Chapter 2

Literature review on Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS)

2.1 General

HIV is a disease that is feared all over the world. It was already discovered in 1981, and 24 years later this disease has reached devastating effects with millions affected all over the world. The disease was first recognised when small clusters of young homosexual men in American cities were reported to suffer rare opportunistic infections like *Pneumocystis carnii* and Kaposi's sarcoma (Hochauser & Rothenberger, 1992). Initially it was not sure if the disease was a "gay disease" and if it was spread by other means as well. By early 1982 reports of Acquired Immune Deficiency Syndrome (AIDS) in recipients of blood transfusions and pooled clotting factors, as well as among injecting drug users indicated that an infectious agent was to blame. The appearance in Africa and in Haiti suggested that the unknown pathogen was already widespread in countries all over the world (Mims *et al.*, 1999).

In 1983 Francoise Barré-Sinoussi and colleagues isolated their first virus from a patient at the Institut Pasteur in France. The patient had persistent lymphadenopathy and the virus was named the lymphadenopathy-associated virus. By April 1984 the French group had already isolated two more, one from an AIDS patient. A month later Gallo's group at the US National Institutes of Health (NIH) reported retroviruses that they named human T-lymphotropic virus type III or HTLV-III (Gallo *et al.*, 1984). Levy *et al.*, 1984 also independently isolated AIDS-related retroviruses. The term Human Immunodeficiency Virus (HIV) was adopted in 1986 (Smith *et al.*, 2001).

By 1986 the drug zidovudine (AZT) had become available, though its effectiveness was still to be measured. As the decade of the 1980's advanced, it became clear that the effects of HIV infection were variable and not necessarily confined to the life-threatening conditions identified in the official definitions of AIDS (Anderson & Wilkie, 1992).

HIV positive refers to a condition where the person is infected with the virus. This does not necessarily mean that the patient will show symptoms, or will feel any different than a HIV negative person. It is only until the disease progresses to AIDS when the person starts to show symptoms and it is often recognised by the development of HIV-related diseases such as pneumonia and tuberculosis.

Several stages in the development of an HIV infection to the condition of AIDS have been identified (Figure 2.1). After infection with the virus, the person will enter the window period, with no signs or symptoms indicating infection. The virus will infect mostly CD4 cells. CD4 receptor sites on helper T-cells serves as a marker to distinguish them from other T-cells. That is the reason for these cells to be named CD4 cells or T4 cells. After infection the body's immune system will produce antibodies against the foreign virus particles called antigens. It takes six to eight weeks for these antibodies to be produced. The virus can not be detected during the window period, because conventional HIV tests test for the antibodies produced against the virus, which is not present in high enough quantities during the first six to eight weeks. People are therefore advised to repeat the test after eight weeks to eliminate the window period, and detect the antibodies that would have been formed after eight weeks or longer.

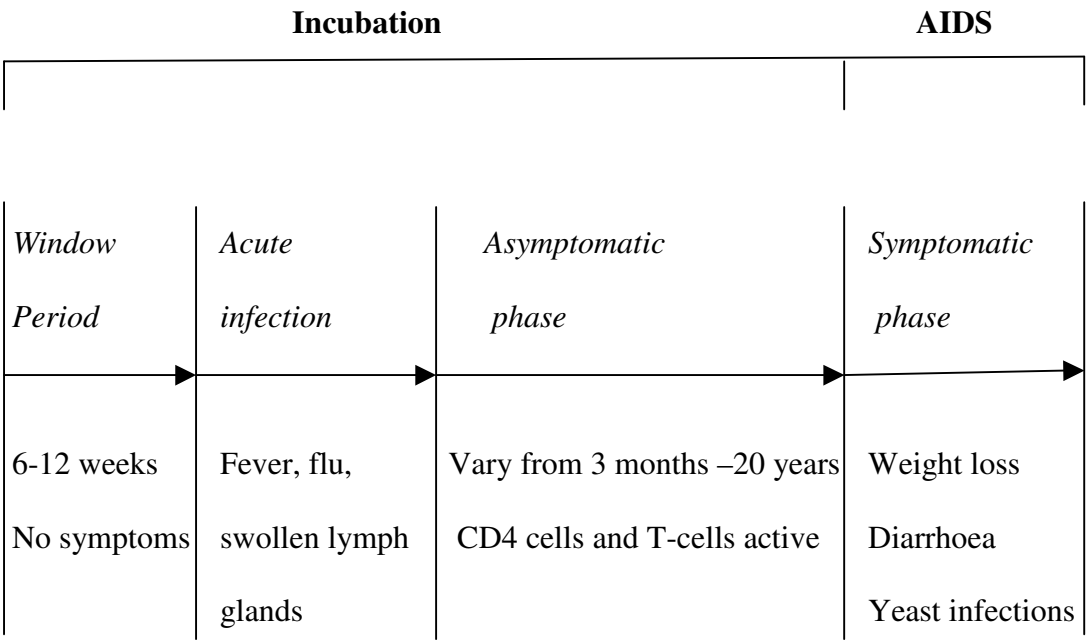

Figure 2.1: Timeline of HIV infection, with associated symptoms and duration.

After the window period a short acute period follows with very mild symptoms like flu, fever and swollen lymph glands, which could last for a day or two. The symptoms are so mild and common that few people would recognise these symptoms as warnings signs of HIV infection. People with HIV may remain healthy and show no symptoms for many years during the asymptomatic phase. This phase varies between individuals, depending on the strength of the body and the immune system, and might only last for a few months or could continue for many years. This phase has been monitored in individuals for twenty years or even more. Later in the course of infection, harmful changes to the immune system may be observed, and the development of HIV-related problems might occur. These people can also develop opportunistic infections (OI) and cancers that can be life threatening. OI will only

surface during the symptomatic phase which also indicates the onset of the infection turning into AIDS (Hochshauser & Rothenberger, 1992).

The clinical manifestations of AIDS include OI that thrive in the immuno-suppressed host. Some of these are common microbes that are seldom pathogenic in immuno-competent individuals. *Pneumocystis carinii*, *Candida albicans* and *Aspergillus* are fungal infections that do not cause more than a mild infection in healthy individuals. Various latent herpes virus infections frequently become reactivated to cause severe illness and AIDS. Some of these OI are therefore correlated with the stage of degeneration caused by HIV (Figure 2.2). Herpes simplex virus 1 (HSV-1), Herpes simplex virus 2 (HSV-2) and varicella-zoster viruses can develop life-threatening OI's in AIDS. The Epstein-Barr virus and Kaposi's sarcoma herpes virus allow tumours to occur at higher frequency during AIDS than in healthy persons (Mims *et al.*, 1999).

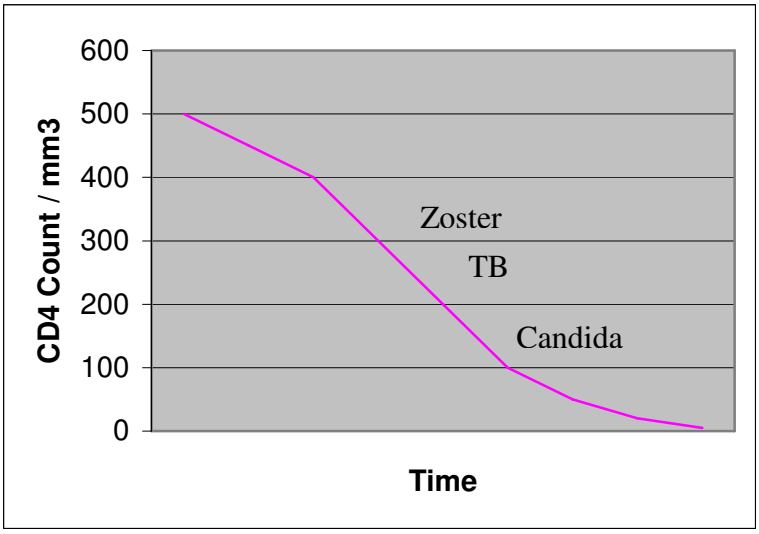

Figure 2.2 Correlation between the number of CD4 cells, and different OI associated with decreased CD4 levels (Smith *et al.,* 2001).

HIV comprise two distinct viruses, HIV-1 and HIV-2, which differ in origin and gene sequence. In 1986, a similar but not identical virus, HIV-2 was identified among people with AIDS of West African origin. So far, there have been comparatively few instances of infection with HIV–2 in Europe and the USA (Anderson & Wilkie, 1992). Both viruses cause AIDS with similar symptoms, although central nervous system (CNS) diseases may be more frequent in HIV-2. It appears that HIV-2 is less virulent than HIV-1 as HIV-2 takes longer to progress to AIDS. In some cases however it has been found that HIV-2 progressed at a similar pace as HIV-1 (Smith *et al.*, 2001).

Since 1986 numerous research projects have been conducted on HIV, and today much more is known about the virus, its infection, pathogenesis and the effects on the body. The genomes of the two types of viruses (HIV-1 and HIV-2) compare very well and only small differences can be detected. There are a variety of types that form the HIV group of viruses, and the fact that viruses mutate continuously make treatment and drug development a difficult task. This virus illustrates Darwinian selection perfectly. It is this selectivity that is responsible for the resistance developed against every new drug that is introduced to stop virus infection (Smith *et al.*, 2001). There are several complementary reasons for this great diversity. The process of reverse transcription does not include an editing device to correct mutations. The RNA genomes of retrovirus particles are also diploid and genetic recombination occurs during reverse transcription. Each infected individual therefore possesses an immense pool of HIV variants, allowing substantial genetic and antigenic drift to occur within each infected individual. It is the high rate of replication that provides the conditions for numerous immune escape and drug-resistant mutants to be regenerated. During the long

asymptomatic incubation period before AIDS develops, the virus is not latent, but is actively replicating producing millions of virions per day (Anderson & Wilkie, 1992).

Humans harbour three major groups of HIV-1, named M, N and O, with group M representing all the subtypes or clades A-H that have spread to cause the worldwide pandemic. HIV-1 groups N and O, in contrast are largely confined to Gabon, Cameroon and their neighbouring countries. The gene sequences of M, N and O are however very different from each other. HIV-2 is endemic to West Africa, but has spread to Europe and India. HIV-2, like HIV-1 are also subdivided into a number of major groups.

2.2 Structure of a virus

Viruses are much smaller than other disease causing organisms. The basic structure of a virus consists of the envelope, capsid and the core of genetic material in the form of either RNA or DNA (Figure 2.3). The envelope is additional to the capsid in some viruses protecting the virus. The basic structure of the virus particles are similar but there is some genetic variability. The capsid surrounds the genetic material, the viral RNA and reverse transcriptase, and it consists of two coats of core proteins namely p18 and p24. These protein coats, in particular p24, are of importance in testing for the presence of the virus (Anderson & Wilkie, 1992). The lipid membrane that makes up the outer envelope of the virus and the gp 120 protein together with another protein gp 41, to which it is anchored, protect the inner parts of the virus containing the RNA and essential enzymes (Hochhauser & Rothenberger, 1992).

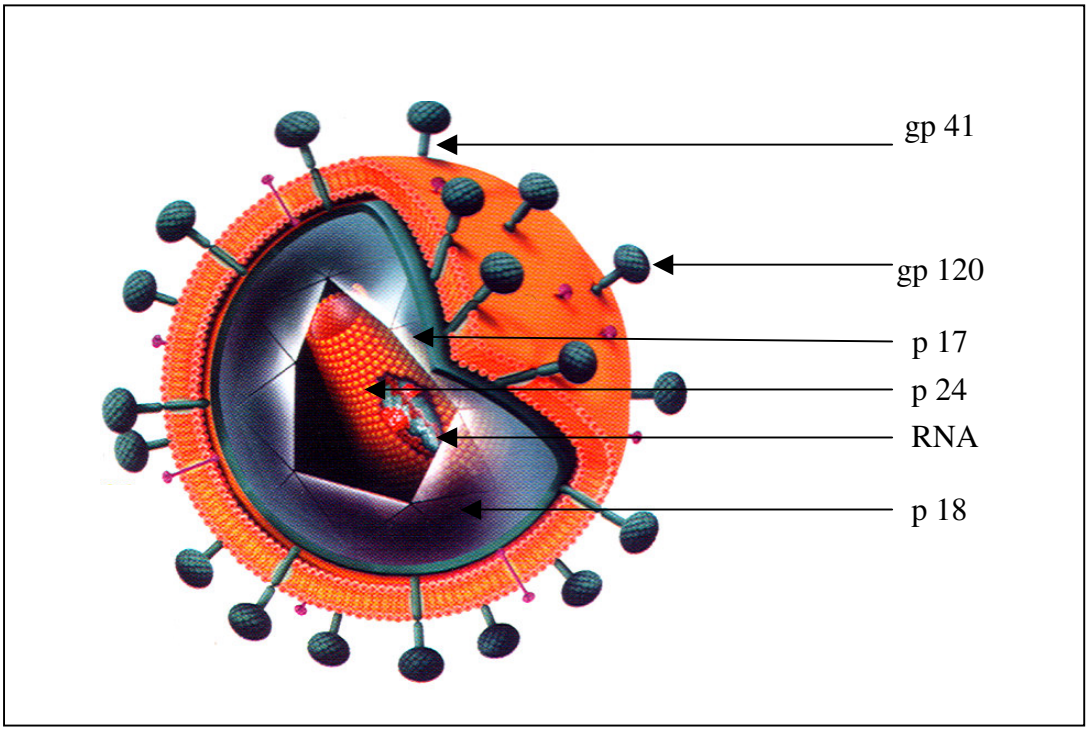

Figure 2.3 The basic structure of HIV (Mims *et al.,* 1999).

HIV comprises of a very small genome, with only nine genes (Figure 2.4). In common with all retroviruses, the gag gene encodes the structural proteins of the core (p24, p7, p6), and matrix proteins of the virus particle (p17), and the env genes encodes for the glycoproteins (gp120, gp41) that comprise the viral envelope antigens. These antigens will interact with the cell surface receptors (Smith *et al.*, 2001). The pol gene encodes the enzymes crucial for viral replication namely reverse transcriptase (RT) to convert RNA into DNA, integrase (IN) to incorporate the viral DNA into the host genome and protease (PR) to cleave the precursor gag and pol genes into their component parts. RT and PR inhibitors represent the current generation of anti-retroviral drugs given in combination to lower the viral load. The

tat gene encodes a protein that promotes transcription or production of HIV RNA from the DNA provirus while rev ensures that the correctly processed mRNA and genomic RNA is exported from the nucleus to the cytoplasm. The function of the other accessory HIV genes is not well understood (Smith *et al.*, 2001).

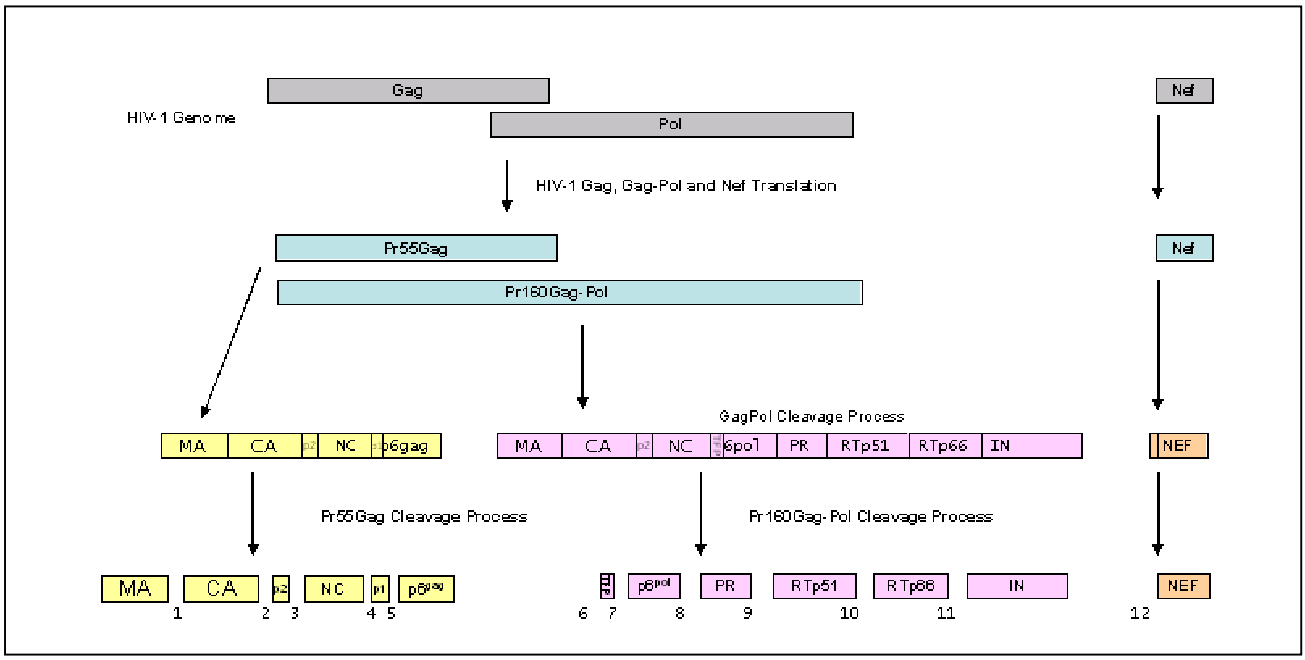

Figure 2.4 The genome of HIV (Mims *et al.,* 1999).

2.3 Pathogenesis

HIV is part of a group of viruses called retroviruses. These viruses contain RNA as genetic material and not DNA. The information then needs to be changed into the form of DNA before it can be incorporated into the genetic material of the host. The DNA is then built into the genetic blueprint of the host cell (Figure 2.5).

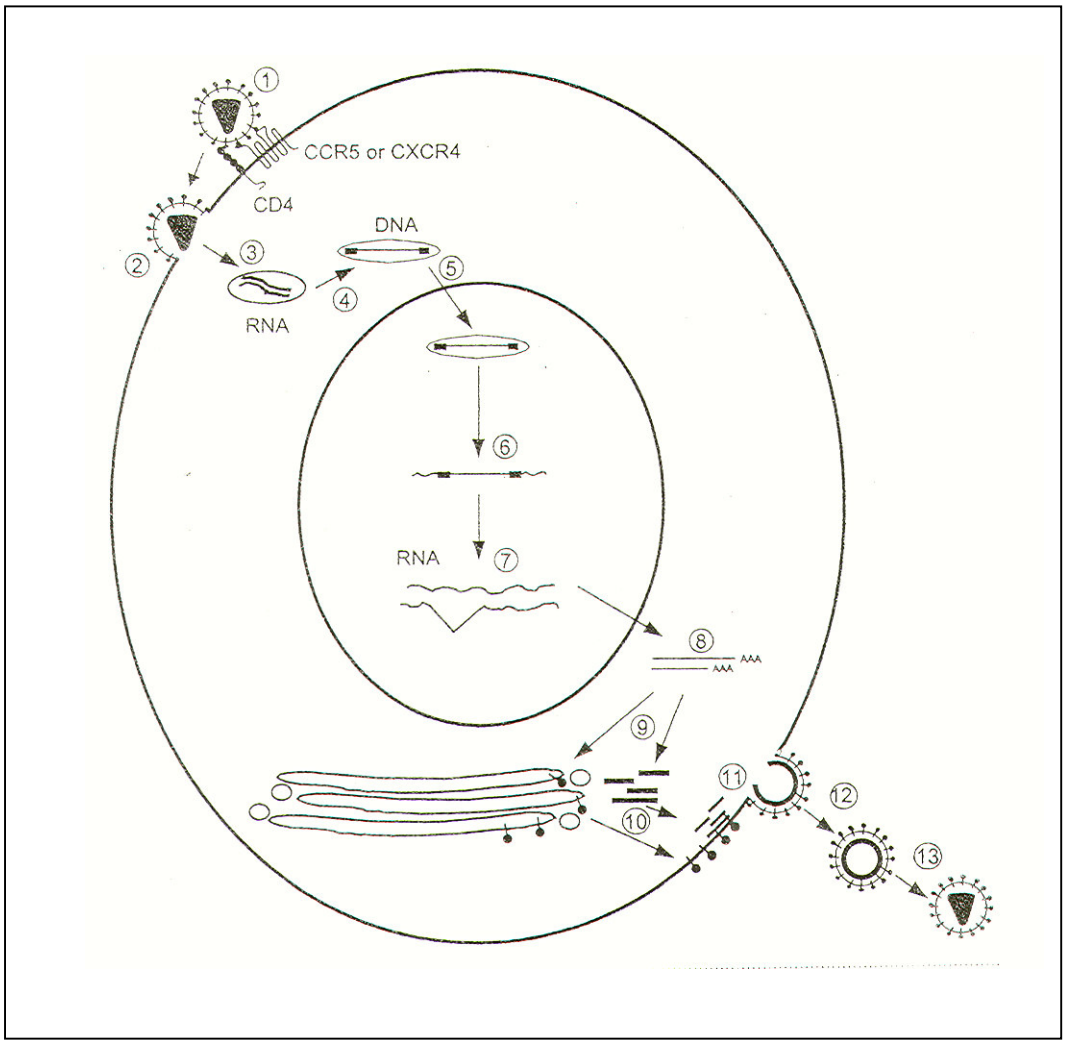

Figure 2.5 Stages in the replication cycle of HIV. (1) Attachment, (2) fusion, (3) entry, (4) RT, (5) nuclear transport, (6) chromosomal integration of DNA, (7) transcription of RNA, (8) nuclear transport of RNA, (9) translation and processing, (10) membrane transport, (11) assembly, (12) budding and (13) assembly (Smith *et al.,* 2001).

The genetic information of all cellular organisms, which allow them to copy themselves, is contained in their DNA or RNA. The DNA is then replicated to produce multiple copies of the virus, with the DNA encoding all the information needed to build an exact same copy. DNA is used to produce RNA that is in turn responsible for protein production. These proteins will form a new cell and in the case of viruses a copy of the virus (Anderson & Wilkie, 1992).

The first step of viral entry into a cell occurs when a protein on the viral envelope, known as gp 120 binds to a molecule on the surface of the CD4 cell. The CD4 receptor sites are present in considerable quantities in certain cells of the immune system namely the T-helper lymphocytes. These cells are also the targets of HIV. There are some CD4 receptor sites on the surface of other cells of the body, such as monocytes, macrophages and in micoglial cells within the brain. The virus can gain entry into all these cells by binding to their CD4 receptors (Hochhauser & Rothenberger, 1992). It became apparent that CD4 receptors are necessary for attachment, but not sufficient for entry into the host cell. Some HIV-2 strains do not depend on CD4 receptors at all. Two chemokine receptors, CCR5 and CXCR4 were identified as co-receptors to CD4 that permit virus entry. These co-receptors have a secondary binding function, assisting binding of the virus to the receptor, and it also opens up the cell wall for the virus to enter. In HIV-1 the CCR5 co-receptor proved to be the most important factor, but later during the course of infection CXCR4 utilising viruses emerged. These strains are more virulent than the initial strains and hasten the depletion of CD4 cells (Smith *et al.*, 2001).

After a virus particle has gained entry into a host cell, the genetic material in the core of the virus becomes integrated into the DNA of the cell. The virus now has 'access' to the cell's own machinery for reproduction, and it will persist like that during the lifetime of the cell. If the virus is integrated into the genetic material, the genetic material may remain latent in the cell, although the cell remains viable (Anderson & Wilkie, 1992).

The enzyme responsible for the translation of RNA to DNA is called reverse transcriptase (RT). Once the RNA is converted to DNA the genetic material can be incorporated into the host genome. When the virus DNA is incorporated into the genetic material of the host, it uses the host's processes to replicate it's own DNA, and to reproduce itself (Anderson & Wilkie, 1992).

RT and integrase (IN) which also integrate DNA into the host genome are the markers for retroviruses. The integrated DNA can remain latent, and be passed to daughter cells during chromosomal replication and cell division. Full replication in T-lymphocytes usually results in cell death, whereas in macrophages lower levels of virus replication permit the host cell to survive for longer periods. Macrophages represent a substantial virus reservoir in the infected host (Smith *et al.*, 2001).

A great deal is known about the dynamics of HIV replication *in vivo*, but there is still little understanding of what eventually tips the balance of infection away from host immunity towards the development of AIDS. It also inhibits the production of an effective vaccine against the infection (Mims *et al.*, 1999).

Figure 2.6 shows the typical course of HIV infection. Primary infection causes a transient fever in the symptomatic phase. The viral load increases sharply within the first three to six weeks that are called the window period. The viral load decreases then concomitantly with the appearance of cytotoxic T-lymphocytes. Following primary infection, HIV is never eliminated and it becomes latent. It will however stay active in the asymptomatic phase, but at a much lower level than in primary infection. The vast majority of untreated people infected with HIV eventually succumb to an AIDS-related death. The asymptomatic period varies greatly among HIV-infected individuals. Progression to AIDS may be within 9-10 years and sometimes even longer, with slowly declining levels of CD4 lymphocytes. These individuals called long-term non-progressors maintain healthy levels of CD4 cells and low levels of viral load for longer periods, whereas others may progress to AIDS within three to five years. CD4 cell replacement is probably playing a major role in determination of the progression to AIDS (Smith *et al.*, 2001).

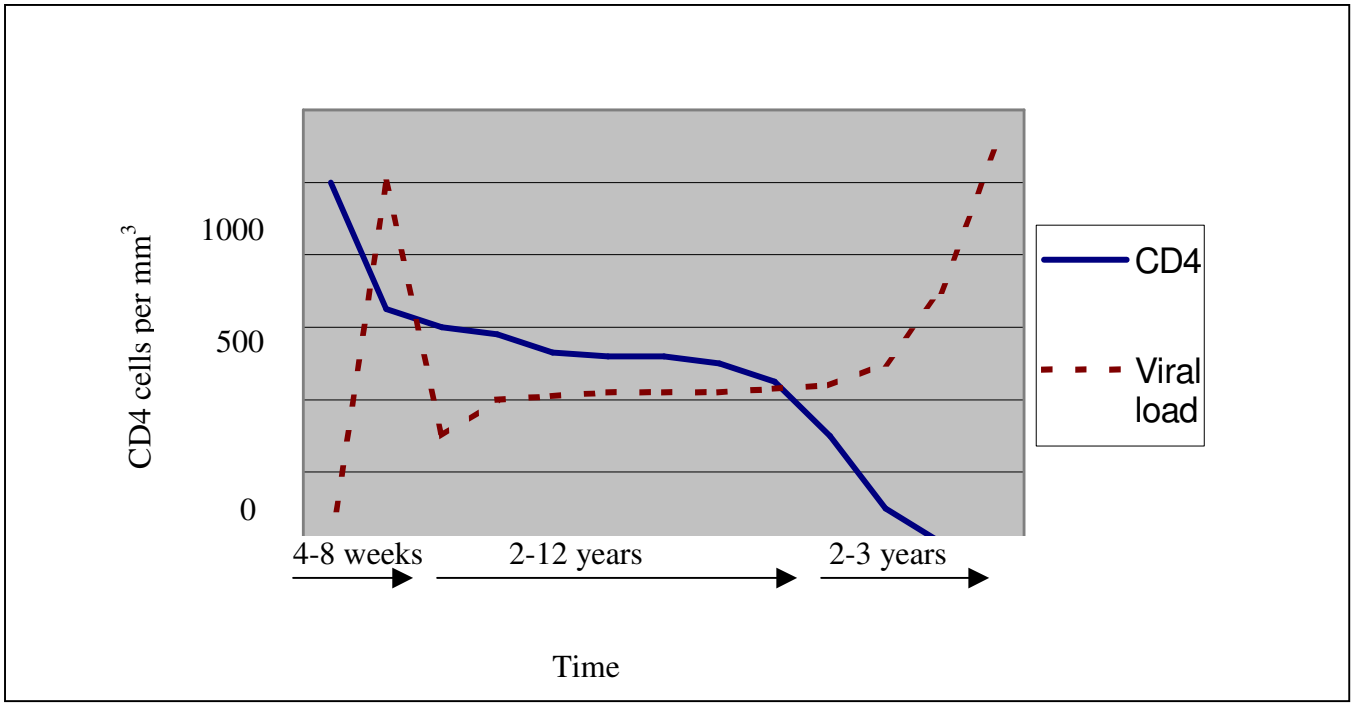

Figure 2.6 Relationship between the CD4 count and the corresponding viral load. 4-8 weeks represents the window period, 2-12 years represents the asymptomatic phase and 2-3 years represents AIDS (Smith *et al.*, 2001).

The overall HIV replication and T-lymphocyte turnover has been estimated to be extremely high, with approximately 10^9 new virions and 3.5 x 10^7 new cell infections per day (Smith *et al.*, 2001). Rising HIV viral load levels and falling CD4 cell counts lead to the onset of AIDS. The phenotype may also change during the course of the infection. These variants tend to have a selective advantage when transmitted from a late stage person to a newly infected one. These variants lead to a fast progression towards AIDS once the host immune system is sufficiently damaged (Mims *et al.*, 1999).

It is macrophage infection that leads to wasting syndrome and CNS disease in AIDS. Micoglia is a type of macrophage in the brain. Their infection leads to signalling of cytokines and chemokines, leading to a loss of neurons and dementia that sometimes occurs in AIDS. Dendritic cells are also infected by HIV. These cells include Langerhans cells of the mucous membranes and these may be a target during sexual transmission. These cells carry HIV to the lymph nodes, where CD4-positive lymphocytes become infected.

2.4 Current anti-retroviral drugs and their mode of action

Anti-retroviral drugs are used to combat the action of HIV. Treatment with these drugs is complex and the field changes rapidly. The drugs currently available inhibit the action of two enzymes vital for the replication of HIV, reverse transcriptase and protease (AIDS Bulletin, 2005).

Drugs that inhibit reverse transcriptase (RT) are called RT inhibitors and are found in two forms: nucleoside and non-nucleoside. The nucleoside RT inhibitors suppress the RT enzyme because they are analogues to the enzyme, and will therefore prevent the enzymes from binding to the active site. AZT is an example of a nucleoside RT drug. The non-nucleoside inhibitors are also RT inhibitors, but they bind to the RT enzymes, and therefore eliminate RT enzymes from producing DNA from the RNA injected into the cell by the virus. Delaviridine is an example of a non-nucleoside RT inhibitor drug currently in use (AIDS Bulletin, 2005).

Drugs that inhibit protease are called protease inhibitors. Protease inhibitors inhibit protease action, which is responsible for cleaving the viral proteins in their active components. These medicines such as Indinavir and Ritonavir bind to the protease active site, and prevent the binding of protease enzymes to cleave the proteins.

Anti-retroviral drugs do not destroy HIV infection, but effectively suppress viral replication. The usual combinations are two nucleoside reverse transcriptase inhibitors together with a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. This is called highly active anti-retroviral therapy (HAART). HAART treatment starts when antigen effects are decreased in the body, and the immune system is therefore not as effective as before. A combination of three drugs commonly used is for example: nevirapine, stavudine and lamivudine.

All these drugs have side-effects. The most common side effects of the nucleoside reverse transcriptase inhibitors are nausea, headache, muscle pain, insomnia and sometimes anaemia and other blood abnormalities. The non-nucleoside reverse transcriptase inhibitors can cause rashes, fever, nausea, headache and liver problems. All the protease inhibitors cause abnormal fat distribution, high cholesterol and triglycerides, and resistance to the hormone insulin that is involved in the metabolism of glucose to fat (AIDS bulletin, 2005).

2.5 The immune system

The immune system of the body that provides protection from disease is a very complex system. It identifies and deals with the very large number of potentially

harmful microorganisms that exist in our environment (Hochhauser & Rothenberger, 1992). Aside from the physical barriers to infection such as the skin and mucous membranes, the body possesses a wide array of chemical agents and specific types of cells that can detect and destroy microorganisms. There is a broad distinction between non-specific defences and specific defences against disease in the human body. The immune system evolved as a defence against infectious disease. Specific immunity is only called into play when microorganisms bypass the non-specific mechanism (Underwood, 2000). Many non-specific mechanisms prevent invasion of microorganisms and are given below:

- Mechanical barriers are highly effective and their failure results in infection.
- Secretory factors present effective chemical barriers to many organisms.
- Cellular factors include leukocytes and macrophages that phagocytose and kill microorganisms.
- Complements are a complex series of interacting plasma proteins (Underwood, 2000).

The non-specific mechanism consists of phagocytes, macrophages, neutrophills and killer cells. A large number of cells are known as phagocytes. Individual types such as macrophages and neutrophills, can act against a wide range of microorganisms. They act by detecting the foreign particle, binding to it and engulfing it. HIV however can gain entry into macrophages. Natural killer cells are also important, and are capable of directly attacking and killing virus-infected, or cancerous body cells.

Interferons and complements form a significant part of the body's general (non-specific) chemical defence. Interferons are a class of small proteins which are

released by virus-infected cells. The interferons assist in protecting uninfected cells from viral entry as well as mobilising the immune system. The term complement refers to a group of different plasma proteins that act to kill bacteria and several other cells. They also enable macrophages and neutrophils to adhere to and engulf microorganisms more rapidly, and intensify the body's inflammatory response to infection (Hochhauser & Rothenberger, 1992).

Specific defences produce a defence that is precisely targeted against specific microorganisms. These microorganisms produce antigens in the infected host, which the immune system will recognise and destroy or neutralise (Anderson & Wilkie, 1992). The immune system has four essential features:

- Specificity
- Diversity
- Memory
- Recruitment of other defence mechanisms

A specific immune response consists of two parts: a specific response to an antigen and a non-specific augmentation of the effect of that response. There is always a quicker and larger response the second time a particular antigen is encountered. An immune response has two phases: the recognition, involving antigen-presenting cells and T-lymphocytes, in which the antigen is being recognised as being foreign. The effector phase follows in which antibodies and effector T-lymphocytes eliminate the antigen, often by recruiting non-specific mechanisms such as complement or macrophage activation (Underwood, 2000).

2.5.1 Antigens

Antigens are substances able to provoke an immune response and react with the immune products. They react with both the T-cell recognition receptor and with the antibody. Antigens are conventially divided into thymus dependent and thymus-independent antigens. Thymus dependent antigens require T-cell participation and provoke the production of antibodies where the thymus-independent antigens require no T-cell co-operation for antibody reproduction (Underwood, 2000).

B-cells within the immune system are involved in the production of antibodies. Antibodies are made up of different types of immunoglobulin (Ig). They are able to recognise foreign proteins or sugars on the surface of antigens, and they will bind to that antigen. Memory cells are produced which is capable of being activated on subsequent encounters with an infectious agent. Antibodies circulate within the blood or lymph where they can bind to bacteria, free viruses or bacteria produced toxins (Anderson & Wilkie, 1992).

2.5.2 Antibodies

Humoral immunity is dependent on the production of antibodies and their actions. All antibodies belong to the immunoglobulin class of proteins and are produced by plasma cells, derived from B-lymphocytes (Underwood, 2000). Antibodies act against infectious agents in various ways. Phagocytes, complement or activated T-cells mark, destroy and neutralise toxic chemicals produced by bacteria, by binding to specific sites on viruses that prevent the viruses from binding to receptor sites on tissue cells. Antibodies play therefore an important role in destruction of micro-organisms, although they cannot penetrate the cells, and therefore have a limited

function in preventing the replication of viruses within the cells (Anderson & Wilkie, 1992).

2.5.3 T-cell receptors

There are mainly four types of T-cells:

- Cytotoxic T-cells (killer T-cells)
- Delayed hypersensitivity T-cells (memory cells)
- Helper T-cells
- Suppressor T-cells

Like B-cells, T-cells are committed to a given antigen. T-cells can recognise antigens that are attached to or displayed on the surfaces of cells. The cytotoxic T-cells or killer T-cells, can be activated to recognise cells which are displaying these antigens. The killer T-cells will then destroy the cells containing the antigens (Anderson & Wilkie, 1992). CD4 T-cells differentiate either into inflammatory or helper cells (Underwood, 2000). CD8 T-cells produce cytotoxins with which they eliminate tumour cells and target cells infected with viruses and other microorganisms (Haslett *et al*., 1999).

T-cells play an important role in regulating the overall activity of the immune system. The helper T-cells activate and co-ordinate the immune response. Once they are activated, they stimulate the production of other T-cells including killer T-cells and B-cells that initiate the process of producing antibodies. Suppressor T-cells slow or stop the activity of T-cells and B-cells once the infection is suppressed. When the memory

cells recognise the same antigen again, they release chemicals which enhance the defence system against the antigen (Hochhauser & Rothenberger, 1992).

2.5.4 Cytokines

Cytokines are soluble mediators secreted by lymphocytes or by macrophages. They act as stimulatory or inhibitory signals between cells. Cytokines which act between cells of the immune system are called interleukins, while those which induce chemotaxis of leukocytes are called chemokines. All the chemokines share the same common features:

- Short half lives
- Rapid degradation
- Local action within the environment of cells
- May act on cytokine receptors on the surface of the cell of production to promote further activation and differentiation
- May affect multiple organs in the body
- Exhibit overlapping functions

The immune system consists therefore of antibodies that are produced to eliminate and destroy antigens which are foreign bodies to the immune system. T-cells have different functions in strengthening and activating the immune response while cytokines stimulate and transport signals between the cells. All of these components work together during HIV infection to oppose the virus.

2.5.5 The effect of HIV on the immune system

One of the most important targets of HIV is the T-cells. The principle way in which HIV compromises the immune system is by damaging the helper T-cells by binding to the CD4 receptor sites which are present on helper T-cells. Later the number of T-cells decline markedly, and the normal ratio of helper to suppressor T-cells are disturbed. The helper T-cells cannot recognise the antigens and the activation of the immune system is suppressed. This leads to considerable problems in the normal functioning of the immune system in the body. It appears as if HIV has a less damaging effect on the other cells of the defence system. The decline in the body to defend itself is sometimes described as immuno-compromised, and these people may be subject to a range of OI (Anderson & Wilkie, 1992).

CD4 receptors sites on helper T-cells serves as a marker to distinguish them from other T-cells. That is the reason for these cells to be named CD4 cells or T4 cells. Killer T-cells and suppressor cells which can be detected by a CD8 marker on the surface are often referred to as CD8 cells or T8 cells (Anderson & Wilkie, 1992).

2.5.6 Antibody tests

As HIV infects the body and the immune system, the foreign antigens will be recognised by the host immune system. This will lead to the production of antibodies against the viral antigens. The detection of the virus is normally achieved by taking a blood sample and detecting antibodies to HIV in the serum. The most common methods used to test for the presence of antibodies to HIV are the ELISA (enzyme-linked immuno-absorbent assay) and the Western Blot test.

If the antibodies are present in the serum the person is HIV positive. If a negative result was obtained, it means that the antibodies were not detected but it might give incorrect results if a person was infected in the recent past. It takes three to eight weeks for antibodies to be produced. This period is also known as the window period of HIV infection. People that have been exposed to a risk of infection in the recent past are advised to repeat the test after three months to eliminate the window period, as the test only detects antibodies in the serum (Hochhauser & Rothenberger, 1992).

2.5.7 HIV antigen tests

This type of test directly detects the antigen of the viral material itself. The tests in clinical settings identify the p14 protein found in the core of the virus. This test can play a part in detecting HIV shortly after infection. Circulating HIV material including p14 can be detected soon after infection but prior to the development of antibodies. In most individuals the level of p14 antigens declines to undetectable quantities in the body as the body begins to produce specific antibodies to HIV. If the level of antibodies falls later during infection, the p24 antigen generally reappears in the serum. This also indicates a decline in the functioning of the immune system (Anderson & Wilkie, 1992).

2.5.8 Monitoring the effects of HIV

An important test for monitoring the functioning of the immune system is the CD4 (T4) lymphocyte count. The normal range of the CD4 count is 500 to 1500 per mm^3 blood. If the CD4 count drops below 200 per mm^3, a more rapid development of symptoms will be experienced (Anderson & Wilkie, 1992). This will be the start of developing OI, because the immune system does not function properly. People

reaching this stage, normally start the use of anti-retroviral treatment (ART) in South Africa, that takes them back to the asymptomatic phase where the CD4 count increases and stabilises for another undetermined period of time.

2.6 Statistics on HIV/AIDS

2.6.1 Sub-Saharan Africa

Sub-Saharan Africa has just over 10% of the world's population, but is home to more than 60% of all people living with HIV (De Oliveira, 2005). Of the 5.6 million new infections in 1999, two thirds occurred in sub-Saharan Africa, and almost a quarter in south and southeast Asia. Africa has been, and continues to be hardest hit. Subtype C, mainly found in sub-Saharan Africa, now accounts for almost 50% of all new infections (Figure 2.7). This subtype may prove to be a virulent strain.

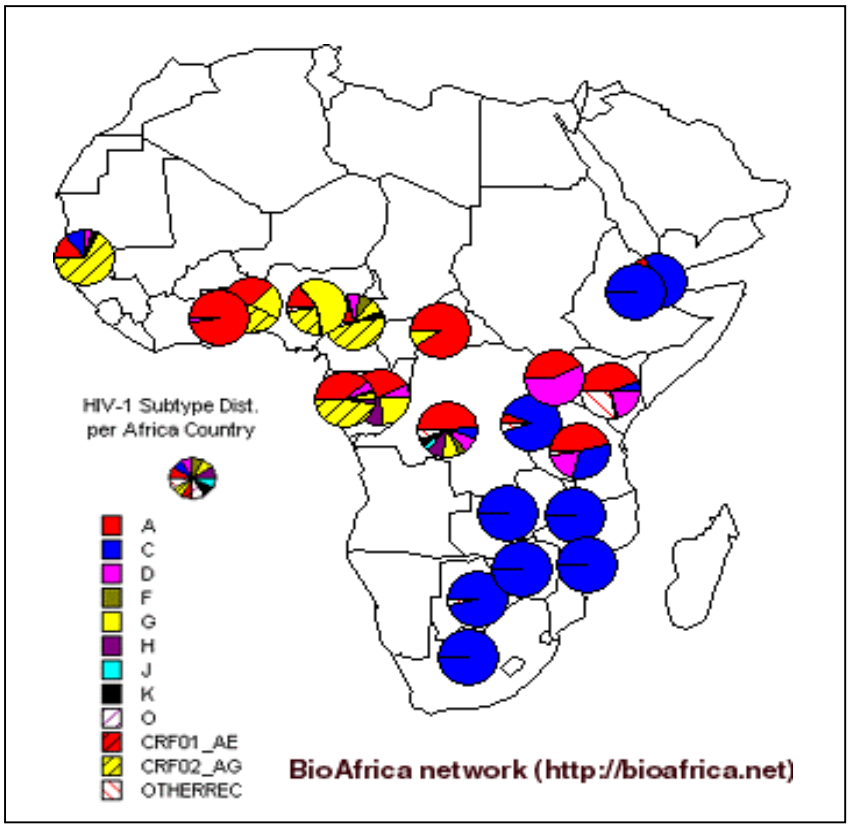

Figure 2.7 Diagram indicating the different subtype distribution in Africa (De Oliveira, 2005).

It is not only the type of virus that determines the prevalence, but also co-infections that favours the transmission of HIV. It is now clear that sexual transmission is enhanced by the presence of other sexually transmitted diseases (STDs), and helps to explain the rapid spread of HIV in countries with high occurrence of STDs. Herpes simplex virus 2 (HSV-2) is highly prevalent in many developing countries, and could increase the risk of HIV transmission by causing genital ulcers that provide a portal of entry for the virus (Smith *et al.*, 2001).

The AIDS estimates for sub-Saharan Africa, at the end of 2004 are given in Table 2.1 below.

Table 2.1: Statistics of HIV/AIDS infection in sub-Saharan Africa (UNAIDS, 2004).

Category	**Percentage or number**
Adult (15-49) HIV prevalence rate	7.4%
Adults and children living with HIV (0-49)	25 400 000
Women (15-49) living with HIV	13 300 000
Adults and children newly infected with HIV in 2004	3 100 000
Adults and child deaths due to AIDS in 2004	2 300 000

HIV infection is becoming endemic in sub-Saharan Africa. The havoc wrought will shape the lives of several generations of Africans. Southern Africa offers only faint hints of impending declines in HIV prevalence. With the exception of Angola each country in this region is experiencing national prevalence of at least 10%. This means that an estimated 11.4 million people are living with HIV in the nine sub-Saharan African countries. This is almost 30% of the global number of people living with HIV in an area where only 2% of the total world population resides (UNAIDS, 2004).

Across the region, women are disproportionately affected with HIV. On average there are 13 women living with HIV for every 10 infected men, and the gap continues

to grow. In most countries women are also infected at an earlier age than men. Recent studies suggest that there are on average 36 young women living with HIV for every 10 young men in sub-Saharan Africa (UNAIDS, 2004).

2.6.2 South Africa

The latest results released at the end of 2003, estimated that 5.3 million South Africans were infected with HIV, the largest number of individuals living with the virus in a single country. Unfortunately, there is no sign yet of a decline in the epidemic. Latest data suggest prevalence levels are still increasing in all age groups, except for pregnant women older than 40 years of age (UNAIDS, 2004).

The HIV and AIDS estimates for South Africa, at the end of 2003 are given in Table 2.2 below.

Table 2.2: Statistics of HIV/AIDS infection in South Africa.

Category	**Percentage or number**
Adult (15-49) HIV prevalence rate	21.5%
Adults living with HIV (15-49)	5 100 000
Women (15-49) living with HIV	2 900 000
Adults and children living with HIV (0-49)	5 300 000
AIDS deaths (adults and children) in 2003	370 000

The national HIV infection rate among pregnant women attending antenatal services in 2003 was 27.9%. Commitment to tackling the epidemic in South Africa is backed by increased domestic financial resources. In 2003, the government approved a Comprehensive National Plan on HIV and AIDS Care Management and Treatment, which provides access to antiretroviral treatment to more than 1.4 million South Africans by 2008 (UNAIDS, 2004).

These figures coincide with the release of a report on the National Indicators of the Demographic Impact of HIV/AIDS in South Africa, 2004 by the Centre for Actuarial Research (CARe) at UCT, The Burden of Disease Research Unit of the MRC and the AIDS Committee of the Actuarial Society of South Africa (ASSA). The report also shows that 5 million out of a total of 46 million South Africans (11%) are infected with HIV. It is also speculated that the population growth of 0.8% is set to fall to half of that level by 2010. In the absence of ART AIDS deaths would be expected to rise to nearly 500 000 by 2010. With ART the number is expected to fall to 380 000. The life expectancy at birth in South Africa is currently 50 years (AfroAIDS info, 2004).