# Section 1
# INTRODUCTION

# 1 Introduction to Human Immunodeficiency Virus

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## Key Points

- The HIV pandemic is one of the greatest threats to human health in history.
- Seventy per cent of worldwide deaths from AIDS occur in sub-Saharan Africa.
- Without treatment for HIV, worsening immunocompromise leads to the development of opportunistic infections and certain cancers.
- Factors associated with more rapid HIV disease progression include older age, poor nutrition and co-infection with tuberculosis and hepatitis C.
- Preventative strategies, such as behaviour change, screening of blood products, post-exposure prophylaxis and treatment of HIV during pregnancy, help decrease rates of HIV transmission.
- Improved access to treatment worldwide has reduced the annual number of HIV-associated deaths and may also reduce the number of new HIV infections globally.

## 1.1 Introduction

HIV-1 and HIV-2 are related viruses, both of which gradually destroy the body's immune system. Since 1981, more than 25 million people have died from the complications of HIV infection, making the HIV pandemic one of the greatest threats to human health in history.

HIV-1 is found throughout the world and is responsible for the global epidemic (UNAIDS, 2009). It is more infectious than HIV-2 and causes a more rapid decline in the immune system resulting in a shorter time between infection and death. HIV-2 is less easily transmitted than HIV-1 and is found primarily in West Africa (Jaffar *et al.*, 2004). HIV-1 is responsible for the global epidemic and will be the focus of this book.

There is evidence that HIV originated as Simian Immunodeficiency Virus (SIV) in non-human primates in West-Central Africa and transferred to humans early in the twentieth century (Worobey *et al.*, 2008). AIDS was first recognised as a clinical syndrome in 1981 and the HIV-1 virus was first identified in a French laboratory in 1983. HIV-1 is classified into three groups (M, N and O), each of which arose from a separate transmission of SIV into humans. Whilst N and O are extremely rare, M (major) is further divided into 11 subtypes (A to K) which differ from one another

in their genetic make-up and their geographic distribution. The commonest subtype worldwide is subtype C, whereas subtype B is the predominant subtype in the USA and Western Europe (Lynch *et al.,* 2009). There is evidence that untreated subtype D has a worse prognosis than other subtypes (Baeten *et al.*, 2007) but the response to treatment between subtypes is similar (Geretti *et al.*, 2009).

## 1.2 Current state of the epidemic

### 1.2.1 Worldwide

Globally, an estimated 33.4 million [31.1 million–35.8 million] people were living with HIV as at December 2008. This number has increased from around 8 million in 1990.

Sub-Saharan Africa remains the worst affected region globally with 22.4 million [20.8 million–24.1 million] adults and children living with HIV. This compares with 850 000 [710 000–970 000] adults in Western and Central Europe and 1.4 million [1.2 million–1.6 million] in North America. Overall, 5.2% [4.9%–5.4%] of sub-Saharan African adults between 15 and 49 years old are HIV-infected (UNAIDS, 2009).

Sixty-one per cent of people infected with HIV in sub-Saharan Africa are women and several population-based surveys in Africa have found extremely high rates of infection amongst young women – for example, HIV infection rates of 51% among women between 25 and 29 years in rural South Africa (Welz *et al.*, 2007).

During 2008 alone, 2.7 million people [2.4–3.0 million] were newly infected with HIV and 2.0 million people [1.7–2.4 million] people died from AIDS. Since new cases outnumber deaths, the number of people living with HIV therefore continues to increase (see Figure 1.1, UNAIDS, 2009).

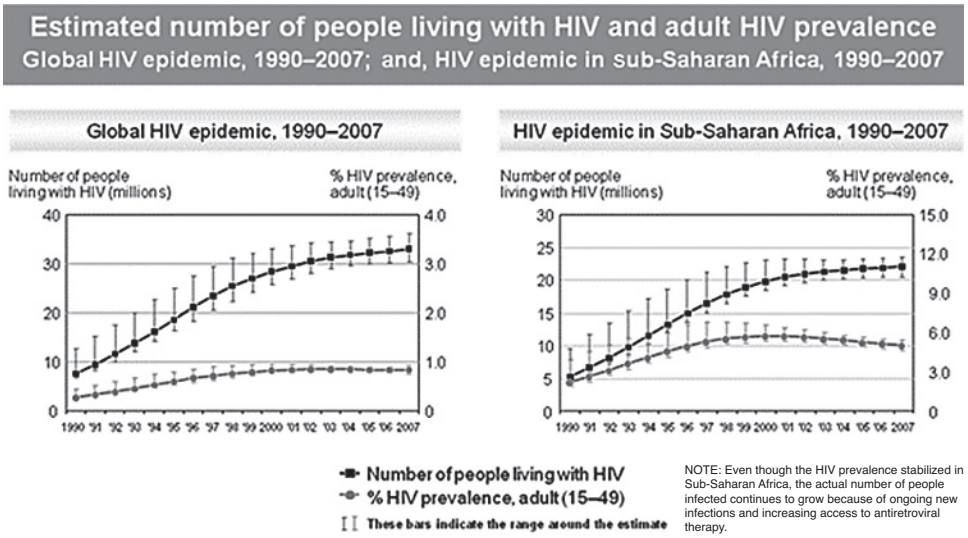


**Figure 1.1** HIV global trends over time. With permission from the UNAID 2008 Report on the global AIDS epidemic.

### 1.2.2 UK and USA

An estimated 83 000 people are living with HIV in the UK. An estimated 58% of people newly diagnosed in 2007 acquired their infection through heterosexual contact and 38% from sex between men. Three quarters of those infected heterosexually probably acquired their infection outside the UK. In 2007, an estimated 6% of UK men who have sex with men (33 300 individuals) aged 15 to 44 years were HIV-infected (Health Protection Agency, 2009).

The HIV prevalence rate in the USA is considerably higher than in the UK at 448 per 100 000 population (1.1 million adults and adolescents). In 2006 Black Americans accounted for 49% of HIV cases diagnosed. The HIV prevalence rate among black people (1715.1 per 100 000) is 7.6 times that of white people (224.3 per 100 000), demonstrating the association between social marginalisation and HIV risk. Seventy-five per cent of prevalent cases were men with the greatest risk factor being sex with men (Centers for Disease Control, 2008).

According to anonymous HIV testing data, around 1 in 4 people with HIV in the UK remain undiagnosed. In 2008, 32% of adults newly diagnosed with HIV in the UK were diagnosed late with a CD4 cell count below 200 cells/mm$^3$ (Health Protection Agency, 2009).

Late diagnosis is the most important factor associated with HIV-related morbidity and mortality in the UK. At least a quarter of the deaths reported in HIV-positive individuals in the UK between 2004 and 2005 may have been prevented if HIV diagnosis had occurred earlier. Late presentation also means that opportunities to reduce HIV transmission by reducing high-risk behaviours or by reducing HIV viral load (and hence infectivity) through treatment are missed (Girardi *et al.*, 2007).

### 1.2.3 AIDS-related mortality

HIV remains the single greatest cause of death in sub-Saharan Africa – responsible for more than 20% of deaths in the region. In 2008, 70% of all deaths worldwide from AIDS occurred in sub-Saharan Africa (UNAIDS, 2009). Since the start of the epidemic, HIV/AIDS has more than reversed gains in life expectancy made in many African countries since the 1960s. For example, in Lesotho, where 1 in 4 adults are estimated to be living with HIV, life expectancy at birth between 1990 and 1995 was nearly 60 years. This fell to 34 years by 2005 to 2010 as a result of AIDS-related mortality (United Nations Population Division, 2005).

As many as 14.1 million (11.5–17.1 million) children in sub-Saharan Africa have lost at least one parent due to AIDS. This has devastating effects on communities and on the economy of affected countries (UNAIDS, 2009).

With the advent of effective antiretroviral therapy (ART), the crude mortality rate among HIV-infected persons in the UK declined from 4.7% in 1997 to 0.95% in 2006. Due to co-morbidities, such as hepatitis C, the mortality rate among injecting drug users in the UK remained considerably higher at 2.9% per year in 2006 (May *et al.*, 2007).

## 1.3 HIV transmission

The commonest route of HIV transmission is through unprotected sexual intercourse and contact with infected genital secretions. HIV may be transmitted vertically (from

mother to child) either in utero, during labour or through breast-feeding. HIV is also transmitted via contaminated blood and blood products, for example through sharing contaminated needles for injection of drugs and via transfusions of unscreened blood products.

Receptive anal intercourse is associated with a 10- to 20-fold greater risk of HIV transmission than vaginal intercourse. This is at least partly attributable to the immunology of the rectal mucosa. Only a single layer of columnar epithelium separates the rectal lumen from the lamina propria, a layer of immunologically active cells which contain a broad range of HIV target cells expressing CD4 co-receptors (see below) (Royce *et al.,* 1997; Boily *et al.*, 2009).

Studies have identified several specific, biological risk factors for infection: The presence of other sexually transmitted infections increases the risk both of becoming infected and of infecting a partner with HIV (Cohen, 2004). Circumcised men are less likely to become infected with HIV (Mills *et al.,* 2008).

A high HIV viral load in body fluids also increases the risk of HIV transmission. In a study of couples in Uganda where one partner was HIV-infected and the other was not, an HIV-1 viral load above 50 000 copies/ml in the HIV-positive partner was associated with a rate of HIV transmission of 23 infections per 100 person years, whereas no infections occurred in couples where the HIV-positive partner had a viral load below 1500 copies/ml (Quinn *et al.*, 2003).

Despite the high rates of infection amongst women in Africa, women do not have an intrinsic biological vulnerability to HIV infection. At any given viral load, women are as likely to become infected with HIV as men (Boily *et al.,* 2009). Rather, the increased vulnerability of young women is due to societal structures and unequal gender roles which render women unable to negotiate safe sexual relations or force them to have sex to survive (Chersich and Rees, 2008; Jukes *et al.,* 2008; MacLachlan *et al.,* 2009).

## 1.4 About the virus

HIV (human immunodeficiency virus) is a retrovirus that uses the enzyme reverse transcriptase to produce proviral deoxyribonucleic acid (DNA) from ribonucleic acid (RNA). HIV primarily attacks white blood cells, particularly T-helper lymphocytes containing the CD4 receptor. It also infects other cells expressing CD4 receptors, including macrophages, Langerhans' cells, monocytes and microglial cells (Wang *et al.,* 2000) T-helper cells have an essential role in cell-mediated immune responses. As a result of this selective destruction of the immune system, people infected with HIV are more susceptible to illnesses and opportunistic infections. (Munier and Kelleher, 2007)

### 1.4.1 Structure of HIV

The HIV particle contains three components: the core, the surrounding protein matrix and the outer lipid envelope. The core contains the viral genetic material, RNA, encapsulated by the capsid protein p24, which contains enzymes (reverse transcriptase, integrase and protease) involved in viral replication. The glycoproteins

gp41 and gp120, which are attached to the envelope, enable HIV to bind and fuse with target host cells (Wang *et al.*, 2000).

### 1.4.2 HIV life cycle

#### *Recognition, binding, fusion and entry*

HIV can only replicate inside human cells. The HIV particle binds to a host cell containing protein receptors (Figure 1.2), of which CD4 is the most important. The binding of the HIV enables the viral envelope to fuse with the host cell. The viral RNA contents are released into the cell, leaving the envelope behind (Figure 1.2) (Nisole and Saïb, 2004).

#### *Reverse transcription and integration*

Inside the host cell, the enzyme reverse transcriptase converts the viral RNA into DNA (Figure 1.2). This DNA is transported to the nucleus, where it is incorporated into the human genome by the enzyme integrase (Figure 1.2). Once integrated, the HIV DNA is called a provirus (Nisole and Saïb, 2004).

#### *Transcription and translation*

The HIV provirus can lie dormant within the cell for a long period. Once activated, the DNA is converted back to RNA, is transported outside the nucleus and is translated into new HIV proteins and enzymes (Wang *et al.,* 2000).

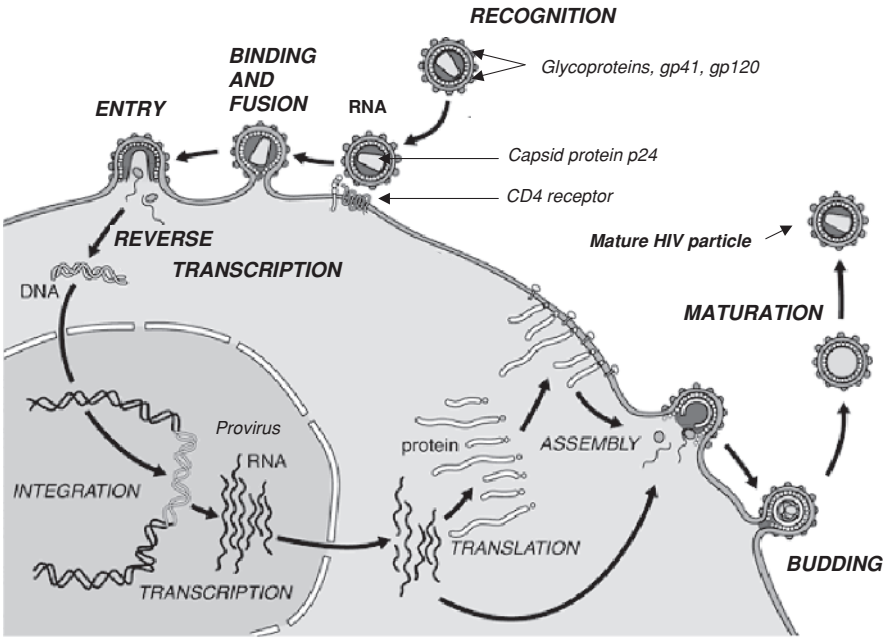


**Figure 1.2** The HIV life (Source: http://media.wiley.com/CurrentProtocols/PH/ph1205/ph1205-fig-0001-1-full.gif).

### *Assembly, budding and maturation*

The enzyme protease is involved in cleaving long protein strands into smaller ones that are incorporated into the HIV particle (Figure 1.2). At the host cell surface, the new HIV proteins and enzymes combine with viral RNA to form new HIV particles. These newly matured HIV particles are released from the host cell. They are ready to infect new cells and restart the replication cycle. The entire process is very active and large numbers of HIV particles are released daily (Gomez and Hope, 2005).

## 1.5 Diagnosis of HIV

### 1.5.1 The HIV test

Until recently, HIV tests detected only antibodies produced by the infected host in response to infection with HIV. Most people develop detectable HIV antibodies within 6 to 12 weeks of infection. This meant that the 'window period', i.e. the time from HIV infection until these tests become positive, was around 3 months.

The HIV test currently recommended by the British HIV Association and widely used internationally is a 'fourth generation HIV test' which detects both HIV antibodies and the p24 antigen. These are very accurate tests with sensitivities and specificities greater than 99%. Because the test can detect the p24 antigen (i.e. a part of the virus itself) the fourth generation HIV test has reduced the window period to around one month (Weber *et al.,* 2002; BHIVA, 2008b).

The rapid HIV test, also known as the point of care test (POCT), can give results either from a finger prick or from an oral swab sample in 15 minutes. Rapid tests do not require laboratory facilities and are useful in resource limited settings and other clinical scenarios where routine blood testing is not possible or where the rate of return for results is low. However, as with most screening tests there is a relatively high rate of false positive results particularly in areas of low HIV prevalence. Therefore all positive results should be confirmed by a conventional test.

It is generally recommended that HIV testing is performed in a health care setting and pretest discussion should establish informed consent for the test. Specific guidance regarding pretest discussion is available from the British HIV Association. These guidelines also suggest routine HIV testing of all patients presenting to a range of hospital departments with so-called 'indicator conditions', i.e. conditions which may be caused or worsened by HIV. Examples include severe psoriasis and seborrheic dermatitis which may be the first manifestations of undiagnosed HIV infection (BHIVA, 2008b).

Conventional tests for HIV are unable to distinguish recent infections from long-standing infections. Recent laboratory advances have made it possible to identify HIV infections which have been acquired during a recent time frame – usually around 6 months. The generic term 'Serological Testing Algorithm for Recent HIV Seroconversion' (STARHS) covers several serological methods (also called 'detuned' or sensitive/less sensitive assays (S/LS)) which can identify recent infections (UNAIDS, 2001).

## 1.6 Measurement of CD4 cells

Because HIV infects CD4 cells and uses them to produce more HIV copies, HIV infection is characterised by a progressive fall in the number of T-helper/inducer

CD4 positive cells. Assessment of the degree of immunosuppression in HIV may be done in a number of ways.

The absolute CD4 count is the measurement of the number of CD4 cells per cubic millimetre of blood (CD4 cells/$mm^3$). The normal absolute CD4 count in adolescents and adults ranges from 500 to 1500 cells/$mm^3$ of blood (Laurence, 1993). The CD4 count can vary slightly due to other factors such as infections, stress, smoking, exercise, the menstrual cycle and the contraceptive pill.

The threshold marking a substantially increased risk of clinical disease progression is a CD4 cell count of 200 cells/$mm^3$. UK, USA and European guidelines recommend that antiretroviral medication is started at any CD4 count below 350 cells/$mm^3$ to prevent the development of AIDS-related illnesses and for optimal long-term outcomes (BHIVA, 2008a; EACS, 2009; Panel on Antiretroviral Guidelines, 2009). In resource-constrained settings, guidelines recommend starting antiretroviral treatment before the CD4 count falls below 200 cells/$mm^3$ (WHO, 2006b).

CD4 percentage (the percentage of all white blood cells that are CD4 cells) is another useful clinical indicator of disease progression and of response to treatment (UK Collaborative HIV Cohort (CHIC), 2007). Compared to the CD4 count, the CD4 percentage tends to vary less due to other factors. A typical CD4 percentage in a person without HIV infection is around 40%. A CD4 percentage below 14% in a person infected with HIV is thought to reflect the same degree of immunosuppression as an absolute CD4 count of <200 cells/$mm^3$.

A third approach is the CD4:CD8 ratio, in which the number of CD4 cells in a sample of blood is compared with the number of CD8 cells. The CD4/CD8 ratio is rarely less than 1.0 in HIV-negative individuals, but may drop as low as 0.1 in patients with very advanced HIV infection. The lower the CD4/CD8 ratio, the worse the level of immune suppression.

Both the CD4 percentage and the CD4:CD8 ratio are affected by changes in the number of CD8 cells, which tends to rise through the course of HIV infection (Taylor *et al.,* 1989).

### 1.6.1 Measurement of viral load

The number of HIV particles in the blood is measured by a viral load test. Commonly used tests measure HIV RNA and report the results as the number of HIV RNA copies per millilitre (mL) of blood. The amount of HIV RNA in the blood correlates strongly with progression to AIDS (Mellors *et al.,* 1996).

The results of the viral load test may range from undetectable to millions of copies per mL of blood. Depending on the assay used, the lower limit of detection is either below 40 copies or below 25 copies in developed world settings. In some countries, older assays only measuring as low as 400 copies/ml are still commonly used.

Due to high numbers, a logarithmic scale with a factor of 10 is often used to express changes in viral load. For example, if the viral load test detects 500 000 copies of virus and treatment reduces this by 1 log, this means that the level has fallen by 10 times to 50 000 copies per mL. Similarly, an increase in the viral load of 2 logs equates to a 100-fold increase and a half a log increase to approximately a threefold increase (Pattman *et al.*, 2005).

Only about 2% of the total virus in an infected person's body is in circulating blood. The rest is in the lymphatic tissue and other body tissues, sometimes referred to as sanctuary sites. Changes in viral load in the blood are usually mirrored in the

tissues, but complete elimination of HIV from sanctuary sites is not possible with current therapies (Saksena and Potter, 2003).

Antiretroviral treatment is discussed in depth in Chapter 12 'Medications, Adherence and Interactions with Food'.

## 1.7 Natural history of untreated HIV infection and AIDS

HIV disease is a term broadly used to describe the illness caused by infection with the human immunodeficiency virus. If untreated, the disease typically progresses slowly from asymptomatic infection. Worsening immunocompromise finally results in the Acquired Immune Deficiency Syndrome (AIDS). This process may take many years. The median time from HIV-1 infection to death in the absence of antiretroviral treatment is 9.4 years, i.e. 50% of infected individuals die within 10 years of becoming infected (Morgan *et al.*, 2002).

As HIV progressively damages the body's ability to protect itself from infectious organisms, HIV-infected individuals become susceptible to opportunistic infections (so called because they take advantage of the body's weakened immune system), including certain types of cancers caused by viruses which rarely occur in people with healthy immune systems.

Since the depressed immune system renders the individual vulnerable to many illnesses, almost any symptom may occur in HIV infection. Specific conditions and opportunistic infections occur at more or less predictable levels of immune suppression as reflected in the CD4 cell count (see Table 1.1). Most complications occur with increased frequency at lower CD4 cell counts. The commonest AIDS-associated conditions are candidiasis (thrush), pneumonia, tuberculosis, Kaposi's sarcoma (cancer of the lining of the blood vessels), toxoplasmosis (a parasitic infection affecting the central nervous system), cryptococcal meninigitis (an indolent fungal meningitis) and cytomegalovirus (CMV) infection (a common viral infection that can cause retinitis and blindness).

The rate of CD4 cell decline and of HIV disease progression varies among individuals (Pantaleo *et al.*, 1995; UK Collaborative HIV Cohort (CHIC), 2007) and depends on interactions between the human host and viral and environmental factors.

Factors associated with more rapid HIV disease progression include older age, poor nutrition and co-infection with tuberculosis and hepatitis C. Psychological factors such as depression, impaired intellectual functioning, drug use and social deprivation may also adversely affect health-seeking behaviour and adherence to antiretroviral medication and may therefore be associated with more rapid progression to AIDS.

A small number of HIV-infected individuals (5–10%) remain well for many years with virtually normal immune systems. These so-called 'long-term non-progressors' have certain genetic characteristics which are protective against progression of HIV (Pantaleo *et al.,* 1995; Stewart *et al.,* 1997).

## 1.8 Staging and classification of HIV disease

HIV staging and classification systems provide clinicians and patients with important information about HIV disease stage and clinical management. They are also vital tools used in clinical and epidemiologic research – particularly in settings where CD4 monitoring is not available (CDC, 1993, WHO, 2006a).

**Table 1.1** Natural history of untreated HIV infection.

| Stage | CD4 cell count/mm$^3$ | Potential complications |
|---|---|---|
| Primary HIV infection | >500 | Asymptomatic – high viral load and a decrease in CD4 cells |
| Early | >500 | Usually asymptomatic or<br>• Persistent generalised lymphadenopathy (PGL)<br>• Acute retroviral syndrome (a flu-like illness which occurs soon after infection)<br>• Candidal vaginitis (thrush)<br>• Skin disorders, e.g. dermatitis and apthous ulcers |
| Middle | 200–500 | Asymptomatic/mildly symptomatic or<br>• Recurrent herpes simplex infection<br>• Varicella zoster (shingles)<br>• Bacterial pneumonia<br>• Pulmonary tuberculosis<br>• Diarrhoea, weight loss and fever may develop<br>• Lymphomas (Hodgkins/B Cell)<br>• Kaposis's sarcoma<br>• Oral hairy leukoplakia (white plaques in the mouth caused by Ebstein Barr virus)<br>• Cervical cancer |
| Advanced | 50–200 | Manifestations of AIDS<br>• Wasting<br>• Pneumocystis jirovecii pneumonia<br>• Kaposi's sarcoma<br>• Lymphomas<br>• Mycobacterium avium complex (MAC)<br>• Progressive multifocal leukoencephalopathy (PML)<br>• Peripheral neuropathy<br>• HIV-associated dementia<br>• Toxoplasmosis |
| Late | <50 | Very high viral load<br>• Wasting<br>• Disseminated cytomegalovirus (CMV)<br>• Disseminated MAC<br>• Neurological manifestations/central nervous system lymphoma |

Adapted from Pattman *et al.*, 2005. *Oxford Handbook of Genitourinary Medicine, HIV and AIDS*.

Two main staging systems are currently in use: the U.S. Centers for Disease Control and Prevention (CDC) classification system and the World Health Organization (WHO) Clinical Staging and Disease Classification System (CDC, 1993; WHO, 2006a). Both staging systems reflect the fact that specific opportunistic infections and HIV-related conditions occur at particular levels of immune suppression as shown in Table 1.1.

The CDC disease staging system classifies the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions. The definition of AIDS

**Table 1.2** Classification system for HIV infection and AIDS in adults and adolescents.

| | Clinical categories/symptoms | | |
|---|---|---|---|
| CD4 Cell Categories | A | B | C |
| ≥500 cells/μL | A1 | B1 | C1 |
| 200–499 cells/μL | A2 | B2 | C2 |
| <200 cells/μL | A3 | B3 | C3 |

Adapted from centers for disease control (CDC, 1993).

includes all HIV-infected individuals with CD4 counts below 200 cells/μL (or CD4 percentage below 14%) as well as those with specific HIV-related conditions and symptoms.

The CDC classification recognizes three stages (Table 1.2). Stage A represents 'Acute retroviral syndrome', i.e. generalised lymph node enlargement or asymptomatic infection.

Stage B ('Symptoms of AIDS-related complex') includes specific symptoms suggestive of immunosuppression but which may also occur in individuals without HIV, e.g. candidiasis and shingles.

Stage C ('AIDS-defining conditions') includes cancers, e.g. lymphomas and Kaposi's sarcoma, opportunistic infections, e.g. cryptosporidiosis and specific HIV-related syndromes, i.e. HIV wasting syndrome, HIV encephalopathy and progressive multifocal leukoencephalopathy (a form of dementia caused by JC virus)(CDC, 1993).

All patients in categories A3, B3, C1, C2 and C3 have an AIDS diagnosis. This definition has been used for finding and reporting AIDS in the United States. It is less useful since the advent of ART, because, where possible, patients are treated before these problems arise.

In contrast to the CDC system, the World Health Organisation Clinical Staging and Disease Classification System (developed in 1990 and last revised in 2005) can be readily used in resource-constrained settings without access to CD4 cell count measurements or other laboratory testing methods (WHO, 2006a).

The WHO Staging (see Appendix 1) is based on clinical findings that guide the diagnosis, evaluation and management of HIV/AIDS. This staging system is used in many countries to determine eligibility for ART (WHO, 2006b).

WHO stages are categorized as 1 to 4 and are defined by specific clinical conditions or symptoms which cover a continuum from asymptomatic infection to advanced AIDS. For example, whilst Stage 1 represents primary HIV infection (i.e. acute seroconversion illness – flu-like symptoms which may occur a few weeks after HIV infection), Stage 2 includes moderate unexplained weight loss (<10% of presumed or measured body weight). Stage 3 has progressed to severe weight loss (>10% of presumed or measured body weight) and Stage 4 to HIV wasting syndrome (WHO, 2006a).

## 1.9 Monitoring the HIV pandemic

HIV *prevalence* refers to all HIV infections regardless of duration. HIV *incidence* refers only to recent infections – usually those acquired in the previous year. Whilst successful prevention efforts which reduce the number of new HIV infections *reduce*

the prevalence of the infection slowly over time, continuing new infections and fewer deaths of HIV-infected persons on ART *increase* the prevalence of HIV – as does migration of HIV-infected individuals into a particular area.

To be able to understand the contribution of all these factors to the HIV prevalence in every country, sophisticated HIV/AIDS surveillance systems have been set up to better understand the global HIV epidemic and to monitor trends (UNAIDS, 2001). This includes anonymous HIV testing of pregnant women attending antenatal clinics and HIV surveys of vulnerable groups, e.g. sex workers. In the last 5 years, approximately 20 countries have conducted national, household HIV surveys, producing more accurate estimates of global HIV prevalence (UNAIDS, 2009).

Historically, HIV epidemics have been regarded as 'concentrated' if the prevalence in the general population is below 1% and generalised if the prevalence is greater than 1%. In a 'concentrated epidemic', HIV transmission is primarily attributable to HIV vulnerable groups, e.g. men who have sex with men, sex workers and injecting drug users. In contrast, HIV in a generalised epidemic is firmly established in the general population and protecting high-risk groups would not impact on HIV transmission (UNAIDS, 2001).

An understanding of the epidemiology of HIV in a particular country offers opportunities for more effective control measures. An example is Accra in Ghana, where the HIV prevalence in the general population is 2% but that among sex workers is 80%. An estimated 75% of HIV infections among young adult men are attributable to sex work (Cote *et al.,* 2004). In such a concentrated epidemic, interventions aimed at protecting sex workers and their clients would dramatically reduce the number of new HIV infections.

In contrast, only between 1 and 9% of HIV infections can be attributed to sex workers and their clients and other so-called 'bridging populations' such as soldiers and truck drivers in African countries with generalised epidemics (Leclerc and Garenne, 2008). Widespread change in community norms and sexual practices are required to change the course of such generalised epidemics.

The long time period between HIV infection and the onset of symptoms (typically between 8 and 11 years) makes the interpretation of trends in the prevalence of HIV difficult. Conventional tests for HIV are unable to distinguish recent infections from long-standing infections. The use of STARHS testing (discussed above) for surveillance purposes allows monitoring of HIV incidence as an indicator of HIV transmission. Increasing or decreasing numbers of recent infections provide important information about the impact of HIV prevention programmes (UNAIDS, 2001).

## 1.10 Prevention

Blood and blood products have been screened for HIV within the UK since 1985. For prevention of sexual transmission, condoms can be up to 95% effective (Pinkerton and Abramson, 1997). Condoms were a mainstay of some of the earliest prevention strategies such as the 'ABC' approach: 'Abstain', 'Be faithful' and 'Consistent and correct use of condoms' (Green *et al.,* 2006) continue to be important for prevention, particularly within high-risk groups such as sex workers or in sero-discordant relationships (i.e. where only one partner has HIV).

Prevention of mother to child HIV transmission (MTCT) with Zidovudine (AZT) was shown in 1994 to reduce the MTCT rate by two-thirds (Connor *et al.,* 1994).

MTCT rates within the UK are now less than 2% (Townsend *et al.,* 2008) and, with the use of ART, mothers who maintain undetectable viral loads can now choose to deliver vaginally. For sero-discordant couples with a positive male partner, the use of sperm washing to remove viral particles and artificial insemination of virus-free sperm has been used successfully (Bujan *et al.,* 2007).

Post-exposure prophylaxis for needlestick injuries has been used for many years. Current recommendations are to take three antiretroviral drugs for 4 weeks following an accidental exposure. Post-exposure prophylaxis for sexual exposure (PEPSE) is also now routinely offered following high-risk sexual exposures (European AIDS Clinical Society, 2009). Trials of pre-exposure prophylaxis (PreP) (i.e. taking antiretroviral drugs prior to an anticipated high-risk exposure) are underway (Derdelinckx *et al.,* 2006).

Other strategies such as treatment of intercurrent sexually transmitted infections have been shown to reduce HIV risk and circumcision decreases HIV transmission rates among heterosexual males (Cohen, 2004; Mills *et al.*, 2008).

Several countries in Africa reported reduced HIV prevalence rates by 2005. Whilst this reduction was partly due to improved surveillance and HIV-related deaths, there was also evidence that behaviour change was starting to occur. In Uganda, where HIV prevalence has declined dramatically in the past 10 years, population-based surveys of sexual behaviour have provided evidence for behaviour change (Green *et al.*, 2006). This has been mirrored in several African countries (UNAIDS, 2009).

Despite the devastating effects of the pandemic, the 2009 UNAIDS epidemiological update showed some encouraging trends: a reduction in the number of annual new HIV infections globally and a reduction in HIV-associated deaths, partly attributable to improved access to treatment (UNAIDS, 2009).

## 1.11 Effect of antiretroviral therapy on the HIV epidemic

Seventy five percent of HIV-infected persons who accessed care in the UK in 2008 received ART (Health Protection Agency, 2009).

In developing and transitional countries, 6.7 million people are in immediate need of ART. Although there has been a dramatic scale-up of antiretroviral treatment programmes outside of industrialised countries, only 31% of the 9.7 million people needing HIV treatment worldwide were receiving it at the end of 2007 (UNAIDS, 2009).

Apart from the humanitarian imperatives for increasing access to ART globally, there is also a public health argument that treatment of infected individuals reduces their HIV viral load and therefore their infectiousness and the number of new HIV infections (Castilla *et al.*, 2005). The availability of treatment also encourages more people to test for HIV with the opportunity for behaviour change and reduced onward transmission by those who are infected.

## 1.12 Stigma

The stigma of HIV is often added to the stigma already experienced by vulnerable individuals – sex workers, drug users, the homeless and men who have sex with men. Stigma includes both the individual internalized feelings regarding HIV status and external experiences of discrimination. There is an increasing body of research on interventions to reduce HIV-related stigma and on the direct, negative effects of

stigma on HIV prevention and treatment behaviours (Doherty *et al.*, 2006; Rintamaki *et al.*, 2006). This includes evidence of stigmatizing behaviours brought to bear by health care workers – even in industrialized settings (Mahendra *et al.*, 2007).

Stigma may result in the rejection of HIV-infected individuals by their families, partners and communities. The fear or experience of stigmatisation has been shown to reduce the likelihood of having an HIV test, of disclosing HIV status to relatives and sexual partners, of engaging with HIV treatment services and of adhering to ART. Stigma therefore directly results in the continued spread of HIV and in preventable HIV-related deaths.

Stigma is increasingly recognised as a significant contributor to the success or failure of HIV interventions and many HIV programmes now have stigma-reduction components (Mahajan *et al.*, 2008). Interventions to reduce stigma will increase in importance as other obstacles to testing and treatment for HIV are addressed worldwide.

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