

# 21 The immuno-compromised client

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## Introduction

For almost everyone, happiness and well-being are related to the attainment and preservation of good health or the restoration of health following acute episodes of illness. A variety of factors influence the potential of each person to achieve these goals, including social, political, economic and occupational circumstances and inherited attributes. Freedom from infectious diseases is an additional critical influence underpinning both individual and community health. Throughout the world, and especially in resource-poor regions, acute and chronic infections account for a substantial and preventable amount of misery, ill-health, disability and premature deaths.

Having an effective immune system for preventing or containing and minimising the consequences of inevitable incidents of infection during life is an essential prerequisite for good health. However, for many, individual genetic characteristics, life events, external circumstances, and infections and diseases can temporarily or permanently impair the ability of their immune system to provide this protection. Immunosuppression is relatively common in many populations throughout the world, significantly increasing the global burden of infectious diseases.

In order to facilitate an understanding of the causes of immunosuppression, this chapter begins with a brief review of the salient features of the immune system, followed by a brief account of the range of immunodeficiency disorders. The remainder of the chapter will focus on the care and support of persons who are immuno-compromised as a result of chronic infection with the human immunodeficiency virus (HIV), the most prevalent and challenging cause of progressive immunosuppression in people throughout today's world. Following an exploration of the pathophysiology of HIV disease, essential elements of the care and support of clients will be discussed, including clinical monitoring, anti-retroviral therapy and infection control. A principal goal of clients with chronic disease is to manage their condition effectively. Using the experience gained over many years in London with the HIV Positive Self-Management Programme (PSMP), this chapter will conclude with a detailed consideration of the role of community-centred programmes led by 'expert patients' in supporting clients to develop knowledge, skills and attitudes to help them better manage their chronic condition and improve the quality of their lives.

## Immune system

Immunity (that is, the body's physiological ability to resist infectious diseases) has evolved in humans over many millennia and affords crucial protection without which survival would be impossible. An understanding of normal immune mechanisms is necessary to appreciate the underlying pathophysiology and clinical consequences of disorders of immunity and to develop appropriate and relevant individualised care and support strategies for immuno-compromised persons.

The immune system is composed of a network of organs, tissues, cells and molecules which respond to and interact with each other in the recognition and containment and/or destruction of invading disease-causing (pathogenic) micro-organisms or other antigens, i.e. any foreign (non-self) material. These coordinated responses are derived from both innate (non-specific) and adaptive (acquired) immune mechanisms.

*Innate immunity* is inborn and consists of physical barriers (intact skin, mucous membranes and ciliated cells), chemical secretions (gastric acid, digestive enzymes, other bactericidal lysozymes and bacteriostatic fatty acids of the skin), the complement system and natural killer (NK) and phagocytic cells. Although many cells in the body engage in phagocytosis, the principal phagocytes are specialised white blood cells: granulocytes (neutrophils, eosinophils) and monocytes and their progeny, circulating macrophages. Other macrophages are fixed in tissues strategically located throughout the body (e.g., lungs, liver, spleen). NK cells especially target and destroy virus-infected and tumour cells.

Phagocytic cells engulf antigens, such as pathogenic micro-organisms, digest them and then project minute fragments of these antigens (epitopes) on their cell surface. This process transforms phagocytic cells into antigen-presenting cells (APC) which circulate throughout the lymphatic system and bloodstream, 'presenting' the antigen to the lymphocytes. When these cells recognise a specific antigen, they rapidly increase in numbers and initiate the antibody and cell-mediated responses described below.

Innate immune mechanisms are non-specific, i.e. they attempt to prevent the invasion of pathogens or neutralise and/or destroy any invading material they recognise as foreign. These mechanisms do not need to differentiate between the different types of pathogens that may infect persons; they just need to recognise self from non-self. Consequently, the development of immunological memory is not a facet of innate immunity. That important role is reserved for enhanced immune mechanism we acquire in the process of adapting to our changing environment and circumstances, i.e. adaptive immunity.

*Adaptive immunity* is gained after birth and is highly specific, targeting a specific micro-organism or groups of micro-organisms which are closely related. This type of immunity is governed by the actions of a group of white blood cells known as lymphocytes. These originate as stem cells in the bone marrow and mature as either B-lymphocytes or T-lymphocytes. These two types of lymphocytes govern antibody-mediated (B-lymphocytes) or cell-mediated immune responses (T-lymphocytes).

### *Antibody-mediated immunity*

B-lymphocytes are transformed into antibody-secreting plasma cells when they are presented with and recognise a specific antigen. These 'y-shaped' antibodies (also

known as immunoglobulins, abbreviated 'Ig') are protein molecules that are designed to be equally specific (e.g. antibodies to hepatitis A virus will only combine with that virus, and will not bind to hepatitis B virus). When combining with a specific antigen, an immune complex is formed which activates a system of plasma proteins known as complement (because they complement the activity of antibodies). Activated complement attach to immune complexes causing the cell membrane to rupture (lysis) and provoking an inflammatory response that leads to their destruction.

There are five classes of antibodies which are sequentially secreted by plasma cells. During primary infection (i.e. the initial few weeks following infection), the first antibody, known as IgM, is produced by plasma cells but recedes after a few months and then disappears as the plasma cells stop producing it and change to producing the second antibody, IgG. Unlike IgM, this antibody is long-lasting and a profile of IgG produced in response to previous infections can be identified in all individuals. Consequently, the presence of IgG is generally used in testing for previous exposure to infections and/or existing chronic productive infections (e.g. Hepatitis C, HIV disease).

### *Cell-mediated immunity*

When presented with an antigen they recognise, T-lymphocytes differentiate into two different types of helper cells (CD4<sup>+</sup> T-lymphocytes): helper cell 1 (TH1) and helper cell 2 (TH2). These two activated immune cells deliver their help by secreting a distinct profile of cytokines, soluble protein molecules that act as cell-to-cell messengers to stimulate or inhibit the growth of immune cells and amplify or depress immune responses. Examples of cytokines include interferons and interleukins. Cytokines secreted by TH1 cells provoke the activation of cytotoxic T-lymphocytes (CD8<sup>+</sup> cells) that, like NK cells, hunt down and kill virus-infected cells. TH2 cells secrete a collection of cytokines that provide programming instructions to plasma cells, facilitating the production of specific and highly effective antibodies. When the pathogen has been destroyed or the infection has been contained, suppressor T-lymphocytes will down-regulate the activation and return adaptive immune responses to their normal steady-state of vigilance.

Working together, innate and adaptive immune responses provide all persons with an impressive armoury of weapons needed to protect them from the constant threat of infection by pathogenic micro-organisms. However, not everyone has or retains an effective immune system and, without this immuno-competence, their health and well-being will be in peril.

### **Immunodeficiency disorders**

Temporary or permanent immunosuppression, regardless of the cause, greatly increases individual vulnerability to infectious diseases. There are many different types of immunodeficiency disorders which are classified as being either primary or secondary.

Primary (congenital) immunodeficiency disorders are genetically determined and are almost always seen in male infants and children. Over 200 different primary immunodeficiency disorders are recognised, some with complex aetiologies. Many

of these are extremely serious, if not life-threatening (e.g. infants with 'severe combined immunodeficiency' (SCID)). Some primary immunodeficiency disorders can be treated by transplanting bone marrow stem cells donated by a sibling with an identical human leucocyte antigen (HLA) genetic match, or, in some cases, by a parent. If transplantation is not an option, other treatments, such as anti-microbial drugs (for prophylaxis and treatment for infections) and intravenous human normal immunoglobulin (HNIG), may be used. Experimental gene therapy for treating some types of primary immunodeficiency disorders shows some promise but is currently not in widespread use due to adverse events in those treated with this technique.

Fortunately most people are born with a competent immune system but later in life some acquire an immunodeficiency disorder as a result of another medical condition or life circumstances and events (see Table 21.1). These are known as secondary immunodeficiency disorders and although many resolve, others progress to chronic immunodeficiency.

One of the most common global causes of chronic immunodeficiency is malnutrition. Most of the enzyme systems involved in immune responses are protein-based and people who are severely malnourished are, by definition, chronically immunosuppressed. However, because HIV disease has become perhaps the most defining and enduring pandemic disease of our times, and arguably the most frequent cause of chronic immunodeficiency throughout the world, it will feature as the main focus of the remainder of this chapter.

### HIV infection and AIDS

Since its recognition as a new communicable disease in the early 1980s, the global pandemic of HIV infection and AIDS expanded rapidly in many regions throughout the world. In some countries, particularly in sub-Saharan Africa, progress made in previous decades in reducing infant mortality, increasing maternal and child health and extending life expectancy has been eradicated by national epidemics of HIV infection. During the past quarter of a century there has been an annual global increase in the estimated number of people living with HIV infection (Figure 21.1) (UNAIDS 2007). However, there are, perhaps, some encouraging changes now being observed in the epidemiological direction of this maturing pandemic.

Table 21.1 Secondary causes of immunodeficiency

Renal disease – e.g. nephrotic syndrome, renal insufficiency
Endocrine diseases – e.g. diabetes mellitus
Liver disease – e.g. chronic hepatitis
Neoplastic disease – e.g. leukaemia, end-stage cancer
Infections – e.g. Epstein–Barr virus, measles virus, varicella-zoster virus, human immunodeficiency virus, <i>Mycobacterium tuberculosis</i>
Rheumatologic diseases – e.g. rheumatoid arthritis, systematic lupus erythematosus (SLE)
Malnutrition (and alcoholism)
Burns
Radiation
Splenectomy
Chemotherapeutic drugs – e.g. corticosteroids, immunosuppressants, anti-cancer drugs

## Epidemiology

During 2007, an estimated 33.2 million people in the world were living with HIV (67 per cent of them in sub-Saharan Africa), both men and women being equally affected. Add to this the 25 to 30 million people who have already died from AIDS and the magnitude of the pandemic becomes startling. Each day during 2007 over 6800 persons became infected with HIV, 50 per cent of these being under the age of 25. Every day during 2007, more than 5700 people died from AIDS (see Table 21.2) (UNAIDS 2007).

Although the percentage of people in the world who are infected with HIV (the global prevalence) has stabilised since 2001, the actual number of persons living with HIV is increasing each year owing to the accumulation of continuing new infections in people with longer survival times in a continuously growing general world population. This has resulted in an annual global increase in the estimated number of people living with HIV (Figure 21.1) (UNAIDS 2007). However, more encouragingly, during 2007 there have been localised reductions in prevalence in specific countries and a reduction in both HIV-associated deaths (due to better availability of and access to anti-retroviral treatment) and in the number of annual new HIV infections globally (UNAIDS 2007).

An analysis of epidemiological trends by UNAIDS (2007) has indicated that this maturing global pandemic has developed into two broad patterns. Generalised epidemics that are sustained in general populations is the pattern seen in many sub-Saharan African countries, especially in the southern part of the continent, and in some countries outside of Africa (e.g. Haiti and Papua New Guinea). In the rest of the world, epidemics are mainly concentrated among populations most at risk of exposure and infection (e.g. men who have sex with other men, injecting drug users, sex workers and their sexual partners).

Sub-Saharan Africa, with an estimated 22.5 million adults and children living with HIV in 2007, has been the most severely affected region in the world, where AIDS remains the leading cause of death. More than two out of every three persons (and 90 per cent of children) infected with HIV live in this region where more than three in four (76 per cent) of AIDS-associated deaths occurred. Other regions with large

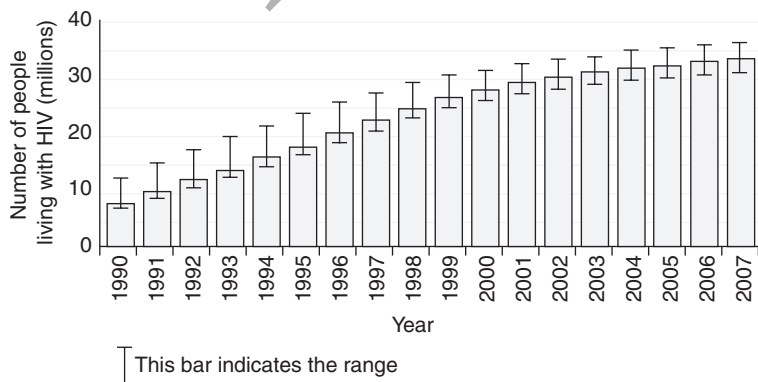


Figure 21.1 Estimated number of people living with HIV globally (1990–2007) (source: courtesy of UNAIDS/WHO. Reproduced with permission).

Table 21.2 Global summary of the AIDS epidemic, December 2007

Number of people living with HIV in 2007	Total	33.2 million [30.6–36.1 million]
	Adults	30.8 million [28.2–33.6 million]
	Women	15.4 million [13.9–16.6 million]
	Children under 15 years	2.1 million [1.9–2.4 million]
People newly infected with HIV in 2007	Total	2.5 million [1.8–4.1 million]
	Adults	2.1 million [1.4–3.6 million]
	Children under 15 years	420,000 [350,000–540,000]
AIDS deaths in 2007	Total	2.1 million [1.0–2.4 million]
	Adults	1.7 million [1.6–2.1 million]
	Children under 15 years	290,000 [270,000–320,000]

Source: Courtesy of UNAIDS/WHO.

numbers of persons living with HIV are South and South-East Asia (4.0 million), Latin America (1.6 million), Eastern Europe and Central Asia (1.6 million) and North America (1.3 million) (UNAIDS 2007). In a current global population of approximately six and a half billion people, it is salutary to remember that China and India together are home to almost one-third of all the people in the world. As relatively new national epidemics continue to expand in these two countries, it is disturbing to contemplate the impact this will have on the future course of the global pandemic.

The prevalence of adults and children living with HIV in Western and Central Europe is estimated to be 760,000 (UNAIDS 2007). The countries with the largest number of cases are the United Kingdom (UK), France, Italy and Spain (UNAIDS 2008). In the UK, the annual number of newly diagnosed HIV infections has more than doubled from 4154 in 2001 to 8925 in 2006. The UK has one of the highest rates of new HIV diagnoses in Western and Central Europe (149 per one million population) in 2006, which is exceeded only by Portugal's 205 per one million population (EuroHIV 2007; UNAIDS 2008). There were an estimated 73,000 persons living with HIV in the UK in 2006 (121 persons living with HIV per 100,000 population) (Health Protection Agency 2007). Although London continues to be the epicentre, accounting for 41 per cent of new HIV diagnoses in 2006, significant increases in new HIV diagnoses have occurred in the East Midlands, Northern Ireland and Wales (Health Protection Agency 2007).

### *Transmission*

Early in the pandemic, the means by which HIV is transmitted from one person to another became clear. HIV is transmitted by blood (including menstrual blood), semen and pre-ejaculate fluid, vaginal fluids and breast milk. It is not spread by tears, sweat or saliva.

### *Sexual transmission*

Unprotected, penetrative sexual intercourse remains the usual means by which most people are exposed to this virus. Worldwide, heterosexual transmission is the principal way people become infected and is the predominant transmission pattern in

1 generalised epidemics in general populations, such as national epidemics in Africa.  
2 Although vaginal intercourse is the most frequent type of sexual activity, unpro-  
3 tected anal intercourse can also transmit HIV, whether it occurs between heterosex-  
4 ual men and women or between men who have sex with other men. Oral sex may  
5 transmit HIV but it is generally considered a lower risk activity than vaginal or anal  
6 intercourse. However, repeated exposure to semen and pre-ejaculate fluid or to  
7 vaginal fluids (and menstrual blood) may increase the risk to the person perform-  
8 ing oral sex (Public Health Agency of Canada 2004).

9 The presence of another sexually transmitted infection, either an inflammatory  
0 condition, such as gonorrhoea or an ulcerative disease (e.g. primary syphilis or  
1 genital herpes), significantly facilitates both the transmission and acquisition of  
2 HIV. There is extensive high-quality research to show that male circumcision pro-  
3 tects against the sexual transmission of HIV from women to men (WHO 2007). This  
4 is because the penile shaft and outer surface of the foreskin is covered by a tough  
5 keratinised, stratified squamous epithelium which provides a barrier against HIV  
6 transmission. However, the inner mucosal surface of the foreskin is not keratinised  
7 (Barreto *et al.* 1997) and is richly supplied with Langerhans' cells which are suscept-  
8 ible to HIV infection (Hussain and Lehner 1995). During vaginal intercourse, the  
9 foreskin is pulled back down the penile shaft and the whole inner surface of the  
0 foreskin is then exposed to vaginal secretions, providing a large area where HIV  
1 transmission can take place (Szabo and Short 2000). Results of three randomised  
2 controlled trials have shown that male circumcision performed by well-trained  
3 medical professionals was safe and reduced the risk of acquiring HIV infection by  
4 approximately 60 per cent (WHO 2007).

5 Finally, patterns of sexual behaviour influence vulnerability to infection. In  
6 Africa, it is not unusual for people to be members of a network of concurrent part-  
7 ners, i.e. simultaneous long-term sexual relationships with more than one partner  
8 at one time. Referred to as concurrent relationships (Epstein 2007), this may be  
9 more risky than sequential monogamy (a more common pattern in Europe and  
0 North America) as friendship and trust within the network may lessen the consist-  
1 ent use of condoms and a single person's infection can spread rapidly through a  
2 group. Where concurrent relationships are the rule rather than the exception, net-  
3 works can efficiently accelerate the sexual transmission of HIV throughout a  
4 society.

### 6 *Mother-to-child transmission*

7 Throughout the world, and especially in resource-poor regions, mother-to-child trans-  
8 mission (MTCT) is the second most frequent means of person-to-person transmission.  
9 HIV can be transmitted by an HIV-infected woman to her infant during pregnancy,  
0 during birth when the newborn infant comes into contact with infected maternal birth  
1 fluids, and shortly after birth or during the early months and years of life while being  
2 breastfed. Most children become infected during the peripartum period, i.e. during or  
3 shortly after delivery (Pratt and Pellowe 2006). There is a wealth of good-quality  
4 research evidence to show that antenatal screening for HIV infection and a combina-  
5 tion of interventions for women found to be infected can significantly reduce the risk  
6 of MTCT. These interventions include: anti-retroviral treatment for the pregnant  
7  
8

women (if indicated) or anti-retroviral chemoprophylaxis, elective caesarean section delivery, and modifications in infant feeding practices (Pratt and Pellowe 2006).

### *Injecting drug use*

HIV is efficiently transmitted by sharing blood-contaminated needles, syringes and injection paraphernalia, a common phenomenon among injecting drug users (IDUs). In Europe and North America, IDUs account for a significant number of persons living with HIV. However, drug users are, by and large, sexually active individuals and are often sex workers. Consequently, they may also acquire HIV infection as a result of sexual exposure (Pratt 2003). Needle and syringe exchange programmes can reduce the transmission of syringe-borne viruses without increasing illicit drug use and are effectively used in many countries as part of a wider harm-reduction strategy (Heimer 1998; Allgeier 2006). It is worth noting that some non-injectable drugs, such as alcohol, crack cocaine and more notoriously, flunitrazepam (Rohypnol™) or GHB (gamma-hydroxybutyrate), the so-called 'date rape drugs', can render a person incapable of making responsible and safe judgements and result in increasing their risk of sexual exposure to HIV.

### *Healthcare transmission*

HIV has been transmitted to patients from healthcare interventions and from infected patients to healthcare workers. In many parts of the world, patients are at considerable risk of being infected with HIV (and other blood-borne viruses) as a result of unscreened transfusions of contaminated human blood and blood components, transplantation of infected donor organs, tissues and semen, the use of unsterilised HIV-contaminated needles and syringes and other equipment used for invasive procedures. Healthcare workers are at risk of potential exposure to blood-borne viruses if they come into contact with the blood, other body fluids or the moist mucous membranes of their patients. The risk of accidental transmission of HIV to patients or healthcare workers is greatest in resource-impooverished regions of the world where healthcare infrastructures are weak, healthcare practice is poor, and safe, affordable and effective healthcare provision is not easily available.

Standard infection prevention and control precautions, an essential element of strategies designed to protect healthcare workers and patients from blood-borne viruses, have been developed and are in wide use in the UK and other countries in the industrialised world (Pratt 2003; Pratt *et al.* 2007). The consistent incorporation of these precautions into everyday clinical practice provides the best available protection against occupational exposure to HIV and other blood-borne viruses during healthcare practice.

### *Diagnosis of HIV infection*

There are two major variants of HIV, known as HIV-1 and HIV-2. The former is the dominant AIDS-causing virus in the world whereas HIV-2 is fairly restricted to the west coast of Africa. However, both types of infection are seen in the UK.

The standard diagnostic test for HIV infection throughout the world is the HIV antibody test. This uses a laboratory technique known as enzyme immunoassay (EIA) to detect HIV-specific antibody G (IgG) in an infected person's blood, saliva

1 or urine. This test is very accurate, having a high degree of both sensitivity and specificity. Most people will develop detectable IgG antibodies (i.e., seroconvert) within  
 2 two to eight weeks (average 25 days) following infection, and virtually all newly  
 3 infected persons will seroconvert by 12 weeks. In the UK, all antibody tests test  
 4 simultaneously for HIV-1 and HIV-2 IgG.

5 Testing for viral proteins is more frequently being done to detect early infection  
 6 as this protein is present in the blood before IgG appears. Antibody tests are not  
 7 used to identify infection in newborn infants (as they would only detect passively  
 8 transferred maternal antibodies); rather a nucleic-acid amplification test (NAT) is  
 9 used, known as PCR DNA (polymerase chain reaction DNA). A variety of 'rapid'  
 0 tests are available in clinics where results can be available within 20 minutes and, in  
 1 the USA and other countries, government-approved self-testing kits for use at home  
 2 and internet testing are available.

### 6 **Pathogenesis**

7 During the first few months following infection (primary infection), some people will  
 8 develop a generally self-limiting seroconversion syndrome, commonly experiencing  
 9 fatigue, fever, rash, lymphadenopathy, diarrhoea, candidiasis and other diverse symptoms.  
 0 During primary infection, increasing viral replication provokes an antibody and  
 1 cell-mediated immune response, and the level of virus in the blood (viral load) is suppressed  
 2 (see Figure 21.2). Towards the end of primary infection, IgG antibodies to  
 3 HIV can be detected in the blood, i.e. seroconversion has taken place.

4 Following this, a productive infection is established and the infected person  
 5 enters a long asymptomatic period (clinical latency) of generally many years.  
 6 However, the virus continues to replicate at an approximate rate of ten billion new  
 7 copies every day, and, although waning immune responses steadfastly continue to  
 8 suppress viral replication, it cannot keep up with the relentless rate of replication,  
 9 and over time there develops a steady increase in viral load corresponding to a progressive  
 0 loss of immune function as measured by the numbers of CD4<sup>+</sup>  
 1 T-lymphocytes in the peripheral blood (see Figure 21.2).

2 Towards the end of clinical latency, infected persons will start to feel unwell with  
 3 various constitutional systems (e.g. weight loss, fevers, night sweats, diarrhoea), and  
 4 are classified as having early symptomatic disease. Without specific anti-retroviral  
 5 treatment, these persons will quickly progress to late symptomatic disease (i.e. the  
 6 acquired immunodeficiency syndrome (AIDS)) where they will experience a variety  
 7 of opportunistic infections and cancers and associated multi-system pathology, and  
 8 die. Globally, tuberculosis is the most frequent opportunistic infection people with  
 9 AIDS develop.

### 1 **Anti-retroviral therapy**

2 Unrelenting viral replication will eventually cause fatal damage to the immune  
 3 system and this can be measured by monitoring the level of specialised immune  
 4 system cells, the CD4<sup>+</sup> helper T-lymphocytes. A normal CD4<sup>+</sup> T-cell count in an adult  
 5 in the UK is generally around 1000 cells per cubic millimetre (cells/mm<sup>3</sup>). As the  
 6 CD4<sup>+</sup> cell count decreases over time with a corresponding increase in the amount of  
 7 HIV in the blood (viral load), anti-retroviral therapy (ART) is eventually required.  
 8

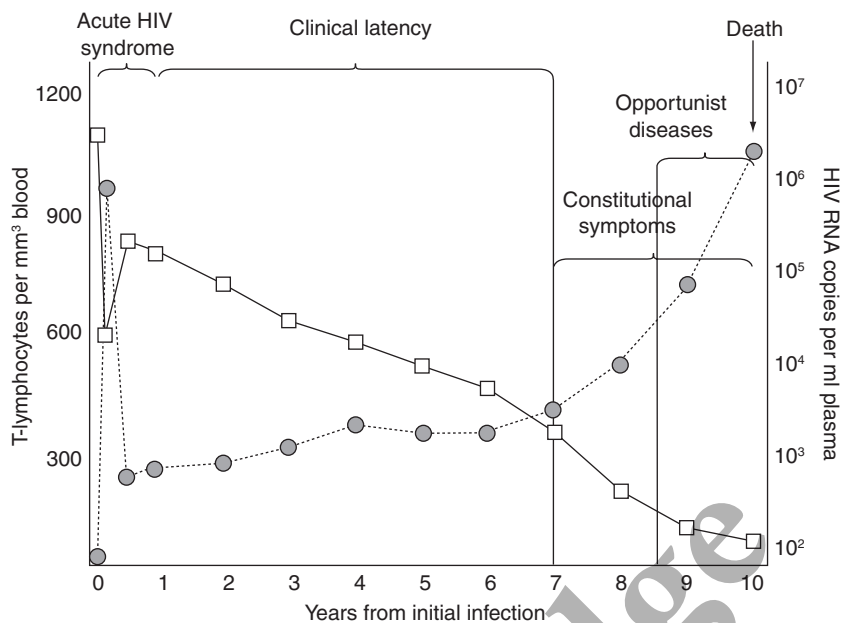


Figure 21.2 The clinical course of HIV infection and disease in relation to the CD4<sup>+</sup> T-lymphocyte cell count and the viral load (source: Pratt *et al.* (2005)).

Current guidelines in both the UK and the USA recommend starting ART in all persons with a CD4<sup>+</sup> cell count of 350 cells/mm<sup>3</sup> (or lower) (British HIV Association 2008).

Effective ART has been available in the UK since the early 1990s and consists of a regimen of a combination of different anti-retroviral drugs that either inhibits viral enzymes used by HIV to replicate, or block cell-surface receptors which HIV uses to attach to and enter cells it has targeted for infection. These drugs inhibit HIV from replicating; they do not eliminate the virus from the body and once these drugs are stopped (or the patient becomes resistant to them), the viral load will rebound to pre-treatment high levels with consequent new damage to an already compromised immune system.

Newly introduced anti-retroviral drugs, such as the integrase and entry inhibitors, offer an increasingly powerful and effective armoury of anti-retroviral agents to depress replication and drive down the viral load below the level of detection. This has the effect of increasing or, more usually, restoring the patient's health and well-being, and decreasing (but not eliminating) their level of infectiousness to other people.

### Self-management

Managing chronic conditions such as HIV can be a complex, time-consuming and challenging process. However, due to the nature of long-term illness it is often the patients, rather than healthcare professionals, who are responsible for the routine management of their day-to-day physical, psychological and emotional health. This 'self-management' will often involve:







