HIV and AIDS

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1. Introduction

Description

Human immunodeficiency virus (HIV) is one of the most important communicable diseases in the UK.
HIV infection is associated with serious morbidity and significant mortality. Whilst early diagnosis and access to treatment is associated with 'near normal' life expectancy, the costs of treatment and care are high, as are the number of potential life years lost. [1]
There is a prolonged 'silent' period when the infection may be undiagnosed.

Historical background

The first UK case of AIDS, in a haemophilia patient, was identified in 1981. By 1982, the UK AIDS surveillance scheme had been started to monitor the incidence of Kaposi's sarcoma and opportunistic infections.

When it was discovered, it is thought HIV was already widespread, with the earliest infections having occurred before the 1950s.

The first diagnostic blood test for HIV was available by 1984.

Incidence and prevalence

Globally HIV has affected 60 million people and been responsible for more than 30 million deaths. [2]
The highest prevalence rates are known to be in sub-Saharan Africa and other parts of the developing world. In some African countries the impact has been as great as to reverse population growth, and also to reduce life expectancy significantly.
In some high prevalence countries there has been a recent decline in incidence. Elsewhere there are still large scale epidemics of HIV (in India, Eastern Europe and the Russian federation).

Incidence and prevalence in the UK

There was a first peak of HIV diagnoses in 1985 (with a rapid rise of AIDS cases and deaths between the late 1980s and early 1990s). There was a further peak of AIDS diagnoses in 1994 followed by a peak of deaths in 1995.

Latest figures from 2011 estimate the number of individuals living with HIV in the UK to be 96,000. Of importance, this includes an estimated 24% who are undiagnosed and unaware of their infection.

Since 2005 when there was a peak of 7,820 reported new diagnoses there has been a year on year decline.
In 2011, in the UK there were 6,280 people newly diagnosed with HIV. The male to female ratio was 4470 to 1810. The number of HIV infections acquired in the UK, in heterosexuals and 'men who have sex with men' (MSM) continues to rise. Between 2001 and 2011 the UK acquired new diagnoses more than doubled, and these are now greater than those from

abroad (in 2011 UK acquired new diagnoses were 4,059 and new diagnoses acquired abroad were 2,221).
Reported deaths amongst people with HIV in 2011 were 500, and in that year there were 460 cases of AIDS reported.

2. Aetiology

In 1983, the causative retrovirus was isolated, the human immunodeficiency virus. HIV-1 is the cause of the world pandemic. A second retrovirus HIV-2 was found in West Africa, but this has remained largely confined to that geographical location.

Although regarded as a complex retrovirus, HIV has only 9 genes. An understanding of the cellular biology of HIV has been instrumental in the development of effective treatment.

The cell-surface receptor for HIV is CD4, expressed on T-helper lymphocytes which are the cells which become depleted in AIDS. Other target cells for HIV infection include macrophages, Langerhans dendritic cells in mucous membranes and microglial cells in the brain.

Transmission of HIV

There are 3 main modes of transmission of HIV infection. In the context of a disability assessment, intrusive enquiry about the mode of transmission is not required and is never appropriate.

Sexual transmission

This accounts for most new cases of HIV, and in the UK the most common route of transmission is unprotected vaginal or anal intercourse. The presence of other sexually transmitted infections (especially if genital ulcers are a feature) is known to increase the risk of acquiring HIV through sexual contact.

Mother to child transmission

This can occur in utero during late pregnancy, during labour or through breast feeding.

Blood or blood product transmission

In industrialised countries where screening of blood products and heat treatment of factor VIII takes place the risk in therapeutic settings has been minimised. The same cannot be said in resource-limited countries.

Similarly, countries where effective needle exchange and prescribing programmes for drug addicts have been introduced have fewer new infections in injecting drug users.

At risk groups

In recent years, the major risk group in the UK has been ‘men who have sex with men’ (MSM). Also important are heterosexually acquired infections among African-born people, and to a lesser extent, in terms of numbers, people who inject drugs. The changing demographics of HIV infection has been reflected in an increase in the incidence of heterosexually acquired new infections amongst non-African men and women.

3. Diagnosis

Description of clinical stages

Various stages of infection can be described. In industrialised countries it is more useful to consider progressive HIV disease as a continuous spectrum.

In resource limited countries, clinical case definitions for AIDS surveillance have been superseded by the WHO clinical staging system (see **Appendix A**). This assumes that an HIV test has been carried out, as these days rapid HIV tests can be done even in field conditions.

Primary HIV infection

A few weeks following exposure to HIV a proportion of those infected (50 to 70%) develop a mild illness similar to infectious mononucleosis. Features of this include fever, malaise, lymphadenopathy, myalgia and pharyngitis. A feature specific to HIV is the development of an erythematous maculopapular rash affecting the face and trunk. Oral or genital ulceration may also feature. The illness is sometimes referred to as acute retroviral syndrome or seroconversion illness.

The illness is usually of sudden onset and lasts only a couple of weeks. Often severity of symptoms is so mild that medical advice is not sought. It is usual for there to be a transient drop in CD4 lymphocytes.

A high index of suspicion is required for the diagnosis to be made. Current UK guidelines outline at risk groups and when a routine test should be offered (even if symptoms or reported risk are absent). [3] Even when the illness does present itself clinically, the diagnosis may be missed due to failure to elicit a history of exposure to the virus or reluctance to test for HIV. [4]
A recent study showed that even within genitourinary services, documented risk factors may not lead to clinical suspicion of primary HIV infection thus missing the opportunity for early counselling or treatment to reduce onward transmission. [5]

In some cases a different clinical picture is seen, with more long lasting symptoms and neurological complications such as encephalitis or neuropathy. These cases may have poor prognosis with an accelerated progression to AIDS. There may be a substantial drop in CD4 lymphocytes and opportunistic infections such as oral or oesophageal candidiasis, and in rare cases pneumocystis pneumonia.

By definition, primary HIV infection precedes seroconversion, so if testing is limited to viral antibodies then there may be negative or borderline results. Direct testing for viral antigen (p24 antigen) or nucleic acid (HIV RNA) will usually confirm the diagnosis.

Treatment of primary HIV infection with antiretroviral drugs is recommended if certain criteria (such as neurological involvement, an AIDS defining illness or CD4 cell count < 350/mm^3) are present. [6]

Early HIV infection

After the primary illness an asymptomatic period, lasting on average 10 years may be expected (without antiretroviral therapy). Viral turnover is rapid during this period with 10^9 to 10^{10} viral particles replicated daily. The half life of circulating CD4 lymphocytes is also greatly reduced.
In many, physical examination is normal at this time, but in about a third of individuals there is persistent generalised lymphadenopathy (due to reactive follicular hyperplasia) with cervical and axillary nodes most commonly affected. Lymph nodes that are asymmetrical, painful or rapidly enlarging should be biopsied to exclude tumour or opportunistic infection.

Where HIV is untreated minor opportunistic conditions often develop in the skin and mucous membranes. These include fungal, viral or bacterial infections; as well as skin conditions such as eczema, dermatitis and psoriasis.

Periodontal disease can cause gingivitis, or more extensive periodontitis. Two types are specifically associated with HIV. One type being a linear gingival erythema with characteristic appearance, and the other a more serious extensive periodontitis that can lead to loss of dentition.

Oral hairy leukoplakia may be a clue to a positive HIV status. A sign of worsening immunodeficiency is oropharyngeal candidiasis. This gives rise to sore mouth and throat and is one of the more characteristic clinical presentations of HIV disease.

As the condition progresses other non-specific symptoms may develop:

- anorexia
- lethargy
- weight loss
- fever and night sweats
- diarrhoea

Symptomatic HIV disease (AIDS)

Complications of late-stage HIV disease include:

- opportunistic infections
- opportunistic tumours
- direct HIV effects (for example encephalopathy or dementia)

The proportion of symptomatic patients who do not fulfil the criteria for AIDS has increased along with effective prevention of opportunistic infections.

AIDS defining illnesses

In the past 10 years the commonest AIDS defining illnesses have been:

- pneumocystis jiirovecii pneumonia (previously known as pneumocystis carinii pneumonia)
- mycobacterium tuberculosis (TB)
- Kaposi's sarcoma
- oesophageal candidiasis

Clinical indicator diseases for adult HIV infection

This table shows clinical indicator diseases for adult HIV infection grouped as AIDS defining conditions, and other conditions where current testing guidelines suggest HIV testing should be offered. [3]

Condition category	AIDS defining conditions	Other conditions where HIV testing should be offered
Respiratory	Tuberculosis Pneumocystis	Bacterial pneumonia Aspergillosis
Neurology	Cerebral toxplasmosis Primary cerebral lymphoma Cryptococcal meningitis Primary progressive leucoencephalopathy	Aseptic meningitis Aseptic encephalitis Cerebral abscess Space occupying lesion of unknown cause Guillain-Barre syndrome Transverse myelitis Peripheral neuropathy Dementia Leucoencephalopathy
Dermatology	Kaposi's sarcoma	Severe or recalcitrant seborrhoeic dermatitis Severe or recalcitrant psoriasis Multidermatomal or recurrent herpes zoster
Gastroenterology	Persistent cryptosporidiosis	Oral candidiasis Hairy oral leukoplakia Chronic diarrhoea of unknown cause Weight loss of unknown cause Salmonella, shigella or campylobacter infection Hepatitis B or C infection
Oncology	Non-Hodgkin's lymphoma	Anal cancer Anal intraepithelial dysplasia

		Lung cancer Seminoma Head and neck cancer Hodgkin's lymphoma Castleman's disease
Gynaecology	Cervical cancer	Vaginal intraepithelial neoplasia Cervical intraepithelial neoplasia grade 2 or above
Haematology		Any unexplained blood dyscrasia including thrombocytopenia, neutropenia or lymphopenia
Ophthalmology	Cytomegalovirus retinitis	Infective retinal diseases including herpesviruses and toxoplasma Any unexplained retinopathy
ENT		Lymphadenopathy of unknown cause Chronic parotitis Lymphoepithelial parotid cysts
Other		Mononucleosis-like syndrome (primary HIV infection) Pyrexia of unknown origin Any lymphadenopathy of unknown cause Any sexually transmitted infection

Non- progressors

Between 10 and 15% remain clinically well for 15 to 20 years. These long-term healthy survivors are known as non-progressors. It is thought that they represent the tail end of a normal distribution of progression rates. [7]

Late complications of HIV

HIV is a complex condition. Any or all of the bodily systems may be involved producing a very wide range of possible clinical pictures.
The clinical manifestations of the later stages of HIV infection have become much less common with the advent of antiretroviral treatment.

Pneumocystis jiroveci pneumonia

The incidence of this condition had been reduced by primary prophylaxis and anti-retroviral therapy. In 85% of cases the CD4 count is below 200/mm^3 and in most the CD4 count will be below 100/mm^3.
Typical symptoms usually develop over a few weeks and include dry cough, increasing shortness of breath and fever. These may be accompanied by constitutional symptoms such as fatigue or weight loss. There may be some chest signs (crackles) on examination but these are not usually marked.
Chest X-ray may be normal or show the characteristic changes of bilateral mid-zone interstitial shadowing.

Bacterial pneumonia

HIV increases the risk of bacterial pneumonia, which can be recurrent. The most common organism causing bacterial pneumonia is Streptococcus pneumoniae, but other common bacteria such as Haemaophilus influenzae may be responsible. Presentation may be atypical and there can be various X-ray appearances, some mimicking pneumocystis pneumonia. Lung abscesses, pleural effusion and empyema can all occur.

Gastrointestinal disease

This includes oesophageal candidiasis. It presents with retrosternal pain on swallowing and is an AIDS defining condition (indicating advanced immmunosuppression). Oesophagitis can also be due to cytomegalovirus or herpes simplex virus.
Intestinal infections can arise from various protozoa and include a cholera-like diarrhoea due to Cryptosporidium parvum.
Some patients with HIV, particularly in the tropics, present with diarrhoea and malnutrition for which no specific opportunistic infection can be found. This HIV enteropathy is not fully understood but may be due to cytokine activity secondary to HIV infection.

Neurological disease

The nervous system is a major site of involvement in HIV, at all stages of infection, and all parts may be involved. During progressive HIV disease, this is relatively common and may be due to opportunistic infection, tumours such as lymphoma, or HIV replication in the brain or spinal cord causing tissue damage.
The most frequent CNS infection is cerebral toxoplasmosis, occurring when the CD4 count drops below 200/mm^3. This is due to reactivation of toxoplasma cysts in the brain, with focal lesions (usually multiple) forming. Symptoms, which present subacutely, include headache, confusion, convulsions and fever with focal neurological disturbance.
Cryptococcal meningitis arises most commonly in association with HIV infection. Presentation is subacute and symptoms and signs may be non-specific, or less frequently it may present with psychiatric disturbance,

cranial nerve palsies or focal intracerebral lesions. Without secondary prophylaxis and in the absence of antiretroviral treatment relapse rate is high.
Progressive multifocal leukoencephalopathy occurs in advanced HIV disease. It is a progressive demyelinating condition caused by a polyomavirus (JC virus). Presentation is with focal neurological deficits, ataxia or personality change. Multiple white matter lesions are seen on brain MRI scan. This condition has no specific treatment, and carries a very poor prognosis.

Primary cerebral lymphoma presents in a similar fashion to toxoplasmosis, with focal signs or seizures. The disease is usually multi-focal, though investigation will often only show a single space-occupying lesion. Prognosis is poor, though treatment (radiotherapy, steroids and chemotherapy may all be used) may prolong median survival to several months.

Peripheral neuropathy is possible at any stage (even at seroconversion), but occurs most commonly in those with advanced disease (10 to 15% are affected) where the picture is of a distal symmetrical sensorimotor neuropathy of axonal type. Pain and paraesthesia may limit walking. There can also be distal weakness and atrophy. Drugs used to treat HIV are also known to cause or worsen peripheral neuropathy.

Other possible neurological presentations include mononeuritis multiplex and an acute inflammatory polyneuropathy resembling Guillain-Barre syndrome.
The spinal cord may be involved directly by HIV (vacuolar myelopathy). Bilateral leg weakness and sensory symptoms may progress to spastic paraparesis, ataxia and incontinence. In rare cases myelopathy can occur.

HIV-associated dementia

A variety of clinical pictures can present due to direct infection of the nervous system with HIV. Those with brain involvement may be asymptomatic or have only mild functional impairment. Up to 10% develop the features of dementia with cognitive, behavioural and motor abnormalities. In the early stages, dementia may mimic depression (mood changes and impairment of memory or concentration). Progression of dementia leads to severe motor and intellectual impairment and severe disability.

Ocular disease

HIV retinopathy features small, pale retinal lesions (without haemaorrhages). These lesions are benign, and may come and go.
In those who have not had antiretroviral therapy, who have AIDS and a CD4 count below 50/mm^3 reactivation of cytomegalovirus as a severe retinitis occurs in up to 30%. This will progress rapidly to involve all of the retina and macula, causing blindness. Cytomegalovirus retinitis is much less common in developed countries.

Haematological conditions

Thrombocytopenia associated with antiplatelet antibodies affects 5 to 15% of those with HIV infection. Whilst not usually symptomatic until the later stages it can be how the illness presents. Mild neutropenia is common at all

stages of infection. In advanced HIV infection, anaemia is common. It may be linked to medication, or human (B19) parvovirus infection.

HIV-associated nephropathy

Glomerular and tubular epithelial cells in renal tissue can be directly infected with HIV. This results in an HIV-associated nephropathy (usually caused by a collapsing focal glomerulosclerosis). It is more common in Africans and African Americans. The clinical picture is of a nephritic syndrome with little oedema. Whilst improvement in renal function may be expected with antiretroviral therapy some individuals will go on to develop chronic renal failure (with the need for renal replacement therapy i.e. dialysis or transplantation). Another important cause of renal impairment in those with HIV is drug toxicity (from a range of drugs used for treatment).

Skin conditions

Skin manifestations are common in those who present late, occurring at higher CD4 counts and before the more severe AIDS defining illnesses. These include seborrhoeic dermatitis, severe eczema, severe psoriasis, shingles, herpes and eosinic folliculitis.

HIV – related tumours

Kaposi's sarcoma usually presents as skin nodules. Lesions can also appear on mucosal surfaces such as the hard palate. These mucocutaneous lesions are rarely important clinically, but can have great significance cosmetically or psychologically for those affected. However, visceral disease affecting lungs or gastrointestinal tract is an important cause of morbidity, and in some cases mortality. Early Kaposi's sarcoma may be halted or even reversed by highly active antiretroviral therapy.

The incidence of Non-Hodgkin's lymphoma is 60 to 100 times higher in HIV-positive individuals than the general population. Tumours tend to be extra-nodal and whilst the majority are large cell B-cell lymphomas they can also be Burkitt's type, T-cell, non-B cell or non-T cell in type. Those associated with Epstein-Barr virus (about 50%) are more aggressive with poorer prognosis.
As with other complications the incidence of HIV-related lymphomas has declined in developed countries in recent years.

Other tumours

The frequency of some other forms of cancer (not regarded as HIV-related) is increased in those who are HIV positive. These include Hodgkin's disease, hepatocellular carcinoma, lung cancer, cervical cancer, skin tumours and head and neck cancers.

HIV and hepatitis virus coinfections [8]

Co-infection with HIV, hepatitis B (HBV) and hepatitis C (HCV) is increasing, due to shared common risk factors for blood-born infections.
Screening of all new HIV-positive patients for hepatitis B and C is recommended. Those with chronic hepatitis B or C should be offered liver biopsy for diagnosis and disease staging. Assessment of liver fibrosis can also be made using non-invasive techniques if necessary.
For hepatitis B, the HBV DNA level and CD4 count determine whether

treatment is needed.
Co-infection with HIV and HCV is widely recognised as having potential morbidity and mortality. HCV treatment can be prolonged (6 to 12 months) and there may be significant and debilitating side-effects.
Those with HIV/HCV infection have a high prevalence of psychiatric co-morbidity.

Tuberculosis and HIV

In global terms the most frequent life threatening opportunistic infection in AIDS is tuberculosis (TB). An interaction between TB and HIV was apparent early on in the HIV epidemic. The World Health Organisation (WHO) has estimated that a third of the HIV positive world population are co-infected with TB.
Most cases are thought to be reactivation of dormant bacilli, but with research suggesting up to 40% are new infections.
The current view is that all patients who present with active TB should be tested for HIV.
Patients with HIV who present with unexplained symptoms should have TB considered as a possible cause.
Active TB can present at any stage of HIV infection, but presentation during early stage-HIV tends to be typical clinically (cough, fever and weight loss) whilst during late-stage HIV there may be unusual chest findings or extrapulmonary involvement.
Diagnosis may be problematic, as the tuberculin skin test may be negative if the CD4 count is low. Invasive procedures may be needed to obtain suitable specimens to confirm TB.

Treatment of TB in HIV

The standard 6 month regimen (with 3 or 4 anti-TB drugs) will usually be effective, unless there is resistance to one or more of the drugs.
When deciding on a drug regimen, drug interactions (for example rifampicin and protease inhibitors) should be considered.
Initial public health measures should include patient isolation of those with pulmonary TB, and contact tracing to ensure preventive therapy can be offered to those at particular risk (HIV-positive contacts of those who are smear-positive for TB).
Adverse reactions to anti-TB medication occur in up to 20% of HIV patients treated. Liver toxicity can occur with rifampicin, and peripheral neuropathy can occur with isoniazid (this side-effect is more common in those with HIV).
The timing of initiating antiretroviral therapy in those with HIV-associated TB has been the focus of research. The studies in those with pulmonary TB concluded that HAART (Highly Active Anti-retroviral therapy see page 18) and anti-TB therapy should commence together if the CD4 count is less than 50/mm^3. Antiretroviral therapy can be delayed for 8 to 12 weeks, but no longer than 12 weeks in those whose CD4 count is more than 200/mm^3 (to reduce the likelihood of immune reconstitution inflammatory syndrome or IRIS).

NB: - For further information on medication side effects see www.bnf.org

Mycobacterium avium complex

Mycobacterium avium is an organism of low pathogenicity found in domestic water supplies. Historically, many of those in industrialized countries with AIDS were reported to develop Mycobacterium avium complex (MAC) infection. MAC infection becomes widely disseminated in those with advanced HIV and is resistant to most first-line anti-TB drugs. Treatment may need to be lifelong to prevent relapse, if the individual is not receiving antiretroviral therapy.

Late HIV diagnoses

Routine HIV testing has been offered in antenatal and sexual health clinics for the past 10 years. The proportion of late diagnoses still remains unacceptably high. In 2011, 47% of HIV diagnoses were made at a late stage of infection, at a point when treatment should have been started. This suggests a clear need for expanded HIV testing in other clinical settings. [1]

Prompt diagnosis of HIV allows the risk of onward transmission to be reduced by ensuring viral load is low (by monitoring and use of antiretroviral therapy as appropriate). Early partner notification and behaviour change counselling can also be started.

Psychological sequelae

The incidence of psychological and psychiatric conditions amongst those with HIV infection is increased compared with the general population. [9]
Emotional distress can arise from particular events (such as receiving an HIV diagnosis). Depression is thought to be about twice as common in those with HIV. Anxiety may accompany depression, or be experienced on its own.
Screening for drug and alcohol misuse, acute stress disorder, risk of self-harm and cognitive difficulties is recommended within the first 3 months of receiving an HIV diagnosis. Thereafter, annual screening to assess psychological support needs is recommended. [10]
Some drug treatments for HIV are known to cause psychological side effects in some individuals (efafirenz can cause nightmares and sleep disturbance whilst rilvipirine can cause depression and mood changes).
Psychological sequelae may be compounded by the fact that HIV infection remains a highly stigmatised condition.

Investigations

At the time of diagnosis baseline investigations should include the following:

- full blood count
- biochemical screen (liver profile, bone profile, estimated GFR and lipids)
- screening for hepatitis B and C, syphilis and other STDs
- screening for previous infection with CMV and toxoplasmosis

Assessment of the individual for management purposes should also include

determination of risk factors for HIV infection, and the presence of cardiovascular risk factors should also be established.

Other more specific tests should include:

- CD4 lymphocyte count
- a quantitative estimation of HIV RNA in the blood plasma (viral load)
- HIV genotypic resistance testing
- tissue typing for HLA-B*5701 (a marker for abacavir hypersensitivity)
- in women- cervical cytology (an annual test is recommended)

From the perspective of prognostic value, the two best laboratory markers are the CD4 count and viral load.

CD4 count

This is a reliable indicator of immune impairment due to HIV. The count is normal at or above 600/mm^3 but there can be wide variability even in the absence of HIV infection.
In the UK, those living with HIV are recommended to start treatment when their CD4 count is around 350/mm^3.
Without antiretroviral therapy, the risk of opportunistic infections in those with a CD4 count that has fallen below 200/mm^3 is about 80% over 3 years. However, clinical progression is known to vary, and a minority will remain well for several years with stable low CD4 counts. Differences in viral load can partly explain this variability.
The spectrum of potential infections is generally determined by the level of CD4 lymphopenia (see **Appendix B**).

HIV viral load

Tests for HIV viral load are widely available in industrialised countries. Various techniques are used, which are highly sensitive with very low detection limits (40 copies/ml)

Screening [3]

As many HIV positive individuals will be unaware they are infected, targeted screening programmes aim to reduce the risk of both sexual and perinatal transmission.
The recommended first-line assay tests for both HIV antibody and p24 antigen at the same time (fourth generation assay). This reduces the time from between infection and testing HIV positive to one month.
Viral load tests may produce false positives so are not recommended for screening purposes.
All new HIV diagnoses should have testing of a second sample and further confirmatory assays.

In some situations, point of care testing (POCT) may be appropriate (certain clinical settings, in the community etc). This allows a result to be given within minutes (from fingerprick or mouth swab sample). Results are less accurate, and further confirmatory tests will be needed.

Currently, rates of HIV testing in the primary care setting are low. For most GPs HIV will be an uncommonly made diagnosis which may be a reason

rates have remained low. Recent research suggests patients find the offer of testing in primary care acceptable, and most proceed to having a test. Increasing HIV testing in primary care would help target some of the HIV positive individuals who remain undiagnosed which would benefit both those individuals and reduce the likelihood of further onward transmission. [11]

4. Treatment

Knowledge of cell biology has enabled the development of pharmacological agents to treat HIV infection. The advent of antiretroviral therapy has transformed HIV to a chronic condition from one that was universally fatal. Current treatments interrupt the life cycle of the virus, suppressing HIV replication by inhibiting HIV enzymes.

The benefits of treatment are closely linked to early diagnosis of the infection.

The 2012 British HIV Association Guidelines recommend starting treatment when the CD4 cell count falls to 350 cells/ mm^3. The guidelines also suggest that in older people consideration should be given to starting treatment at higher CD4 counts because of the higher risk of disease progression in this group.

In the UK, retention in HIV care is high with an estimated 90% of adults with HIV regularly attending services. A further 4% attend intermittently. Whilst there are some known factors linked to 'loss to follow up' (female sex, age <35, recently diagnosed, infected outside the UK, black African) the reasons for this are not yet fully understood.

Management of care for adults with HIV, in resource-rich countries, is almost entirely through outpatient services.
Once commenced treatment is lifelong, and should if at all possible continue uninterrupted. This requires commitment from both patient and health care team.

For antiretroviral therapy to be effective, adherence of greater than 95% is needed. Medication needs to be taken as prescribed (at the right time of day, with food etc). Social support needs to be sufficient to meet the challenges of adherence.

Medication [2][12]

Between 2002 and 2011, the proportion of HIV diagnosed people receiving antiretroviral therapy increased from 71% to 84%.

To optimise first-line therapy resistance tests to drugs are carried out on HIV patients before they start treatment.

There is no evidence to indicate that treatment with antiretroviral therapy can ever effect a 'cure' or completely eradicate HIV. However, treatment is highly effective at keeping those with HIV well and allowing a near-normal life expectancy. It has also been shown that antiretroviral therapy can make someone living with HIV virtually unable to transmit HIV to someone else, by reducing viral load to undetectable levels.

Current guidelines recommend treatment should be considered if HIV

symptoms develop, or the CD4 count falls to around 350 /mm^3.
Other factors that should be taken into account include the rate of CD4 decline, viral load, age, co-infections (hepatitis B or C) and whether or not the individual has a partner who is HIV negative.
The results of a major prospective trial looking at the timing of initiating therapy (Strategic Timing of Anti-Retroviral Treatment – START) are expected in 2015. The trial will look at whether treatment should start immediately on diagnosis, when CD4 count falls to below 350 /mm^3 or when the individual develops AIDS.

Highly active anti-retroviral therapy (HAART) comprises at least 3 drugs from 2 different drug classes. There are a number of initial regimens with comparable efficacy.

Antiretroviral therapy

A number of different drugs are used in combination (see **Appendix C** for a table of the principal antiretroviral agents).

Nucleoside analogue reverse transcriptase inhibitors

Zidovudine (AZT or ZDV) was first shown to be active against HIV (in vitro) as long ago as 1985. Once in use, there was still clinical progression after a year or two of therapy due to drug resistance developing.
This prompted the use of combination therapy, to reduce drug resistance.
The nucleotide agent tenofovir is usually grouped with the nucleoside analogues. As less toxic and easier to use alternatives are available, AZT is used infrequently now.

Non-nucleoside reverse transcriptase inhibitors

Efavirenz is the most commonly prescribed drug from this class of antriretrovirals.Other drugs in this class licensed in the UK include nevirapine, etravirine and rilpiravine.

Protease inhibitors

Inhibitors of HIV protease act synergistically with nucleosides, and greatly inhibit HIV replication as a result. These days the pharmokinetics of a protease inhibitor will usually be boosted by the additional use of ritonavir (in low dose).

Entry inhibitors

This newer class of drug targets viral entry into cells. There are 2 subgroups, called fusion inhibitors and co-receptor antagonists (the role of this subgroup in management terms is still to be determined).
Enfuvirtide is licensed for use in treatment-experienced patients as part of a combination therapy. Administration is by sub-cutaneous injection, and a disadvantage is the high rate of injection site reactions. This means Enfuvirtide is rarely prescribed now.

Integrase inhibitors

This is another new class of drug, with the first licensed drug being raltegrivir. The drug inhibits the enzyme integrase which is needed to integrate HIV proviral DNA into the host cell genome.

Combination therapy

Treatment has been shown to be most effective if 3 drugs are used, and this has become the standard of care.

Combinations include:

- 2 nucleosides and 1 non-nucleoside reverse transcriptase inhibitor or

protease inhibitor
- 3 nucleoside analogues (but this is less effective and not routinely recommended)

Treatment failure

There is no agreed definition of treatment failure, but those who fail to show viral load suppression to less than 40 copies/ml within 6 months or who show a rise in viral load after an initial suppression should be considered for treatment change (3 new drugs).
Inadequate treatment is the most important cause of treatment failure. Factors that may lead to irregular taking of drugs include non-adherence or lack of availability of drugs. Poor absorption may also be a factor in failed treatment.

Of concern is that sub-optimal therapy is known to be a factor in the development of drug resistance mutations.

Toxicity may also necessitate a change in therapy.

Drug resistance

One of the major factors in treatment failure is drug resistance. Resistant mutants are known to arise spontaneously, but when HIV replicates in the presence of sub-optimal levels of anti-retroviral therapy the selection of drug-resistant mutants occurs rapidly. This selection can be stopped if HIV replication can be completely suppressed by effective drug treatment.

Genotypic assays for drug resistance are widely used, being relatively easy to perform and low cost.
It is recommended that baseline resistance testing is carried out at diagnosis, to identify resistance mutations at an early stage.

'Salvage' therapy

This is treatment following exposure to multiple antiretroviral drugs in the past. Usually, there will be numerous drug resistance mutations present. Achieving sustained viral suppression below detection level is much less likely in this situation. However studies suggest being able to reduce the viral load does lead to clinical improvement.
At least 2 new drugs should be used in the regimen, but it may be possible to recycle drugs used in the past as well.

Drug toxicity

This occurs commonly and may be a factor in reduced drug compliance. Side effects can range in severity from minor GI disturbance to a serious adverse reaction (see **Appendix D** for further details).

Antiretroviral treatment can cause metabolic effects. Lipodystrophy syndrome is the collective term for:
- insulin resistance
- dyslipidaemia
- fat redistribution (loss of subcutaneous fat, increased abdominal fat, 'buffalo hump' and breast enlargement)

Some drugs (stavudine, didanosine and zidovudine) which are associated with a higher risk of lipoatrophy should only be used in the absence of suitable alternative drugs. [12]

Drug interactions are also possible, and of particular importance in advanced HIV disease.

Immune reconstitution inflammatory syndrome (IRIS)

Unusual signs and symptoms have been reported in patients on HAART, some time after starting therapy. This syndrome arises when the CD4 count is increasing. Another name used is immune reconstitution disease (IRD). It may take the form of an unusual presentation of a previously subclinical opportunistic infection, or an exacerbation of a previously treated opportunistic infection.

Absence of an agreed definition means incidence is difficult to ascertain, but it is thought up to 20% on HAART may be affected. HAART should be continued, and although there is no trial data to support their use, steroids may be prescribed. Most cases of IRIS are self-limiting.

Prevention of opportunistic infections

Low-dose co-trimoxazole is used routinely as PCP prophylaxis once the CD4 count is consistently below 200/mm^3. This also reduces the risk of cerebral toxoplasmosis and possibly bacterial pneumonia.

In some countries, isoniazid is used prophylactically (for a year) in high risk groups to reduce the risk of developing active TB.

Management of late complications

First line treatment for pneumocystis jiroveci pneumonia (PCP) is high-dose co-trimoxazole for 3 weeks. Alternative treatments include clindamycin and primaquine, trimethoprim and dapsone or intravenous pentamidine (this is used infrequently due to toxicity). [13]

In moderate to severe PCP, use of high dose steroids has been shown to reduce morbidity and mortality. Ventilatory support may be needed if respiratory failure develops.

Focal cerebral lesions are treated as for cerebral toxoplasmosis as standard practice (as toxoplasmosis is by far the commonest cause). Should there be no clinical improvement in 7 to 10 days; biopsy of a lesion would be carried out.

Cryptococcal meningitis is best treated with amphotericin B and flucytosine together. Close monitoring for adverse reactions is needed. Secondary prophylaxis with fluconazole is effective in preventing relapse. Without this, the relapse rate is 50 to 80%.

First-line treatment of Cytomegalovirus retinitis is with intravitreal ganciclovir injection or implant.

Other management

Those susceptible can be immunised against hepatitis B and should also receive flu and pneumococcus vaccination.

Psychological support and counselling are key components of the management of HIV infection. A high level of understanding and motivation will help adherence to treatment.
Skilled support from trained professionals may improve patient adherence to treatment regimens.

Management should also include advice on lifestyle factors:

- avoidance of illicit drug use (particularly intravenous)
- avoidance of excess alcohol
- minimising stress
- adequate exercise
- maintaining adequate nutrition
- safer sex practices
- maintaining positive social contacts/ hobbies and interests

Recent published guidelines advising on provision of psychological support advocate a ‘stepped care model’ for managing the specific mental health needs of those with HIV. [14]
The model has 4 steps:

- Information and support
- Enhanced support
- Counselling and psychological therapies (HIV specialist)
- Specialist psychological and mental health intervention (general or other specialist)

5. Special Situations

HIV in children

Infection in children is usually through mother-to-child transmission (MTCT). Advanced maternal HIV disease, vaginal delivery and breast feeding all increase the risk of MTCT.
In resource- rich countries the use of HAART in pregnancy and elective caesarean section has reduced the risk of transmission to less than 1%.
Diagnosis during the first year of life is absolutely key, as about 20% of HIV-infected children will progress rapidly to AIDS. As uninfected children may have maternal HIV antibody up to the age of 18 months, the diagnostic approach taken is to use virus detection techniques (HIV DNA by PCR). This allows for HIV infection confirmation in 95% of all non-breastfed perinatally infected children by the age of 1 month.

Common AIDS diagnoses in infancy include pneumocystis pneumonia and HIV encephalopathy. Developmental delay is common with 10% severely affected, and 40% having some evidence of delay.

The management of children with HIV should be in specialist units (from paediatricians who have experience in HIV management).
In the first year, prophylaxis against pneumocystis is usually given regardless of the CD4 count. In older children, the principles of monitoring and treatment are similar to that taken for adults.

Occupational exposure [15]

A study looking at 3000 instances of occupational exposure to HIV showed the risk of HIV infection after needlestick injury/ percutaneous exposure to be 0.3%. The risk after mucous membrane exposure was lower at 0.1%.
In spite of lack of direct evidence, current recommendation is for a high risk occupational exposure (deep wound, direct blood vessel cannulation involved or exposure from patient with advanced HIV disease) to be treated with 2 nucleoside inhibitors and a protease inhibitor for one month.
All instances of occupational exposure merit careful and prompt risk assessment, to maximise potential benefit of treatment.

6. Prognosis

In the UK, HIV can now be regarded as a chronic manageable disease rather than a fatal illness.
From the mid-1990s and the advent of antiretroviral therapy there was a sharp decline in the number of AIDS-defining diseases. However, over the past decade AIDS diagnoses have continued (460 reported in 2011). The majority are in those diagnosed late.

Whilst the average time between HIV infection and progression to AIDS is 10 years, about 20% of those infected with HIV progress rapidly within 5 years.
Where HIV is acquired later in life the prognosis is less favourable.
Other poor prognostic factors include acquiring the infection through intravenous drug use, and high viral load/ low CD4 count when HAART is initiated.

Several studies have highlighted that treated HIV patients still have a reduced life expectancy compared with an uninfected population. The incidence of cancer, liver disease and cardiovascular disease is higher in this group. Conditions which may be regarded as phenomena of the normal aging process may be seen at an earlier age in those with HIV infection. This may be due the long term effects of HIV treatment as well as HIV itself. [9] [16]

Liver disease

Hepatitis C co-infection has led to an increasing number of deaths and cases of cirrhosis. Hepatitis B and alcohol abuse are also possible additional risks for liver disease that may be seen.

Heart disease

This is assuming increasing importance due to the hyperlipidaemic effects of antiretroviral drugs, and the enhanced risk of diabetes. Myocardial infarction, angina and peripheral vascular disease are occurring in unusually young age groups (who may also have the additional risk of a heavy smoking habit).

Life Expectancy

With prompt diagnosis, and timely antiretroviral therapy normal or near-normal life expectancy may be expected.
The risk of death in the first year following diagnosis is increased 10 fold in those diagnosed late compared with those who have an early diagnosis. [1]

7. Main Disabling Effects

As mentioned previously HIV is a complex condition, with many possible clinical presentations and the capacity for any or all bodily systems to be affected.
Many individuals receiving care and treatment remain well for years after infection, and early or mild symptoms are unlikely to have any disabling effects.

Variability and fluctuation of the disabling effects of the condition or its treatment may be experienced by individuals, and will need careful consideration. Fluctuating symptoms may be multiple and can affect both physical and mental function adversely. Variability or fluctuation in disability may, or may not be predictable. [17]

Good response to treatment does not guarantee absence of potentially disabling symptoms or disabling side-effects.
Where HIV is more advanced, disabling features may be severe and widespread and arise from opportunistic infections, malignant disease, neurological impairment, severe cognitive impairment and sensory impairment.

Treatment side-effects giving rise to disability include cardiovascular disease, diabetes and lipodystrophy.

Treatment side effects may be long lasting, and patients may retain serious impairment from the poorer efficacy of earlier treatments, even if currently responding well to more modern treatments.

Self-care needs

May be affected by:

- fatigue
- general debility
- muscle weakness
- impaired balance
- severe night sweats/ sleep disturbance
- severe diarrhoea
- cognitive impairment due to dementia
- psychological sequelae (such as depression)

Mobilising needs

May be affected by:

- fatigue
- general debility
- muscle weakness
- osteoporosis and bone density loss
- peripheral neuropathy

- breathlessness
- visual impairment

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Appendix A - WHO Clinical Staging System[2]

WHO Clinical Stage	HIV-associated symptoms	Examples of defining conditions
1	Asymptomatic	• Asymptomatic • Persistent generalised lymphadenopathy
2	Mild symptoms	• Recurrent respiratory tract infections • Herpes zoster • Seborrhoeic dermatitis
3	Advanced symptoms	• Unexplained severe (>10%) weight loss • Persistent oral candidiasis • Pulmonary tuberculosis • Severe bacterial infections
4	Severe symptoms	• HIV wasting syndrome • Extrapulmonary tuberculosis • Recurrent severe bacterial pneumonia • Kaposi's sarcoma

Appendix B - Principal Complications (Untreated HIV Infection) [2]

Principal complications of untreated HIV infection		
Infections	**Neoplasms**	**Direct HIV effects**
Early/intermediate HIV infection (CD4>200/mm^3)		
Herpes zoster	Non-Hodgkin's lymphoma[a]	Persistent generalised lymphadenopathy
Oral hairy leukoplakia	Cervical intraepithelial neoplasia	Atopy; eczema
Oral candidiasis; candidal vaginitis	Anal intraepithelial neoplasia	Recurrent aphthous ulcers (oral and gastrointestinal tract)
Pulmonary tuberculosis[a]		Immune thrombocyopenia
Bacterial pneumonia, especially pneumococcal		Neutropenia
Bacteraemia, especially pneumococcal and salmonella		Neuropathy (mononeuritis multiplex; Guillain Barre syndrome)
Bacillary angiomatosis		HIV associated nephropathy (HIVN)
		Lymphocytic interstitial pneumonitis (LIP)
Late HIV infection (CD4<200/mm^3)		
Pneumocystis pneumonia[a]	Kaposi's sarcoma[a]	HIV enteropathy
Candidal oesophagitis[a]	Primary cerebral lymphoma[a]	Peripheral neuropathy (distal, axonal)
Cerebral toxoplasmosis[a]	Hodgkin's lymphoma	Autonomic neuropathy
Cryptococcal meningitis[a]	Conjuctival carcinoma	Myelopathy
Chronic cryptosporidial[a] diarrhoea	?cervical carcinoma[a]	HIV dementia[a]
Chronic isosporiasis[a], microsporidiosis	?anal carcinoma	Wasting syndrome[a]
Chronic HSV[a] ulceration		Cardiomyopathy
Extrapulmonary tuberculosis[a]		
Disseminated M.avium complex (MAC)[a]		
CMV (retinitis and disseminated)[a]		
Progressive multifocal leukoencephalopathy[a]		
Recurrent bacterial pneumonia[a]		
Recurrent bacteraemia, especially salmonella[a]		
Disseminated histoplasmosis[a], and P. mameffei		

(a) AIDS-defining condition, incomplete list. ? – suspected but unproven association

Appendix C - Principal Antiretroviral Agents [2]

Principal Antiretroviral Agents			
Nucleoside Reverse Transcriptase Inhibitors	**Non-Nucleoside Reverse Transcriptase Inhibitors**	**Protease Inhibitors**	**Entry Inhibitors**
Zidovudine (AZT/ ZDV)	Nevirapine	Lopinavir[a]	**Fusion Inhibitor**
Lamivudine (3TC)	Efarivenz	Ritonavir	Enfuvirtide
Emtricitabine (FTC)	Etravirine	Azatanavir	
	Rilpirivine		
Abacavir (ABC)		Saquinavir[a]	
Didanosine (ddl)		Fosamprenavir[a]	Maraviroc
Stavosine (d4T)		Indinavir[a]	
Nucleotide Reverse Transcriptase Inhibitor		Nelfinavir	
Tenofovir (TDF)		Tipranavir[a]	**Integrase Inhibitors**
		Duranavir[a]	Raltegrivir

(a) Given with low dose ritonavir for pharmakinetic enhancement

Common Fixed Dose Drug Combination Preparations	
Name	**Drug combination**
Truvada	tenofovir, emtricitabine
Kivexa	abacavir, lamivudine
Atripla	tenofovir, lamivudine, efavirenz
Eviplera	tenofovir, emtricitabine, rilpivirine

Appendix D - Principal Drug Toxicities [2]

Nucleoside Reverse Transcriptase Inhibitors (NRTI)		
Class effects	GI disturbances, raised liver enzymes, hepatic steatosis, lactic acidosis	
AZT	Headache, nausea (usually resolves in 2 to 4 weeks)	
	Anaemia (avoid if anaemic at baseline)	
	Macrocytosis (benign)	
	Nail pigmentation	
	Myopathy (rare on lower doses 500-600 mg/day)	
	Lipodystrophy with facial wasting (long-term effect, unknown incidence)	
ABC	Hypersensitivity 5%; may be fatal if rechallenged (closely associated with HLA B*5701)	
ddI	Pancreatitis, peripheral neuropathy	
d4T	Lipodystrophy with facial wasting; peripheral neuropathy	
3TC, FTC	No major toxicities	
Nucleotide RTI		
Tenofovir	Renal failure (case reports, rare, incidence unknowm)	
Non-nucleoside RTI (NNRTI)		
Efavirenz		Neuropsychiatric disturbances (8%) – vivid dreams, impaired concentration, mood changes usually transient, <4 weeks duration; rash
Nevirapine		Rash (20%, severe 6%); rarely Stevens-Johnson syndrome; hepatitis (esp in women with CD4>250/mm^3 or men with CD4>400mm^3 –avoid)
Protease Inhibitors (PI)		
Class effects	GI disturbances; hyperlipidaemia, truncal fat accumulation, diabetes, bleeding in haemophiliacs, raised liver enzymes	
Lopinavir	Diarrhoea	
Ritonavir	Circumoral and peripheral parasthesiae (unusual in low dose)	
Saquinavir	Rash, peripheral neuropathy	
Nelfinavir	Diarrhoea	
Indinavir	Renal calculi, haemolysis	
Atazanavir	Hyperbilirubinaemia, jaundice	
Tipranavir	Rash (caution in sulphonamide allergy), liver dysfunction	
Darunavir	Diarrhoea, rash (caution in sulphonamide allergy)	
Entry Inhibitors		
Fusion Inhibitors		
	Injection site reactions (painful, erythematous nodules); headaches, dizziness, nausea, eosinophilia	
CCR5 Antagonists		
Maraviroc	Cough, muscle and joint pain, diarrhoea, sleep disturbance, raised liver enzymes (and possibly hepatitis)	
Integrase Inhibitors		
Raltegravir	Nausea, diarrhoea, headache; raised CPK in some patients	