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ISBN: 1-905310-07-2

First published in Great Britain by Bridgehead Pharmedicalensing Group in January 2005 under ISBN: 0-9545760-9-8.

This edition published in Great Britain in May 2005 by

Bridgehead International Limited
Pera Innovation Park
Nottingham Road
Melton Mowbray
Leicestershire LE13 0PB, UK

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1 Introduction to HIV

1.1 Learning objectives

On completing this section, the reader should be able to:

- describe the human immunodeficiency virus
- describe the strains, classification and epidemiology of HIV
- understand how HIV infection occurs
- discuss the conditions secondary to HIV infection.

1.2 Introduction

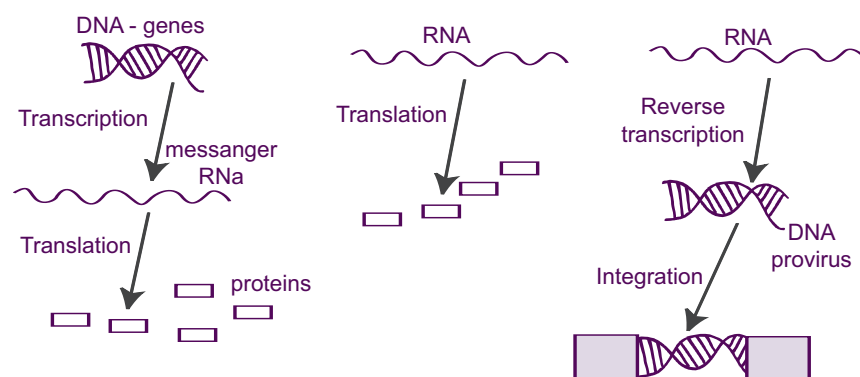
Since the first cases of AIDS were identified in 1981, more than 20 million people with HIV/AIDS have died, with 2.9 million deaths (including an estimated 490,000 children younger than 15 years) in 2003 alone. As of the end of 2003, an estimated 37.8 million people worldwide (35.7 million adults and 2.1 million children younger than 15 years) were living with HIV/AIDS.

An estimated 4.8 million new HIV infections occurred worldwide during 2003. This included approximately 1,700 children under the age of 15 years, and 6,000 young people aged 15 to 24 years becoming infected with HIV every day.

1.2.1 Viruses

Viruses possess either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), but not both. There are, therefore, two kinds of viruses: DNA viruses and RNA viruses. The human immunodeficiency virus (HIV) belongs to a family of RNA viruses known as the **retroviridae**. When the virus enters a cell, a DNA copy of the viral genes (known as a **provirus**) is made which controls the synthesis of proteins. The proviral DNA integrates into the DNA of the host cell using an enzyme called **reverse transcriptase** (RT, figure 1.1). It then directs the formation of messenger RNA for the manufacture of viral proteins. The key discovery of RT answered a major question as to how viruses make DNA from an RNA template.

Figure 1.1 The three types of viral replication: (A) DNA virus; (B) RNA virus; (C) retrovirus, using reverse transcriptase. (Adapted from BD Shoub, 1999)



1.3 Human immunodeficiency virus

Human immunodeficiency virus type 1 (HIV-1) was isolated in 1983, and linked with acquired immunodeficiency syndrome (AIDS) in 1984. In 1986, a second type of HIV, called HIV-2, was isolated from AIDS patients in West Africa. Studies of the natural history of HIV-2 are limited but there are some similarities between HIV-1 and HIV-2: both have the same modes of **transmission** and both are associated with similar opportunistic infections and AIDS. However, there are notable differences:

- immunodeficiency appears to develop more slowly and to be less aggressive in individuals infected with HIV-2
- people infected with HIV-2 are less infectious early in the course of infection compared with HIV-1

Since the first cases of AIDS were identified in 1981, more than 20 million people with HIV/AIDS have died

AIDS is derived from the human immunodeficiency virus (HIV), which belongs to a family of RNA viruses known as retroviridae

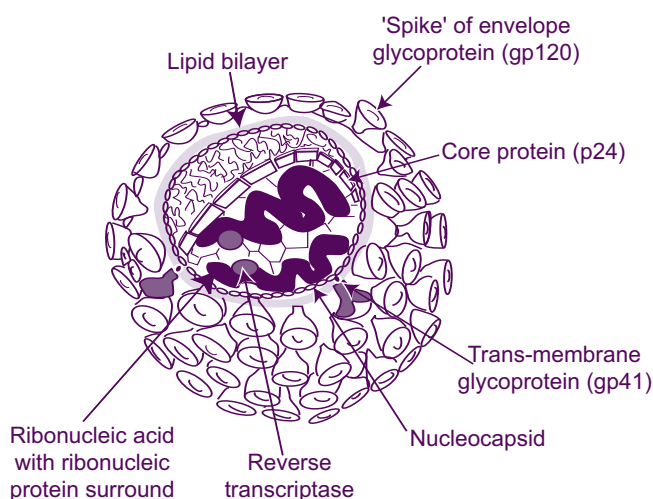
1.6 Introduction to the virology of HIV

1.6.1 The structure of HIV

HIV is approximately 100–150 nm in diameter and roughly circular in shape (figure 1.2). However, the viral envelope is very pliable and the shape may change from spherical to an oval or irregular outline.

HIV is approximately 100–150 nm in diameter and roughly circular in shape

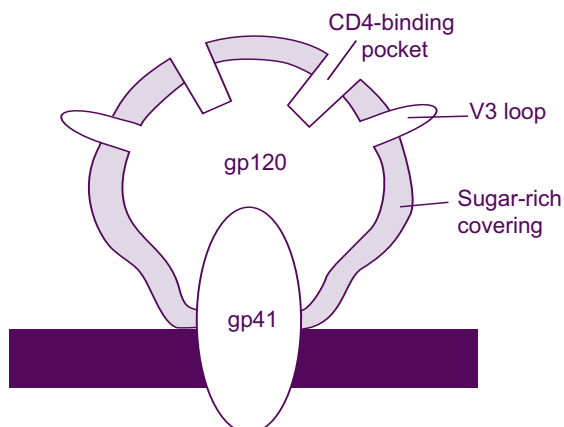
Figure 1.2 Schematic diagram of HIV (adapted from BD Shoub, 1999)



The envelope is in part derived from the cell membrane of the host cell that the virus buds through in the final stages of its replication. Protruding from the outside of the envelope are two viral proteins that are anchored into the outer surface of the envelope (figure 1.3). These are gp120 (a knob-like protein; 120,000 Daltons) and gp41 (a smaller spike-like protein; 41,000 Daltons). These proteins are critical for the initial attachment of the virus to its cellular receptor site and are the most important **antigens** of the virus; as surface molecules they are the most likely to be encountered by the host's defenses. The antibodies they elicit will be those that may confer protection by preventing the virus from attaching to the cellular receptor sites.

Two viral proteins are anchored into the outer surface of the HIV envelope, these are gp120 and gp41

Figure 1.3 Diagram of the structure of the envelope glycoprotein of HIV (adapted from BD Shoub, 1999)



The inner core of the virus (**capsid**) surrounds the nucleic acid and is the chief feature used to recognize the virus under the electron microscope. The main protein of the core of the virus is referred to as p24.

Slightly different forms of the virus are found across individuals as well as across populations. The variability in the virus is due mainly to the inaccuracy of the viral genetic copying mechanism, with 10-20 mistakes made during each replication cycle of the virus. In addition, the enzyme reverse transcriptase (RT) is prone to errors when making a DNA copy from the RNA template. These errors can create **quasispecies**.

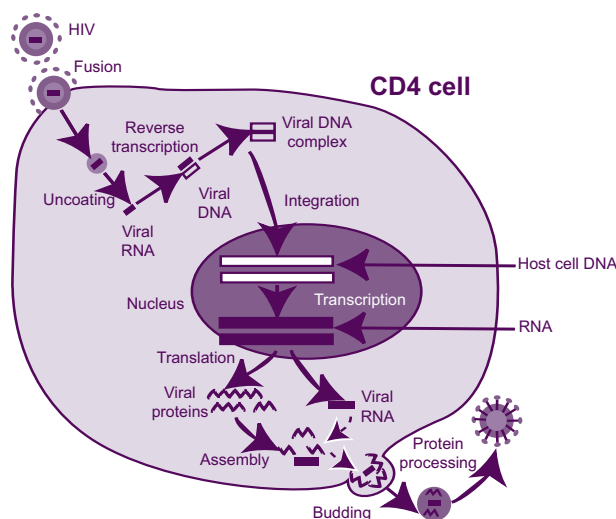
1.7 HIV lifecycle

Viruses cannot reproduce without the aid of a living cell. HIV causes a reduction in the number of T-cells in the body, eventually resulting in an increased risk of other infections. The life cycle of HIV consists of several stages (see figure 1.4):

- viral attachment
- penetration or fusion
- uncoating
- **reverse transcription**
- **integration** into host DNA
- viral latency and protein synthesis
- cleavage and viral assembly
- budding.

HIV causes a reduction in the number of T-cells in the body, which eventually result in an increased risk of infection

Figure 1.4 Diagram representing life cycle of HIV (adapted from Lee K, Gulick RML, 2001)



1.7.1 Viral attachment

Once HIV comes into contact with a T-cell, it must attach itself to the cell so that it can fuse with the membrane, thereby allowing its RNA to gain access to host DNA. Attachment occurs via a specific binding between proteins on the surface of the virus and proteins that serve as receptors on the surface of the T-cell. The two receptors most commonly used by HIV to latch onto the cell are:

- CD4
- a beta-chemokine receptor (either CCR5 or CXCR4).

In order for RNA to gain access to host DNA HIV must attach and fuse with the cell membrane

On the surface of the viral envelope, two sets of proteins called gp120 and gp41 attach to CD4 and CCR5/CXCR4. The postulated route of entry of HIV into cells is shown in figure 1.3. The initial step is the attachment of the V3 loop of the gp120 envelope protein onto its specific receptor site, the CD4 protein (1). This initial step causes structural changes to the surface of the virus, allowing it to attach to the co-receptor that brings the gp41 protein of HIV into closer contact with the cell membrane (2). The gp41 protein can then mediate fusion of the viral envelope with the cell membrane (3), permitting the virus to penetrate the cell and start replicating (4).

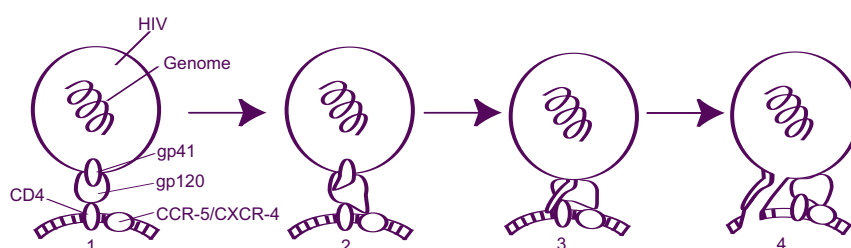
1.7.2 Penetration/fusion

After attachment is completed, viral penetration occurs, allowing injection of the viral **nucleocapsid** directly into the cytoplasm. gp120 actually contains three sugar-coated proteins (glycoproteins) and, once gp120 attaches itself to CD4, these three proteins spread apart. This exposes the gp41 protein, permitting its binding to the chemokine receptor. Once this has occurred, the viral envelope and the cell membrane come into direct contact. Cells that express the CD4 receptor include:

- CD4⁺ T-cells
- **dendritic cells**
- **macrophages** (figure 1.5)
- monocytes.

Penetration of the cell membrane allows injection of the viral nucleocapsid directly into the cytoplasm

Figure 1.5 Diagram representing the steps in the infection of a macrophage by HIV (adapted from BD Shoub, 1999)



1.7.3 Uncoating

Having penetrated the cell membrane, in order for HIV to replicate, it must release its RNA into the cell. The viral RNA is protected by the nucleocapsid, which needs to be partially dissolved to allow conversion of the virus RNA into DNA, for incorporation into the T-cell DNA.

The nucleocapsid must be partially dissolved to allow conversion of the virus RNA into DNA and subsequent incorporation of the virus RNA into the T-cell DNA

1.7.4 Reverse transcription

Before the virus RNA can be incorporated into the CD4⁺ cell DNA, it must first be converted to DNA in a process known as reverse transcription. HIV uses an enzyme called reverse transcriptase, which utilizes nucleotides in the cell cytoplasm. The result is the conversion of single-stranded viral RNA into a double strand of DNA.

Conversion of virus RNA into DNA uses an enzyme called reverse transcriptase

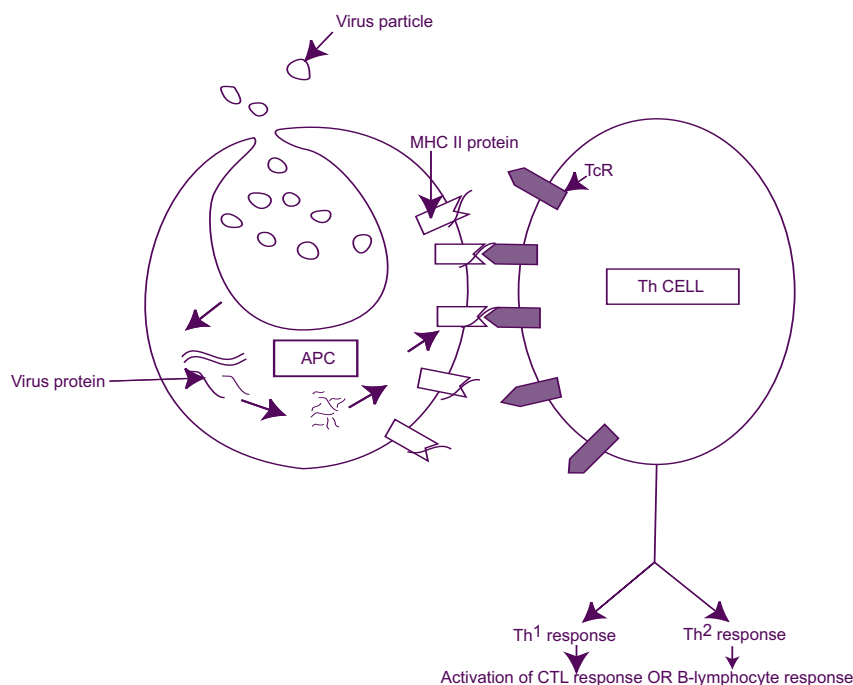
2 Immunology and virology of HIV infection

2.1 Learning objectives

On completing this section, the reader should be able to:

- describe the basics of the immune system
- understand the response to infection
- discuss monitoring HIV and AIDS progression.

Figure 2.1 Diagram representing the presentation of virus antigens to the immune system (Adapted from BD Schoub, 1999)



At the same time that viral proteins are being made and assembled into new virions, proteolytic degradation of viral proteins is occurring in the cytoplasm. The proteolytic fragments are then transported into the endoplasmic reticulum, where they form a complex with a developing class I molecule, and are then transported to the cell surface.

2.4.2 The role played by lymphocytes in fighting infection

Both CTL and CD4⁺ T-helper-cell responses appear to contribute to immune control of viral infection, although in situations in which **neutralizing antibody** responses are limited, **cellular immune responses** appear to increase in importance. Entry of a virus to a cell causes production of TNF α and β , which activates antiviral mechanisms in nearby cells, thereby increasing their resistance to infection. In addition, IFN γ enhances the efficiency of the adaptive immune response by activating macrophages and natural killer cells and by increasing levels of MHC class I and class II molecules.

CTL are generated in response to infection and inhibit virus replication by at least two mechanisms:

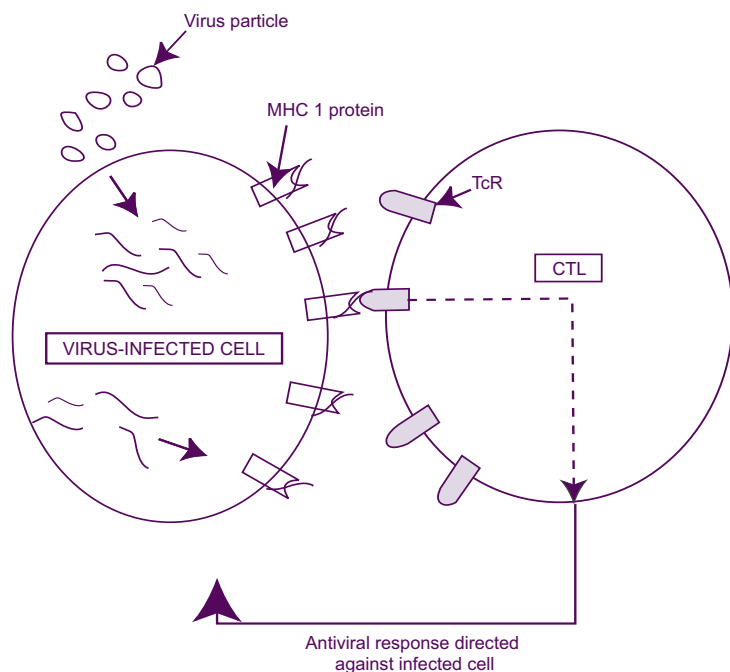
- direct killing of infected cells
- release of soluble antiviral factors.

The presence of a viral protein (usually 9–10 amino acids in length) within the peptide-binding cleft of a class I molecule is a signal to the immune system that a foreign invader is present within that cell. This then triggers CTL to kill the infected cell through a direct recognition mediated by the TCR on the CTL (figure 2.2).

CTL and CD4⁺ T-helper-cell responses, both appear to contribute to immune control of viral infection

The presence of a viral protein complexed to a class I molecule triggers the CTL to kill the infected cell through a direct recognition mediated by the TCR

Figure 2.2 Diagram representing the recognition of a viral-infected target cell and the antiviral CTL response (Adapted from BD Schoub, 1999)



Activation of the CTL leads to the release of antiviral agents including the beta **chemokines**, which are able to inhibit infection by any progeny virions that may already have been produced. At the same time that CTL are activated to kill virus-infected cells, they produce soluble factors that have been shown to inhibit HIV replication. These include the chemokines RANTES, MIP-1 α , and MIP-1 β , which have been shown to inhibit the ability of HIV-1 to infect new cells by competing with virus for binding to certain co-receptors present on the cell surface that are necessary for viral entry. Other soluble factors, including **defensins**, are also released. If CTL arrive after new **progeny viruses** have been produced, then the release of soluble factors might be expected to inhibit those progeny viruses from infecting other cells.

In addition to CTL, the cellular immune response is also associated with the generation of virus-specific T-helper cells, which recognize viral proteins that have been taken up into antigen-presenting cells (APCs), processed to smaller peptides, and then presented at the cell surface within the peptide-binding groove of the class II molecule. These cells are required for the maintenance of CTL in a number of chronic viral infections.

2.4.3 Memory cells

An offshoot of the management section of the immune system is the creation of a biological memory bank for storage of details of the foreign body. Should the foreign body be encountered again, the immune response is accelerated and it is dispatched much more rapidly, usually even before any clinical signs or symptoms of a potential disease are manifest.

New observations suggest that considerable damage is caused to the immune system during the acute phase of the infection, resulting in a substantial early

In addition to CTL activity, virus-specific T-helper cells recognize viral proteins that have been taken up into antigen-presenting cells and presented at the cell surface complexed with class II molecules

Memory cells allow the immune response to be accelerated upon second exposure to an antigen

3 Antiviral therapy

3.1 Learning objectives

On completing this section, the reader should be able to:

- discuss different types of HIV therapeutics on the market
- understand the toxicities of these therapeutics
- discuss new therapies in development

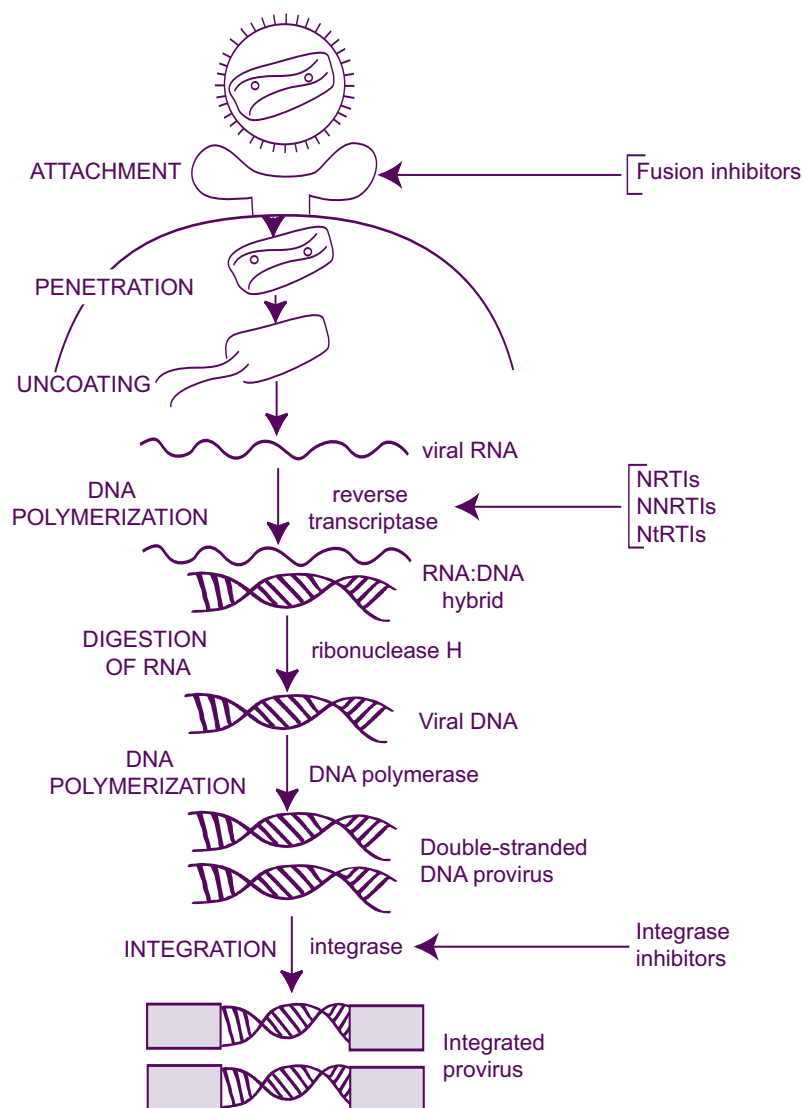
3.2 Introduction

Current anti-HIV therapy consists of four major treatment modalities:

- NRTIs
- NNRTIs
- PIs
- fusion/entry inhibitors.

The stages during the HIV replication process at which these agents exert their effect are outlined in figure 3.1.

Figure 3.1 Steps in the early stage of HIV replication (adapted from BD Shoub, 1999)



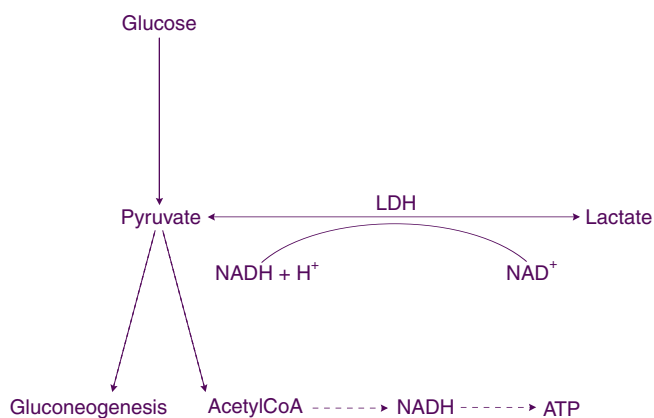
3.8.1 Nucleoside reverse transcriptase inhibitors

All NRTIs can potentially cause mitochondrial injury, producing a decrease in mitochondrial DNA that may be irreversible as well as an increase in mutant mitochondrial DNA. It is currently hypothesized that much of the recognized long-term NRTI-associated toxicity can be attributed to mitochondrial damage. Some of the other major side effects include:

- lactic acidosis (mechanism outlined in figure 3.5)
- hepatic steatosis
- hyperlactatemia.

All NRTIs can potentially cause mitochondrial injury, producing a decrease in mitochondrial DNA that may be irreversible as well as an increase in mutant mitochondrial DNA

Figure 3.5 Mechanism by which NRTI therapy interferes with glycolysis (Montessori et al)



A list of side effects for antiviral agents is documented in tables 3.4–3.6.

4 The importance of resistance

4.1 Learning objectives

On completing this section, the reader should be able to:

- understand the problems associated with resistance
- discuss the mechanism of resistance development
- appreciate potential strategies for the management of resistance.

5 Opportunistic infections and AIDS-related conditions

5.1 Learning objectives

On completing this section, the reader should be able to:

- discuss the types of opportunistic infection associated with HIV

6.2 Glossary

active site: the part of the enzyme molecule that is involved in effecting its action in its substrate

acute HIV syndrome: the first stage of HIV infection

acute retroviral syndrome: primary HIV infection

adaptive: part of the immune system in which responsiveness to invading organisms generally increases on subsequent exposure

AIDS Clinical Treatment Group: the US governmental group that co-ordinates drug trials. It is part of the National Institutes for Health (NIH)

AIDS-related complex: the fourth stage of HIV infection

antibody: protein produced by the immune system of humans and higher animals in response to the presence of a specific antigen

antigen: a substance which, when introduced into the body, is capable of starting the production of a specific antibody by the immune system

antigen-presenting cells: blood cells that present antigens to the immune system

autonomic: relating to or controlled by the autonomic nervous system

bacillary angiomatosis: An infectious bacterial disease characterized by cutaneous vascular lesions. It is caused by *Bartonella henselae* and is seen in AIDS patients and other immunocompromized hosts

basal ganglia: group of nerve cells located at the base of the brain that participates in the regulation of motor performance. It is composed of the putamen, caudate, globus pallidus, and substantia nigra

binding pocket: the part of the active site of the enzyme to which the substrate binds

capsid: inner core of HIV

CD4⁺: a T-helper cell on which the CD4 protein is embedded. The CD4 protein is also used by HIV to infect these cells

cellular factors: relating to the cell-based immune system

cellular immune response: response to infection based on T lymphocytes

chemokines: cytokines that attract leukocytes

clades: subtypes of HIV

codons: groups of nucleic acids on DNA that code for polypeptides or proteins

combination therapy: antiviral therapy using a combination of drugs—combinations are generally more effective than single drugs

cycloSal: nucleotide delivery system

6.3 Recommended reading

AIDSmap <http://www.aidsmap.com>

AIDSMeds <http://www.aidsmeds.com>

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