	1000–2000	200–500	1B	2B	3B	4B
C	<1000	<200	1C	2C	3C	4C

Treatment of HIV-infected people in developing countries

General approach

The general approach to treatment in developing countries should ideally be no different from that in the industrialised world, but is hampered by lack of infrastructure and resources for diagnosis and treatment. As for other diseases in resource-poor countries, treatment must often be decided on the basis of very limited information. Patients should be counselled about HIV infection and prevention of its transmission.

Treatment of opportunistic infections

Specific opportunistic infections should be treated as recommended (see chapter 9). Patients with some common diseases, such as tuberculosis and pneumococcal infection, usually respond well to standard treatment. Toxoplasmosis also responds well to treatment if diagnosed early, but as with many HIV-related diseases, is likely to relapse unless maintenance treatment is taken. In situations where precise diagnoses cannot be confirmed, a syndromic approach may be more practical. Individual symptoms such as diarrhoea or prurigo should be treated symptomatically if no treatable cause can be identified.

Prevention of opportunistic infections

Clinical trials have demonstrated the efficacy of preventive regimens against tuberculosis (for example, using isoniazid) among HIV-infected people in developing countries, and co-trimoxazole has been shown to reduce morbidity and mortality among HIV-infected individuals in Côte d'Ivoire. Both these interventions are now recommended by UNAIDS but have yet to be introduced on a large scale, particularly in the poorest countries, and will need to be evaluated under operational conditions. Pneumococcal polysaccharide vaccine was recently found to be ineffective in preventing invasive pneumococcal disease among HIV-infected people in Uganda; conjugate pneumococcal vaccines may be more effective, and are currently being investigated in children.

Antiretroviral therapy

Antiretroviral therapy is currently available to only a very small minority of HIV-infected people in developing countries. As

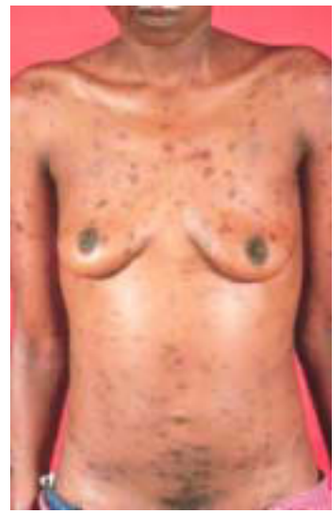


Figure 10.11 Kaposi's sarcoma: multiple skin nodules and plaques (courtesy of Dr AC Bayley)

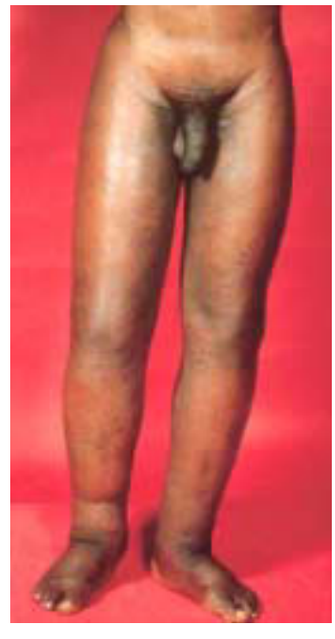


Figure 10.12 Kaposi's sarcoma: bilateral leg oedema and inguinal lymph node enlargement, without any evident skin lesions (courtesy of Dr AC Bayley)

antiretrovirals become less expensive, they will inevitably become more widely available and used. However, widespread implementation poses huge challenges in resource-poor countries, including identifying HIV-infected people before the stage of terminal disease; monitoring the response to therapy; continuity of drug supply; adherence, especially to complex regimens; and managing treatment failures. A priority will be to minimise the development of antiretroviral drug resistance by using rational and effective regimens, and maximising continuity of treatment and adherence. Resistance is probably inevitable unless triple drug regimens are used. Some populations will be easier to reach through existing infrastructures, such as occupational health schemes; tuberculosis programmes could also potentially be built upon if more resources were available.

Public health priorities

In response to the global epidemic of HIV/AIDS, WHO established the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 1994. HIV/AIDS is the only disease for which a joint programme between several United Nations agencies has been established.

Essential components of public health programmes for HIV/AIDS

The key elements of public health programmes for HIV/AIDS are listed in Box 10.4. The global response to the HIV pandemic is based on fundamental principles, but HIV/AIDS prevention and control is implemented, successfully or unsuccessfully, at the local level. Involvement of heavily affected communities and non-governmental organizations has been crucial to a successful response. Key requirements of programmes are prevention of new infections, as listed in Box 10.4: youth (both in- and out-of-school), especially young women, are an important target group for HIV awareness and life-skills training. Preventing mother-to-child transmission is also important: antiretroviral drugs are most cost effective when used for this purpose, and effective and safe strategies for the reduction of transmission via breast feeding are also needed. Other important areas include prevention of discrimination and assurance of confidentiality for HIV-infected people, integration of sexually transmitted diseases control into HIV/AIDS prevention activities, and provision of services for HIV/AIDS care. Because of the close interrelationship between HIV/AIDS and tuberculosis, some countries have integrated tuberculosis and HIV/AIDS control activities.

Box 10.4 Essential components of HIV/AIDS programmes

Prevention of new infections
- Reduce sexual transmission
  - Awareness and life-skills education, especially youth
  - Condom promotion
  - STD control, including for commercial sex workers
  - Partner notification
- Blood safety
  - HIV testing of transfused blood
  - Avoid non-essential blood transfusion
  - Recruitment of safe donor pool
- Interventions to reduce transmission among injecting drug users (where necessary)
- Reduce mother–child transmission
  - antiretroviral therapy
  - avoidance of breast feeding (where safe): consider replacement feeding, or early weaning

Surveillance for HIV infections and AIDS

Voluntary counselling and testing

Mitigation of HIV-related disease
- Rational approach to care for HIV-related disease, especially tuberculosis
- Appropriate preventive therapies

Mitigating social impact
- Minimising stigma: respect for confidentiality, protection against discrimination
- Care for AIDS orphans

11 Injection drug use-related HIV infection

RP Brettle

Introduction

A variety of important medical problems, both infective and non-infective in nature, are associated with injection drug use (IDU) including the blood-borne viruses such as HIV, hepatitis B (HBV) and hepatitis C (HCV), all of which may be transmitted via the sharing of injection equipment. Consequently the medical care of patients using drugs requires a knowledge of both drug- and infection-associated conditions. The use of recreational drugs either occasionally or continually should not be a bar to or be used as a means of discriminating against access to health care in the UK as has been alleged recently. This right of access was explicitly addressed in the updated "*Guidelines on Clinical Management, Drug Misuse and Dependence*" published by HMSO in 1999. This report stated that:

- Drug misusers have *the same entitlement* as other patients to the services provided by the NHS.
- It is the responsibility of *all doctors* to provide care..., *whether or not the patient is ready to withdraw from drugs*.
- This should include *the provision of evidence-based interventions*, such as hepatitis B vaccinations, and providing harm minimisation advice.

Although combination therapy for HIV is not specifically mentioned in this document, because it is an evidenced based intervention the same principles apply.

Medical care systems

The difficulties of engaging drug users for medical care should not be underestimated. There are some particular characteristics of IDU that it may be helpful to be aware of, and the details will vary with geographical location (Box 11.1).

Drug users usually require a substantial supply of money to fund their addiction 'habit', which in itself results in other problems.

Not surprisingly the problems and illegality associated with the use of recreational drug use is associated with a number of difficulties for any health service in delivering medical care for drug users. For the health service these numerous crises, whether social, financial, legal, etc., lead to the impression of a chaotic lifestyle; in reality hospital appointments usually have a fairly low priority because of the enormity of their problems.

The social effects of HIV infection are similar for all risk groups – the infection effectively impoverishes the patient; however in the case of drug users these effects may be a little more dramatic.

More importantly the inability to fund a drug habit can have important consequences for a health service which are often not appreciated:

- A need to find additional sources of income – benefits fraud, drug dealing, hospitalisation (save money on food, etc.) – all of which increase the pressure on the NHS to prescribe addictive drugs (which may be greater than actual habit in order to provide additional funds).
- The physical weakness and mental slowing leads to peer victimisation.
- Practical problems such as problems with visitors, unexplained absences from ward, frequent self-discharge,

Box 11.1 General characteristics of IDU in UK

- Mainly an illegal activity
- Male dominated (10–30% females)
- Usually involves the young and initially healthy – 2 years before any contact with NHS
- Do not seem to be particularly health conscious
- Have often spent time in prison (up to 70%)
- Tend to have a crisis lifestyle
- Are often associated with violent or unpredictable behaviour, which in part is related to an excess of or withdrawal from recreational drugs and is more often than not related to problems with their peers

Box 11.2 Specific problems relating to drug addiction

- Expensive to maintain (£100–£200/day) and may be funded by a variety of means such as:
  - theft – car crime, burglary
  - fraud – credit and cheque cards, DSS benefits
  - drug dealing
  - prostitution – male or female
- Are often short of money
- May need to avoid police "warrants"
- Live for today (shortened "future time perspective")
- May require 3–4 shots per day for opiates and every hour for cocaine

Box 11.3 Recreational drug use and health care

"Unreliable" individuals with chaotic type of lifestyle

- Irregular attendances – missed appointments, wrong day, frequent self-discharges from ward
- Suspect motives for many of symptoms
- Unexplained absences from wards
- Disruptive visitors
- Day/night reversal
- Self-medication and drug dealing
- Theft from other patients and staff
- A threat for patients and staff
- Attention seeking, demanding of time and often noisy
- Aggressive behaviour both verbal and physical
- Utilise a number of offensive weapons – knives, guns

Come with a variety of staff "attitudes"

- "Others more deserving" of care
- "Manipulative" of staff
- "Dangerous"
- "Frightening"
- "Upset other patients"
- "Not enough time"
- "Never change"

day/night reversal, theft of hospital property (related to a falling income), noise, manipulation of staff or other patients and attention-seeking behaviour.
- Increased frequency of verbal and physical abuse of both staff and other patients.

The net result may be an inability to cope in the community or the hospital, resulting in frequent precipitous admissions and discharges – "revolving door" type admissions with considerable frustration for patients, relatives and staff.

Without a *modified* healthcare system which understands and considers these problems, drug users have a tendency to record a high default rate in terms of attendance or frequent discharges from hospital units. The aim of an IDU service should be to initiate and maintain contact primarily in order to deliver health care and health education. The initiation and maintenance of that contact may require a variety of initiatives as described in box 11.5.

A system of providing both drug services as well as medical care from the same site by the same doctors seems to be an efficient model of care for drug users, whereas a system of delivering care via two distinct physical sites (one for drugs and one for physical care) is less efficient and seems to provide either a poor medical and/or a poor HIV service.

The dependency needs of IDU-related HIV are both physical and psychological. The physical care varies from mildly ill to high dependency, whilst on the psychological side it may vary from being entirely well to toxic confusional states, obsessive-compulsive states, anxiety and agitation as well as frank psychosis. The differential diagnosis is extensive and admission is commonly required to exclude the diagnosis of an organic psychosis. The time that patients may remain in a medical unit varies from a few days to over a month and this mixture of serious physical and mental ill health is rarely found in other areas of medicine. There is also the danger of fire from careless cigarettes, since the majority of patients smoke heavily and consume excessive amounts of sedative drugs. Because addiction to cigarettes seems to be greater or at least equal to opiates, it appears impossible to enforce a total no smoking policy for the inpatient areas if the policy of maintaining contact with patients is to be followed. In addition to the difficulties described above, there are also the problems of nursing individuals in some form of isolation. The requirement for cubicles is high as a consequence of an increased risk of infectious agents associated with HIV and IDU, such as tuberculosis. There is also an increased need for privacy because of mixed sexes (one third are female), mixed risk groups (homosexuals and drug users) and disturbed patients.

Management strategies for IDU-related HIV

There are a number of strategies which may be adopted in order to cope with IDU-related HIV admissions, including higher staffing levels, avoidance of high occupancy levels and continuity of care by both nursing and medical staff. Other issues are as listed overleaf:

Box 11.4 Social effects – physical and mental slowing

- More vulnerable to exploitation from peers
- More likely to get caught by the law
- Reduced income – "criminal unemployment"
- Increased demands on NHS to replace the missing funds
  - pressure for prescribed drugs
  - pressure for access to state benefits

Box 11.5 Initiatives for initiation and maintenance of contact with drug users

- Needle exchange
- Methadone prescribing
- Social provisions such as helping with housing
- Medical care

Box 11.6 Specific problems of IDU-related HIV for a health service

- Mixture of physical and psychological dependency
- Frequent security and fire incidents
- Increased need for cubicles
- Need for increased staffing levels

Box 11.7 Management strategies for IDU-related admissions

- Continuity of care from medical and nursing staff
- Increased numbers of nursing and medical staff
- Response to violence is to call police
- Tight control on drug prescribing
- A written smoking policy which is given to every patient on admission
- Coordination of drug prescribing between different agencies around admissions and discharges
- Increase contact with healthcare system gradually
- Clear guidelines and policies which all staff sign up to
- Such policies to be supportive and caring and based on health and safety principles
- Avoid situations leading to confrontation
- Avoid withdrawals in ward area but make it clear that no guarantee of increases on discharge
- Awareness of need for relief of pain and psychological distress

Box 11.8 Strategies for coping with IDU-related HIV admissions

- Violent activities, assaults, etc. are managed by calling the police. Patients need to be informed that recreational drug use is just as illegal in hospital as out, that other patients may complain to the police via a local drugs hot line if they observe illegal drug dealings or use on the wards and this could result in police raids.
- There is tight control of prescribed drugs early on in the disease process with accompanying harm reduction messages. The message concerning prescribing is that its function is to provide a safety net for the physical discomfort of addiction rather than to provide a free buzz or "stone".
- There is a gradually increasing level of contact between hospital and patient over time which allows the service to get used to the behaviour of patients and for them to get used to the hospital's routines. This is one form of re-socialisation for the individual with problem drug use.
- The aim is to provide a supportive and caring environment associated with firm discipline over misbehaviour and illegal activities. Wherever possible the rules are based on health and safety principles rather than moral or legal ones. Injecting in the hospital is forbidden because of the dangers to staff. Similarly being stoned is discouraged because of the increased risks of hypostatic pneumonia or fire hazards from concomitant smoking.
- A written smoking policy is provided to every patient on admission. It is based on health and safety principles and the need to reduce the danger of fires for everyone's sake.
- The regime for outpatient appointments is reasonably flexible (anytime on a set day) in order to allow for missed appointments. However the patients are made aware of the need for some structure in the system by making the patient aware of the hospital's limitations.
- The law relating to the prescribing of drugs such as methadone is explained in verbal and written instructions.
- Confrontation is generally avoided in situations that cannot be resolved. This means adapting the regime or removing the patient from the environment that they find difficult; this may require us either to allow the patient to self-discharge or if necessary to discharge the patient from the unit. The patients are always offered an outpatient appointment if they leave the hospital or are discharged.
- Treatment in the community is often arranged in order to avoid long spells in hospital. Increased drug taking in hospital or difficult behaviour is often a symptom of boredom and much can be done to avoid this, for instance by providing satellite TV or computer games.
- Coordination of substitute prescribing with other carers is very important to avoid double prescribing via hospital admissions. Careful prescribing on discharge is also required to avoid similar problems in the community.
- Illegal drug use in the ward requires careful discussion in order to arrive at a compromise over the amount of drugs prescribed and the amount of drugs used illegally. Generally this compromise is achieved by suggesting that the dose of prescribed drugs will be reduced until a satisfactory level of consciousness is achieved that reduces the fire risk and the necessity for increased nursing observation. Such reductions result in increased cost for the patient in terms of the need to purchase black market supplies of drugs.
- On occasions, in order to deliver inpatient care, illegal or extra drug use needs to be covered. In such situations the patients are warned that this does not imply any sort of contract or obligation for increased doses on discharge. If the admission is prolonged then an offer of detoxification to the doses prescribed would be made.
- Obvious withdrawal symptoms (alcohol or opiates) during a physical illness would be covered with extra doses of opiates or short courses of benzodiazepines (diazepam or chlodiazepoxide). Agitation from recent stimulant use would also be covered for inpatients. The prime aim would be to reduce the chance of agitation and disturbed behaviour in the wards.
- Fear of pain may be a major problem for drug-using patients. We have generally used either a subcutaneous infusion of opiate over and above maintenance drugs or the use of oral slow-release morphine preparations. Provided observation reveals that the patients are not excessively sedated from a health and safety point of view there is no upper limit on the doses employed to relieve pain.
- There may be concern amongst the staff over the level of prescribing of sedative drugs. The nursing staff need to have confidence in the medical management policy relating to sedative and pain control prescribing. A number of patients, particularly drug users, request high levels of sedation prior to death and this may cause concern amongst a number of staff, medical and nursing as well as relatives.

Management of IDU-related problems

Controlled Drug prescriptions

A working knowledge of the regulations surrounding Controlled Drug prescriptions is important when managing drug users. Attention to detail when a patient is admitted is imperative if centres are to avoid the problems of double prescribing. The front pages of the BNF give exact guidelines on how to prescribe Controlled Drugs legally and additional information is available via the updated *Guidelines on Clinical Management, Drug Misuse and Dependence* published by HMSO in 1999.

The medical effects of recreational drugs

Carers need to have a working knowledge of the effects of recreational drugs and equivalent doses of drugs (methadone or diazepam) if patients need to be temporarily covered for the effects of withdrawal. Tables of equivalence for opiates and benzodiazepines can be found in *Guidelines on Clinical Management, Drug Misuse and Dependence* (HMSO 1999). The differential diagnosis in a patient with IDU-related HIV is extensive and requires consideration of both infective and non-infective disorders. These are summarised in Table 11.1.

When patients are admitted with respiratory problems there is the dilemma of how to manage opiate prescribing.

- For those patients with mild respiratory depression a discussion over a temporary reduction in oral drugs by around 10–20% or splitting the daily dose into 3 or 4 doses may suffice.
- In those with more severe respiratory depression rapid improvement in pulmonary function is required. However if the opiate withdrawal is excessive as with intravenous bolus injections of naloxone, the patient may become disruptive with loss of venous access.
- The preferred solution is a naloxone infusion (2 mg in 500 ml perhaps starting at around l0 ml per hour) to achieve an acceptable improvement in respiratory rate (and therefore oxygenation) without too great an increase in physical arousal. The aim is to improve oxygenation rather than induce withdrawal from opiates. This improved oxygenation can be assessed by respiratory rate, oxygen desaturation or arterial blood gases. Such an infusion may be required for up to 48 hours in those on methadone because of its relatively long half-life compared to other opiates. In the event of a lack of venous access then regular small doses of intramuscular nalaoxone (0.2 mg i.m. every 1 hour initially) can also be employed to maintain oxygenation.

Excessive doses of benzodiazepines also produce drowsiness and/or coma which can usually be managed by simple supportive therapy with care over respiratory rate, etc. In extreme cases it is possible to utilise the antagonist flumazenil but there is a danger of inducing fits in those on chronic long-term doses. *It is therefore preferable to reverse the opiate element first (with an infusion of naloxone) before resorting to flumazenil.*

Opiate withdrawals should be considered in any agitated patient known to be on opiates, particularly those who have recently commenced drugs that induce liver enzymes such as rifampicin, rifabutin, phenytoin, etc.

Table 11.1 Medical (non-infection) problems of drug use

Problem	Medical complications
Drug effects	
Excess opiate	Narcosis, coma, small pupils, respiratory depression, aspiration pneumonia, and *rhabdomyolysis secondary to pressure*
Opiate withdrawal	Mild "URT" (sweating, coryza, lacrimation), pupillary dilatation, insomnia, nausea, vomiting, diarrhoea, lethargy, muscle weakness, myalgia, muscle twitching, tachycardia and hypertension
Excess cocaine	Apprehension, dizziness, syncope, blurred vision, dysphoric states, paranoia, confusion and aggressive behaviour, seizures, coma, hyperthermia, respiratory depression, apnoea, sudden death, spontaneous rhabdomyolysis
Excess amphetamine	Headaches, anorexia, nausea, tremors, dilated pupils, tachycardia and hypertension
Stimulant withdrawal	Sleepiness, lethargy, increased appetite, food binging, depression or even suicide
Trauma	
Frequent injecting	Track marks and skin scars, lack of veins and thrombophlebitis, deep venous thrombosis, persistent peripheral oedema, venous stasis and ulcers secondary to chronic venous obstruction
Misplaced injections	Arterial damage and insufficiency with secondary tissue damage, muscle compartment syndrome and traumatic rhabdomyolysis, false aneurysms and pulmonary emboli, traumatic neuropathy
Immunology	
IDU	Enlarged nodes, elevated IgM, false positive syphilis serology
Endocrinology	
Opiate use	Increase prolactin levels and gynaecomastia, amenorrhoea (may be secondary to weight loss)
Cannabis	Oligospermia, impotence and gynaecomastia
Neurology	
Stimulants	Psychosis, depression, cerebral infarcts and haemorrhages (CVAs)
Chronic use of benzodiazepines or barbiturates	Brain damage
Cardiology	
Cocaine	Cardiac arrhythmias such as sinus tachycardia, ventricular tachycardia and fibrillation as well as asystole, myocardial infarction, severe hypertension
Adulterants of illicit drugs, for example quinine	Cardiac arrhythmias and death
Tricyclic antidepressants	Cardiac arrhythmias and death
Cannabis	Sinus tachycardia and postural hypotension
Pulmonary	
Inhaled cocaine	Excessive use of Valsalva – spontaneous pneumomediastinum and pneumopericardium
Excess sedatives or stimulants	Respiratory depression, coma and pneumonia
Opiate withdrawals	Mild "URT"
Stimulant use, for example cocaine	Tachypnoea
Opiates or cocaine	Pulmonary oedema
Hepatitis B	Polyartertis nodosa
Foreign body emboli, (particles injected intravenously) for example talc granulomas	Pulmonary hypertension (and right heart failure) abnormal pulmonary function eg reduced DCO, restrictive defect due to interstitial lung disease

Medical problems of HIV-infected drug users

The extent of IDU-related conditions requires consideration of not only the clinical features of IDU but also the associated medical conditions such as HIV since confusion may arise as to the aetiology of specific symptoms. (See Box 11.9)

Pre-AIDS deaths

The phenomenon of pre-AIDS death amongst HIV-infected drug users was described soon after the onset of the AIDS epidemic in the USA. The IDU non-AIDS death rate was 2.5/100 person-years in Edinburgh (compared to 0.9/100 person-years in other risk groups), 3.8/100 person-years in Amsterdam and 2.6/100 person-years in New York. In Edinburgh 20% of pre-AIDS deaths were expected and related to conditions not ostensibly related to HIV. Liver disease was the single commonest cause of these deaths, accounting for 75% of expected pre-AIDS deaths or 25% of all pre-AIDS deaths, and is presumably related to the heavy co-infection with hepatitis B and C.

Respiratory infections

A review of pneumonia in all HIV positive patients suggested an increased annual incidence of bacterial pneumonia; 97–290 per 1000 compared to 21 per 1000 for HIV negative individuals. IDU-related HIV patients also have an overall higher incidence of bacterial infections; 12% (mortality of 2.2%) compared to 3% (mortality of 0%) in HIV negative drug users. The overall rate of bacterial sepsis in Edinburgh drug users was 7.0 per 100 person-years whilst in the Bronx cohort of drug users the rate was 8.0 per 100 person-years. In Spain 60% of the pneumonias in the HIV-infected patients occurred before a diagnosis of AIDS, in 55% of patients the problem was recurrent and the mortality was increased for HIV-infected patients (19% vs. 4%). *Streptococcus pneumonia* and *Haemophilus influenzae* were the commonest organisms involved in the pneumonias. Additional susceptibility factors for drug users may be the use of opiates themselves because they are known to depress the cough reflex as well as the immune system. Latterly it has been suggested that the inhalation of drugs as well as the injection of drugs may increase the risks of bacterial pneumonias. The odds of developing pneumonia were twice as great for those reporting smoking cocaine, crack cocaine and marihuana and over 20-fold increased for those also having prior PCP and a low CD4. The effects of tobacco were not examined since all patients utilised this drug. The incidence of tuberculosis is much higher in HIV-infected drug users than in other risk groups outside the tropics, or in HIV negative drug users. In the USA, most patients with AIDS and tuberculosis have been drug users. One study showed a prevalence of 15% in drug users with AIDS but only 4% in other risk groups within a New York hospital. In New York the rate of tuberculosis was 4% among HIV positive drug users compared to 0% in HIV negative drug users. The 36% increase in reported cases of tuberculosis between 1984 and 1986 has been largely ascribed to infection amongst HIV positive drug users.

Hepatitis

Drug users with a history of IDU are highly likely to be co-infected with hepatitis B and C viruses (anywhere from 40% to 100% depending on location).

Anti-HIV drugs have long been associated with hepatitis and it is uncertain at present whether modern combination therapy for HIV will have a deleterious effect on those

Table 11.1 *continued*

Smoking of tobacco, heroin, marijuana	Abnormal pulmonary function for example reduced DCO, COAD
"Snorting" stimulants	Chronic rhinitis, rhinorrhoea, anosmia, atrophy of the mucosal membranes, ulceration and perforation of the nasal septum
"Snorting" opiates	Recurrent sinusitis

Box 11.9 Associated medical problems of IDU

- Lymphadenopathy is associated with both HIV and the injection of foreign materials.
- Fatigue, lethargy and excessive sweating are features of HIV as well as mild withdrawal from opiates.
- Diarrhoea, a common presentation of early symptomatic HIV (CDC stage IVA), is also a common symptom of opiate withdrawal.
- Weight loss and fever are both key symptoms of the constitutional symptoms associated with HIV (CDC stage IVA), infection with mycobacteria as well as heavy opiate or stimulant (amphetamines or cocaine) use.
- Epileptic seizures require consideration of cerebral toxoplasmosis in HIV, the intermittent use of benzodiazepines or even hepatic encephalopathy.
- The excessive use of cannabis and benzodiazepines interferes with memory and other cognitive functions in a similar manner to HIV as does frequent head injuries. Thus early dementia is difficult to detect in current drug users especially since reducing drugs will also help the dementing patient to improve function in relation to activities of daily living.
- Syncopal attacks in HIV may be associated with an autonomic neuropathy or a failing adrenal cortex but it is also associated with the use of antidepressant tricyclic drugs such as amitriptylene.
- Jaundice may be a result of acute or chronic hepatitis B or C infection, excessive alcohol ingestion or a side effect of the treatment of mycobacterial infections in HIV.
- Lastly shortness of breath and a persistent cough are common early symptoms of *Pneumocystis carinii* pneumonia (PCP) but can occur with endocarditis, bacterial pneumonia, excessive smoking, recurrent bronchitis and obstructive airways disease.

Greater detail can be obtained from the web site of the Regional Infectious Diseases Unit, Western Infirmary, Edinburgh (www.med.ed.ac.uk/ridu/History.htm).

Box 11.10 Co-infection of HIV and hepatitis viruses

Hepatitis B

- 10% of drug users will be carriers of hepatitis B
- Re-emergence of carriers (HbsAg) with CD4 counts of < 200 cells/μl may occur

Hepatitis C – data contradictory and may vary with risk groups because of length of HCV infection which is often unknown

- HCV RNA levels rise with falling CD4 counts
- Increased progression of both HIV and HCV disease reported in haemophiliacs
- Studies on drug users have reported no change of HIV progression
- Increased rate of HCV progression also reported in drug users

co-infected with HCV or not. There are reports in the literature of therapy improving, worsening or having no effect on concomitant HCV. Thus despite a greater risk of hepatotoxicity in HIV/HCV co-infected patients on highly activated retroviral therapy (HAART), this is not a reason to withold therapy from HCV HIV co-infected patients but rather such patients require more carefully monitoring. There is also the problem of additional hepatotoxicity associated with the use of antituberculous drugs in HIV/HCV co-infected individuals.

Although treatment for HCV is now available in the form of interferon and ribavirin, tolerance and interactions with HIV therapy are likely to be problematical since ribavirin has been reported to interfere with the phosphorylation of nucleosides such as zidovudine.

HIV dementia and encephalitis

HIV/AIDS is unusual in that it combines both immunological, neurological and psychiatric disorders and as a consequence patients may develop a variety of disabilites ranging from wasting disorders, severe pain, neurological dysfunction such as paralysis or cognitive impairment and psychological symptoms. These combinations of problems may result in considerable problems for both patients and carers. Autopsy studies in Edinburgh (prior to modern antiretroviral therapy (ART)) have shown that as many as 60% of IDU-related HIV patients have evidence of HIV encephalitis although only 6–7% have frank dementia.

AIDS

As for AIDS itself, little variation between the risk activities with regard to presentation has been reported. In the USA, figures available to the Centers for Disease Control show that conditions such as Kaposi's sarcoma are unusual in the absence of homo/bisexuality. In drug users, Kaposi's sarcoma, cytomegalovirus and chronic cryptosporidiosis are all significantly less common than for all other risk groups notified with AIDS, while PCP, tuberculosis, oesophageal candidiasis and extrapulmonary cryptococcosis are more common.

Progression from HIV to AIDS

No evidence has been found for a role of alcohol, opiates or other psychoactive drugs in accelerating the progression of immunodeficiency in HIV-seropositive homosexual and bisexual men. The major factors identified in the progression of HIV appear to be age and HLA type. Al B8 Dr3 and Bw 35 are all associated with more rapid progression whilst B27 is associated with slower progression to AIDS and death.

Survival after the development of AIDS

Without treatment, in general, around half of patients with AIDS survive for one year but only a fifth for three years and the median survival time is around 18–20 months. In Edinburgh the one- and three-year post-AIDS survival rates were 66% and 25%. Older age at AIDS diagnosis and HLA type A1 B8 DR3 were associated with shorter survival. Whilst it had been generally assumed that the survival for injection drug users with AIDS would be shorter than for other risk groups, several studies including our own counter this presumption.

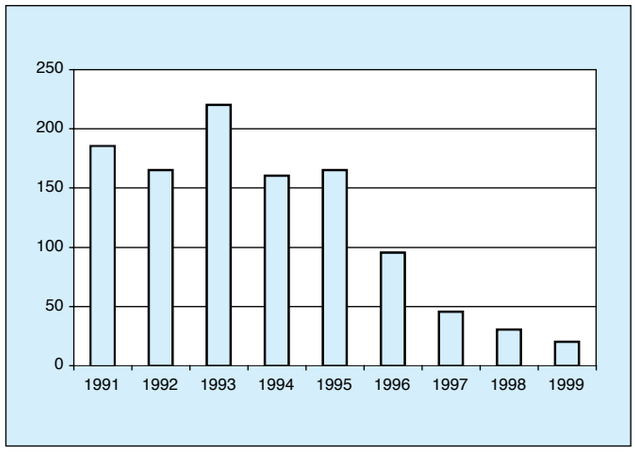


Figure 11.1 Opportunistic events/100 patient-years: Regional Infectious Diseases Unit, Edinburgh

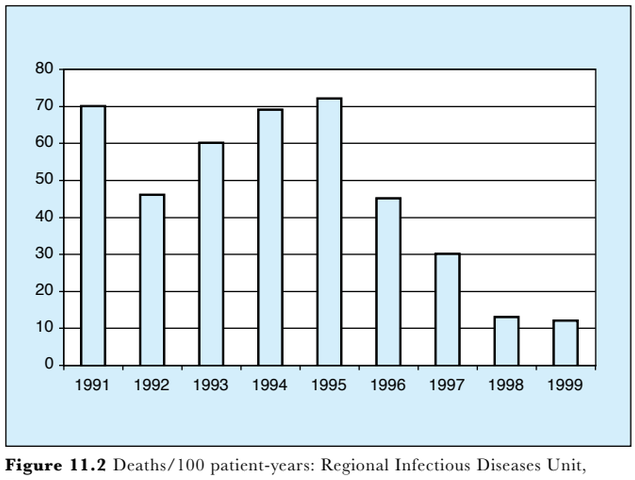


Figure 11.2 Deaths/100 patient-years: Regional Infectious Diseases Unit, Edinburgh

Problems of pain management in IDU-related HIV

The investigation of pain in IDU-related HIV is a major problem for carers, particularly since it is a useful complaint to increase the size of opiate prescriptions. Considerable experience is required in both the investigation and management of pain in order to avoid ever larger prescriptions.

The commonest problem in the management of pain in drug users is that of insufficient doses as a consequence of existing high levels of opiate use and/or disagreement from carers over whether pain is real or being treated adequately. Self-medication is a common problem which increases the uncertainties around prescribing. The use of inappropriate drugs such as Diconal or Temgesic should be avoided because these drugs are highly sought after as recreational drugs in the community.

Our own practice has been to utilise increasing doses of existing drugs such as methadone, oral solutions of morphine, slow-release morphine preperations such as MST (although this also has some street value since it can be injected), morphine/diamorphine solutions via subcutaneous infusions or fentanyl patches.

There is the additional problem of providing adequate sedation during procedures. Patients may require unusually large doses of medazolam as a consequence of their regular intake of benzodiazepines. If adequate doses of medazolam are not used then there is no loss of memory for the procedure which can be quite distressing for the patients. Alternatively, particularly if the patient uses illicit benzodiazepines or opiates, excessive sedation occurs with even quite small doses. As with the elderly, some HIV/AIDS patients also exhibit an unusual sensitivity to neuroleptics such as carbamazepine or antidepressants, possibly because of the concomitant presence of HIV encephalopathy. Care is therefore required in the introduction of such drugs for pain control.

Box 11.11 Common causes of pain in drug users

Dental caries
Traumatic neuropathies
Abdominal pain
- Constipation
- Cholecystitis
- Appendicitis
- Chronic hepatitis
- Lymph node enlargement
  - MAI
  - Lymphoma

Antiretroviral therapy

It is perfectly possible to treat drug users with antiretroviral therapy although there are a number of simple difficulties such as venous access for monitoring of therapy.

When considering combination therapy for recreational drug users a number of important principles need to be understood by the drug users. Whilst these may seem obvious to ourselves this is not the case for the patients.

A number of groups have been exploring drug regimens thought to be particularly suitable for drug users, usually because they provide the possibility of a once-daily regimen, and therefore the option of employing directly observed combination therapy (DOCT) at a suitable location. Whilst DOCT may be offered to a patient as an option it should perhaps be seen as a means to an end rather than as a long-term solution.

Box 11.12 Problems of antiretroviral therapy in drug users

- Regular venous access required – consider external jugular rather than femoral artery
- Improved health may encourage a return to IDU – continue with harm reduction strategy

Drug interactions

Drug interactions are an ever present problem with modern antiretroviral therapy for all patients, but even more so for those taking recreational drugs where there is the ever-present possibility of serious increases in the levels of pharmaceutical or recreational drugs. Of course from the patient's point of view reduced levels of recreational drugs is also an important problem.

Box 11.13 Important principles in modern antiviral combination therapy

- Intermittent combination therapy is a major disadvantage because of the development of resistance which will impair future therapy choices
- Almost total (95%) adherence is required for the best chance of long-lasting success (undetectable viral load)
- Increasing the number of drugs used in combination therapy does not increase "wellness", it simply increases the chance the regimen will be successful for a longer period
- However more antiviral drugs increase the chance of an adverse drug related event
- Intermittent recreational drug use is more dangerous and difficult to adjust for than regular recreational drug use (time and patience required by both patient and doctor) in terms of interactions with combination therapy

The most extensively investigated interactions are with methadone since it is commonly used long-term for heroin substitution. Little other investigational work has been undertaken possibly because of the difficulties of working with illegal drugs such as cocaine or amphetamine and some lack of interest on the part of pharmaceutical companies. One proviso when discussing interactions is our relative lack of knowledge of methadone levels and symptoms of withdrawal. Very little work seems to have been carried out in this area recently and much more is required if we are to better understand the interactions that do occur.

Other drugs used in HIV

It is important also to remember that a number of other drugs commonly used in HIV medicine such as rifampicin or phenytoin also dramatically reduce methadone levels by enzyme induction and cause problems with acute withdrawal. Increased zidovudine levels have also been reported with sodium valproate, a drug that is commonly used to control seizures.

In summary the use of recreational drugs certainly affects the choice of anti-viral drugs and possibly also the time at which therapy starts. Individual regimes to suit particular problems are important. Because of the complexity of the interactions it is important to get over to the patient how vital it is to know what drugs are actually taken rather than what drugs are prescribed. Misinformation may be fatal and they need to understand why the information needs to be accurate. This will only work of course if the patient is truly persuaded of the need for therapy. The risks of not taking therapy have to be very real and to outweigh the risks of the therapy – which after all in the case of ecstasy and ritonavir could be sudden death – not a very good outcome measure for combination therapy. For drug users the risks of disease may not outweigh therapy until the CD4 count is below 200 cells/microgram when the immediate risk of ill health is 20% or one in five for the next 12 months and 80% or four in five for the next three years. By comparison, the risk of a drug-related adverse event lies somewhere between 3% and 30%. At levels of CD4 count of 350 or 500 the risks of an adverse event are likely to outweigh the risk of serious HIV disease.

Despite all these difficulties, in Edinburgh with around 50% of our patients being drug users, we have managed to achieve the same reductions in opportunistic infections and deaths noted in other areas.

Thus recreational drug use related HIV can be managed successfully via attention to drug dependence needs, social needs and the medical care needs.

Box 11.14 Substitute recreational drug therapy and interactions with HAART

NRTI (Nucleoside Reverse Transcriptase Inhibitors)
- Zidovudine
  - ZDV levels increased by opiates (AUC increased x 2)
- Stavudine and Didanosine
  - Absorption decreased by co-administration with methadone
- Abacavir
  - Rate but not extent of absorption of decreased by co-administration with methadone
  - Increased clearance of methadone – dose adjustment may be needed

NNRTI (Non Nucleoside Reverse Transcriptase Inhibitors)
- Nevirapine and efavirenz
  - AUC of methadone reduced by as much as 30% – dose adjustment may be needed
- Delavirdine
  - AUC of methadone increased – to date no reports of dosage adjustment required

PI (Protease Inhibitors)
- Ritonavir
  - No change in methadone dosage required
  - Heroin and morphine levels reduced
  - Dextropropoxyphene and pethidine levels increased
- Indinavir
  - Initially need to reduce methadone doses but after a few weeks return to previous levels
- Nelfinavir
  - Methadone levels reduced and dosage adjustment usually necessary

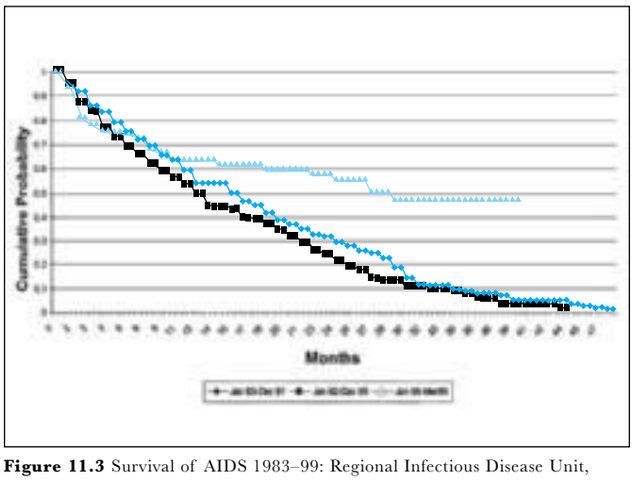


Figure 11.3 Survival of AIDS 1983–99: Regional Infectious Disease Unit, Edinburgh

12 HIV infection in children

Gareth Tudor-Williams, Diana Gibb

Epidemiological aspects

By the end of 2000, there were an estimated 1.4 million children under 15 years of age living with HIV infection worldwide and 4.3 million had died. Of these, UNAIDS estimates that 600 000 became infected during 2000 alone, over 90% via mother-to-child transmission (MTCT). Over 90% of people with HIV live in the developing world and, of these, over two-thirds live in countries in sub-Saharan Africa. Here HIV is reversing gains in child survival and significantly lowering life expectancy. Although the burden of HIV disease borne by African children is enormous, over half of the world's population live in the Asia/Pacific region. The HIV epidemic is at a much earlier stage here than in Africa and the explosive increase seen this decade is alarming.

Around half of women who acquire HIV become infected before 25 years of age and die before their 35th birthday, in the prime of their child-bearing years. As a result, by the end of 1999, the epidemic had left behind 13.2 million AIDS orphans under the age of 15 years. The difficulties that poor communities in Africa face in trying to care for this increase in children without parents is enormous and is largely dependent on existing family and social support structures already greatly affected by the AIDS epidemic.

For a vertically infected child in sub-Saharan Africa the probability of death by 12 months is estimated to be between 23% and 50%, and over 75% will not live to see their fifth birthday. HIV-infected children in Western Europe and North America contribute <1% to the total number of children worldwide living with the disease today. Over the last 5 years the epidemiology of paediatric HIV infection in affluent countries has changed as a result of a number of factors:

- First, there has been a dramatic decrease in MTCT as a result of widespread implementation of interventions for pregnant infected women and their newborns, resulting in few infected children.
- Second, new HIV infections increasingly occur either in children whose mothers acquired the disease in a country with a high prevalence of HIV, or come to light in older children who were themselves born elsewhere.
- Third, with the advent of potent antiretroviral therapy, children are living longer with HIV infection – for example, one-quarter of the 10 000 children living with HIV in the USA are now teenagers and the age of children in Europe is also increasing.

Unlinked anonymous monitoring of HIV through testing newborn dried blood spot (Guthrie) cards provides an unbiased estimate of the prevalence of HIV infection among women having live babies. This is being undertaken in the UK and covers 70% of births (see Figure 12.3). In 1999, the prevalence of maternal infection was 0.25% (1 in every 400 births) in London, compared with approximately 1 in 6000 births outside London. There has been an increase of around 30% in the number of pregnant HIV-infected women being reported in the last 2 years, which may in part reflect an increasing desire for infected women to have children in the new knowledge that the risk of MTCT is low. In London, three-quarters of seropositive

Table 12.1 End 2000 global HIV/AIDS estimates in millions

	Children	Total
People living with HIV/AIDS	1.4	36.1
New HIV infections in 2000	0.6	5.30
HIV/AIDS Deaths in 2000	0.5	3.0
Cumulative HIV/AIDS deaths	4.3	21.8

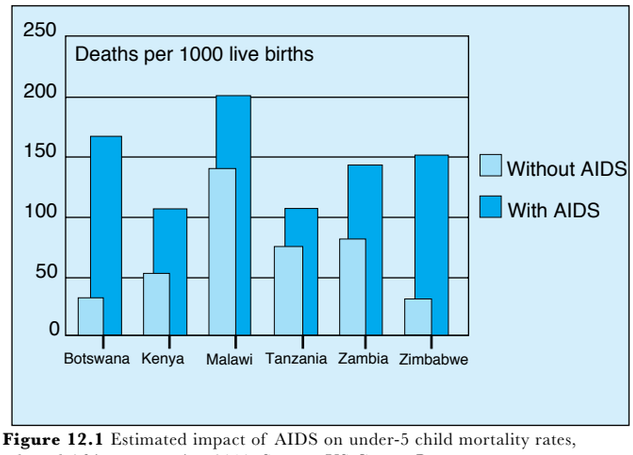


Figure 12.1 Estimated impact of AIDS on under-5 child mortality rates, selected African countries, 2010. Source: US Census Bureau

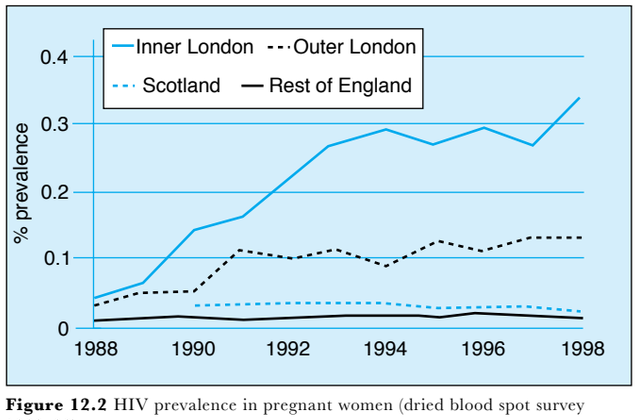


Figure 12.2 HIV prevalence in pregnant women (dried blood spot survey 1988–98)

newborns are delivered to mothers born in sub-Saharan Africa, and similar patterns are seen in European countries such as France and Belgium. In Scotland, Ireland and Southern Europe a high proportion of seropositive children are still born to women with IDU as a risk factor, but here too the proportion of women acquiring HIV from heterosexual transmission is increasing. Romania has the largest number of HIV-infected children in Europe, making up nearly half of the estimated 10 000 children living with HIV/AIDS in East and Western Europe. The majority belong to a cohort of children who were uniquely infected with HIV through contaminated blood products and needles in the late 1980s and early 1990s. Although many have died, there remain a considerable number of these children now entering their teenage years in Romania.

Box 12.1 Mother-to-child transmission of HIV infection

- HIV infection is transmitted to about 15–20% of babies born to HIV infected women *(between 1 in 5 and 1 in 6)*.
- The transmission rate doubles if a woman breastfeeds to about 30% *(1 in 3)*.
- In non-breast fed infants, approximately 70% of transmission occurs around the time of delivery
- Transmission is increased if a women has a high HIV viral load, low CD4 count and/or AIDS.
- Factors around delivery influence transmission.

Antenatal testing and mother-to-child transmission

Most observational studies estimate the risk of MTCT without interventions to be around 15–20% in Europe and the USA and over 30% in African populations. Postnatal breastfeeding doubles the overall risk of transmission and accounts for most of the difference. In non-breastfeeding women, approximately 75% of perinatal transmission occurs around the time of delivery. Other factors independently affecting the rate of transmission include the HIV viral load and CD4 cell count of the mother at the time of delivery, duration of rupture of membranes, prematurity and mode of delivery. In the last five years, the MTCT rate has been reduced to less than 2% in the USA and most European countries by the introduction of antenatal testing, highly active antiretroviral therapy (HAART) for mother's requiring therapy, use of antiretroviral therapy perinatally even if not indicated on the grounds of the mother's disease status, delivery by elective caesarean section, and refraining from breastfeeding. A recommendation that HIV testing should be offered to all women in pregnancy has been successfully implemented in many European countries, notably France, Italy and Spain where the prevalence of HIV in pregnant women was highest.

In the UK, universal offer of HIV testing during the antenatal period has been recommended in London because of the high prevalence since 1992. However, until 1999, it was recommended that antenatal HIV testing should only be offered to women considered at high risk (selective testing) outside London. An economic analysis was published in 1999 showing that a universal offer policy was cost-effective throughout the UK provided that a high uptake of testing was achieved. Department of Health guidelines endorsing this approach were published in August 1999. In low prevalence areas, up to 50 pooled samples can be tested in batches to reduce costs. During most of the 1990s, detection of previously undiagnosed HIV in pregnancy has been low everywhere in the UK. However, during 1999, and more dramatically, during the first half of 2000, there has been a marked improvement in antenatal detection rates, with about 75% of all HIV infected women being aware of their diagnosis before their baby is born in inner London and Scotland, 66% in outer London and about 50% elsewhere in the UK. In most European countries and in the USA, a marked decrease in AIDS cases reported in infancy reflects the high proportion of pregnant women receiving appropriate care to reduce MTCT.

Among UK women who either knew their HIV status before pregnancy or are diagnosed during pregnancy, MTCT rates of 2% or less are being reported among those taking up

Box 12.2 Interventions to reduce transmission from mother-to-child

- Not breastfeeding
- Antiretroviral therapy
- Elective caesarean section delivery (ie before the onset of labour or membrane rupture)
- **IMPLEMENTING ALL 3 CAN REDUCE TRANSMISSION RATES TO 2% OR LESS**

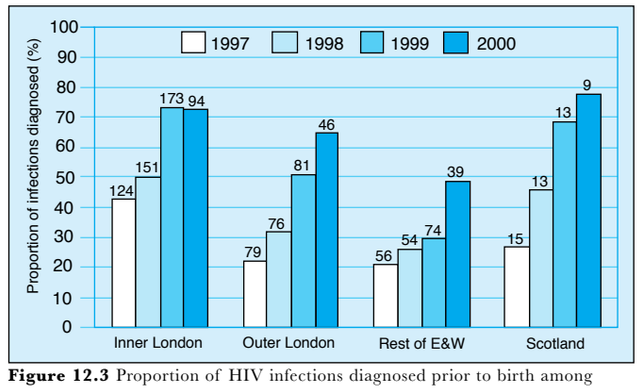


Figure 12.3 Proportion of HIV infections diagnosed prior to birth among pregnant women

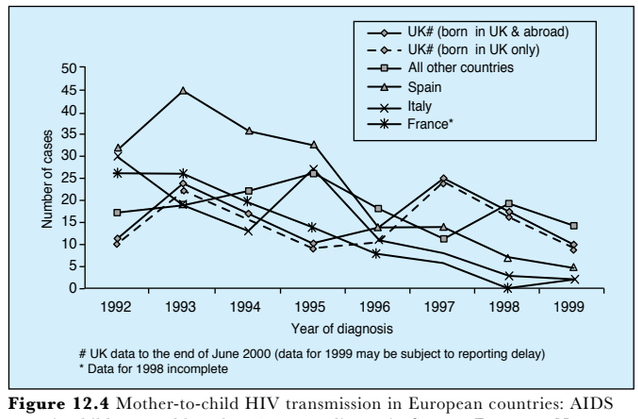


Figure 12.4 Mother-to-child HIV transmission in European countries: AIDS cases in children aged less than 1 year at diagnosis. Source: European Non-aggregate AIDS data set. June 1999. European Centre for the Epidemiological Monitoring of AIDS, Saint Maurice, France

interventions. Women taking HAART for their own disease who have undetectable HIV viral load at delivery have a very low risk of transmitting HIV to their baby. For those women not needing therapy for themselves, most guidelines recommend zidovudine and elective caesarean section (CS) delivery, which limits exposure of mother and baby to antiretroviral drugs and is associated with a transmission rate of <2%. There have been recent concerns about the possible link between mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues, particularly zidovudine (ZDV) and lamivudine (3TC). This was reported from the French cohort in 1998, but extensive retrospective analysis of US and other European data have not revealed additional cases. In Europe and the USA, it has been agreed that the benefits of antiretroviral therapy (ART) in reducing MTCT outweigh the possible adverse effects, but that it is important to prospectively follow all infants born to infected women as the long-term effects of exposure to ART *in utero* is unknown.

A European trial and a meta-analysis of cohort data from the USA and Europe showed that in women taking no ART or ZDV monotherapy, elective CS delivery decreased the risk of MTCT by approximately 50% compared with vaginal or emergency CS delivery. This approach has been widely adopted in Europe for women taking mono ART in pregnancy to prevent MTCT. However, it has been less widely adopted in some countries such as the USA, where women are more likely to be given triple HAART in pregnancy in order to reduce viral load to below the level of detection. In this situation the additional benefit of an elective CS delivery remains unclear. There is probably no place for dual ART with ZDV and 3TC in pregnancy, as this is rarely able to fully inhibit viral replication, adds little to reducing transmission with ZDV and elective CS, increases the potential for toxicity in the infant and has been associated with rapid selection of 3TC-associated mutants.

In the developing world, a number of major studies have evaluated the efficacy of cheaper and less complicated perinatal ART regimens. These include short-course ZDV and most notably the use of a single dose of the non-nucleoside reverse transcriptase inhibitor (NNRTI) drug nevirapine to the mother during labour and to the infant within the first three days of birth. This extremely cheap regimen has been shown to reduce transmission by nearly 40% compared with a regimen of intrapartum and neonatal ZDV for a week, even in breastfeeding women over a period of 12 months. It is now being implemented alongside antenatal HIV testing programmes in many parts of the developing world. A concern that resistance to nevirapine, which occurred in about 15% of women, might compromise its use in subsequent pregnancies is probably unfounded as virus returns to wild type in the months following delivery. However, there are concerns that giving a single dose of nevirapine during labour in addition to other ART to women in Europe and the USA who fail to achieve undetectable viral load, could compromise the woman's future ART options to any NNRTI drug because of the rapid selection of HIV strains resistant to nevirapine even after a single dose. Resistance testing to guide therapy choice is routinely recommended for all HIV-infected pregnant women in many developed countries because of *de novo* acquisition of drug-resistant strains of HIV-1.

Diagnosis

IgG antibodies to HIV are passively transferred to virtually all babies born to infected mothers, unless they are born extremely preterm or the mother has profound hypogammaglobulinaemia. Standard IgG antibody assays are so sensitive that traces of

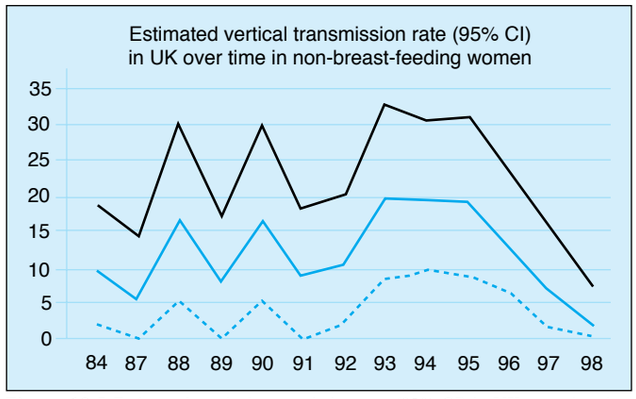


Figure 12.5 Estimated vertical transmission rate (95% CI) in UK over time in non-breastfeeding women (from Doung, BMJ 1999)

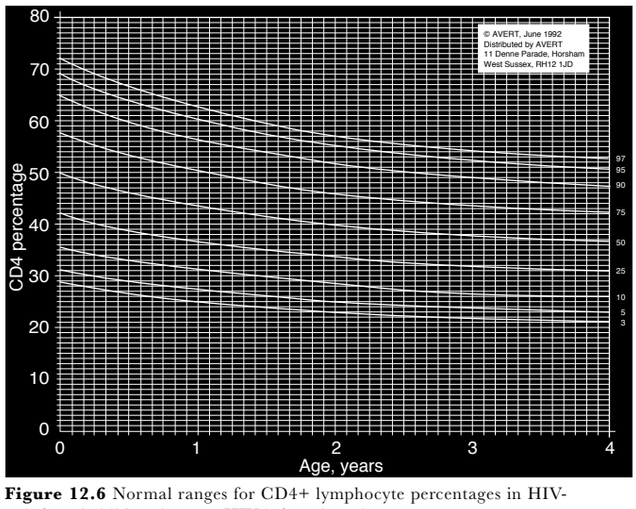


Figure 12.6 Normal ranges for CD4+ lymphocyte percentages in HIV-uninfected children born to HIV-infected mothers.

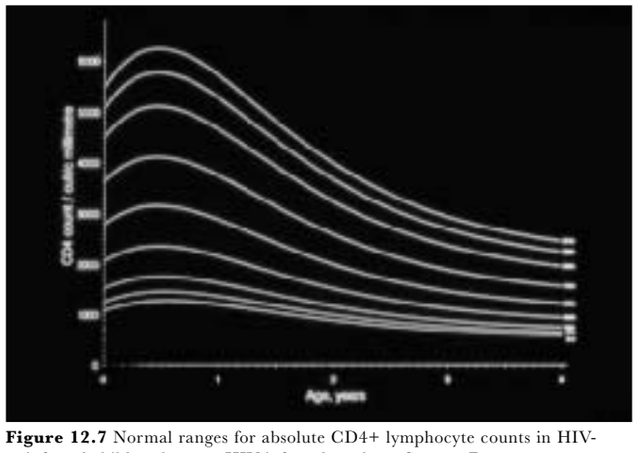


Figure 12.7 Normal ranges for absolute CD4+ lymphocyte counts in HIV-uninfected children born to HIV-infected mothers. Source: European Collaborative Study

Table 12.2 Suggested follow-up of infants born to HIV-infected mothers

Age	Action	Comment
Birth to 4–6 weeks	Give antiretroviral prophylaxis to baby	Usually zidovudine monotherapy, but modified in light of maternal therapy
24–48 hours	Proviral DNA PCR*	If positive, suggests intrauterine transmission or high intrapartum innoculum: may be associated with more rapid disease progression. Not helpful if negative, as less than 50% of infected babies can be detected within 48 hours of birth
3–6 weeks	Proviral DNA PCR	Should detect 95% of infected infants. A positive result must be confirmed on two separate blood samples
4–6 weeks	Stop antiretroviral prophylaxis. Start PCP prophylaxis**	See text for PCP prophylaxis recommendations
3–4 months	Proviral DNA PCR	If all assays are negative and there are no clinical concerns, child is almost certainly uninfected. PCP prophylaxis can be stopped
18 months	HIV antibody test	Performed until seroreversion documented

*Initial infant sample should be tested in parallel with maternal sample obtained around the time of delivery, to ensure maternal strain of HIV can be detected.
**For very low risk infants paediatric specialists increasingly are not recommending PCP prophylaxis.

maternal antibody are frequently detectable in the baby up to 18 months of age. Waiting for antibodies to become undetectable ("seroreversion") is therefore a slow way to establish the child's infection status. Using techniques that detect proviral HIV DNA, by polymerase chain reaction (PCR) or other amplification techniques, 93% of infected infants can be diagnosed by one month of age, and virtually all by three months. Quantitative RNA assays are now widely available but are not licensed for diagnostic purposes because of problems with false positive results and variable performance with non-B clade viral isolates. Whichever test is used, it is essential to ensure that it efficiently detects the maternal strain of HIV.

Virus culture is a highly specialised assay that is available only in research laboratories and has been largely superseded by amplification assays. Immune complex dissociated p24 antigen assays (ICD p24 ag) detect the nuclear capsid antigen of the virus by a commercial ELISA kit. This is a cheap but less sensitive method of diagnosis. Similarly IgA assays are highly specific but lack sensitivity, particularly during the first three months of life.

If PCR assays which reliably detect the mother's strain of HIV are negative on the infant's blood at three different time points, with at least one set performed at or after three months of age, and there are no clinical concerns, the parents/guardians can be informed that their baby is almost certainly not infected (Table 12.2).

T-cell subsets and measurement of immunoglobulins (Ig) are non-specific tests. Reversal of the CD4 : 8 ratio and high Ig (>2 × upper limit of normal) are suggestive of infection but, for diagnostic purposes, should be supported by at least one other test that detects the virus directly. It is important to realise that absolute CD4 counts are physiologically much higher in infants and young children than in adults (Figures 12.7 and 12.8).

All children presumed to be uninfected should be followed until seroreversion is confirmed, and longer term follow-up to ensure normal development until four to five years is advised in children exposed to ART perinatally.

Natural history and clinical manifestations

As in adults, HIV-infected children present with a spectrum of signs and symptoms reflected in the revised Centre for Disease Control classification system (Box 12.3). The differences between adults and children with HIV disease are summarised (Box 12.4). In the absence of HAART, disease progression is generally faster than in adults, with 15–20% of children

Box 12.3 Centers for Disease Control 1994 revised classification system for HIV infection in children less than 13 years old

Category N: no symptoms

Category A: mildly symptomatic
- Lymphadenopathy
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent upper respiratory tract infections, sinusitis or otitis media

Category B: moderately symptomatic
Examples of conditions in clinical category B include:
- Anaemia, neutropenia or thrombocytopenia
- Bacterial infections: pneumonia, bacteraemia (single episode)
- Candidiasis, oropharyngeal
- Cardiomyopathy
- Diarrhoea, recurrent or chronic
- Hepatatis
- Herpes stomatitis, recurrent
- Lymphoid interstitial pneumonia
- Nephropathy
- Persistent fever > 1 month
- Varicella (persistent or complicated primary chickenpox or shingles)

Category C: severely symptomatic
Any condition listed in the 1987 surveilllance case definition for AIDS, *with the exception of LIP*. For example:
- Serious bacterial infections, multiple or recurrent
- Candidiasis (oesophageal, pulmonary)
- Cytomegalovirus disease with onset of symptoms at age >1 month
- Cryptosporidiosis or Isosporiasis with diarrhoea persisting 1 month
- Encephalopathy
- Lymphoma
- *Mycobacterium tuberculosis* disseminated or extrapulmonary
- *Mycobacterium avium* complex or *M. kansasii*, disseminated
- *Pneumocystis carinii* pneumonia
- Progressive multifocal leucoencephalopathy
- Toxoplasmosis of the brain with onset at age > 1 month
- Wasting syndrome

developing AIDS-defining illnesses by 12 months. This subset of perinatally infected children typically present with PCP at around three to four months of age (Figure 12.8). Progression rates to AIDS in infancy have been shown to be reduced by the use of primary PCP prophylaxis with Septrin from 4 to 6 weeks of age onwards.

Approximately 70% of perinatally infected children will have some signs or symptoms by 12 months (Figure 12.14). In the absence of antiretroviral therapy, the median age at which children progress to AIDS is about six years, and 25–30% have died by this age. The median age of death is around nine years. In many cases, the child is the first family member to be diagnosed as HIV infected. Some children, however, do not present until the second decade of life. Disease progression in children in developing countries is more rapid (Figure 12.15). Survival following an AIDS diagnosis has greatly improved over the past 10 years, but even where antiretroviral therapy is available the mortality amongst children with PCP and CMV is appreciable (Figure 12.13). This is yet another reason for antenatal HIV testing which can render PCP in infancy wholly preventable.

Children with HIV infection frequently present with signs and symptoms that are common in general paediatrics and are non-specific. The most usual clinical features associated with HIV infection include persistent generalised lymphadenopathy, hepatosplenomegaly, chronic or recurrent diarrhoea, fever, and recurrent otitis or sinusitis.

Persistent oral candidiasis, bilateral parotitis or neurological signs are more specific of HIV infection. Herpes zoster (shingles) in childhood is uncommon and suggests a defect in cellular immunity justifying an HIV test in the absence of other explanations. Similarly, thrombocytopenia can be a presenting feature, and HIV should be considered in the differential diagnosis of idiopathic thrombocytopenic purpura.

Recurrent and often severe bacterial infections are frequent and include pneumonia, cellulitis, local abscesses, osteomyelitis, septic arthritis and occult bacteraemia. The common causative organisms are similar to those seen in children with hypogammaglobulinaemia and include pneumococci, salmonellae, staphylococci, streptococci and *Haemophilus influenzae*. This reflects the B-cell defect that accompanies the destruction of the CD4+ helper T cells. Children with HIV infection frequently have hypergammaglobulinaemia due to dysregulated polyclonal B-cell activation. The antibodies are generally non-functional.

Pulmonary disease is an important cause of morbidity and mortality and may be one of the first manifestations. Lymphoid interstitial pneumonitis (LIP), characterised by multiple foci of proliferating lymphocytes in the lung interstitium, occurs in 20–30% of vertically infected children, but is rare in adults. It presents with persistent bilateral reticulonodular shadowing on chest X-ray (Figure 12.9) and clinical features ranging from asymptomatic to chronic hypoxia. It may be an abnormal response to primary Epstein–Barr virus (EBV) infection. Co-infection with *Mycobacterium tuberculosis* is an increasing problem in children, and can be difficult to distinguish radiologically from LIP. Clinically a child with bilateral infiltrates due to TB would be highly symptomatic, as opposed to LIP which may be clinically silent.

Opportunistic infections, apart from PCP and primary disseminated CMV disease in the subset of children with very rapid disease progression, are usually a late complication of HIV infection and result from severe immunosuppression. The most common are oesophageal candidiasis, multidermatomal varicella zoster, disseminated mycobacterium avium complex (MAC) or CMV infections, cryptosporidiosis, and more rarely,

Box 12.4 Differences between children and adults with HIV disease

- More rapid disease progression:
  - 20% of children develop AIDS by 12 months
  - Child may be the first family member to present
- Higher viral loads at presentation
- Physiologically higher absolute CD4 counts
- Growth faltering common (affects height and weight)
- Encephalopathy presents with developmental delay and hypertonic diplegia
- Opportunistic pathogens encountered for the first time
  - primary illnesses often more severe than OIs in adults
- Poor primary responses to childhood infections/immunisations
- Lymphoid interstitial pneumonitis common
- Malignancy uncommon (accounts for less than 2% of AIDS-defining presentations in children)
- More rapid clearance of antiretroviral drugs, requiring higher than adult equivalent doses particularly in very young children

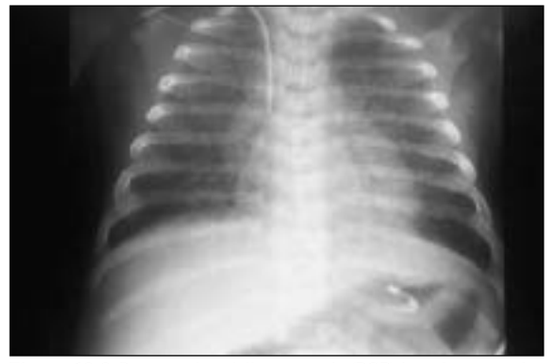


Figure 12.8 *Pneumocystis carinii* pneumonia (PCP) in a three month old. Diffuse bilateral ground-glass opacification, tending to confluence in right upper and both lower lobes. Air bronchograms are seen, which imply air space disease which is a late feature of disease. The earliest infiltrates are usually perihilar. The absence of pleural effusion or hilar adenopathy is typical. Less typical presentations include miliary, coin and nodular lesions, lobar consolidation and cavitations

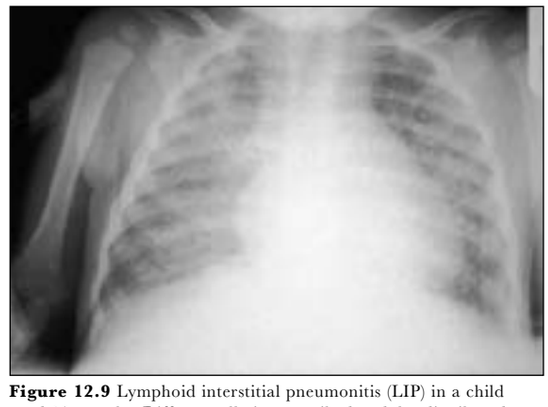


Figure 12.9 Lymphoid interstitial pneumonitis (LIP) in a child aged 12 months. Diffuse, well-circumscribed nodules distributed uniformly throughout both lung fields. May be associated with hilar adenopathy. A radiological spectrum is seen in LIP, ranging from fine linear interstitial infiltrates to large nodules that tend to confluence in the right middle and lingular lobes

toxoplasmosis. MAC should be considered in any child with advanced disease and unexplained fevers, weight loss and abdominal discomfort.

Encephalopathy due to effects of HIV infection on the central nervous system is seen most frequently in the subgroup of children with rapid disease progression. The most common neurological manifestations are hypertonic diplegia, developmental delay (particularly affecting motor skills and expressive language) or acquired microcephaly. Cranial imaging studies may show basal ganglia calcification and cerebral atrophy and MRI scans may show evidence of white matter damage. Seizures are not usually a feature of HIV encephalopathy which does not tend to affect the grey matter. The majority of school age children are attending normal school without requiring additional support in the classroom.

Malignancy, such as Kaposi's sarcoma or lymphoma, is a relatively uncommon feature of paediatric HIV disease, accounting for only 1–2% of AIDS-defining illness in children.

Prognostic markers

The most widely used surrogate markers for predicting disease progression in children, as in adults, are the CD4 values and viral load. Very high viral loads are frequently found in infected children, particularly following perinatal transmission (Figure 12.10). Absolute CD4 counts are physiologically higher in children compared with adults (Figure 12.7). CD4 percentages vary rather less, and according to the CDC classification system can be used across all age ranges; >25% is considered evidence of no immunosuppression, 15–25% moderate and <15% severe immunosuppression (Figure 12.6).

Tables 12.3–12.5 contain data from a pre-antiretroviral trial of intravenous immunoglobulin in the USA that illustrate the independent prognostic value of these markers, although positive predictive values of each are low. Age-adjusted rates of change for viral load and CD4 counts may be of higher positive predictive value for disease progression: an analysis of combined European and US data is presently underway to evaluate this concept.

Management

The aim of any intervention for HIV-infected children should be to maintain the best possible quality of life for the children as long as possible, with the hope that they will be able to take advantage of potential curative therapy in the future. This inevitably means balancing the potential benefits of new treatments against the need for increased monitoring, possible toxicities and limiting future therapeutic options.

As a result of advances in ART, there has been a shift in focus from diagnosing and managing opportunistic infections (OI) to preventing them by restoring and maintaining cellular immunity. For most established opportunistic infections, the best treatment is HAART.

Antiretroviral therapy

Virus replication in children, as in adults, is occurring at all stages of HIV infection and, as improved drugs and drug combinations become available, treatment is likely to be offered increasingly early. Highly encouraging results have been reported with three or more drug combinations in selected, infected infants, which demonstrate that complete viral suppression and maintenance of entirely normal immune development can be achieved and sustained for at least three years. These observations, and studies of adults treated during primary infection, provide a rationale for early aggressive therapy of infants.

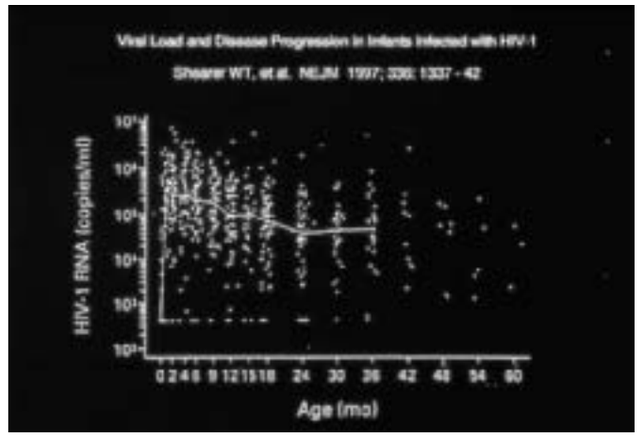


Figure 12.10 Plasma viral load (HIV-l RNA copies/ml) over time in a cohort of perinatally infected, non-breast-fed infants. Solid line represents median values at each time point. Note that median viral load on days 1–3 of life was below the limit of detection (<400.copies/ml). Most non-breast-fed infants are infected during labour or delivery, resulting in a lag before viral replication reaches detectable levels in the circulation

Table 12.3 Association of baseline CD4+ lymphocyte percentage with long-term risk of mortality in HIV-infected children

Baseline CD4+ percentage	Patients (no.)	Deaths (no.)	% mortality
25%	189	50	26
15–24%	93	31	33
5–14%	59	35	59
<5%	33	32	97

Table 12.4 Association of baseline HIV RNA copy number with long-term risk of mortality in HIV-infected children

Baseline HIV RNA (copies/ml)*	Patients (no.)	Deaths (no.)	% mortality
Undetectable	25	6	24
4001–50 000	69	19	28
50 001–500 000	105	34	32
500 001–1 000 000	20	8	40
>1 000 000	35	25	71

*Tested by NASBA RNA QT Amplification system on frozen stored serum (lower limit of detection=4000 copies/ml)

Table 12.5 Association of baseline HIV RNA copy number and CD4+ cell percentage with long-term risk of mortality in HIV-infected children

Baseline viral load/ CD4+ percentage	Patients (no.)	Deaths (no.)	% mortality
100 000 copies/ml			
15%	103	15	15
<15%	24	15	63
>100 000 copies/ml			
15%	89	32	36
<15%	36	29	81

Mean age = 3.4 years, mean follow-up = 5.1 years

* Data taken from the National Institute of Child Health and Human Development Intravenous Immunoglobulin Clinical Trial. Reproduced from Mofenson L *et al. Journal of Infectious Disease* 1997;**175**:1029–38.

Less impressive results have been documented outside clinical trials. Some children have failed due to inadequately defined pharmacokinetics for drugs like nelfinavir in infants, many of the infants have now been exposed to all three classes of ART and have few therapeutic options left, and adverse consequences of early prolonged therapy are unknown. Considerable support is required to enable families to sustain high levels of adherence long term. US guidelines recommend HAART for all infants, but European practice tends to be more conservative (Figure 12.11).

Older children presenting for the first time are a selected group who are not rapid disease progressors. For these children it is reasonable to monitor CD4 counts and only offer treatment if counts are declining steadily below 25%. There is no consensus level of viral load above which treatment must be started.

When starting HAART, most prescribers would initiate triple or even quadruple combination therapy, ideally sparing at least one class of drugs. The protease inhibitors (PI) are more difficult to formulate into palatable suspensions for children compared with the nucleoside analogues and non-nucleoside reverse transcriptase inhibitors. No data in children provide evidence to conclude that PI-containing or PI-sparing regimens have greater long-term clinical efficacy.

The management of heavily pretreated children who are failing therapy requires careful evaluation of past drug history, adherence, unused treatment options, possibly genotypic or phenotypic resistance testing, and pharmacodynamics. It has become clear that many drugs are more rapidly cleared in children. The problem of underdosing in infancy has already been mentioned. Adolescents may require higher than adult doses until reaching Tanner IV or V stages of puberty. Increasingly therapeutic drug monitoring will be used to understand population pharmacokinetics, and to tailor individual therapy.

Short- and long-term toxicities of specific drugs and drug classes are broadly similar in children as in adults, with 58% of children presenting with at least one side-effect in a recent national Italian survey of children on HAART. The most common toxicities are gastrointestinal symptoms and skin rashes. Lipodystrophy is increasingly described, particularly in adolescents who may wish to switch or discontinue therapy as a result. Lipid metabolism abnormalities with significantly raised fasting cholesterol and/or triglyceride levels are particularly associated with PI-containing regimens. Long-term consequences are not yet known and no consensus has emerged regarding the use of statins, but early onset cardiovascular complications are a potential risk.

It is likely that long-term control of viral replication in children will require adjunctive immune-based treatment, and several approaches are under investigation. The role of strategic treatment interruptions is also being evaluated. The long-term goal is to restore the child's HIV-specific immune responses to the point where HAART is no longer needed.

In view of the many uncertainties regarding optimal treatment, it is strongly recommended that children should be offered treatment as part of a clinical trial. Paediatricians in Europe and Brazil are collaborating in a series of studies coordinated by the Pediatric European Network for the Treatment of AIDS (PENTA). Information about the PENTA studies is available through the Medical Research Council Clinical Trials Centre in London (telephone +44 (0) 20 7670 4791/2, fax +44 (0) 20 7670 4814) or INSERM in Paris (telephone +33 1 4559 5201, fax +33 14559 5180).

Box 12.5 Issues to consider when starting therapy in Children

- Parental (and child) readiness
- Likelihood of good longterm adherence
- What formulations could this child take (taste testing: let child chose)?
- What pharmacokinetic data are available for infants/children/adolescents?
- What experience have other family members had on antiretroviral drugs?

Box 12.6 Drug combinations consider:

- Pill/liquid burden
- Ease of adminstration
- With/without food
- Number of times per day (avoid school hours, ?once daily for adolescents)
- Creative use of drug–drug interactions (boosting with ritonavir)
- Pill-swallowing techniques
- Adherence aids (sticker charts, dosette boxes etc.)
- Gastrostomy tubes to improve quality of life if this is severely eroded by difficulties taking medicines orally

Box 12.7 Recommendations for use of HAART in children (adapted from PENTA, 2001)

- Must start HAART if
  Clinical stage C or immunological stage 3 disease (CD4<15%)
- Consider HAART if
  Clinical stage B or
  Steadily declining CD4% falling below 25%, or
  High viral load (>10^6 RNA copies/ml if age <1 year, >10^5 if age over 1 year)
  Infant <12 months, regardless of CD4 or viral load
- Defer HAART if
  Stage N or A disease
  CD4>25%
  Low viral load:
  <10^5 in children between 1 and 30 months
  <50 000 copies/ml in children >30 months

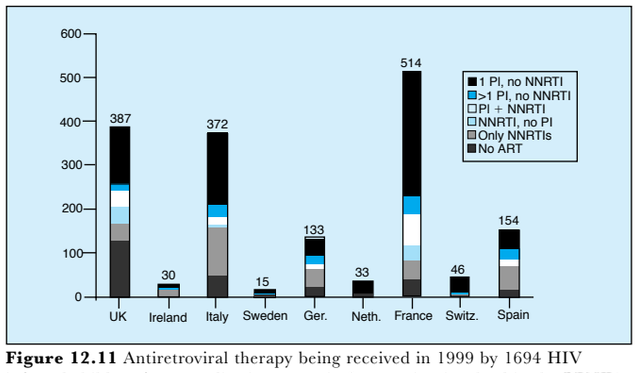


Figure 12.11 Antiretroviral therapy being received in 1999 by 1694 HIV infected children from paediatric centres in 9 countries, involved in the PENTA network of trials (unpublished data, Paediatric European Network for the Treatment of AIDS)

Prophylactic measures

Early-onset PCP is a preventable disease (Table 12.2). Infants at higher risk of acquiring HIV, whose mothers are identified during pregnancy, can be started on PCP prophylaxis from around 4 to 6 weeks of age onwards. Prophylaxis can be stopped once it has been established that the baby is uninfected. Infected children should continue on prophylaxis throughout the first year of life, as CD4 counts are unreliable indicators of risk (see Figure 12.7). Thereafter, it is not unreasonable to stop prophylaxis for children with CD4 counts consistently above 15%, provided the family are reliable clinic attendees and the child's clinical status and immune function can be regularly monitored. Any child with rapidly declining CD4 counts or counts consistently less than 15% should be on prophylaxis. Co-trimoxazole is the drug of choice. Regimens vary, but one convenient dosage regimen is suggested in Table 12.5. Rashes and bone marrow suppression due to co-trimoxazole may require switching to alternative prophylactic agents such as dapsone.

Routine active immunisation schedules should be followed for HIV-infected or -exposed infants, with the exception that BCG should not be given to symptomatic infected children because of the risk of dissemination. There is a theoretical risk of paralytic poliomyelitis in immunocompromised contacts of children excreting live polio vaccine virus. Inactivated polio vaccine (IPV) may be recommended by injection instead of the live oral polio vaccine. In practice it can be difficult to obtain supplies of IPV in the UK, and in view of the very low transmission rate of HIV, many units now condone giving oral polio vaccine (OPV), and advise carers about thorough hand-washing when changing nappies.

Pneumococcal polysaccharide vaccine has been recommended for HIV-infected children over two years of age, but is likely to be superseded soon by conjugate vaccines which can be given to younger children. Influenza vaccine is generally offered each winter, although data demonstrating its efficacy in this population are lacking.

Passive immunisation of symptomatic children is recommended if they are in contact with varicella zoster virus (VZV) and are either VZV naive or have no detectable specific antibodies to VZV. Varicella zoster immunoglobulin (VZIG) ideally should be given within 72 hours of contact. VZIG may prolong the incubation period to 28 days, so clinicians need to consider isolating these patients at clinic visits. Similarly normal human immunoglobulin should be given for susceptible symptomatic children in contact with measles. If children are stable on HAART with CD4 counts above 15%, passive immunisation is unnecessary.

Regular intravenous immunoglobulin infusions (400 mg/kg every 28 days) should be reserved for children with recurrent bacterial infections despite good compliance with co-trimoxazole prophylaxis, or those with proven hypogammaglobulinaemia. Higher doses may be useful in the management of thrombocytopenia (0.5–1.0 g/dose every day, for three to five days).

HIV-infected children who are household or day care contacts of individuals with open pulmonary tuberculosis should be carefully assessed, bearing in mind skin testing is frequently unhelpful because of anergy. If there is no evidence of infection, prophylactic isoniazid for six months, or isoniazid plus rifampicin for three months, is recommended. There is little enthusiasm for prophylaxis against *Mycobacterium avium intracellulare* in children because of adverse reactions and the potential for resistance and breakthrough on single agents such as rifabutin. The most appropriate prophylaxis for all OI is to optimise antiretroviral therapy to restore and preserve immune function.

Table 12.6 Suggested doses of co-trimoxazole for prophylaxis for *Pneumocystis carinii* pneumonia, to be given once daily on three days per week (usually Monday, Wednesday and Friday). Dose is based on 900 mg/m² dose

Surface area (m²)	Dose of co-trimoxazole (mg)
0.25–0.39	240
0.40–0.49	360
0.50–0.75	480
0.76–1.0	720
> 1.0	960 (adult dose)

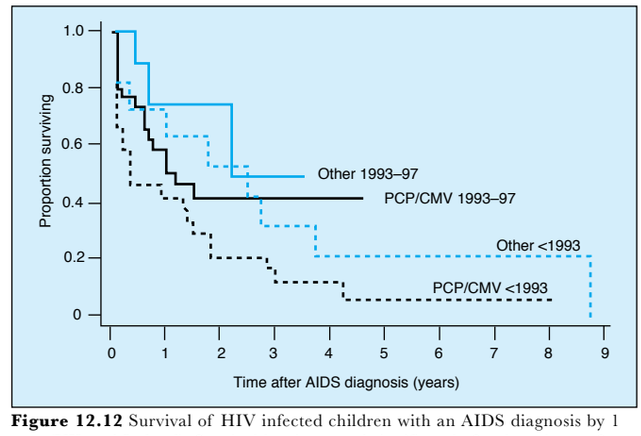


Figure 12.12 Survival of HIV infected children with an AIDS diagnosis by 1 year (UK and Ireland). Survival has improved significantly for those born after 1993 CMV, Cytomegalovirus infection; PCP, pneumocystis carinii pneumonia. Reproduced from Williams A *et al.* PCP and CMV infection in children with vertically acquired HIV infection. *AIDS* 2001;**15**: 1–5

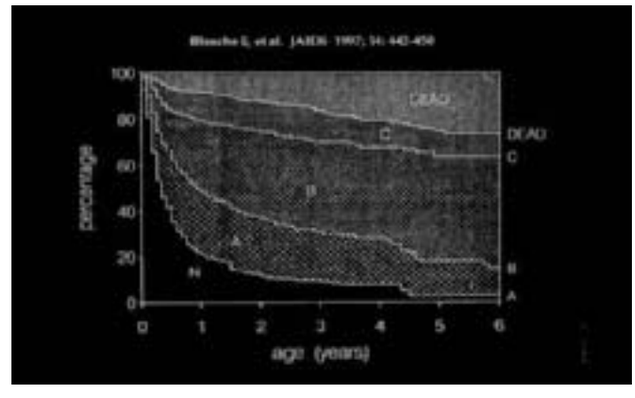


Figure 12.13 Morbidity and Mortality in European children vertically infected by HIV-1

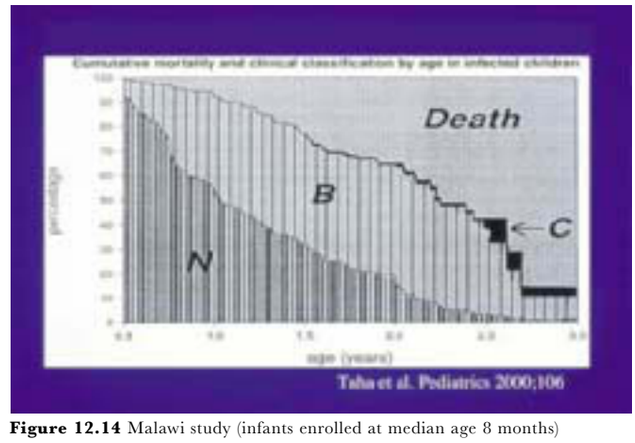


Figure 12.14 Malawi study (infants enrolled at median age 8 months)

Supportive care

Unlike almost any other life-threatening disease of children, HIV simultaneously threatens the parents and other siblings. The parents' own health, their social isolation and feelings of guilt compound the difficulties of caring for a sick child. An effective well-coordinated multidisciplinary team is required to address the changing needs of infected and affected children and their caregivers. Continuity of care between inpatient and outpatient services, local referring hospitals and the community needs to be developed. Ideally adults and children should be treated in family-based units. All too often parents will ignore their own health needs because they put their children first.

Increasingly the work of the multidisciplinary team has shifted towards ways of helping families achieve long-term adherence to HAART. As children survive longer, meeting the needs of adolescents and planning transition to adult clinics is placing new demands on services.

The decision as to who should be informed should be tailored individually. Families may need help in explaining the diagnosis to older children. This needs to be undertaken at the child's pace, and is frequently most effectively achieved in gradual steps. It is not mandatory to tell staff at schools, as universal precautions should be employed for all children with cuts and abrasions. The risks of transmission from casual contacts in school or day care settings are virtually nil. Ensuring that adolescents are well informed and responsible before they become sexually active themselves is a priority.

The child's developmental needs require careful monitoring and support, with access to a clinical psychologist, a physiotherapist, occupational therapist and speech therapist.

The multidisciplinary team should include a dietician, as nutritional problems and growth faltering are very common complications. Balanced supplements are sometimes required and enteral feeding through gastrostomy tubes and occasionally intravenous parenteral feeding may be necessary. Gastrostomy tubes have been used with success to allow unpalatable medicines to be given, even when they were not required for nutritional supplementation.

Because children below the age of eight years very rarely complain of symptoms of unilateral eye disease, regular monitoring of young children with CD4 counts less than 5% by a paediatric ophthalmologist is desirable. Chorioretinitis due to CMV is usually treated by intravenous induction therapy with ganciclovir followed by regular maintenance intravenous treatment five days per week. Paediatric formulations of oral ganciclovir are poorly bioavailable. Intravitreous injections and, in older children, implants have been used.

Pain management is of critical importance in late-stage disease. Complementary therapies such as therapeutic touch and aromatherapy may be useful and require evaluation. It is a testament to the success of HAART that very few children in industrialised countries are needing palliative or terminal care. However unless new treatment strategies become available, the next few years may see some children running out of therapeutic options.

Prevention remains the top priority in managing HIV infection in children. Reducing national perinatal transmission rates to below 2% is an achievable target that can only be realised if HIV-infected mothers can be identified prenatally and offered appropriate interventions. This will require continued effort by health professionals, public health planners and community organisations.

13 HIV counselling and the psychosocial management of patients with HIV or AIDS

Sarah Chippindale, Lesley French

What is HIV counselling?

Counselling in HIV and AIDS has become a core element in a holistic model of healthcare, in which psychological issues are recognised as integral to patient management. HIV and AIDS counselling has two general aims: (1) the prevention of HIV transmission and (2) the support of those affected directly and indirectly by HIV. It is vital that HIV counselling should have these dual aims because the spread of HIV can be prevented by changes in behaviour. One-to-one prevention counselling has a particular contribution in that it enables frank discussion of sensitive aspects of a patient's life – such discussion may be hampered in other settings by the patient's concern for confidentiality or anxiety about a judgemental response. Also, when patients know that they have HIV infection or disease, they may suffer great psychosocial and psychological stresses through a fear of rejection, social stigma, disease progression and the uncertainties associated with future management of HIV. Good clinical management requires that such issues be managed with consistency and professionalism, and counselling can both minimise morbidity and reduce its occurrence. All counsellors in this field should have formal counselling training and receive regular clinical supervision as part of adherence to good standards of clinical practice.

When is HIV counselling necessary?

Pre-test discussion

A discussion of the implications of HIV antibody testing should accompany any offer of the test itself. This is to ensure the principle of informed consent is understood and to assist patients to develop a realistic assessment of the risk of testing HIV antibody positive. This process should include accurate and up-to-date information about transmission and prevention of HIV and other sexually transmitted infections. Patients should be made aware of the "window period" for the HIV test – that a period of 12 weeks since the last possible exposure to HIV should have elapsed by the time of the test.

Patients may present for testing for any number of reasons, ranging from a generalised anxiety about health to the presence of HIV-related physical symptoms. For patients at minimal risk of HIV infection, pre-test discussion provides a valuable opportunity for health education and for safer sex messages to be made relevant to the individual. For patients who are at risk of HIV infection, pre-test discussion is an essential part of post-test management. These patients may be particularly appropriate to refer for specialist counselling expertise. In genitourinary medicine clinics where HIV antibody testing is routinely offered as a part of sexual health screening, health advisers provide counselling to patients who have been identified as high risk for testing HIV positive.

The importance of undertaking a sensitive and accurate sexual and/or injecting drug risk history of both the patient and their sexual partners cannot be overstated. If patients feel they cannot share this information with the physician or counsellor then the risk assessment becomes meaningless; patients may be inappropriately reassured, for example, and be unable to disclose the real reason for testing. Counselling skills are clearly an essential part of establishing an early picture of the patient

Box 13.1 Counselling

Prevention
- Determining whether the lifestyle of an individual places him or her at risk
- Working with an individual so that he or she understands the risks
- Helping to identify the meanings of high-risk behaviour
- Helping to define the true potential for behaviour change
- Working with the individual to achieve and sustain behaviour change

Support
- Individual, relationship and family counselling to prevent and reduce psychological morbidity associated with HIV infection and disease

Box 13.2 Different HIV counselling programmes and services

- Counselling before the test is done
- Counselling after the test for those who are HIV positive and HIV negative
- Risk-reduction assessment to help and prevent transmission
- Counselling after a diagnosis of HIV disease has been made
- Family and relationship counselling
- Bereavement counselling
- Telephone "hotline" counselling
- Outreach counselling
- Crisis intervention
- Structured psychological support for those affected by HIV
- Support groups

Box 13.3 Pretest discussion checklist

Indications for further counselling and referral to counsellor
- People who have been sexually active in areas of high HIV prevalence
- Men who have sex with men
- Current or previous sexual partners HIV positive
- Client presenting with clinical symptoms of HIV infection
- High-risk sexual behaviour
- High-risk injecting drug practices
- Learning or language difficulties

Points for counsellor and/or physician to cover
- What is the HIV antibody test (including seroconversion)?
- The difference between HIV and AIDS
- The window period for HIV testing
- Medical advantages of knowing HIV status and treatment options
- Transmission of HIV
- Safer sex and risk reduction
- Safer injecting drug use
- If the client were positive how would the client cope: personal resources, support network of friends/partner/family?
- Who to tell about the test and the result
- Partner notification issues
- HIV status of regular partner: is partner aware of patient testing?
- Confidentiality
- Does client need more time to consider?
- Is further counselling indicated?
- How the results of the test are obtained (in person from the physician or counsellor)

and his/her history and of how much intervention is needed to prepare him or her for a positive result, and to further reinforce prevention messages. It is at this stage that potential partners at risk are identified which will become an important part of the patient's management if HIV positive.

Post-test counselling

Results

HIV results should be given simply, and in person. For HIV negative patients this may be a time where the information about risk reduction can be "heard" and further reinforced. With some patients it may be appropriate to consider referral for further work on personal strategies to reduce risks, for example one-to-one or group interventions. The window period of 12 weeks should be checked again and the decision taken about whether further tests for other sexually transmitted infections are appropriate.

HIV positive patients should be allowed time to adjust to their diagnosis. Coping procedures rehearsed at the pre-test discussion stage will need to be reviewed in the context of the here and now; what plans does the patient have for today, who can they be with this evening? Direct questions should be answered but the focus is on plans for the immediate few days, when further review by the counsellor should then take place. Practical arrangements including medical follow-up should be written down. Overloading the patient with information about HIV should be avoided at the result giving stage – sometimes this may happen because of the health professional's own anxiety rather than the patient's needs.

Newly diagnosed patients

Counselling support should be available to the patient in the weeks and months following the positive test results. Immediate issues often include disclosure to others which may present a complex challenge to the patient. Current and previous sexual partners at risk will have been identified at the pre-test discussion stage and possible ways of informing these people will be explored with the counsellor. It is also important to discuss safer sex with those diagnosed with HIV. Pregnant women who test HIV positive need information and advice on the management of their pregnancy, including: options on reducing the risk of materno-fetal transmission, options for their own treatment and referral to specialist medical and counselling support. Although testing HIV positive is not a reason *per se* for seeking a termination of pregnancy, all women should be given the opportunity to discuss this if appropriate. Families may be a source of support but in many instances patients need time to come to terms with their diagnosis and to fully understand its implications before they have the capacity or resources to raise it with parents, siblings and/or loved ones who will inevitably be distressed. Being identified HIV positive may facilitate constructive planning for the future, such as deciding on the future welfare and care of children, although this tends to happen later in the counselling process when the early shock has resolved.

Counselling involves understanding a person in their social and familial contexts and many patients will derive crucial support and strengthening of coping mechanisms from this intervention during this vulnerable period. Counselling support can also help a patient engage in wider medical care and monitoring. If a person is inadequately prepared for the test, or a positive result is given inappropriately, he or she may reject further intervention including accessing medical care and therefore the likelihood of psychological morbidity and disease progression may be increased. It seems the "getting it right" for patients at early stages of diagnosis has a profound effect upon

Box 13.4 Counselling skills

- Empathy
- Non-judgemental approach
- Active listening
- Clear discussion and information giving
- Ability to establish working relationship with client
- Facilitating appropriate planning by the client
- Motivating appropriate self-care and reflective abilities

Box 13.5 Post Test Counselling – HIV Positive Result

IMMEDIATE FOLLOW-UP

- Time for "ventilation"
- Awareness of shock factor – keep information to a minimum
- Focus on coping today, tonight, next few days
- Who knows the patient is receiving the result today?
- Safer sex/Partners
- Arrangements for confirmatory HIV test
- Follow-up medical and counselling appointment
- Written information – support numbers

Box 13.6 Psychological issues in HIV/AIDS counselling

Shock

- of diagnosis
- recognition of mortality
- of loss of hope for the future

Fear and anxiety

- uncertain prognosis
- effects of medication and treatment/treatment failure
- of isolation and abandonment and social/sexual rejection
- of infecting others and being infected by them
- of partner's reaction

Depression

- in adjustment to living with a chronic viral condition
- over absence of a cure
- over limits imposed by possible ill health
- possible social, occupational and sexual rejection
- if treatment fails

Anger and frustration

- over becoming infected
- over new and involuntary health/lifestyle restrictions
- over incorporating demanding drug regimens, and possible side-effects, into daily life

Guilt

- interpreting HIV as a punishment; for example, for being gay or using drugs
- over anxiety caused to partner/family

their capacity to cope in the subsequent months and years, and to access help appropriately in later stages of disease.

The importance of encouraging and working towards coping strategies involving active participation (to the extent the patient can manage) in planning of care and in seeking appropriate social support has been demonstrated clinically and empirically. Such an approach includes encouraging problem solving, participation in decisions about their treatment and care, and emphasising self-worth and the potential for personal control over manageable issues in life.

Psychological responses to an HIV positive result

Many reactions to an HIV positive diagnosis are part of the normal and expected range of responses to news of a chronic, potentially life-threatening, medical condition. Many patients adjust extremely well with minimal intervention. Some will exhibit prolonged periods of distress, hostility or other behaviours which are difficult to manage in a clinical setting. It should be noted that serious psychological maladjustment may indicate pre-existing morbidity and will require psychological/psychiatric assessment and treatment. Depressed patients should always be assessed for suicidal ideation.

Effective management requires allowing time for the shock of the news to sink in; there may be a period of emotional "ventilation", including overt distress. The counsellor should provide an assurance of strict confidentiality and rehearse, over time, the solutions to practical problems such as who to tell, what needs to be said, discussion around safer sex practices and adherence to drug therapies. Clear information about medical and counselling follow-up should be given. Counselling may be of help for the patient's partner and other family members.

Counselling can also be offered to the patient and their partner together. This should only take place with the patient's explicit consent, but it may be important for the following reasons listed in Box 13.7.

Partners and family members sometimes have greater difficulty in coming to terms with the knowledge of HIV infection than the patients do themselves. Individual counselling support is often required to manage this, particularly role changes within the relationship, and other adjustment issues that may lead to difficulties. This is part of a holistic approach to the patient's overall health care.

In many cases the need for follow-up counselling may be episodic and this seems appropriate given the long-term nature of HIV infection and the different challenges a patient may be faced with. The number of counselling sessions required during any of these periods largely depends on the individual presentation of the patient and the clinical judgement of the counsellor.

Box 13.7 Advantages of counselling patient with their partner

- Adjustments to sexual behaviour and other lifestyle issues can be discussed and explained clearly to both.
- If the patient's partner is HIV negative (i.e. a serodiscordant couple) particular care and attention must be paid to emotional and sexual consequences in the relationship.
- Misconceptions about HIV transmission can be addressed and information on safer sex given.
- The partner's and the patient's psychological responses to the diagnoses or result, such as anxiety or depression, can be explained and placed in a manageable perspective.
- There may be particular issues for couples who have children or who are hoping to have children or where the woman is pregnant.

Box 13.8 Causes of uncertainty

- The cause of illness:
  - Progression of disease
  - Management of dying
  - Prognosis
  - Reactions of others (loved ones, employers, social networks)
- Effects of treatment
- Long-term impact of antiretroviral therapy
- Impact of disclosure and how this will be managed

The worried well

Patients known as the "worried well" present with multiple physical complaints which they interpret as sure evidence of their HIV infection. Typically, fears of infection reach obsessive proportions and frank obsessive and hypochondriacal states are often seen. This group shows a variety of characteristic features, and they are rarely reassured for more than a brief period after clinical or laboratory confirmation of the absence of HIV infection. A further referral for behavioural psychotherapy or psychiatric intervention may be indicated, rather than frequent repetition of HIV testing.

Box 13.9 Characteristics of the worried well

- Repeated negative HIV tests
- Low-risk sexual history, including covert and guilt-inducing sexual activity
- Poor post-adolescence sexual adjustment
- Social isolation
- Dependence in close relationships (if any)
- Multiple misinterpreted somatic features usually associated with undiagnosed viral or postviral states (not HIV) or anxiety or depression
- Psychiatric history and repeated consultation with general practitioners or physicians
- High levels of anxiety, depression and obsessional disturbance
- Increased potential for suicidal gestures

Linking with community and statutory agencies

Counselling and testing should never be provided without clear, working links with services for back-up and complementary management. Links with these services should be planned as an integral part of any HIV/AIDS counselling initiative from the outset. This is particularly important for patients from ethnic minority communities. Such links must be kept open and flexible to ensure that medical information and advice are consistent across all levels of intervention. Finally, the value of groups in HIV psychosocial and stress management is amply demonstrated. Groups are valuable in reducing an individual's sense of isolation, in providing a safe place to express feelings, to share experiences, and to learn successful coping styles from others, for example support groups for those who are newly diagnosed.

HIV counselling and combination antiretroviral therapy

Significant developments in combination antiretroviral therapy have led to a surge of optimism about long-term medical management of HIV infection and people are now living much longer with HIV. Patient adherence is an important factor in the efficacy of drug regimens. However, taking a complicated drug regimen – often taking large numbers of tablets several times a day – is a constant reminder of HIV infection. The presence of side-effects can often make patients feel more unwell than did the HIV and some may be unable to cope with the side-effects. Counselling may be an important tool in determining a realistic assessment of individual adherence and in supporting the complex adjustment to a daily routine of medication.

Discussions on safer sex are important, as drug-resistant HIV strains are emerging which limit treatment options for those acquiring such strains. Many patients diagnosed with HIV some years ago are now feeling well enough to return to work, to study and are, paradoxically, learning to readjust to living as they had formerly adjusted to the possibility of dying. Patients also have to deal with the uncertainty which remains about long-term efficacy of current medical treatment, and there are some who will fail on combination therapy. Even with the significant medical advances in patient management, counselling remains an integral part of the management of patients with HIV, their partners and family.

Box 13.10 Coping strategies

- Using counselling
- Problem solving
- Participation in discussions about treatment
- Using social and family networks
- Use of alternative therapies, for example relaxation techniques, massage
- Exploring individual potential for control over manageable issues
- Disclosure of HIV status and using support options

Box 13.11 Who is HIV and AIDS Counselling for?

- People worried that they might have HIV
- People considering being tested for HIV
- People who have been tested for HIV (both negative and positive)
- People unaware of the risks involved in behaviours that they are, or have been, engaged in
- People with HIV infection and disease, including AIDS
- People needing support with antiretroviral therapies
- People experiencing practical and emotional difficulties as a result of HIV infection
- Family/Partners/Friends of people with HIV/AIDS

14 Palliative care and pain control in HIV and AIDS

Rob George, Chris Farnham, Louise Schofield

This chapter looks at changes in the palliative care of HIV disease before offering practical guidelines in pain and symptom control and managing the days prior to death.

Managing uncertainty vs. managing death

HIV disease constantly challenged the acute/palliative interface with clinical constellations in which "curable" and palliative elements coexist. HAART (highly activated antiretroviral therapy) is the most recent example since which progression beyond "treatability" is less easy to discern. Similarly in cancer, palliative care's role now includes support early in the disease journey to help manage the uncertainties associated with toxic treatments as well as the worries about disability and mortality. Such psycho-emotional, spiritual and social fallout is beyond the capabilities of linear, curative medicine to manage. Palliative (symptom-based) and therapeutic (pathology-based) approaches are not mutually exclusive. The unifying concept of palliative care these days is the management of uncertainty and suffering, only part of which is care of the dying.

A challenging disease

Many patients with HIV/AIDS come from marginalised groups. Characteristically, these minorities take up services late or sit uneasily with conventional care because of different health beliefs or mistrust. Consequently, we cannot approach them all in the same way; neither can we assume what makes a good death nor what comprises a family or close social group. These are the practical realities of patient-centred care.

Flexibility, collaboration and support

Effective care for patients in whom deterioration or death is a real but fluctuating possibility also confronts us with the need to integrate care flexibly. Patients facing chronic ill health or those with acute, highly symptomatic disease may benefit from specialist advice or shared care as much as those may in the terminal phase of their illness. It is only by close collaboration between teams that good outcomes will be achieved. This brings us to our shared problem: that of uncertainty and the ways in which curative and palliative strategies coexist.

The therapeutic dilemma

When palliation is simply supporting aggressive curative therapy, there is no problem. However, when disease is progressive or debilitating, or where prophylactic and maintenance regimens maintain residual health, but compromise the quality of the patient's life, therapeutic decisions must take account of the burdens and benefits in personal as well as pathological terms. This is the idea that treatments may be futile not just by being ineffective, but also by being so destructive to quality of life that they may be worse than useless. Ethicists call this qualitative futility. In order for us to be of genuine benefit clinically, we must find effective ways of living in this tension between cost and benefit.

The quantity/quality equation

Balancing the costs and benefits of treatment formally and explicitly clarifies a patient's best interest, particularly as health

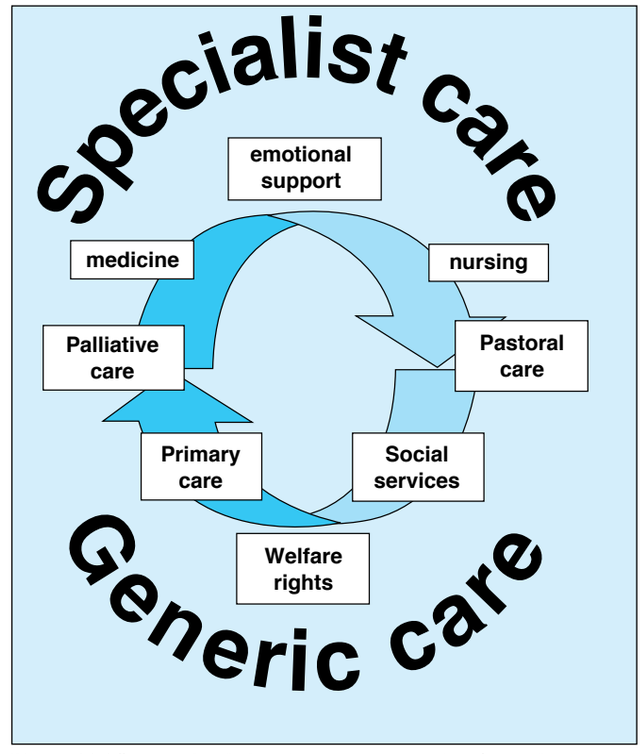


Figure 14.1 Inter- and multidisciplinary care: essential professional groupings necessary for effective supportive and palliative care

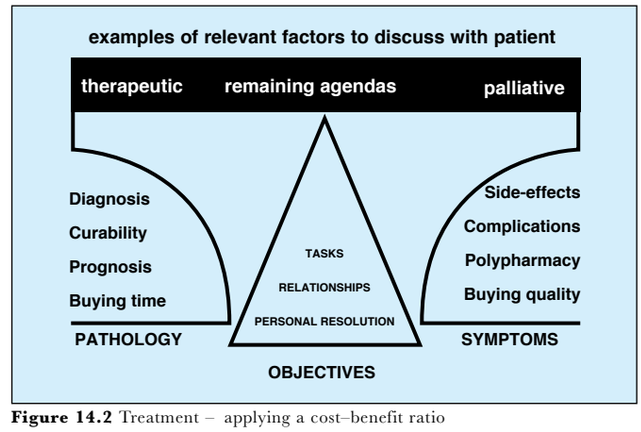


Figure 14.2 Treatment – applying a cost–benefit ratio

begins to fail. Certainties, such as time and energy expended on a course of treatment or immediate and short-term benefits etc. then become increasingly important.

Try not to make assumptions about a patient's views or wishes. The subtle ways in which illness and the individual interact mean that social, psychological and existential/spiritual elements may be every bit as relevant to symptomatology as the underlying pathology. Be sure to discuss these issues with the patient trusting that those not wanting to be involved in decision-making will let you know. Refer on for psychological or pastoral help if you need to.

Box 14.1 The essentials of partnership with patients

- The patient's priorities may be very different from yours
- Try not to make assumptions about a patient's views or wishes
- Quality of life generally, but not necessarily, becomes more important than the quantity as health wanes
- Be sure to discuss costs and benefits openly and in detail

Working with uncertainty

One of the greatest fears for the chronically sick or dying is helplessness. The more a patient and family feel their agendas, wishes and hopes are being taken seriously, the better able they are to cope.

Never make rash promises or be blindly optimistic about all treatments. Patients respond very negatively to hopes that are raised and dashed. Professional denial is the single most common cause of anger expressed by patients against doctors. Avoid presenting options as unchallengeable. There are ways to communicate boundaries or margins of our uncertainty to ensure that patients are informed. Don't forget, consent is a dynamic process.

Box 14.2 The patient is at the centre of decision-making

- Work in partnership with the patient and family
- Share responsibility for making decisions
- Maximise the patient's control over decision-making
- Work in a positive framework
- Agree specific tasks
- Set realistic goals
- Review regularly
- Remain open to creative options

Discussing prognosis

Open sharing of information inevitably leads to questions about prognosis. Always speak to individuals where they are able to express emotions openly. Never do it on an open ward. Include significant others if possible and invite another professional (for example, the key nurse), who can reinforce the discussion and offer support after you have gone. Patients and families need to "re-run" many times and characteristically will hear only the first and last thing that you say.

To gauge a patient's level of knowledge, anxiety or fear, explore their understanding of the situation by starting conversations in an open way, simply by asking what they think is going on or how they feel their disease is fairing.

When you talk about time, according to the stage of illness, break the future into tangible and appropriately small blocks of time such as one to three months. The intervals chosen will depend on each case. Confine your prognostication to this period and use general terms such as better, the same or worse.

Never give a finite prognosis. Always say that the unexpected may happen. If possible arrange to review the discussion to answer outstanding questions. This will also provide the opportunity to revise an opinion.

Box 14.3 Consent is a dynamic process

- Set goals and objectives with the patient.
- Revised them as regularly as necessary – clearly it would be stupid to review weekly when a patient's prognosis is years and equally unhelpful to give a patient a 2-month appointment when you expect them to die in a few weeks.
- Particularly, review aggressive treatment to reach a specific goal immediately that objective is met: a patient's wishes may alter radically as a result of success or failure.
- Be realistic, yet at the same time be prepared to allow a patient to risk things such as travel, provided they are well informed.
- Above all plan positively: people wish to live not to exist.

Box 14.4 Answering questions about prognosis

- Choose a "safe" place
- Include significant others and/or other professionals
- Explore the patient's understanding
- Be honest; don't collude with unrealistic hopes and don't be afraid to say "I don't know"
- Be kind; allow the patient to set the limits on the discussion when exploring painful truths
- Arrange a future contact

Summary

Palliative and curative care are inescapably entwined but changeable and good practice recognises the fluid involvement of different colleagues in care. Palliative care brings: ways of talking about and engaging uncertainty, looking at care planning and dealing with the ethical difficulties around consent and refusals and is valuable at any stage of illness. Palliative care workers should be called on when necessary, not just when you have run out of options and certainly not left until a patient is actually dying.

Symptom Control

General points

The significance of symptoms

Noxious and debilitating symptoms, and pain in particular, can destroy ones quality of life sufficiently to be significant risk

factors for depression and suicide irrespective of whether they are from a disease or its treatment. Symptom control is an essential part of curative treatments.

Interventions may not be conventional, for example using a drug for its side-effect rather than its accustomed indication (for example, opiates for breathlessness), or working psychologically with a patient's perceptions to alter a symptom's impact or its threshold. This idea of a symptom threshold or altering perception may be unfamiliar, but it holds the key to effective symptom control.

Thresholds

Symptoms only become problematical when a threshold is passed and one *perceives* there to be a problem. Anything that changes perception generally (fear, anxiety, etc.) can also alter symptomatology – information (bad news, unexpected deterioration, a new complication etc.) or feelings that are unwanted (fear of failing health, death, guilt, anger, bitterness, etc.) are all examples.

Non-medical symptom control

Equally, symptom thresholds can be raised by psychological interventions and measures that calm, allow patients to unwind or promote a coping mechanism. For example aromatherapy and other complementary therapies, meditation and prayer are effective for some. Massage and acupuncture have solid evidence to support their effects on musculoskeletal and myofascial pain, as do breathing exercises and respiratory pacing in breathlessness. Diet is obviously important in nausea, vomiting and bowel control.

Pain management

Pain is what the patient says it is. Leaving emotion and "soul" for the moment, pain can be classified in several different ways (Table 14.1). This is simplistic, but practical. Nociceptive pain is usually opiate sensitive and neuropathic pain is opioid resistant.

Evaluating pain

Over 90% of pains are controllable. All pain can be improved. Take a proper history and examine the patient to establish exactly what is going on.

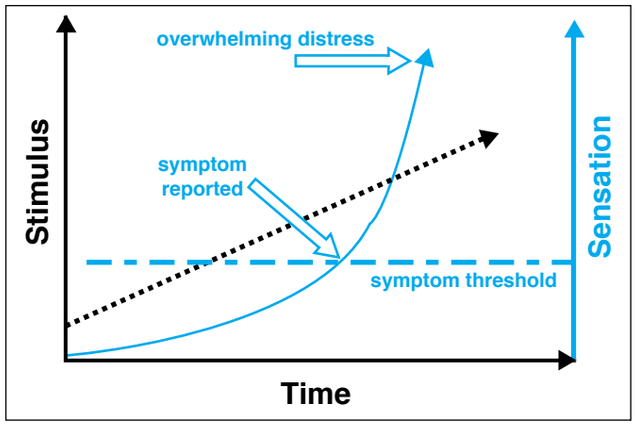


Figure 14.3 Sympton thresholds: the relationship between a noxious stimulus (for example, pain) and the reported symptom is exponential. Once past its threshold, without adequate treatment or a reduction in the process, the symptom will soon become intolerable. If the patient's threshold falls, the symptom will escalate in the same way, even when the underlying disease is stable

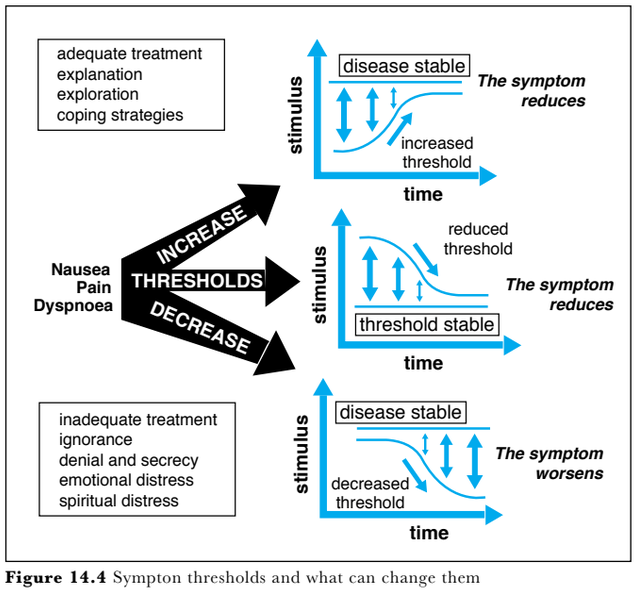


Figure 14.4 Sympton thresholds and what can change them

Table 14.1 Classification of pain

Location	"Source"		Opioid (morphine) Responsiveness			Anti-inflammatory
	Nociceptive	Neuropathic	Full	Partial	Resistant	
Visceral eg liver, bowel, myocardium, pleura	✔ ✔		✔ ✔			✗ (unless from lymph nodes)
Somatic for example, soft tissues damage, inflammatory diseases		✔ ✔		✔ ✔	✔	✔ ✔
Bone pain for example, metastases, infarction	✔ ✔	✔	✔ ✔	✔		✔ ✔
Root irritation for example, compression, inflammation		✔	✔ ✔		✔	✔ ✔ ✔ ✔
Peripheral neuropathy, cord pathology		✔ ✔			✔ ✔	

Table 14.2 Drugs used in pain management

Weaker opioids	Strong opioids	Co-analgesics	Non-opioids
DHC	Oramorph	Anaesthetic agents	Muscle relaxants
Codeine	Diamorphine	Anti-convulsants	NSAIDs
Tramadol (?)	Hydromorphone	Anxiolytics	Paracetamol
Co-proxamol	Fentanyl	Corticosteroids	COX_2 inhibitors
Oxycodone (also used as strong opioid)	Dextromoramide	Tricyclic antidepressants	
	Dipiponone		

To be able to monitor the pain it must be recorded accurately. Use body charts to localise the pain and get an estimate of each element of the pain by asking to score or grade the pain as a score out of 10 for intensity (0 = no pain, 10 = the worst pain you could imagine). This will help in monitoring treatment, but it will also give the patient a sense that pain is not fixed and can improve.

Box 14.5 Fundamentals of pain management

- Any pain, however generated, is a genuine symptom
- Always assume that there is a physical trigger, until proven otherwise
- The vast majority of patients have a combination of pain types
- The correct dose of an analgesic is that which relieves the pain

Opiates and nociceptive pain

Nociceptive pain is managed by using the World Health Organization (WHO) analgesic ladder. Over 90% of such pains are controllable in this way.

When prescribing *any* opiate, nearly all patients need a laxative and nearly 50% need an antiemetic.

Bottom rung: Paracetamol influences other drug's metabolism. However, in general, palliative physicians use doses up to 6 g a day. Similarly gastrointestinal complications (with appropriate prophylaxis) or renal impairment with NSAIDs are not absolute contraindications in patients with a short prognosis and severe pain.

Middle rung: The weak opiates, or compound analgesics (co-codamol, co-dydramol, etc.), may be helpful for mild to moderate pain. Formulations differ slightly in efficacy and prescribing is empirical. Low-dose strong opioid can be used. Dependency is less than 0.1%.

Upper rung: Many strong opiates are available. Morphine is the drug of choice by mouth. Use other opioids *only* where there is a specific problem with morphine. Alternatively using co-analgesics may reduce side-effects.

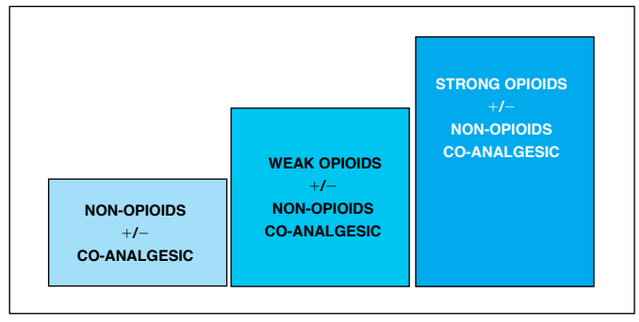


Figure 14.5 The WHO analgesic ladder

Box 14.6 Morphine facts

- Dose range is 1000-fold, (2.5 mg 4-hourly to 2.5 g 4-hourly or more)
- Most patients require less than 200 mg morphine equivalent per day
- It is not addictive when used therapeutically

Box 14.7 Opioid side effects

- *Nausea and vomiting – dose related*
- *Constipation – may be desirable, dose related*
  Peripheral effect
  Always prescribe laxatives
- *Clouding of consciousness – hallucinations rare*
  Central effect, fades with time
  Warn the patient of initial drowsiness
- *Respiratory depression – good for dyspnoea*
  Central + peripheral cough suppression
  Pain has a partially protective effect
  Increase dose carefully where chronic lung disease present
- *Itch – histamine release*

Opiate toxicity

Toxicity is idiosyncratic and dose dependent. For some the therapeutic window may be very small. In poorly controlled pain (usually non-opioid responsive), escalating doses may lead to toxicity: confusion, hallucinations, agitation and myoclonic jerks. Paradoxical pain (loss of analgesia and increasing pain) may occur.

Confusion in the dying is complex and increasing opiates is not the only solution to increasing pain. You may need to stop all opiates until symptoms have subsided. *Seek the advice of an expert*

Box 14.8 Dealing with opiate toxicity

- The half-life of morphine and diamorphine is four hours
- Respiratory rates down to 5 or 10 are acceptable for a few hours
- Central effects can be antagonised, but will lead to rebound agitation and hyperresponsiveness
- It is best simply to stop the opiate and wait
- *In extremis:* naloxone is the specific antidote and reverses all the actions of opiates. Use very small doses
- Physostigmine can be used to selectively antagonise respiratory depression

Good prescribing

Opioid responsive pain can normally be controlled within 24–48 hours. Morphine should be titrated using immediate-release formulations (Oramorph elixir, Sevredol tablets). Their effect peaks within the hour and last four hours. Titrate with a four-hourly regimen with "top-ups" for breakthrough pain of *25–50%* dose and a *25–50%* increase in the next scheduled dose as necessary. In individuals with hepatic or renal impairment the increases should proceed more slowly. Slow-release preparations (for example, MST b.d. or MXL o.d.) are best for maintenance. Immediate release formulations should continue to be available for breakthrough pain at a dose at least one-sixth the final 24-hour dose.

Box 14.9 Prescribing for nociceptive pain

- By the ladder:
  Don't forget that co-analgesics and non-opioids should be added to what you already use
- By the clock:
  NEVER use prn pain control for example, 4-hourly for morphine liquid, 12-hourly for MST
- By the right route:
  Use the mouth where possible, parenteral drug is no more effective

Opioid non-responsive pain

Neuropathic pain: Drugs affecting nerve conduction or central processing usually work. Regimens are empirical as the numbers needed to treat (NTTs) between groups are similar; benefit may take several days to gain; neuropathic analgesics have significant side-effects and dose increases should be made slowly. Patient, family and staff may need support in keeping a steady hand whilst the best combinations are found.

Intractable cases or root or cord problems (for example, CMV) may need a nerve block or long-term epidural. Many different techniques are available. They carry potential morbidity, so use cost–benefit analysis with the patient to decide a plan. Do not make choices on behalf of the patient; immobility and incontinence free of pain may be a valid choice.

Compound pains: Many patients have pain from tissue damage and the nervous system simultaneously. Their treatment requires accurate diagnosis and specific co-analgesics. Morphine may play a part in their management. To read more on this see Further reading on page 95. Make a habit of enlisting specialist support with neuropathic and compound pains.

Total body pain and suffering

This is the difficult area of suffering and the subtle interactions of our psyche, beliefs and body. Some people use the terms "soul", spiritual, or "emotional" pain. It is complex, distressing and very real (Fig 14.6). It stems out of a lowered threshold of distress and may occur with other symptoms as well. For understandable reasons, there is always an element of this in any dying person as they process and face their death and what it means. Fear and guilt are the common roots for many. Don't forget, *paene* (punishment) is the Latin root of pain.

Box 14.10 Neuropathic pain

- Generated in nervous system
- Source can be local nerve to thalamus
- Caused by:
  - Toxins for example, chemotherapy
  - Invasion/compression, for example, by tumour
  - Damage by viruses for example, HSV, CMV, HIV
  - Demyelination of any kind
  - Often coexists with nociceptive pain
  - May not present with classical dysaesthesia
- Seldom opioid responsive

Box 14.11 Neuropathic analgesics

- *Tricyclic antidepressants:*
  - Lofepramine (70 mg 1–3 times/day) or Amitriptylline (10–150 mg nocte +/– day time doses)
- *Anticonvulsants:*
  - Gabapentin (start dose of 300 mg up to 2700 mg)
  - Carbamazepine (100 mg b.d. up to 1600 mg per day),
  - Valproate (ranging from 200 mg to1200 mg per day)
  - Phenytoin (up to 300 mg per day).
- *Benzodiazepines:*
  - Clonazepam (0.5–4 mg nocte),
  - Diazepam, midazolam (parentally)
- *Membrane stabilisers:*
  - Flecainide (100–200 mg b.d.),
  - Lidocaine (lignocaine) (subcutaneous or i.v. infusion in doses of 0.5–2 mg/kg/h)
- *Others:*
  - Clonidine, octreotide, etc. seek advice

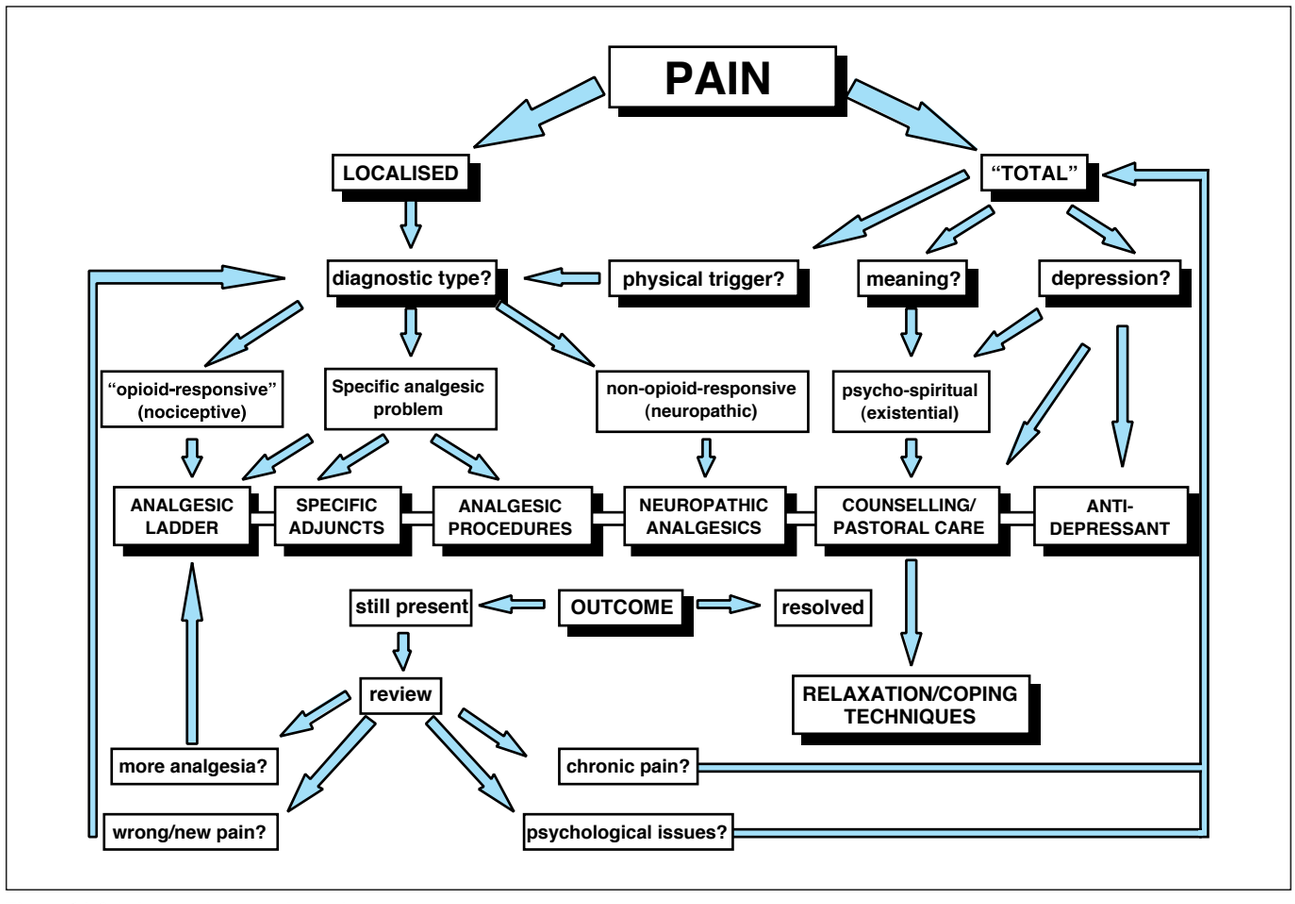


Figure 14.6 A therapeutic approach to pain

Effective management requires one to deal not only with any physical component, but also with the meaning of the symptomatology and the exacerbating effects of fear, anxiety, sleeplessness, loss of future, and of death and its connotations for the individual. In this difficult area do not be afraid to refer for help from a counsellor, psychologist or spiritual adviser.

Nausea and vomiting

These are the second most common symptoms, not least because of the burgeoning numbers of drugs that have gastrointestial side-effects. Careful assessment should ensure a logical and methodical use of antiemetics.

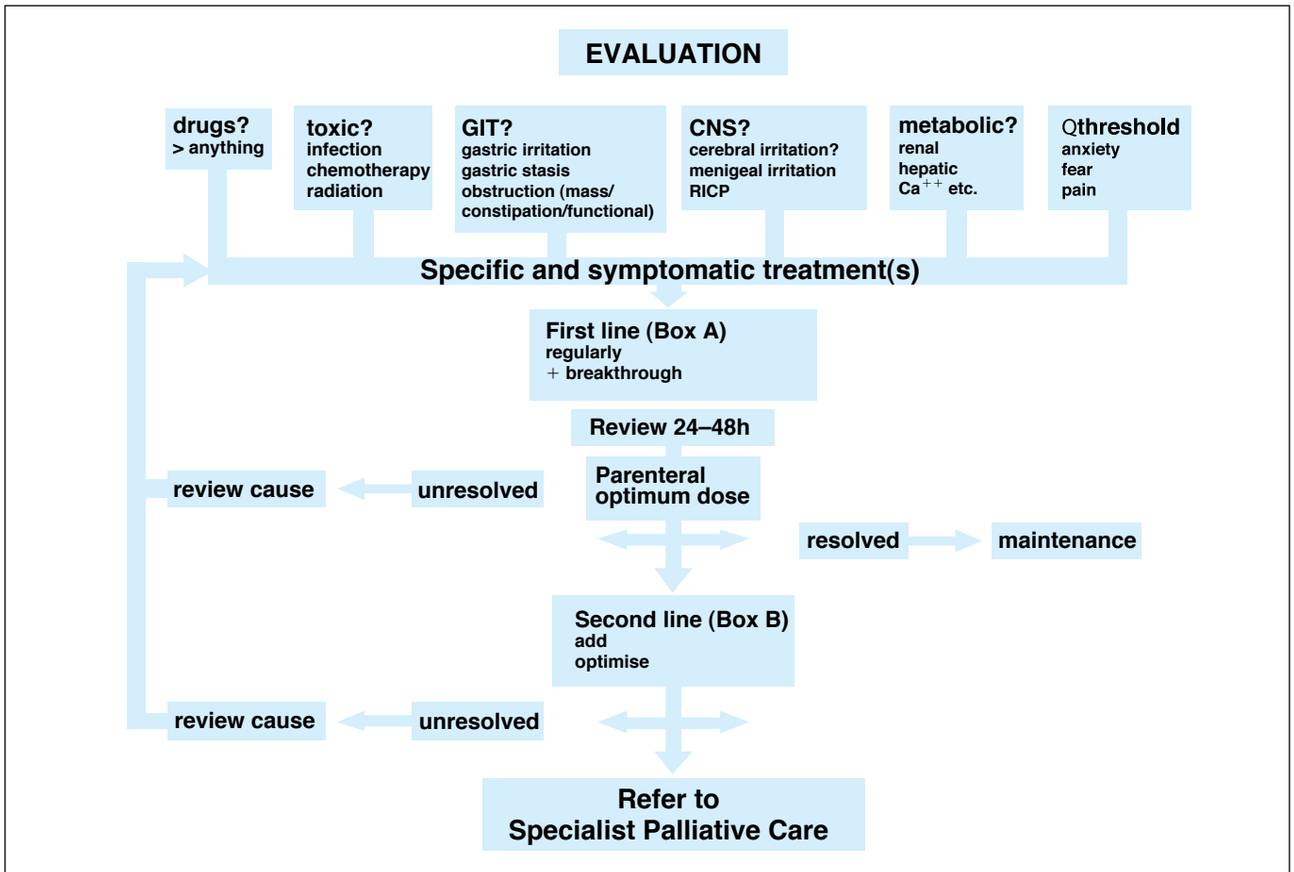
General guidelines

Nausea and vomiting is usually "uncontrolled" because of erratic and illogical prescribing in inadequate doses given orally. These guidelines are therefore common sense, but necessary.

Assess nausea and vomiting separately. Nausea tends not to respond to prokinetics. Treat any potentially reversible causes and stop emetogenic drugs if possible. Anxiety exacerbates nausea and vomiting and may need specific treatment.

Box 14.12 Logical and methodical use of antiemetics

- One-third of patients require more than one antiemetic for satisfactory control
- Select the most appropriate drug for the putative cause
- Use regularly, at optimum dose
- Have a low threshold for parenteral routes
- Careful re-evaluation on a regular basis
- Use adjuvant drugs such as corticosteroids and antisecretory drugs



Box A First-line antiemetics

Prokinetic (gastric stasis, functional obstruction)
Metoclopramide 10 mg stat., then 10 mg t.d.s. or 30–60 mg/24h via subcut. infusion (n.b. inactivated by muscarinic drugs)
Vomiting Centre (RICP, motion, mechanical obstruction)
Cyclizine 50 mg p.o./s.c./i.v. stat then 50 mg p.o. t.d.s. or 150 mg/24h via subcut. infusion
Hyoscine hydrobromide as patch 500 mg/72h
5HT$_3$ Antagonists (metabolic, drugs, radiation, gut distension)
Granisetron 1–3 mg p.o./i.v. stat and b.d. or 9 mg/24 h via subcut. infusion

Box B Second-line antiemetics

Broad spectrum
Methotrimeprazine 6.25 mg stat 12.5–25 mg/24h via infusion
Dexamethasone 4–8 mg daily as one dose mane
Prokinetic:
Cisapride 20 mg p.o. stat and b.d.
Antisecretory drugs:
Hyoscine butylbromide 20 mg s.c. stat and 60–120 mg/24h
Octreotide 100 mg stat and t.d.s. or 300–600 mg/24h via infusion
Cannabinoids:
Nabilone 1–2 mg b.d.

Figure 14.7 Guidelines for pain evaluation

Prescribe the most appropriate first-line antiemetic for the likely cause according to the figure. Prescribe both regularly and as required. If the patient is vomiting, or has been nauseous for some time administer parenterally, preferably by continuous subcutaneous or intravenous infusion preceded by a stat dose. Optimise the dose daily taking into account breakthrough doses and reported level of nausea and vomiting.

If there is no improvement, rather than changing the drug, optimise the dose, and re-evaluate the cause. It may influence your drug choice. After 48 hours, substitute or add an appropriate second-line, broader spectrum antiemetic. A significant minority of patients need more than one antiemetic. Consider non-drug treatments, including acupressure bands, control malodour, and ensure patient avoids foods that may precipitate nausea. If control remains poor, then refer. Only consider converting to equivalent oral regimen after 72 hours of good control and continue antiemetics indefinitely unless the cause is self limiting.

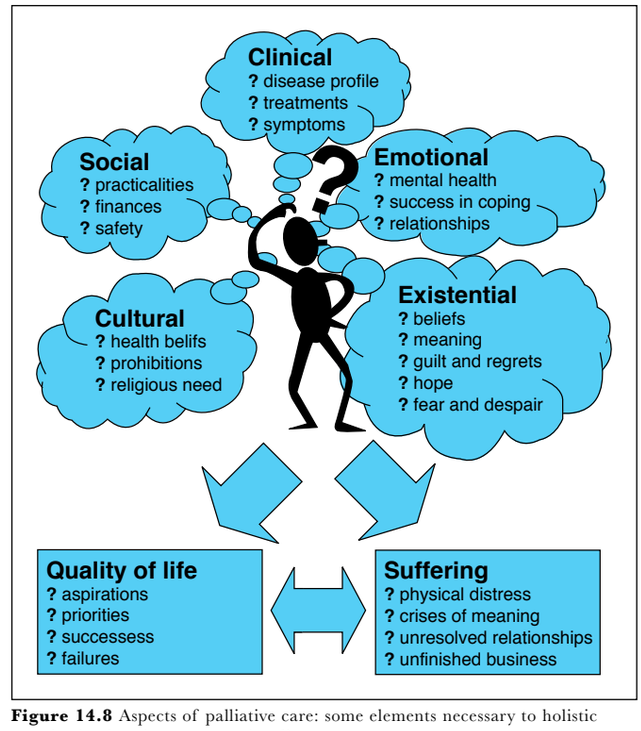


Figure 14.8 Aspects of palliative care: some elements necessary to holistic practice in chronic or progressive disease

Other common symptoms

Other common symptoms are cognitive impairment, weight loss, malaise, weakness, pruritis, cough, diarrhoea, etc. Their differential diagnosis and appropriate investigations and management are covered more widely in the *ABC of Palliative Care*.

Death and dying

When treatment is futile, persevering with treatment and investigation can be obstructive in allowing a patient a dignified and meaningful death. The patient should be at the centre of the decision-making process as much as is possible. It is at this time that the multiprofessional team is so important.

Facilitating choice

If you have been managing your patients properly and involving them in decision-making, the groundwork for managing the last weeks or months should have been done, you will have a good enough relationship to be honest and open and to finish these last preparations. If you have not faced these with your patient in some form, even by flagging that "a time will come…" whilst not failing them as a technician, you will have failed as a doctor. This is the time to check regularly about a patient's wishes. Proper links and services from primary care and social services are essential and friends, family and professionals should be as much "in the know" as possible.

Box 14.13 Preparing for death

- Do they want active treatment if they deteriorate? If so, what level of resuscitation do they want? Is there a time or circumstances in which they wish treatment to be withdrawn or withheld?
- Will they feel more in control if these are written formally? A 'Living Will' or Advance Directive can be of great help to some patients by ensuring that their wishes are known if they become incapable. (See the BMA guidelines "Advance Statements: a guidance to practitioners".)
- Have they said their goodbyes, sorrys and thank yous?
- Are there remaining personal matters to address: a will, funeral preparations, etc?
- Do they want to be at home? If so, is it suitable?

Two additional symptoms

Movement-related pain

This is a common problem in dying patients with HIV and is best managed with NSAIDs. If the patient cannot swallow, then rectal indometacin is very effective.

Pulmonary secretions

Retained secretions in patients too weak to clear them can be controlled with hyoscine 0.6–1.2 mg s.c. over 24 h or glycopyrronium 0.6–1.2 mg s.c. over 24 hours. If they fail to clear, use furosemide (frusemide). Reassure family that noisy breathing of itself is not distressing to the patient.

As death approaches

In the last days of life, pragmatism and sensitivity are essential. Patients have no appetite, are weak and somnolent or unconscious. Altered breathing patterns can last for days. Be calm and reassuring: relieve anxiety for both patient and carers by explanation that these changes are normal and don't cause physical suffering, which is true.

Most importantly continue to visit. The clinical situation can change very quickly. Assess symptoms regularly and change palliative therapeutics as necessary (even several times a day). As swallowing becomes difficult swap to parenteral routes. Most drugs for symptom control can be given continuously via a syringe driver subcutaneously. (Drugs can be mixed, see the charts in Twycross *et al.* 1998.) Figure 14.5 summarises management in the last few days of life.

With the limited communication, problems may manifest themselves as pre-terminal restlessness or distress. Possible physical and psychological/spiritual triggers need to be checked and acted on.

In general encourage the family to talk normally to the patient and to say whatever they need to say. Reassure them that the patient can hear and continue to explain all that you do to the patient and chat normally through procedures. This period of life, when the dying process is actively underway, may be short lived or take many days. In most cases we do not know what is taking place. Where beliefs are unknown or unfamiliar it is best presented neutrally as a time of transition; when our place is to care.

Box 14.14 Pre-terminal restlessness

- Exclude urinary retention
- Treat any suspected pain
- Check that there is not an important visitor that the patient must see or hear
- Check for an important date or anniversary
- Exclude any important religious rite
- Sedate as necessary; midazolam (starting at 10 mg/24 h), levomepromazine (12.5–300 mg/24 h).

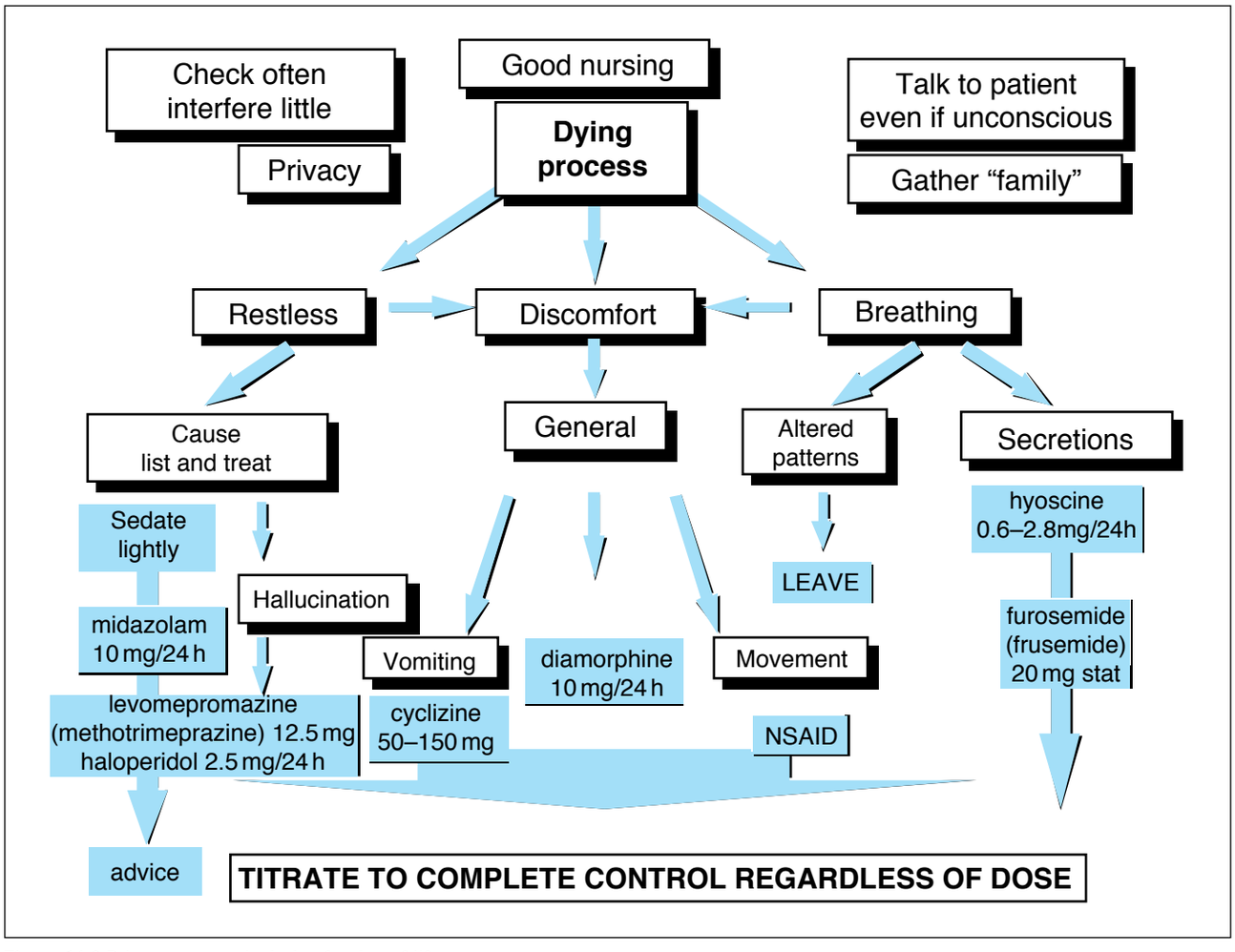


Figure 14.9 Pain management in the last few days of life

It is important to allow those with religious beliefs the opportunity to see their advisors and perform necessary rituals as they wish. This can often lead to conflict if partners and family are of differing opinions. Give time to friends and family to spend talking over what has happened. Obviously you must be aware of the dynamics of the group and you must respect the patient's confidentiality.

Finally, a death affects us and the team involved. Debriefings and supervision work either individually or as a team can be most beneficial.

Further reading

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15 Control of infection policies

IJ Hart, Celia Aitken

Intensive epidemiological studies of HIV infection have shown that it is not transmitted in the community by casual or intimate non-sexual contact.

As of December 1999 there have been 96 documented instances of confirmed occupational transmission of HIV. There have been, in addition, 171 cases of HIV infection, possibly resulting from occupational transmission in exposed individuals with no other known risk of infection. The rate of transmission after a single percutaneous exposure to HIV positive material is 0.32% (21 confirmed infections after 6498 exposures in 25 studies). The risk of infection after exposure of mucous membranes and/or conjunctivae to infected material is 0.03% (one confirmed infection after 2885 exposures in 21 studies).

It is important to design infection control policies which, while protecting staff against the risk of fection, do not compromise medical and dental care. HIV is one of several blood-borne viruses; carriers of these viruses may be perfectly well and individuals may be unaware that they are infected. Some, including the hepatitis viruses B and C, are potentially more infectious than HIV. Thus, healthcare workers and society in general need to adjust to the concept that direct contact with the blood of others may present a potential, albeit low, risk of infection.

In the UK the Department of Health and many other bodies have issued guidelines to educate and protect healthcare and community workers. Routine HIV screening of antenatal patients is now recommended, and testing of all those at risk is encouraged. Awareness of the risks, education, careful attention to work practices, provision of protective equipment and immunisation against hepatitis B, where appropriate, are measures which will reduce to a minimum the risk of infection with all blood-borne viruses.

Box 15.1 Selected guidelines

- United Kingdom Health Departments. *Guidance for clinical health care workers: protection against infection with blood borne viruses. Recommendations of the Expert Advisory Group on AIDS.* London: HMSO, March 1998
- *A code of practice for sterilisation of instruments and control of cross infection.* London: British Medical Association, June 1989
- *The safe disposal of clinical waste.* London: HMSO, 1992
- United Kingdom Health Departments. AIDS/HIV infected health care workers. *Guidance on the management of infected health care workers and patient notification. Recommendations of the Expert Advisory Group on AIDS.* London: DOH, March 1998
- Advisory Committee on Dangerous Pathogens. *Protection against blood borne infections in the workplace: HIV and hepatitis.* London, HMSO, 1995
- Royal College of Pathologists. *HIV and the practice of pathology.* London: Marks & Spencer Publication Unit of the Royal College of Pathologists, July 1995
- United Kingdom Health Departments. *HIV post exposure prophylaxis: Guidance for the UK Chief Medical Officers Expert Advisory Group on AIDS, July 2000.*
- General Medical Council. *Serious communicable diseases.* London: HMSO, 1997

Hospital care

HIV positivity *per se* is not an indication for isolating a patient in hospital. It may be necessary to consider source isolation, however, if there is evidence of active infection with other agents, such as *Mycobacterium tuberculosis*, varicella-zoster virus, or if there is a likelihood of extensive exposure to body fluids from, for example, haemorrhage or severe diarrhoea.

Medical practices should be of a sufficiently high standard to eliminate any risk of patient-to-patient spread of HIV in hospital. This is achieved, as part of general infection control procedures, by using disposables, and by paying careful attention to decontamination and sterilisation. Attempts to recycle disposables or to bypass accepted disinfection procedures may lead to nosocomial infection.

Staff should adopt sensible precautions if contamination with blood or other body fluids is likely. This applies particularly for the management of known virus carriers but should also be the routine for any patient. The concept of "universal precautions" for all patients is being introduced increasingly into healthcare. In most cases precautions entail no more than wearing disposable gloves and an apron, but in certain circumstances, such as bronchoscopy, protective spectacles and a mask may be necessary to protect the eyes and mouth. Most aspects of patient care and examination do not

Figure 15.1 Bronchoscopy in a patient infected with HIV

expose the staff to body fluids, and protective clothing is not required.

Many staff sustain inoculation injuries while manipulating needles and sharp instruments. Education and careful attention to technique will reduce the risks to a minimum. No attempt should be made to resheathe needles unless a safe resheathing device is available, and needles should be placed immediately into safe sharps disposal containers, which should not be overfilled.

Although there is little epidemiological evidence of increased risk, many hospitals assume that special care should be taken during surgery on known or suspected HIV carriers. This usually means adopting pre-existing policies for hepatitis B carriers and may include the introduction of double-gloving and additional protective clothing. Preventing unnecessary exposure to body fluids and trying to reduce the incidence of penetrating injuries to a minimum are the best defence against infections, which may be present, but unsuspected, in any patient.

Reports of transmission of HIV from a dentist to his patients have raised public concerns about the risks of acquiring HIV and other blood-borne viruses from healthcare workers. Guidelines produced by the UK Health Departments identify work practices known as "exposure-prone invasive procedures" as aspects of medical care that present a potential risk of transfer of a blood-borne virus from healthcare workers to patients.

Exposure-prone procedures are those where there is a risk that injury to the worker may result in the exposure of the patient's open tissue to the blood of the worker. These procedures include those where the worker's gloved hands may be in contact with sharp instruments, needle tips or sharp tissues (spicules of bone or teeth) inside a patient's open body cavity, wound or confined anatomical space where the hands or fingertips may not be completely visible at all times.

Healthcare workers who are HIV positive or HbeAg positive carriers of hepatitis B are excluded from exposure prone procedures. HbeAb positive carriers are excluded if there is $>10^3$ copies/ml of HBV DNA in their blood. There are many reports of hepatitis B transmission from staff to patients but only one report of HIV transmission from a surgeon to one of his patients during orthopaedic surgery. The risk of HCV transmission from staff to patient is still not known but may be higher than previously thought. Clearly, the risks to the patient from HIV in health care workers are extremely low but the frequency of inoculation injury to the surgeon during the course of major surgery highlights the need for continued surveillance.

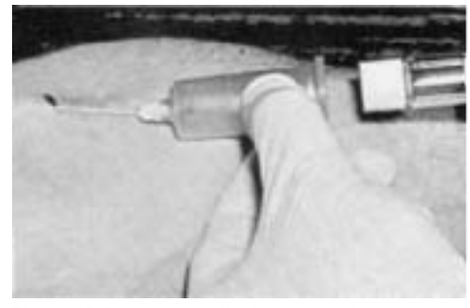


Figure 15.2 A vacuum collection system of the type shown reduces the risk of spillage when large volumes of blood are required

Sharps disposal

Clinical laboratory staff are at risk from certain pathogens which may be present in specimens. The Advisory Committee on Dangerous Pathogens originally produced specific guidelines for work on samples from HIV positive patients. These have now been reissued to encompass potential risks from all blood-borne viruses. The most important aspects of safety in the laboratory are education, training, and prevention of inoculation and skin contact with body fluids. It is important to review all laboratory procedures to reduce the use of needles and the danger of exposure to glass fragments. This may necessitate increased investment in automatic pipetting systems to replace the need for glass pipettes. The absence of evidence of airborne transmission means that HIV positive samples may be handled on the open bench providing the work is conducted in optimal facilities and the operator is free from distraction and

Figure 15.3 Safe sharps disposal

disturbance. The current practice of alerting laboratory staff to samples from known or suspected HIV positive patients by the use of biohazard stickers may be defended on the basis that it reduces risks. It must, however, be emphasised constantly that in the present epidemic no unfixed specimens can be considered free from infection.

Community aspects

HIV carriers m the community present no risk to others from normal day-to-day contact. The combined effects of dilution, temperature and detergent action ensure that standard washing procedures will satisfactorily decontaminate cutlery, crockery and clothing. All blood spillages should be decontaminated with hypochlorite (bleach) and carefully cleaned up. The absence of evidence that saliva can transmit HIV means that nobody should withhold mouth-to-mouth resuscitation from someone who has suffered a respiratory arrest. Members of the rescue services who frequently carry out resuscitation, often in cases in which facial injury exposes them to blood as well as saliva, are provided with masks and other devices. Anyone attempting to use a resuscitation device must be adequately trained as, in the wrong hands, it may prejudice the life of the casualty and in some cases increase the potential risks to the operator by causing bleeding.

Disinfection

An important method of reducing the potential infectivity of viruses is dilution. Thus procedures such as thorough cleaning and handwashing are central to any infection control policy and must never be neglected. HIV has been described as a fragile virus, and this is true to an extent. Although it is effectively inactivated by many different agents, survival of virus may be prolonged at ambient temperatures, and infectious virus may still be present in dried blood after a week. This means that any surfaces and fomites that have been in contact with clinical material must be decontaminated.

The trend towards the use of disposables reduces the need for decontamination in many areas. Thorough cleaning followed by heat sterilisation should be adopted, if at all possible, for any reusable equipment. Although HIV is inactivated by boiling, autoclaving has become the norm in clinical practice. With increasing numbers of HIV carriers in the community it is important for their protection to ensure that instruments are rendered free of all organisms, including bacterial and fungal spores. Organisms that may present no risk to people with normal immunity may lead to opportunistic infections if they are immunocompromised by HIV infection or other agents such as chemotherapeutic drugs.

Liquid disinfectants must always be considered a poor alternative to heat sterilisation. Difficulties exist controlling their potency, most are caustic, and most are rapidly inactivated by organic matter. For hospital or community use, if it is necessary to use a liquid disinfectant, it is sensible to choose one which is known to inactivate hepatitis B and other pathogens such as *Mycobacterium tuberculosis*, as well as HIV.

All waste that is contaminated with blood must be considered potentially infective and treated as "clinical waste" in accordance with the Health Services Advisory Committee's document "The safe disposal of clinical waste". Sharps containers must meet Department of Health specifications and must be incinerated before disposal.

Box 15.2 Community aspects of decontamination

- Cutlery, crockery, clothing
  decontaminated by normal washing
- Decontaminate blood spillages with bleach (hypochlorite)

Figure 15.4 Secure bagging for specimen and request sent to laboratory

Box 15.3 Disinfection

- Autoclave or use disposables if possible
- Hypochlorite (1000 ppm available chlorine) for general decontamination
- Hypochlorite (10 000 ppm available chlorine) if organic matter, including blood, present
- 2% Glutaraldehyde (freshly activated) NB: Beware of dangerous fumes

First aid and inoculation injuries

In the event of exposure to blood, simple first-aid measures should be applied immediately. Any blood or other body fluids on the skin should be washed away with soap and water. Splashes into the mouth or eye should be diluted by washing, and sterile eyewash bottles should be provided in any areas where this is likely to occur. A skin puncture should be encouraged to bleed in an attempt to express any material deposited in the wound. The wound should then be washed thoroughly. Any injury to a member of staff should be reported immediately to the person in charge and then to the occupational health physician or other medical adviser. In hospital this allows for the opportunity to investigate the state of health of the person inoculated and, if necessary, to take protective measures such as hepatitis B prophylaxis or antibiotic cover, or testing the source patient or the use of antiretroviral drugs. At present the recommended drugs for postexposure prophylaxis are zidovudine, lamivudine and indinavir. They should be taken for four weeks. An acceptable recommended alternative regimen is the use of nelfinavir instead of idinavir. However, allowances for pregnancy, drug interactions and potential antiviral resistance in the source may result in some modification to the final regimen. In these circumstances expert advice should be sought. The medical adviser should discuss whether blood samples should be taken for future reference of HIV testing and whether a programme of follow-up consultations should be started.

The medical adviser will need to obtain information about the source patient concerning possible indicators of HIV infection, including risk factors and results of previous HIV tests, medical history suggestive of HIV infection, and details of past and current antiretroviral therapy in patients known to be HIV infected. The source patient should be asked to consent to testing for HIV infection. This will entail pre-test discussion and obtaining fully informed consent. If the patient is unconscious when the injury occurs consent should be sought once the patient has regained full consciousness. If the patient refuses testing, is unable to give consent because of mental illness or disability, or does not regain full consciousness within 48 hours, testing should be considered in exceptional circumstances only, such as where there is good reason to think that the patient may be HIV infected. In this case testing an existing blood sample for HIV infection may be done but only after consultation with an experienced colleague. The decision to test may be challenged in courts so be prepared to justify the decision. Only the source patient and those exposed to the infection may be told the result of the test and the result can only be entered into the patient's personal medical record with the patient's consent. If the patient dies HIV testing can be done if there is good reason to think the source patient may be infected. It is usual to seek the agreement of a relative before testing.

Those concerned with counselling people who have sustained inoculation injuries should have enough knowledge to provide current information about the risks of occupational exposure and should be able to advise on changes in lifestyle such as the adoption of safer sex practices.

In summary, the risk of transmission of HIV within hospitals and to carers in the community is low. Education of staff, good infection control procedures and safe working practices can help to minimise this risk. Due attention to these measures at all times will ensure the protection of patients and staff.

Box 15.4 First aid

- Body fluids on skin, in eyes, or in mouth
  - wash away immediately
- Penetrating wounds
  - encourage bleeding
  - wash with soap and water
  - report to the supervisor and medical officer

16 Strategies for prevention

John Imrie, Anne M Johnson

Introduction

Limiting the spread of HIV relies on health promotion activities to encourage and help sustain behavioural changes that reduce the risk of acquiring or transmitting the virus. Despite advances, the prospect of a widely available effective vaccine remains some distance off and behavioural interventions are likely to remain the backbone of HIV prevention for the foreseeable future. Appropriate prevention strategies are required in both developed and developing country settings and must be specific to the cultural, epidemiological and socio-economic environment of each country. This chapter focuses on HIV prevention strategies in the UK although some of the principles outlined are generalisable to other countries (chapter 10). This chapter deals with sexual and parenteral transmission of HIV. The prevention of perinatal transmission is addressed in chapter 12.

General health education

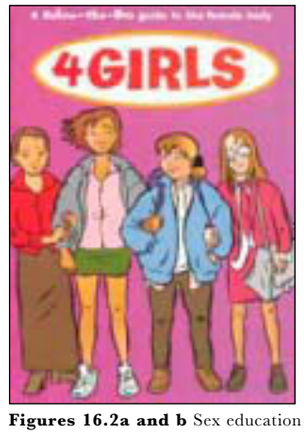
Government information campaigns and media attention in the 1980s raised the general public awareness of HIV/AIDS. Knowledge of transmission routes and risk reduction strategies (for example, condom use and reducing partner numbers) remains high, although public campaigns for HIV risk-reduction no longer have the same profile in the UK. Recent increases in sexually transmitted infections (STI) (for example, chlamydia and gonorrhoea) and high teenage pregnancy rates indicate that safer sexual practises are not consistent among young people. Age at first intercourse continues to decline and while there is some evidence of increased condom use in many countries, there has been little change in the numbers of people reporting multiple sexual partners. Those at greatest risk of poor sexual health outcomes are men who have sex with men, the under 25s, injecting drug users and their partners, inner city populations and some ethnic minority populations

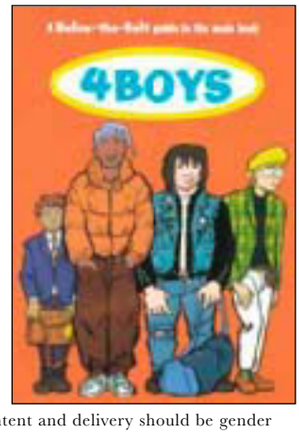
Epidemiological data show an increasing trend in the number of heterosexually acquired HIV infections diagnosed in many developed countries. In the UK in 1999, for the first time the number of newly diagnosed HIV infections acquired hetrosexually exceeded those acquired through sex between men. However the majority of heterosexually acquired infections in the UK remains among those with sexual partners in Africa (chapter 1).

These trends indicate the continued importance of general health education strategies for HIV prevention and sexual health promotion. Prevention messages can be delivered in many different settings, ranging from mass media, school sex education, community and youth organisations, through individual interventions in primary care, contraception services and specialist STD services. All health professionals can provide practical information and personally tailored messages to individuals.

Given the particular risk among young people, education for HIV prevention needs to take place in the broader context of sexual health education in schools, before young people become sexually active, as part of Personal Health and Social Education (PHSE). To remain effective over time, however, school-based sexual health and general HIV education strategies need to be

Figure 16.1 Dutch scratch card shows prevention messages can be delivered in different settings using a range of age appropriate techniques reproduced with permission from the Dutch Foundation for STD Control





Figures 16.2a and b Sex education content and delivery should be gender sensitive and take account of the different needs of boys and girls reproduced with permission from the Family Planning Association

sustained, politically supported by central and local government, financially secure, and routinely assessed and revised to meet the changing needs of new generations of sexually active young people.

Current approaches to sex education in schools include both teacher-led and peer-led approaches. Generally outcomes of sex education have been poorly evaluated and the most effective methods of delivering sex education for achieving improvements in sexual health outcomes are uncertain. However, observational studies have indicated some key components of effective sex education programmes. Several randomised trials are currently under way examining a range of approaches, and they will hopefully provide some more definitive answers.

Box 16.1 Approaches to sex education most likely to improve sexual health outcomes in young people:

1. Begin early (i.e. sex education should start with pre-teens)
2. Cover issues in an incremental and age-appropriate fashion
3. Address knowledge and attitudes, and provide practical skills (for example, using condoms)
4. Provide information, improve knowledge and build confidence to access sexual health and contraceptive services
5. Employ participative approaches (for example, role play)
6. Ensure content and delivery are gender sensitive, taking into account the different needs of boys and girls
7. Ensure understanding of different sexual choices (for example, delaying first intercourse, resisting pressure for sex) and different sexualities
8. Deliver interventions in a range of settings across the community (for example, involve parents and youth services)

Preventing sexual transmission

The epidemiology of HIV within the UK indicates that the greatest risk of infection is still associated with particular behaviours or demographic characteristics. Identified behaviours with the highest risk of HIV infection are: sex between men, injecting drug use; sex with injecting drug users, and sexual contact in parts of Africa and other parts of the world, where heterosexual transmission predominates. In other parts of the world commercial sex workers are at greatly increased risk of HIV. In the UK, other than among sex workers who are also injecting drug users (IDUs), high rates of condom use with commercial partners have maintained low HIV prevalence among prostitutes.

While there has been massive expenditure on HIV prevention over the last decade, until recently there has been a dearth of high-quality evaluation and little evidence from randomised trials to demonstrate effectiveness of different interventions. However, there is now a growing evidence base to support targeted HIV prevention interventions, tailored to the cultural context and needs of particular groups. A small number of randomised trials have shown the interventions to be effective in reducing the frequency of specific risk practices (for example, unprotected penetrative vaginal or anal intercourse) and, in a few cases, the incidence of new STI. In general, these interventions have aimed to provide basic HIV/AIDS education (including instruction on correct and appropriate condom use), enhance motivation for behavioural change, and teach risk reduction and safer sex negotiation skills (including the ability to resist pressure for sex) and have been delivered in community, small group and individual settings.

However, effective interventions in a research setting may not yield the same results in "real life". Careful consideration of local HIV epidemiology with a critical view of the generalisability of the intervention, will help to determine whether a specific intervention is appropriate and prevent spending limited resources on a programme that shows little benefit, or worse still, a negative effect. The literature contains examples of both.

No single intervention strategy is likely to be sufficient to address all of a group's prevention needs. There is no evidence that "single-shot" prevention interventions have enduring effectiveness at a population level. Interventions need to be sustained, with careful monitoring to indicate when changes are necessary, and must adapt, particularly, to the evolving epidemiological, social and cultural changes in successive new generations.

Little has changed with respect to the core content of prevention messages: it requires sexual contact involving the exchange of body fluids or blood-to-blood contact for transmission to occur. Those who know they are HIV negative and in a mutually monogamous relationship, are not at risk of

Box 16.2 Practises that reduce the risk for acquisition or transmission of HIV

- Using condoms for all penetrative sexual intercourse
- Using adequate quantities of water-based lubricant for both vaginal and anal intercourse. (Oil-based products will cause latex condoms to perish. Lubricants containing spermicides (for example, Nonoxyl 9) may cause irritation and have not been demonstrated to be effective in reducing HIV transmission *in vivo*)
- Reducing numbers of sexual partners
- Adopting sexual practises that carry a lower risk for HIV transmission (for example, oral sex, mutual masturbation)
- Avoiding recreational drug use during sexual activity, or when sex is likely to happen
- Ensure timely screening and treatment for suspected STI
- For young people, delaying the age at which first sexual intercourse takes place

infection through sex. To limit sexual risk of infection, the most effective strategies are to reduce numbers of sexual partners, know about partners' previous sexual and drug-use history and adopt safer sex practices (for example, oral sex, mutual masturbation and use condoms). Although condoms do not provide total protection, correct and consistent use will substantially reduce the sexual risk of HIV, STI and pregnancy.

The challenge that remains is how to deliver innovative HIV prevention messages through a range of different community, and individual focused interventions to reduce HIV transmission.

The following sections examine some effective strategies in relation to specific populations at high risk.

Gay, bisexual and other men who have sex with men

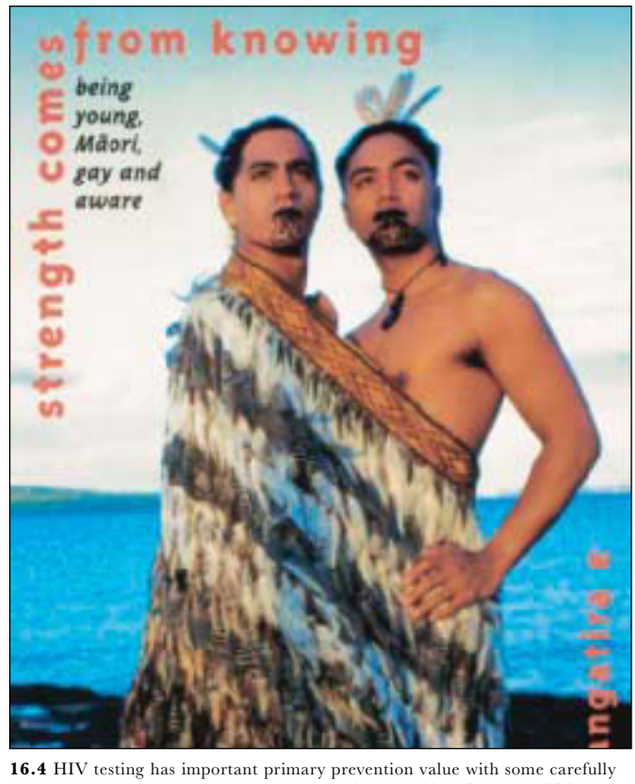
In most industrialised countries, homosexual and bisexual men have been disproportionately affected by HIV/AIDS. Unprotected anal sex is the primary mode of transmission and receptive intercourse carries the greatest risk. The success of early safer sex promotion campaigns primarily led by gay organisations has been highlighted as one of the greatest early successes in HIV prevention with evidence of falling STI rates, stabilisation in HIV prevalence and rapid uptake of safer sex practices. Over time these changes have proved difficult to sustain. Although condom use has become a social norm within the gay community, in recent years increasing proportions of homosexual men are engaging in unprotected anal sex. This particularly involves sex between men who are known to be HIV positive, partners whose HIV status is unknown to each other and younger men (< 25 years) who are likely to have become sexually active in the era of HIV/AIDS, and were not exposed to the intensive campaigns of the mid 1980s.

Factors which may contribute to increasing risk behaviour include: "boredom" with prevention messages; failures to target appropriate messages to a new generation of gay men; and perceived decreased threat of HIV in the era of highly active antiretroviral therapy (HAART).

The content of the successful interventions targeting gay men varies, but have often included motivational training, audiovisual presentations (for example, eroticising safer sex), brief safer sex negotiation skills training, stress reduction training and intensive group counselling. Interventions such as these are likely to attract individuals with particular concerns about their sexual risk behaviours and greater motivation to address them, so such interventions alone are not likely to meet all of the prevention needs of men who have sex with men. These interventions are particularly relevant to men using genitourinary medicine (GUM) clinics and HIV testing services.

Knowing that face-to-face interventions will never be able to reach all of the people at risk, community level strategies offer the potential of reaching those who do not attend services. Broader strategies focused at the community level have been shown to be effective in reaching higher risk and vulnerable men who often do not participate in small group interventions. Prevention programmes involving outreach workers and peer-educators can be used to target men using community venues (for example, bars, clubs, saunas), public sex environments (for example, cruising grounds, public toilets) and other places where homosexual men meet to have sex. These strategies often follow the principals of empowerment or community-building models of health promotion, with the intervention being developed either by gay communities themselves, or in collaboration with public health or sexual health providers. The

Figure 16.3 Face-to-face interventions may be particularly relevant for persons attending health care and other services reproduced with permission from the Terrence Higgins Trust



16.4 HIV testing has important primary prevention value with some carefully defined groups reproduced with permission from the New Zealand AIDS Foundation

content of successful community-focused interventions varies, but among the most important components are peer and opinion-leader delivery of risk reduction messages, community-building activities and peer-outreach providing safer sex materials (i.e. condoms and lubricant). One of the very few rigorously evaluated and effective interventions that specifically targeted young gay men (for example, aged 18–29) was developed using these approaches.

Injecting drug users

HIV transmission between injecting drug users (IDUs) occurs primarily through sharing of HIV-contaminated syringes, needles and injecting equipment. IDUs and their partners are also at risk through sexual transmission. Since many, particularly female, IDUs support their drug habit through commercial sex they may be at risk of sexual transmission both to and from their commercial and non-paying partners.

The epidemiology of HIV infection in IDUs and the social and cultural context of drug use vary substantially between geographical areas. Identifying promising interventions most likely to succeed within a particular setting is reliant upon understanding the local epidemiology and drug-use culture.

Preventing HIV transmission in injecting drug users relies primarily on reducing the frequency of sharing needles, syringes and other paraphernalia used for injecting ("works"), and on ensuring that the risk of sexual transmission for paying and non-paying partners is minimised through safer sex practices. Effective strategies that reduce the risk of HIV transmission through injecting will have other benefits in reducing the incidence of other viral infections (for example, hepatitis B and hepatitis C).

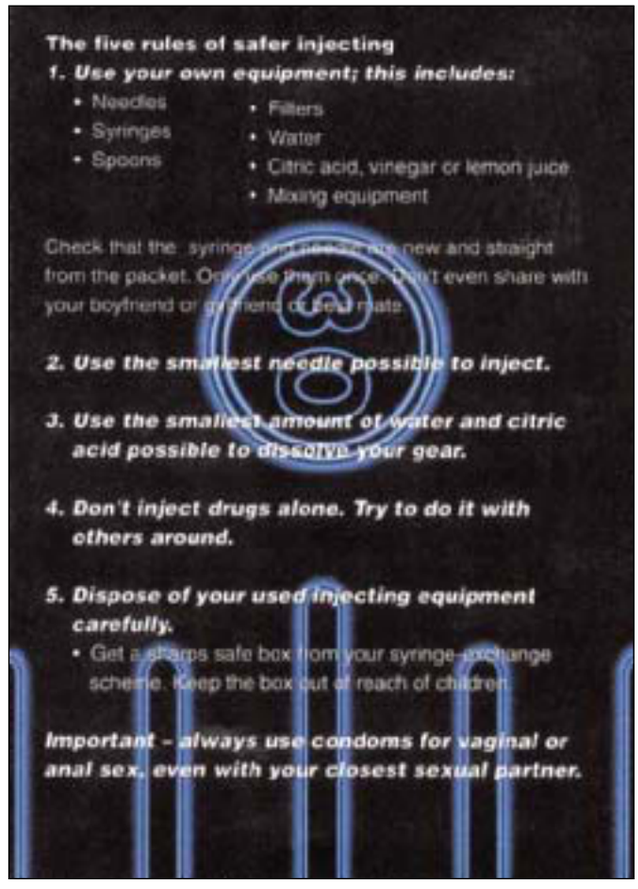
Social, political and legal controversies have hampered prevention strategies to minimise the potential harm of injecting drug use to both the individual and the community, because of particular concerns that increasing the supply of clean injecting equipment would encourage injecting drug use. Research evidence from largely observational evaluations has shown these concerns to be largely unfounded.

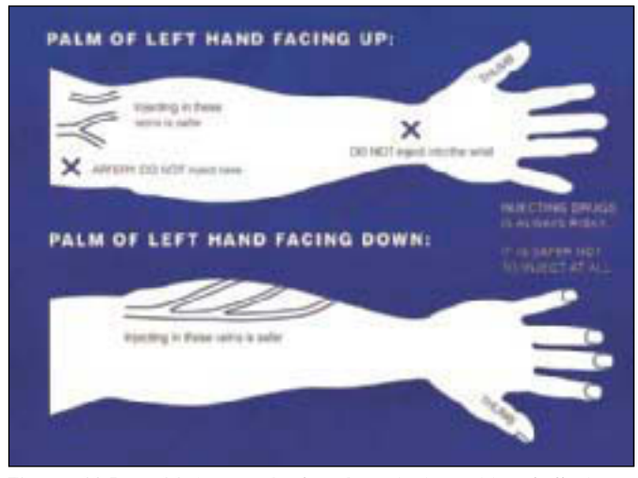
Observational studies have demonstrated that needle exchange programmes (i.e. providing sterile needles and syringes in exchange for used ones) are the most effective base for prevention strategies with drug users. Needle exchange has been successfully delivered within health and social services, through outreach workers, and dispensing machines, and has been demonstrated to be associated with reduced HIV prevalence without increasing levels of drug use. Improved access to bleach cleaning kits (for shared needles and syringes) and training in effective cleaning procedures may reduce HIV transmission through needle sharing. However, the quality of available products and the complex skills required make this a poor substitute to access to clean needles, but better than no intervention at all.

Evidence supports outreach and peer-educators as the most effective way to reach drug users in the community. Former injectors and current injectors have been employed successfully in both roles. Other interventions, specifically low-threshold easy-access drug treatment programmes and oral methadone maintenance, have been shown to reduce overall levels of drug injecting. These interventions bring drug users into regular contact with service providers (whether outreach or service based), where opportunities to deliver other information, education and counselling interventions exist. In particular, treatment and methadone maintenance programmes can offer adjunct social, educational and rehabilitation interventions to break the cycle of drug use and increase the possibility of an individual's integration into routine employment and

Box 16.3 Effective HIV prevention strategies targeting injecting drug users

- Making easily available sterile needles and syringes
- User-friendly, low-threshold drug treatment programmes, including oral methadone maintenance
- Sustained education through outreach programmes and peer education providing information, skills (for example, safer injecting), health services and social support
- Providing access to counselling and HIV testing
- Facilitating access to health care, support and STD services for IDUs with HIV infection
- Special programmes for high-risk subgroups (for example, sex workers, prison inmates, youths in detention)





Figures 16.5a and b An example of good practice in provision of effective accurate information for injecting drug users, reproduced from "A Guide to Safer Injecting". with permission from HIT

mainstream culture. A supportive environment including political, financial and legal support for the programmes at both central government and the local level is essential for the long-term success of comprehensive programmes.

In parts of the world such as the USA where IDUs have suffered a particularly severe HIV epidemic, sexual transmission to the partners of IDUs is a major source of increasing heterosexual transmission. Programmes to prevent sexual transmission among IDUs have received much less attention than those for harm minimisation from injecting and there has been little demonstrable success in changing the sexual behaviour of IDUs. Approaches to changing behaviour in this population clearly need to incorporate those shown to be appropriate to all heterosexual populations. In addition, approaches that have shown some promise specifically among drug users include skills training in correct condom use, voluntary HIV testing and counselling, and sexual negotiation skills. Such programmes need to target in-treatment drug users, sex workers and female sexual partners of male drug users.

African and other ethnic minority communities

African and ethnic minority communities have become an important focus for targeting HIV prevention interventions, however evidence for effective interventions with this group is limited. The few interventions that have been rigorously evaluated have been developed in careful collaboration with the affected communities. They have considered carefully the cultural and social factors influencing sexual attitudes of the communities and treated HIV prevention within the context of wider sexual health, contraception and pregnancy. Within the UK context recent research into the sexual attitudes and lifestyles of diverse ethnic communities has provided guidance for the development of linguistically and culturally appropriate strategies. African communities in the UK are particularly severely affected by HIV. Many within these communities also face the additional challenges of relatively recent migration including problems of language, culture and isolation often along with possible economic and/or legal difficulties associated with refugee status. All these difficulties may in turn limit access to local service for treatment and HIV prevention.

Strategies for people with HIV infection

Until recently targeting prevention interventions to HIV positive individuals has been largely neglected. Affected communities have been understandably concerned about stigmatisation and discrimination, while those responsible for prevention have felt poorly equipped to tackle many of the key issues. As stigma and exceptionalism associated with HIV diminishes, opportunities emerge to build HIV prevention strategies where people living with HIV are partners in development and delivery of the interventions. The advent of highly active antiretroviral therapy (HAART) has led to improved survival and thus to an increasing number of people living with HIV in the population. This brings with it particular public health challenges for individuals and society. Clinicians and policy makers need to be aware that with widespread use of HAART comes responsibility for ensuring that the risk of transmission, and particularly the transmission of resistant or virulent strains, is minimised and that public health is protected. For those living with HIV, HAART may lead to improved quality of life and sexual relationships and increased longevity, but also raises the challenge of maintaining life-long safer sex

Box 16.4 Guidance for enhancing sexual health promotion and HIV prevention in minority ethnic communities

- Facilitating access to appropriate confidential adolescent and adult sexual health and HIV prevention services, including specialist services outside routine clinical settings inline with the expressed needs of the community
- Developing materials using appropriate language and images including materials appropriate for non-native English-speakers
- Early and continued sex education in schools to supplement and support provision in the home
- Assisting parents from cultures where sex in general is rarely discussed to discuss sex education
- Providing focused interventions for young boys in either school or community settings
- Prohibitive messages may be supported by some particularly older generations
- Exploiting and explaining the wider benefits of safer sex in relation to contraception and avoidance of other infections may increase the overall acceptability of messages with all audiences
- Focused work exploring assumptions made about "safe" partners and concurrent relationships in cultures where they are common
- Use of appropriate and community-specific delivery points, for example, settings appropriate to the specific culture
- Awareness of different migration, refugee and acculturation experiences between communities and between generations
- Promoting HIV testing within high-risk ethnic communities is likely to be extremely sensitive and should be treated with careful consideration and caution based on a clear understanding of the individual and community issues

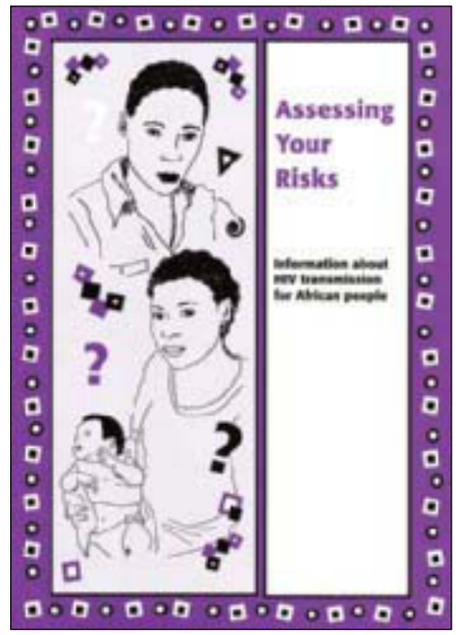


Figure 16.6 Key materials should be available using appropriate language and images for minority groups and for non-native English speakers

practices to avoid infecting others. Collectively, increased survival leads to a larger pool of infected people in the community who may pass on infection and there is already evidence that new HIV infections may once again be increasing in parts of the USA. While there are theoretical reasons to believe that HAART may decrease infectivity by decreasing viral load, at the population level, such gains may be counterbalanced by increased unsafe sexual behaviour, increased incidence of STIs, and the emergence of drug-resistant strains amongst those failing therapy, which in turn may lead to new infections resistant to currently available therapies.

Prevention trials specifically with those living with HIV are scarce. However, recent research and community consultation has provided indications of acceptable primary prevention approaches. Acceptable primary prevention strategies with HIV positive people include providing counselling and support in both one-to-one and small group contexts, providing specialist sexual health and STI screening services for HIV positive people, and offering social, emotional and sexual counselling support within HIV outpatient treatment services. As with other groups, interventions are more likely to achieve success if they occur in genuinely productive partnerships with leadership from the affected communities to overcome wider social prejudice and stigmatisation.

Voluntary counselling and HIV testing

Diagnosis of infected individuals has an important role in secondary prevention, because it allows infected individuals to benefit from treatment to reduce the chance of progression to severe immunodeficiency. Identifying those who are HIV positive in order to work with them to prevent onward virus transmission is also fundamental to primary HIV prevention.

Routine HIV antibody testing of pregnant women is now recommended throughout the UK. Positive women can then benefit from antiretroviral therapy to prevent perinatal transmission of HIV and advice to avoid transmission through breast feeding. Detailed recommendations on the management of HIV positive pregnant women is dealt with in chapter 12.

HIV counselling and testing is widely available in many clinical settings in the UK, particularly in genitourinary medicine (GUM) clinics. Counselling for HIV testing was originally developed in the pre-antiretroviral therapy era and much of the content focused on the nature and interpretation of the test, and the advantages and disadvantages of knowing ones' status in the context of an untreatable infection. All clients were also advised on risk-reduction strategies to prevent the acquisition or transmission of HIV through sex or injecting drug use. In the era of HAART, GUM clinics are increasingly offering routine testing and counselling as part of their clinical services in order to identify HIV positives.

The effectiveness of testing and counselling services in achieving behavioural change for primary prevention is limited and somewhat confusing. Brief client-centred counselling has been shown to be an effective strategy in reducing future STI acquisition in only one large-scale trial, while another study demonstrated its effectiveness in different developing countries using behavioural change endpoints. However, two major reviews of the effectiveness literature have concluded that testing and counselling are only effective as primary prevention strategies for achieving sexual behaviour change within carefully defined groups, including in-treatment drug users, commercial sex workers and post-test counselling and support for those who receive a positive result. Nevertheless, for its secondary prevention benefits and primary prevention value with specific groups, voluntary

Contact addresses and numbers for further information

- National AIDS Helpline: 0800 567123
- Health Development Agency, Trevelyan House, 30 Great Peter Street, London SW1P 2HW. Tel: 020 7222 5300
- National Aids Trust, New City Cloisters, 196 Old Street, London EC1V 9FR. Tel: 020 7814 6767
- The Terrence Higgins Trust, 52/54 Grays Inn Road, London WC1X 8JU. Helpline: 020 7242 1010 (noon to 10 pm every day)
- The Haemophilia Society, Chesterfield House, 385 Euston Road, London NW1 3AU. Tel: 020 7380 6000.
- DrugScope, Water Bridge House, 32–36 Loman St, London SE1 0EE. Tel: 020 7928 1211
- Cardiff AIDS Helpline (10 am to 8 pm Mon-Fri). Tel: 01222 223443
- Northern Ireland AIDS Line, Belfast (7 pm to 10 pm) Mon–Fri. Tel: 01232 326117
- The Sandyford Initiative, 6 Sandyford Place, Sauchiehall St, Glasgow G3 7NP (8.30 am to 4.30 pm Mon, Wed, Fri; 8:30 to 7 pm Tue and Thur.) Tel: 0141 211 8601
- London Lesbian and Gay Switchboard. Tel: 020 7837 7324
- Gay Men's Health, 10A Union Street, Edinburgh EH1 3LU. Tel: 0131 558 9444

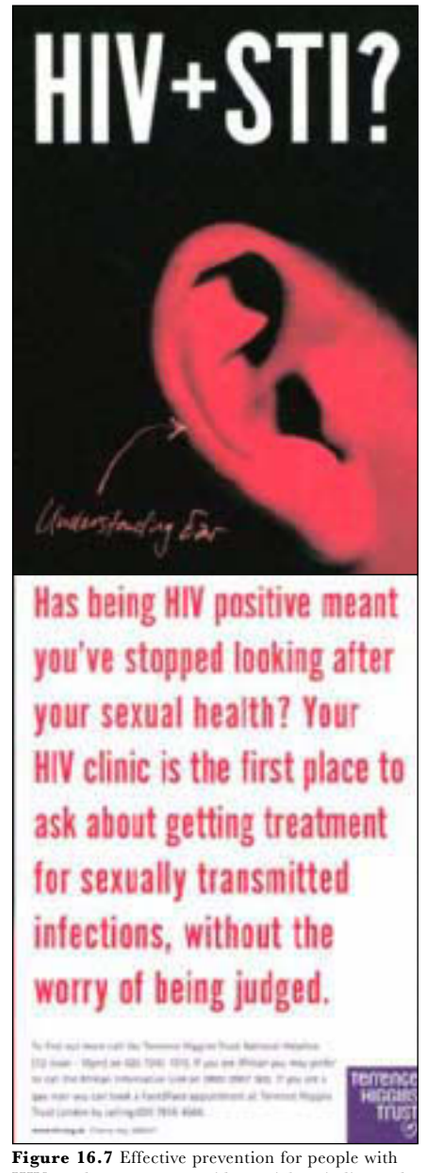


Figure 16.7 Effective prevention for people with HIV needs to overcome wider social prejudice and stigmatisation, reproduced with permission from the Terrence Higgins Trust

counselling and HIV testing is still an important component of any comprehensive HIV prevention strategy.

The testing scenario has much to offer with respect to individually focused prevention. The process of HIV testing offers an opportunity to use a client-centred counselling approach to undertake an individual risk assessment, discuss and develop individually tailored personal prevention strategies and consider the implications of a positive result.

Control of sexually transmitted infections (STIs) and STI screening

There is now substantial evidence from observational, biological and intervention studies to show that STIs (both ulcerative and non-ulcerative) may increase the susceptibility of uninfected individuals to HIV and increase the infectiousness of HIV positive individuals. Control of STIs therefore has an important role in the primary prevention of HIV. In the UK, the network of GUM clinics provides open-access services for screening, treatment and partner notification for STIs. STI control is particularly important among populations at high risk of HIV infection. Screening and treatment offer an opportunity to focus behavioural interventions on those who have STIs. Increasingly, GUM clinics are recognising the importance of offering regular STI screening as part of routine HIV treatment services alongside appropriate counselling on risk-reduction strategies.

In developing countries, where the burden of untreated STIs is much greater and diagnostic and treatment services more limited, syndromic management approaches have been used. These combine clinical history with knowledge of local pathogens to devise treatment algorithms. Such strategies however appear to be most effective in terms of their specificity and sensitivity in identifying STI cases, where the prevalence of STIs is high.

Blood transfusion and blood products

In,the UK and other developed countries, the risk of HIV transmission through blood transfusion has been minimised by testing all blood samples for HIV antibody and excluding those at increased risk from HIV from donating blood. The current categories for exclusion from blood donation in the UK are shown in Figure 16.8.

Travel to countries with high HIV prevalence

In some countries in Africa, HIV prevalence in the general population exceeds 20% and STI rates are much higher than in the UK. Unprotected sex is therefore associated with a high risk of both HIV and STI infections. All travellers to these countries need clear advice on sexual risk reduction through limiting sexual partnerships and always using condoms. There is no risk of transmission from casual contact. However, in some countries, HIV screening programmes for blood transfusions are not always in place, and there may be shortages of sterile medical equipment for injections and intravenous infusions. Sterile needle packs, first-aid kits (including needles, syringes and suture packs) and minor surgery kits are available for purchase or mail order from the Hospital for Tropical Diseases (London) Travel Clinic (2nd Floor Mortimer Market Centre, off Capper Street, London WC1E 6AU, tel. 020 7388 9600). Basic needle packs and larger made-to-order first aid and surgical packs can be ordered from Nomad Travellers Store and Medical Centre (3–5 Wellington Terrace, Turnpike Lane, London N8 0PX, tel. 020 8889 7014).

Figure 16.8 Government advice to those who should not give blood. Reproduced with permission from the Department of Health Publications

17 Being HIV antibody positive

Jonathan Grimshaw

Late in, 1984, when I was tested, HIV had only just been identified as the cause of AIDS. There was no formal counselling before or after testing, no organised emotional or social support in the community and certainly no prospect of treatment. The doctor who gave me the positive test result told me, kindly, that I seemed the sort of person who would be able to cope. I agreed. Never having been confronted by anything like this before I was ignorant of what "coping" would involve.

Initial reactions

I was very frightened. I was convinced I was going to die painfully and soon. I felt very alone. I knew no one else in the same situation. Public fear of AIDS and stigmatisation of "AIDS carriers" were at their height. Confiding in people, even friends, risked hostility and rejection, but I knew equally that friendships would not survive the level of deceit needed to conceal something so devasting. I thought I would never know sexual intimacy or love again. At that time, safer sex was not common behaviour; asking for it could raise the suspicion in a potential partner's mind that you "had AIDS" and no one, I thought, could possibly want to be intimate with or have a relationship with someone who had the "AIDS virus".

I expected, through illness, to lose my income, my security, my independence, my dignity and my self-esteem. I came to realise how much the things that give a life meaning and purpose – aspirations, dreams, motivation, hope, endurance, fulfilment – depend on the unconscious assumption of a future. Coping with HIV meant firstly coming to terms with the loss of that assumed future and secondly trying to give life some meaning and purpose in its absence. This comes with hindsight. At the time I couldn't cope at all and spent much of the first few weeks after diagnosis drunk or tranquillised.

Peer support, counselling and referral

At the end of 1984 the Terrence Higgins Trust established its first support group for people diagnosed with HIV. It gave me and the others there a safe environment in which, for the first time, we could talk openly and honestly about what had happened to us. Most importantly, hearing other people describe feelings and experiences almost identical to one's own made each of us realise that we were not alone. Learning that the frightening and unfamiliar extremes of fear, anger and grief that each of us had felt were a common and natural reaction to the situation we were in was the first step in our being able to see ourselves again as normal people rather than the "AIDS carrier" pariahs of popular perception.

The potential psychological and social impact of a positive HIV antibody test result are now well understood, as is the importance of counselling and referral to agencies that can support people emotionally and practically as they come to terms with the diagnosis and its implications for their lives. For many people, peer support continues to be a key part of that process.

Coping with uncertainty

It took some time for it to sink in that the positive result wasn't necessarily a sentence of imminent death, but no one could tell me how long I had to live. In many ways an AIDS diagnosis would have been easier; it would have given me something concrete to deal with. Being HIV antibody positive was a kind of limbo where you knew the axe would fall, but never when.

How people cope with this kind of uncertainty probably reflects how they cope with uncertainty in other areas of their lives; some avoid thinking about the future if it threatens contentment in the present, some throw themselves aggressively into trying to shorten the odds in their favour, some fatalistically assume the worst and prepare themselves for it.

My way of coping was to throw myself into community work developing services for people with HIV and prevention campaigns and establishing Body Positive. This was the first self-help group in the UK, and perhaps the world, for people with HIV. If I couldn't fight the HIV inside me, I could at least fight the HIV outside me. I became very driven because, like many people confronted at a relatively young age by their mortality, and not knowing how long I had left, I didn't want to die insignificantly. I had a lot to achieve with perhaps very little time.

One would very occasionally hear someone with HIV say that the diagnosis was the best thing that had ever happened to them. More than any other event or crisis, it forced them to think about what was important and re-arrange their lives accordingly. Certainly, the years after my own diagnosis were lived with an intensity and with a sense of fulfilment in my work that would probably not have been achievable without HIV to concentrate the mind.

Retirement

In the early 1990s my CD4 count, which had been declining very slowly over time, suddenly seemed to plummet and I developed some minor illnesses. In fact, the CD4 count never fell below the lower limit of what would be considered a normal range, but I convinced myself that the suddenly rapid decline meant that the deterioration to AIDS had begun. I retired from work, cashed in my pension and bought a nice place by the sea in which to pass my remaining few years. I had achieved what I needed – to feel that I had done something useful with my life – and I was completely ready for death.

After leaving work, my CD4 count stopped declining and I remained well. In retrospect, the retirement was probably necessary as I was almost certainly approaching "burn-out", but it felt at the time as though HIV had fooled me into a premature withdrawal from life.

During 1997 my viral load started to double every three months and I began combination therapy. Since then my CD4 count has dropped below 500 only once, when I became resistant to one of the drugs. Since changing the combination, my viral load has been undetectable.

Living with HIV in the era of combination therapy

It is sometimes assumed that combination therapy has transformed the lives of people with HIV. Well, yes and no. In people who are HIV antibody positive it can postpone illness or an AIDS diagnosis. But in doing so it prolongs the uncertainty. The long-term efficacy of antiretroviral therapy is unknown.

This brings dilemmas of its own. For example, many healthy people in mid-life seeing an advertisement for a pension plan might wish they could put more money aside for their old age. But an HIV antibody positive person has to ask him/herself

"do I spend money and enjoy life now because there may not be an old age to save for, and risk impoverishment if there is; or do I save for old age and risk lying on a hospital bed in a year or two's time regretting not spending my money and living life to the full while I was well?".

I can only imagine how much more acute and agonising dilemmas of this kind – involving trade-offs between present and future – must be in families where a parent and possibly also a child has HIV.

There are other trade-offs, some more difficult than others. Never, for example, during all the years before combination therapy did I have to adapt my life to a medication regimen. It took some time to learn full adherence to the regimen, initially, I would simply forget very occasionally to take a dose when due. But, more fundamentally, adherence involves restricting freedoms that most of us take for granted – to eat what you want when you want, for example. It was difficult to adjust to my freedom being compromised by the treatment rather than the disease itself, although viewed in the light of the benefits of the treatment, these compromises were insignificant.

Although public education has removed much of the fear and prejudice surrounding HIV and AIDS, there are communities where HIV remains highly stigmatised and where people with HIV are discriminated against. Discrimination, real or perceived, restricts the choices one is able to make in life; it limits life's potential – a cruel irony when medicine has found ways to prolong life with HIV.

Nor does combination therapy remove anxieties about falling in love and sexual intimacy. There is still the fear of revealing one's status to a potential partner in case of rejection. Although my viral load is currently undetectable, I can't assume that I'm not infectious. I must still insist on safer sex. The social acceptance of safer sex as normal, or at least sensible, behaviour means that asking for it is less likely to be met with rejection, but having sex with someone entails a risk, however small, that unsafe sex could occur. I know from experience that it isn't always possible to be totally in control of an activity in which someone else is playing an equal part. However much I rationalise that preventing transmission is a shared responsibility, because everyone has a responsibility to protect themselves, and that anyone wanting unsafe sex is probably HIV antibody positive themselves, I know I would feel a tremendous sense of guilt and failure of moral responsibility if unsafe sex did occur.

The HIV "veteran"

I was aware before combination therapy arrived that I had remained well for an unusually long time since diagnosis. Now it seems that combination therapy may keep me alive and possibly well for many years more. During the millennium celebrations it occurred to me that, if adulthood begins at 18 years, I have lived with HIV for over half my adult life.

I read recently that there is sometimes a striking similarity in how long-term survivors of HIV and war veterans describe their feelings about life. Both have had to confront their own mortality in a way that has led them to question, and sometimes reject, many of the assumptions which most people rely on to get through life. Large numbers of their peers and people they loved have died. As time goes on there there are fewer and fewer people with whom they have a shared life experience. War might have made life more intense for a while, but with the perspective of long hindsight there is some bitterness about the damage it has done to their lives. They have a strange sense of not knowing quite where they belong. This describes me pretty well.

18 Having AIDS

Caroline Guinness

I was diagnosed in 1986 when there was very little knowledge of HIV. I had just been diagnosed as having precancer of the cervix, but I felt there was something else wrong – just an instinctive feeling – there was nothing in particular. So I went to my GP, and in fact saw a locum who was very young and enthusiastic. He felt my neck and said my glands were up, which I suppose alerted him to HIV, although he didn't say anything, suggesting it might be glandular fever. He took some blood, and said I should return three days later.

When I went back for the results he said they were negative for glandular fever, but that he had also requested an "AIDS test". I remember feeling really cold when he said that. I knew that maybe that was what it was, because two years beforehand, shortly after my husband left me and I was very vulnerable, I had slept with a bisexual man. I told the doctor that I thought he should have talked to me about it first, and that I wanted the test stopped. He said it was too late as it had already gone to the laboratories. I said in that case I didn't want to know what the result was.

About two weeks later, my own doctor who was back, just turned up at my house. He knew that I didn't want to know the result of the test, but he thought that, as an intelligent woman, I should know that it was positive. Even though I had some suspicions, I found that being told for definite was a different thing altogether. I went into shock. My first reaction was to ask how long I had to live, and he said probably about five years. My next thought was for my daughter, who was three years old at the time, and whether she would be infected too. The doctor didn't think there would be any risk to her as I had obviously contracted it after she was born, but I knew nothing about transmission or anything like that. He suggested another doctor at the practice who had more experience than him, and had been treating a couple of gay men, and that I should go and see her, which I did. She was really sweet, but she didn't know anything about other genitourinary medicine (GUM) clinics, voluntary agencies etc. On the other hand, she was good because she was a very firm believer in complementary therapies, so recommended vitamins and minerals and things which, looking back on it, was actually the best thing she could have done. But not having any counselling and not being in a specialist situation were not good. For the next six months or so I was just in denial – it hadn't sunk in at all. I didn't want to tell anybody because the atmosphere was really bad those days, lots of scaremongering in the Press, calling it the "gay plague" etc.

I did tell a couple of close friends whom I lived with at the time. One, as a gay man, found it very ironic as he thought that if anyone should have tested positive it should have been him, and the other was a girlfriend of mine who sort of panicked. She was OK, but having lost her partner a couple of years before, she couldn't bear the thought of losing somebody else, which of course didn't help me. I didn't want anyone like Social Services to know, as Lee had just started nursery school, and I didn't want it getting out. So I just kept quiet and I continued in my state of denial.

I couldn't cope with work at all – it seemed irrelevant. I told my colleagues that I needed treatment for my cervix which I thought might help explain my lack of concentration. Their reaction was that it wasn't such a big deal, and as I felt I couldn't tell them what was really happening, I resigned. That left me with financial problems, but I didn't want to go to Social Services because of Lee.

I had a partner at the time whom I had been with for six months before being diagnosed, and having to tell him, and him having to get tested was the other thing that was really frightening. Because I didn't know how to tell him, I asked my best friend, whom he got on very well with, if he would tell him. My partner thought that he was going to be told I wanted to split up, so when he realised what it actually was, his initial reaction was one of relief, but the following two weeks, while he got tested and waited for the results, were pretty fraught. We had no information about transmission, but luckily the test came back negative, which was a relief.

My fears about Lee being infected went on for quite some time because I felt I was not getting any real reassurance. I worried about things like her using my toothbrush, and I remembered I had cut my finger and she had helped me put the plaster on, and stuff like that. All those things kept going through my mind. The doctor I was seeing didn't recommend that I had her tested, as she firmly believed Lee would be alright. Looking back on it, I think that if I had just had her tested then I would have felt a lot more reassured, because the whole issue bugged me subconsciously for a long time.

Another very stressful event which happened that year was that a close friend of mine told me he had AIDS. He didn't want anybody to know, and he asked if myself and a couple of other friends could look after him. His health went downhill so quickly and he started getting dementia and incontinence etc, and for me it was like looking in a mirror – very frightening. He did actually go public in the end, but he died shortly before Christmas, so all in all it was quite a bad year.

In 1987, about a year after my diagnosis, through the Terrence Higgins Trust (THT) I finally found out about GUM clinics and I attended James Pringle House, Middlesex Hospital, which made a huge difference to me. I really wanted to meet other HIV positive women – I'd never met any, and still felt as if I was the only woman who had the virus. Someone at THT told me about a support group called Positively Women, who met once a week, so I went along to the group and met a couple of other positive women which helped a lot. I eventually became the Director of Positively Women, and the next three years were really hard work. There was nothing for women at all, so we tried to produce leaflets and information. Despite doing interviews and media work, I never went public about my HIV status. Although our slogan said "For positive women, run by positive women", people never seemed to twig with me; I think they had some vision of what someone with HIV should look like, which I didn't really fit into. Positive women were very much seen as drug users or prostitutes, and most of the women were keeping quiet, usually to protect their families. Through Positively Women, I did many hospital visits to AIDS wards and I used to find that stressful, worrying that I might catch something if I was going to see someone with meningitis or TB.

However, after three years my energy was beginning to dwindle, and I also felt I wasn't spending enough time with Lee, so in 1991, I resigned as the Director, and went part-time. It gave me a bit more time to myself, and because I felt so run down I started using complementary therapies such as acupuncture reflexology, which I'm still having, and which made a difference.

I continued to attend the clinic every three months for a regular follow-up, and the relationship I had with my doctor was very good. She trusted my own judgement on my health, and I found we could work together. She also understood my need for complementary therapies. Seeing the same people on each visit helped maintain continuity and build up a relationship, which was important.

I decided to tell my daughter when she was about 10 years old. She's very bright and reads the newspapers, and it seemed the right time for her. Although I had never gone public about it, I knew it was going to get out at some point, and I didn't want Lee to find out from anyone else. I thought Lee might suspect, but in fact she hadn't. Her first reaction when I told her was to burst into tears, and then she felt embarrassed about crying which made me feel awful as it was quite a natural reaction. For a week or so she kept asking me how I was, and if there was anything in particular that she could do to help. I said she could give me a hand with the housework, but that didn't last very long – I don't think that was what she was expecting! It became immediately apparent that there were no services for children, and she was desperate to meet other kids in the same situation. I suggested to Lee that she didn't tell any friends for a while until she got used to the fact. Anyway she did actually tell a schoolfriend who immediately told everyone else which was exactly what I didn't want to happen.

Her school had been helpful – I had spoken to the Head, her teacher, and the school counsellor before telling her, but she still needed to talk to a trained counsellor, and again she needed to meet other kids in the same situation. None of the organisations offered services for children, but I got a letter from a woman in a similar situation and we met up so that Lee could meet her daughter, which was good for both of them, and at least she knew she wasn't on her own. Lee also started seeing a child psychologist which she really benefited from and she still goes along there when she wants to, but nothing regular.

I think that over the last year or so my energy really hasn't been so good, and as Lee has now reached 13 and is going through everything that 13 year olds do, I could really do with some help now. Her father was in Australia when I was diagnosed, and I didn't want to tell him by 'phone or letter, so I was hoping that he would be coming over to the UK at some point. Because I'd been told that I had about five years to live, I wanted to sort things out as quickly as possible. Anyway, he did come over and I told him, and he had a really odd reaction: he seemed to think I was trying to emotionally blackmail him, which really upset me. It was only later that I found out through a mutual friend that he felt that if he hadn't left me for someone else, I would never have slept with this bisexual man, and so he felt responsible, a thought which had never entered my head. His whole reaction was one of pure guilt, but then over the years that all changed, and for the last few years he's been really supportive.

At the beginning of 1992 I found I was pregnant, and I decided I wanted a termination, and that at the same time I wanted to be sterilised as I didn't want to go through this worry again. I knew enough about transmission at that point to know there was a 10–15% chance that I could pass the virus on, and although that's quite a low risk, I had seen enough other women take the chance and go through the whole nine months and following 18 months not knowing whether the child was infected or not, and I felt I didn't have that in me. I was referred to a hospital and I went there and saw a doctor in outpatients. She knew nothing about HIV – absolutely nothing. She automatically assumed I would want a termination, and before she examined me she removed all the blankets and coverings from the table, so again obviously had no idea about transmission or anything. She also asked the nurse what precautions she should be taking in front of me. It made me feel awful at what was a traumatic time anyway.

About a month ago I was involved in a conference called Living Proof, the first conference for long-term survivors ever, which was really illuminating and quite empowering. There were a lot of other women there which was great to see. I went to three workshops during the two-day event and it was amazing how the experiences of both women and men were so similar. We had all been told first that we probably had five years, then seven years, then 10 years etc. Although my Consultant never said this, it had been the general consensus, and the type of the thing you read in the press, so that when you go past those dates you feel more and more isolated. When you have also suffered so much loss and lost so many people on the way, there is a tinge of guilt that you are still here. Friends whom I told originally have sort of forgotten about it now because it's been going on for so long and they don't seem to realise that I'm still going through it all, and that it takes a large chunk out of my life, that I had to resign my job and go onto benefits.

You feel that people are waiting for you to die. It's still the uncertainty of just not knowing, constantly trying not to be in denial, because there've been enough people I know who have had the virus longer than I have and have died, and I do have definite symptoms. If I was in America I would have been diagnosed as having AIDS a while ago because my CD4 count has been hopping between 150 and 200 over the last two years. Luckily they don't do that here, because psychologically that's a hard one.

When I was admitted into hospital last year, the doctor was trying to be reassuring, saying that it wasn't necessarily HIV-related, but I didn't believe it. I found that most of the nurses had had no specialist training which made me feel a bit vulnerable. One morning I woke to find a young agency training nurse looking at my file; she said, "Oh, you were diagnosed in 1986 and you're still alive – that's amazing", and I thought "I just don't need this, I really don't". I was feeling so ill and didn't really have the strength to deal with it.

When you live in a little closed society like I do medically, where you go into a clinic, where everybody is wonderful and the service is fantastic, you forget about the lack of knowledge and the attitudes outside that world.

Update since 4th edition

It is now the year 2000 and I am still here. I am amazed at just how much my life has changed over the last four years, not to mention the changes in medical advances, from which I have benefitted greatly.

In 1996 I became steadily more and more ill. I was suffering from constant night sweats, my face was covered in molescums, warts appearing everywhere, my hair falling out in huge clumps, my weight plummeting and the most appalling constant fatigue, it was as much as I could do to get a meal together for Lee on her return from school. This was very frightening for her. Finally I came down with pneumonia and having just recovered from that, I immediately got *E. coli* septecaemia and very nearly died. While I was in hospital it was suggested that I start on combination therapy – I felt I had nothing to lose and agreed. The viral load test had just come in and my count was nearly one million, and my T cells were hovering around 50. To my mind I had no choice but to begin treatment.

I started with "Dual Combination" (which is not advisable today). I was taking 3TC and D4T. Almost immediately I started to feel better. My viral load became undetectable, my T cells rose to over 200, my hair stopped falling out, the

molescums disappeared, as did the warts, the night sweats stopped, but the most remarkable thing for me was to suddenly be flooded with masses of energy. I experienced complete euphoria.

The psychological effects were strange. Having prepared myself for death I found myself strangely afraid of life. I had been forced to opt out of the "rat race", which in a way was rather comforting. Now I needed to join it again. I realised that I had missed years of planning for a future. No pension plans, no savings etc… I also felt a strong sense of "survivor's guilt". I had lost so many close friends and colleagues, and asked myself the question "why me"? Out of the 600 or so women who used Positively Women there were only four of us left from the original group. I decided to start from the beginning again and threw myself into working in the music and film business.

After 18 months I developed a strange side-effect – lipodystrophy. My fat just disappeared off my arms and legs, I had no buttocks to speak of and my face aged about 20 years. My breasts grew enormous and I had a bulging stomach. My viral load was at this point about 5000 and my T cells were dropping again. I decided to see if my body would return to its normal shape and to discontinue any form of treatment. I was still on 3TC and D4T.

After about four months, all my old HIV symptoms were reappearing. My viral load reached 650 000 and my T cells were around 50. The lipodystophy had not changed at all – if anything it was worse – but this could have been "AIDS wasting". Time for a new combination. At this point (September 1998), dual combination was not recommended and I started on triple combination – DMP, AZT and DDI. It took longer for this to work than the last combination, but after about three months my viral load was below 50 and my T cells ranged between 200 and 250. I am still on this combination and still undetectable and, much to my doctor's surprise, my body fat has gone back to normal. My triglycerides are still high, but I have the weight back on my buttocks, arms, legs and face – and it seems to get better by the day.

I have recently married a wonderful man, Lee is now 17 and life goes on. I am more confident of a future, but by no means complacent. I see too many of my peers suffering appalling side effects or complete treatment failure for me to take my life for granted. If I am still around for the next edition of the *ABC of AIDS*, I am sure it will all have changed just as radically again – watch this space.

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