

PATHOPHYSIOLOGY OF THE HUMAN IMMUNODEFICIENCY VIRUS

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OBJECTIVES

1. Provide an overview of the healthy immune system.
2. Describe the human immunodeficiency virus (HIV).
3. Describe the major components of the HIV life cycle.
4. Identify the various HIV types and subtypes.
5. Discuss HIV's effects on the immune system.

KEY POINTS

1. The immune system protects the body by recognizing invading antigens on pathogens (bacteria, viruses, fungi, and parasites) and reacting to them.
2. T lymphocytes, or T cells, regulate the immune system and destroy antigens.
3. HIV continuously uses new host cells to replicate itself.
4. The HIV life cycle includes six phases: binding and entry, reverse transcription, integration, replication, budding, and maturation.
5. Once HIV is in the circulatory system, it targets the CD4+ lymphocyte.
6. Two types of HIV cause AIDS: HIV type 1 (HIV-1) and HIV-2.
7. Primary infection refers to the time when HIV first enters the body.
8. Clinical latency refers to the time before onset of symptoms and complications in the HIV-infected individual. In HIV-infected adults, this phase may last 8-10 years.
9. Early signs and symptoms of HIV can include candidiasis, lymphadenopathy, cervical carcinoma, herpes zoster, and peripheral neuropathy.
10. Late signs and symptoms of HIV and AIDS-defining illnesses can include the development of life-threatening infections and malignancies.

OVERVIEW

The human immunodeficiency virus (HIV) is a retrovirus belonging to the family of lentiviruses. Retroviruses can use their RNA and host DNA to make viral DNA and are known for their long incubation periods. Like other retroviruses, HIV infects the body, has a long incubation period (clinical latency), and ultimately causes the signs and symptoms of disease, here AIDS. HIV causes severe damage to the immune system and eventually destroys it by using the DNA of CD4+ cells to replicate itself. In that process, the virus eventually destroys the CD4+ cells.

THE HEALTHY IMMUNE SYSTEM

The immune system protects the body by recognizing antigens on invading bacteria and viruses and reacting to them. An antigen is any substance that induces a state of sensitivity and immune responsiveness. These antigens interact with antibodies and immune cells, initiating an immune response. This process destroys the antigen, allowing the body to be free of infections. Types of antigens include bacteria, viruses, fungi, and parasites. When the immune system is weakened or destroyed by a virus such as HIV, the body is left vulnerable to infections.

The immune system consists of lymphoid organs and tissues, including the bone marrow, thymus gland, lymph nodes, spleen, tonsils, adenoids, appendix, blood, and lymphatic vessels (**Figure 1**). All components of the immune system are vital in the production and development of lymphocytes, or white blood cells. B lymphocytes (or B cells) and T lymphocytes (or T cells) are produced from stem cells in the bone marrow. B cells stay in the bone marrow to complete the maturation process, but T lymphocytes travel to the thymus gland to complete their maturation. There T lymphocytes become immunocompetent, multiply, and become more differentiated.

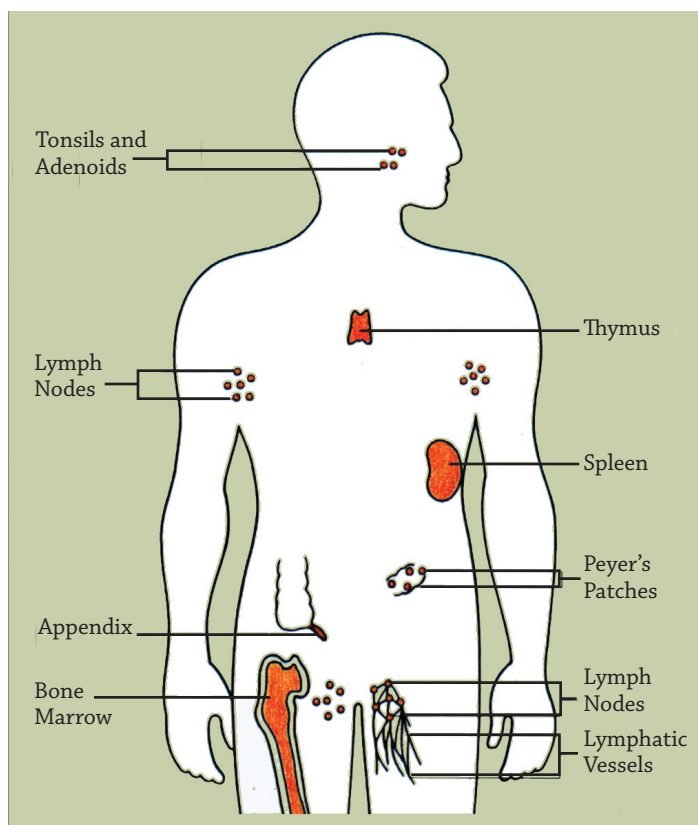


Figure 1. Organs of the Immune System

B Lymphocytes

The main function of B lymphocytes is humoral (antibody) immunity. Each B cell can recognize specific antigen targets and can secrete specific antibodies. Antibodies function by coating antigens, which makes the antigens more vulnerable to phagocytosis (engulfing and ingestion of invading organisms by leukocytes and/or macrophages), or by triggering the complement system, leading to an inflammatory response. Antibodies are highly specialized serum protein molecules. They are grouped into five classes, each having a specialized function: immunoglobulin G (IgG), IgA, IgM, IgE, and IgD.

T Lymphocytes

T lymphocytes have two major functions: regulation of the immune system and killing of cells that bear specific target antigens. Each T cell has a surface marker, such as CD4+, CD8+, and CD3+, that distinguishes it from other cells. CD4+ cells are helper cells that activate B cells, killer cells, and macrophages when a specific target antigen is present. There are two main types of CD8+ cells. The first type, cytotoxic CD8+ cells, kills cells infected by viruses or bacteria, as well as cancer cells. The second type of CD8+

cells, T-suppressor cells, inhibits or suppresses immune responses. Normal CD8+ cell count is between 300 and 1,000 cells in adults and children. The normal CD4+:CD8+ ratio is between 1.0 and 2.0.

T cells can secrete cytokines (chemicals that kill cells), such as interferon. Cytokines can bind to target cells and activate the inflammatory process. They also promote cell growth, activate phagocytes, and destroy target cells. Interleukins are cytokines that serve as messengers between white blood cells. Recombinant (laboratory synthesized) interleukins are currently being studied in clinical trials for patients with HIV infection.

Phagocytes

Phagocytes include monocytes and macrophages, large white blood cells that engulf and digest cells carrying antigenic particles. Found throughout the body, phagocytes rid the body of worn-out cells, initiate the immune response by presenting antigens to lymphocytes, are important in immune response regulation and inflammation, and carry receptors for cytokines. Dendritic cells, another type of phagocyte, also are antigen-presenting cells. They have long, threadlike extensions that help trap lymphocytes and antigens and are found in the spleen and lymph nodes. Neutrophils are granulocytic phagocytes that are important in the inflammatory response.

Complement

The complement system consists of 25 proteins. Complement can induce an inflammatory response when it functions with antibodies to facilitate phagocytosis or weaken the bacterial cell membrane. The complement proteins interact with one another in a sequential activation cascade, promoting the inflammatory process.

Despite the heavy artillery that the immune system has against foreign predators (**Figures 2 and 3**), HIV defeats it over time.

HIV'S STRUCTURE

HIV consists of a cylindrical center surrounded by a sphere-shaped lipid bilayer envelope. There are two major viral glycoproteins in this lipid bilayer, gp120 and gp41. The major function of these proteins is to mediate recognition of CD4+ cells and chemokine receptors, thereby enabling the virus to attach to and invade CD4+ cells. The inner sphere contains two single-stranded

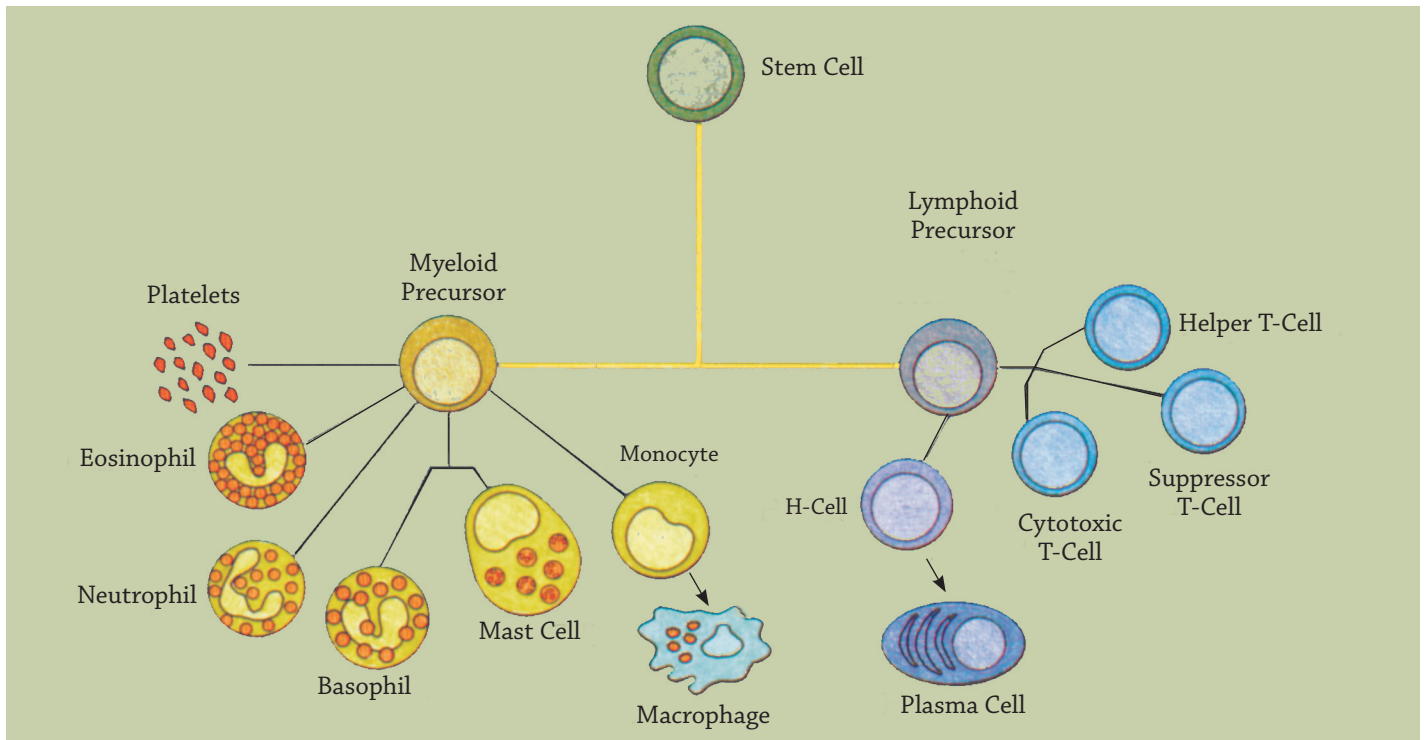


Figure 2. Cells of the immune system

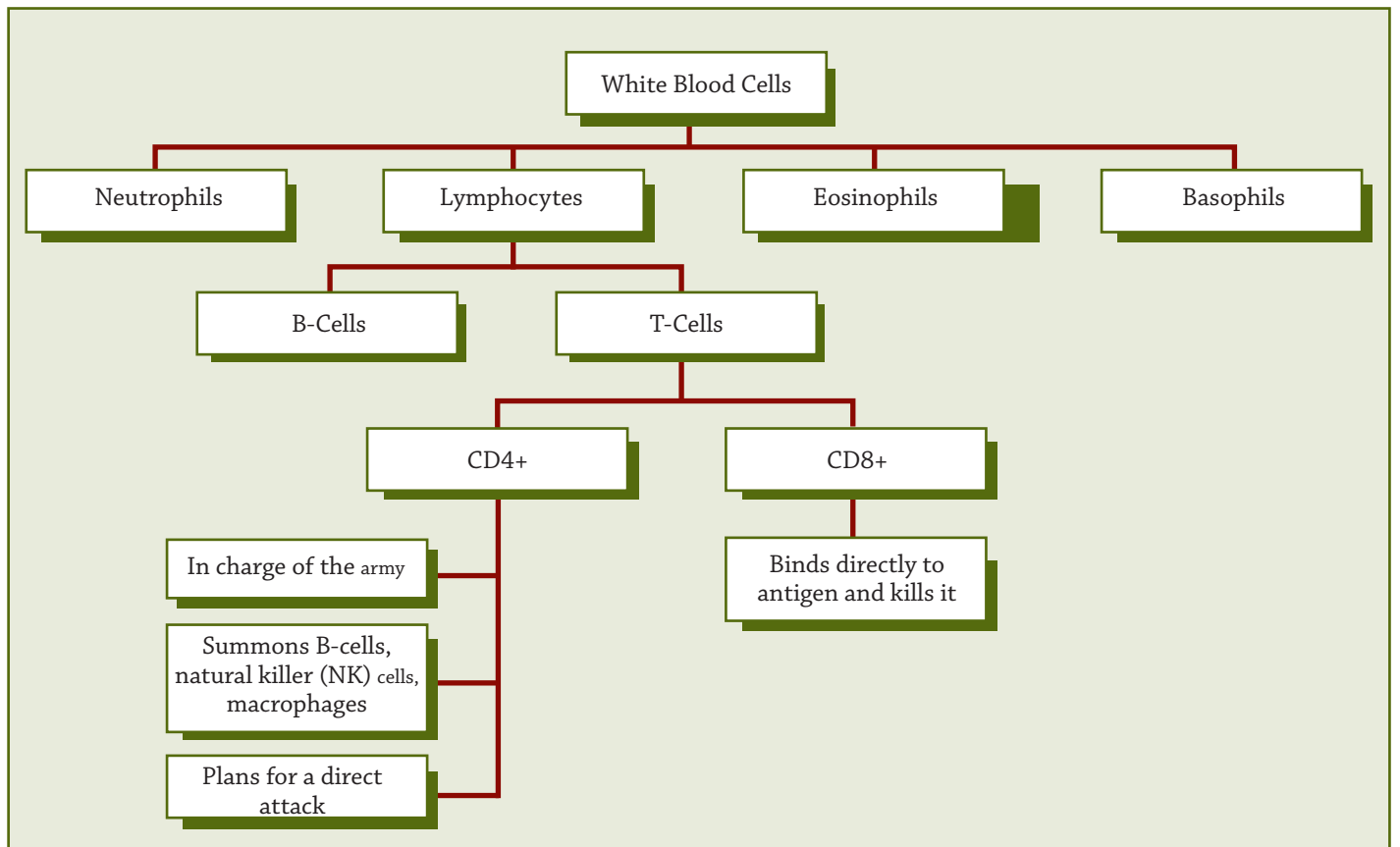


Figure 3. Immune response by white blood cells

copies of the genomic material, RNA, as well as multiple proteins and enzymes necessary for HIV replication and maturation: p24, p17, reverse transcriptase, integrase, and protease (**Figure 4**). Unlike other retroviruses, HIV uses nine genes to code for the necessary proteins and enzymes. The three principal genes are gag, pol, and env. The gag gene encodes core proteins. The pol gene encodes the enzymes reverse transcriptase, protease, and integrase. The env gene encodes the HIV structural components known as glycoproteins. The rest of the genes—rev, nef, vif, vpr, and tat—are important for viral replication and enhancing HIV’s infectivity rate.

HIV’s Life Cycle

Host cells infected with HIV have a shortened life span as a result of the virus’s using them as “factories” to produce multiple copies of new HIV. Thus, HIV continuously uses new host cells to replicate itself. As many as 10 million to 10 billion virions (individual viruses) are produced daily. In the first 24 h after exposure, HIV attacks or is captured by dendritic cells in the mucous membranes and skin. Within 5 days after exposure, these infected

cells make their way to the lymph nodes and eventually to the peripheral blood, where viral replication becomes rapid. CD4+ lymphocytes that are recruited to respond to viral antigen migrate to the lymph nodes. These become activated and then proliferate via complex interaction of cytokines released in the microenvironment of the lymph nodes. This sequence of events makes the CD4+ cells more susceptible to HIV infection, and it explains the generalized lymphadenopathy characteristic of the acute retroviral syndrome seen in adults and adolescents. In contrast, HIV-infected monocytes allow viral replication but resist killing. Thus, monocytes act as reservoirs of HIV and as effectors of tissue damage in organs such as the brain.

The HIV life cycle includes six phases: binding and entry, reverse transcription, integration, replication, budding, and maturation (**Figure 5**).

Binding and Entry

The envelope proteins gp120 and gp41 bind to CD4+ cell receptors and coreceptors on the outside of CD4+ cells

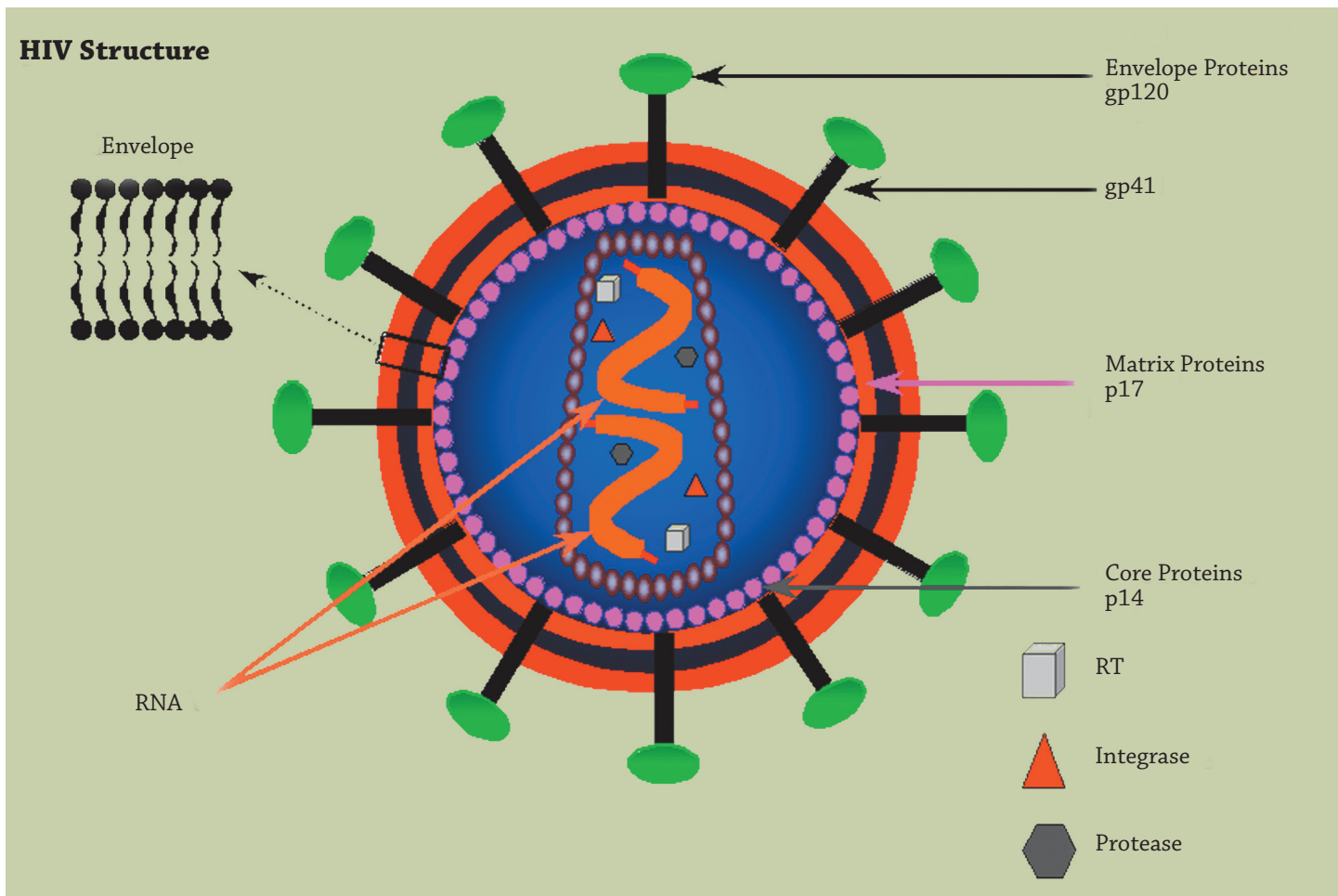


Figure 4. The Human Immunodeficiency Virus

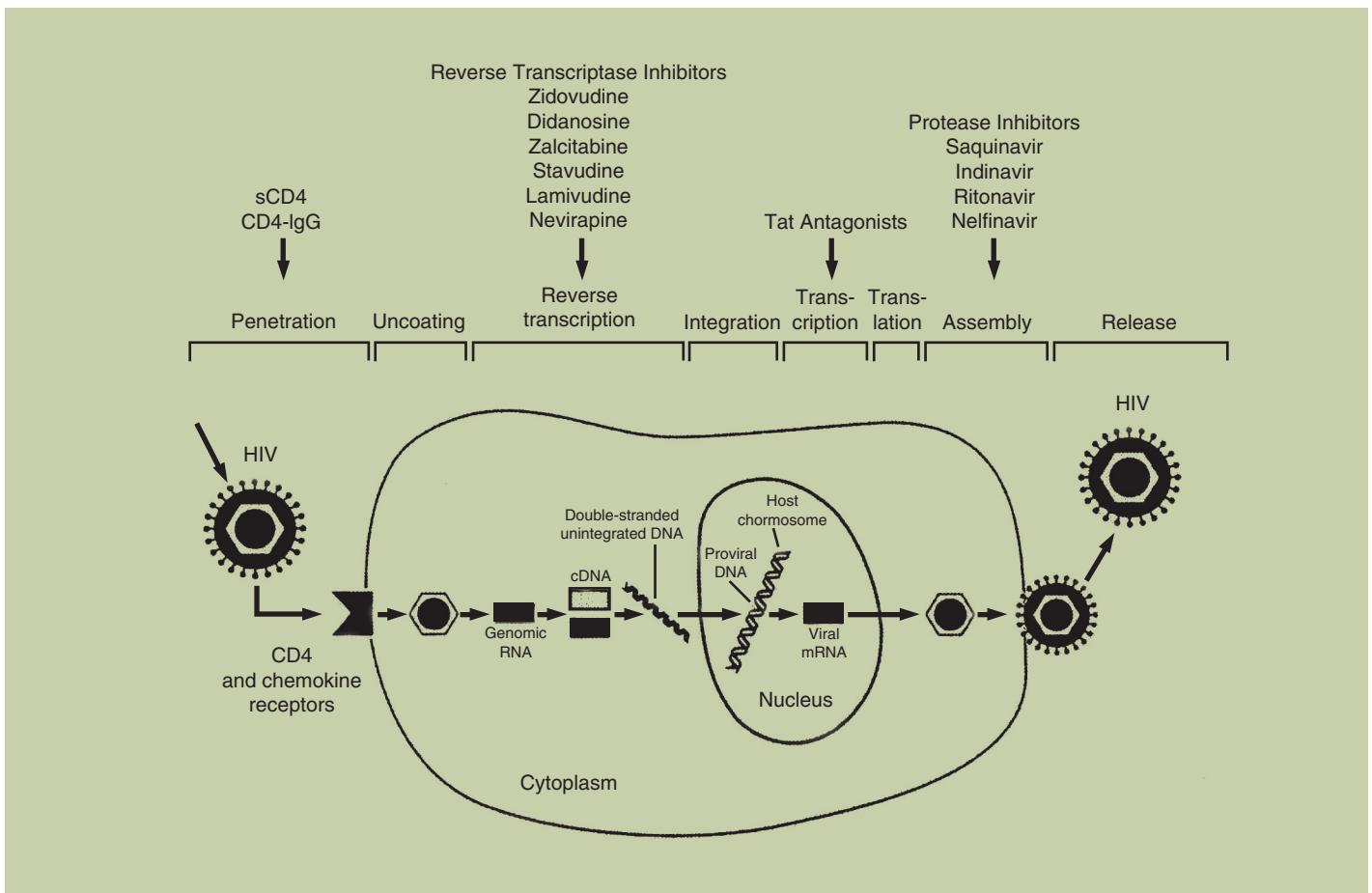


Figure 5. The HIV life cycle This depiction of the HIV life cycle shows the sites of action of some antiretroviral agents.

and macrophages. The chemokine receptors CCR5 and CXCR4 facilitate viral entry. T-cell tropic viruses require CXCR4 to bind, and macrophage-tropic strains of the virus require CCR5. R5 is the most common virus transmitted during acute infection, and later during infection X4 is the virus that is most common. The presence of a homozygous inactive mutation of the CCR5 allele has caused resistance to infection by the R5 virus.

The joining of the proteins and the receptors and coreceptors fuses the HIV membrane with the CD4+ cell membrane, and the virus enters the CD4+ cell and macrophage. The HIV membrane and the envelope proteins remain outside of the CD4+ cell, whereas the core of the virus enters the CD4+ cell. CD4+ cell enzymes interact with the viral core and stimulate the release of viral RNA and the viral enzymes reverse transcriptase, integrase, and protease.

Reverse Transcription

The HIV RNA must be converted to DNA before it can be incorporated into the DNA of the CD4+ cell. This

incorporation must occur for the virus to multiply. The conversion of HIV RNA to DNA is known as reverse transcription and is mediated by the HIV enzyme reverse transcriptase. The result is the production of a single strand of DNA from the viral RNA. The single strand of this new DNA then undergoes replication into double-stranded HIV DNA.

Integration

Once reverse transcription has occurred, the viral DNA can enter the nucleus of the CD4+ cell. The viral enzyme integrase then inserts the viral DNA into the CD4+ cell's DNA. This process is known as integration. The CD4+ cell has now been changed into a factory used to produce more HIV.

Replication

The new DNA, which has been formed by the integration of the viral DNA into the CD4+ cell, causes the production of messenger DNA that initiates the synthesis of HIV proteins.

Budding

The HIV proteins and viral RNA, all the components needed to make a new virus, gather at the CD4+ cell membrane to form new viruses. These new viruses push through the different parts of the cell wall by budding. Many viruses can push through the wall of one CD4+ cell. These new viruses leave the CD4+ cell and contain all the components necessary to infect other CD4+ cells.

Maturation

The new virus has all the components necessary to infect other CD4+ cells but cannot do so until it has matured. During this process, the HIV protease enzyme cuts the long HIV proteins of the virus into smaller functional units that then reassemble to form a mature virus. The virus is now ready to infect other cells.

HIV TYPES

There are two types of HIV that cause AIDS: HIV type 1 (HIV-1) and HIV-2. We know little about HIV-2. Studies have shown striking similarities but also important differences between HIV-1 and HIV-2. They have the same modes of transmission and are associated with the same opportunistic infections, but HIV-2 appears to progress more slowly. Most HIV-2 cases are found in western Africa and in countries related to western Africa in some way such as Portugal, France, Angola, Mozambique, Brazil, and India.

Various subtypes of HIV-1 have been found in specific geographic areas and in specific high-risk groups. A person can be coinfecting with different subtypes. The following are HIV-1 subtypes and their geographic distributions:

Subtype A:	Central Africa, sub-Saharan Africa
Subtype B:	South America, Brazil, United States, Thailand, Europe, Caribbean, India, Japan
Subtype C:	Brazil, India, South Africa
Subtype D:	Central Africa, sub-Saharan Africa
Subtype E:	Thailand, Central African Republic, Southeast Asia
Subtype F:	Brazil, Romania, Democratic Republic of Congo (Zaire)
Subtype G:	Democratic Republic of Congo (Zaire), Gabon, Thailand, Russia, Central Africa
Subtype H:	Democratic Republic of Congo (Zaire), Gabon, Russia, Central Africa
Subtype I:	Cyprus
Subtype O:	Cameroon, Gabon

Subtypes are unevenly distributed throughout the world. Subtype C currently accounts for more than half of all new HIV infections worldwide. Africa has most subtypes, although subtype B is less prevalent. There are no known subtypes of HIV-2.

EFFECTS ON THE IMMUNE SYSTEM

The pathogenesis of HIV is basically a struggle between HIV replication and the immune responses of the patient, via cell-mediated and immune-mediated reactions. The HIV viral burden directly and indirectly mediates CD4+ T-cell destruction. There is destruction of mature CD4+ cells; CD4+ progenitor cells in bone marrow, the thymus, and peripheral lymphoid organs; as well as CD4+ cells within the nervous system, such as microglia. The result of this destruction is failure of T-cell production and eventual immune suppression.

There are many mechanisms of CD4+ cell depletion by HIV infection. Direct HIV-mediated cytopathic effects include single-cell killing as well as cell fusion, or syncytium formation. The syncytium is a fusion of multiple uninfected CD4+ cells with one HIV-infected CD4+ cell via CD4-gp120 interaction. This fusion results in a multinucleated syncytium, or giant cell, which may ultimately serve as a means to produce many virions. The host's natural immune responses also play a role in CD4+ cell depletion, mainly through cytotoxic CD8+ T-cells, antibody-dependent cellular cytotoxicity, and natural killer cells. Other mechanisms include autoimmune responses, anergy, superantigen-mediated activation of T cells, and programmed cell death (apoptosis).

HIV can infect many types of cells. The spread of HIV outside lymphoid organs to the brain, spinal cord, lung, colon, liver, and kidney usually occurs late during illness. **Table 1** gives a partial list of cells susceptible to HIV infection.

The immune systems of HIV-infected children undergo changes that are similar to those in adults. B-cell activation occurs in most children early in the infection, evidenced by the presence of hypergammaglobulinemia (>1.750 g/L) with high levels of anti-HIV-1 antibody. This reflects both dysregulation of T-cell suppression of B-cell antibody synthesis as well as active CD4+ enhancement of B-lymphocyte humoral response. Also, as HIV disease progresses through more severe immunosuppression and depletion of CD4+ cells, the CD8+ count increases, yielding an overall decrease in the CD4+:CD8+ ratio.

Table 1. Cells Susceptible to HIV Infection

System	Cell
Hematopoietic	<ul style="list-style-type: none"> • T-cells (CD4+ OR CD 8+) • Macrophages/monocytes • Dendritic cells • Fetal thymocytes and thymic epithelium • B-cells • NK cells • Megakaryotic cells • Stem cells
Central Nervous	<ul style="list-style-type: none"> • Microglia • Capillary endothelial cells • Astrocytes • Oligodendrocytes
Large Intestine	<ul style="list-style-type: none"> • Columnar epithelium
Other	<ul style="list-style-type: none"> • Kupfer cells (liver) • Synovial cells • Placental trophoblast cells

Adapted from Levy L.A. Microbiological Reviews, 57:183-289, March 1993

CLINICAL CATEGORIES OF HIV INFECTION

Children infected with HIV often have severe disease when first evaluated, or they may develop AIDS over time, much like adults infected with HIV. Infants and young children normally have higher CD4+ counts than those of adults. The normal CD4+ count in children varies with age, but it is equal to the adult value by the time the child is 6 years old. Immunologic and clinical categories are used to evaluate the HIV disease status in children and to make treatment decisions.

Primary Infection, or Acute Retroviral Syndrome

Primary infection refers to the time when HIV first enters the body. At the time of primary infection with HIV, a person’s blood carries a high viral load, meaning that there are many individual viruses in the blood. The number of copies of virus per milliliter of plasma or blood can exceed 1 million. Newly infected adults often experience an acute retroviral syndrome. Signs and symptoms of acute retroviral syndrome include fever, myalgia (muscle pain), headache, nausea, vomiting, diarrhea, night sweats, weight loss, and rash. These signs and symptoms usually occur 2–4 weeks after infection, subside after a few days, and often are misdiagnosed as influenza or infectious mononucleosis. An important

differentiating symptom that is often absent is the presence of a runny nose or nasal congestion.

During primary infection, the CD4+ count in the blood decreases remarkably but rarely drops to less than 200 cells/μL. The virus targets CD4+ cells in the lymph nodes and the thymus during this time, making the HIV-infected person vulnerable to opportunistic infections and limiting the thymus’s ability to produce T lymphocytes. HIV antibody testing using an enzyme-linked immunosorbent assay or enzyme immunoassay may yield positive or negative results depending on the time of seroconversion. DNA PCR and RNA PCR will be positive, but confirmation with Western blot analysis may yield an indeterminate result because seroconversion can take up to 2–8 weeks to occur. The average time to seroconversion is 25 days.

Clinical Latency/Asymptomatic Disease (Clinical Stage 1)

Although patients recently infected with HIV usually experience a “clinically latent” period of years between HIV infection and clinical signs and symptoms of AIDS, evidence of HIV replication and host immune system destruction exists from the onset of infection. Early during this time, referred to as Clinical Stage 1, the immune system produces antibodies in an attempt to protect itself from HIV. This is when the “viral set point” is established. The viral load of the set point can be used to predict how quickly disease progression will occur. People with higher viral load set points tend to exhibit more rapid disease progression than those with lower viral load set points.

During latency, HIV-infected patients may or may not have signs and symptoms of HIV infection though persistent lymphadenopathy is common. In HIV-infected adults, this phase may last 8–10 years. The HIV enzyme-linked immunosorbent assay and Western blot or immunofluorescence assay will be positive. The CD4+ count is greater than 500 cells/μL in children over 5 years of age.

Mild Signs and Symptoms of HIV (Clinical Stage 2)

HIV-infected people may appear to be healthy for years, and then minor signs and symptoms of HIV infection begin to appear. They may develop candidiasis, lymphadenopathy, molluscum contagiosum, persistent

hepatosplenomegaly, popular pruritic eruptions, herpes zoster, and/or peripheral neuropathy. The viral load increases, and the CD4+ count falls is between 350-499/uL in children older than 5 years. Once patients are in this stage they remain in stage 2. They can be reassigned stage 3 or 4 if a condition from one of those occurs, but they cannot be reassigned to Clinical Stage 1 or 2 if they become asymptomatic.

Advanced Signs and Symptoms of HIV (Clinical Stage 3)

HIV-infected patients with weakened immune systems can develop life-threatening infections. The development of cryptosporidiosis, pulmonary and lymph node tuberculosis, wasting, persistent fever (longer than one month), persistent candidiasis, recurrent bacterial pneumonia, and other opportunistic infections is common. These patients may be wasting, or losing weight. Their viral load continues to increase, and the CD4+ count falls to less than 200-349 cells/ μ L in children older than 5 years.

Clinical Stage 4

Patients with advanced HIV disease, or AIDS, can continue to develop new opportunistic infections, such as *Pneumocystis jirovecii* pneumonia (formerly *Pneumocystis carinii* pneumonia), cytomegalovirus infection, toxoplasmosis, *Mycobacterium avium* complex, cryptococcal meningitis, progressive multifocal leukoencephalopathy, Kaposi sarcoma and other infections that commonly occur with a severely depressed immune system. The viral load is very high, and the CD4+ count is less than 200 cells/ μ L in children older than 5 years. At this point in the disease course death can be imminent.

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