HIV Infection

How does HIV infect human cells? The human immunodeficiency virus (HIV) is the causative agent of acquired immune deficiency syndrome (AIDS). Left untreated, AIDS is a lethal condition because HIV destroys the body's immune system, rendering it defenseless against disease-causing organisms (e.g., bacteria, protozoa, and fungi, as well as other viruses) in addition to some forms of cancer.

HIV (**Figure 1**) is a lentivirus, a member of a group of RNA viruses called the retroviruses. Retroviruses are so named because they contain an enzymatic activity reverse transcriptase, which catalyzes the synthesis of a DNA copy of an ssRNA genome. A typical retrovirus consists of an RNA genome enclosed in a protein capsid. Wrapped around the capsid is a membranous envelope that is formed from a host cell lipid bilayer.

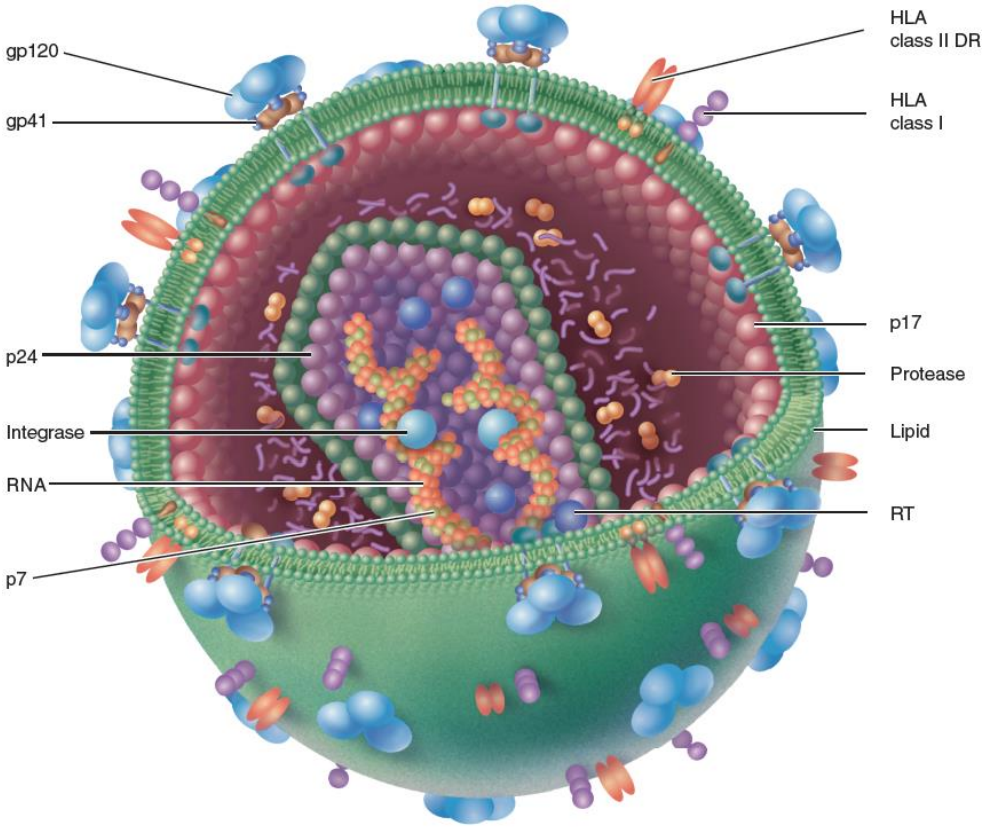

FIGURE 1

HIV Structure

The surface of the virus is a lipid bilayer in which are embedded the viral glycoproteins gp120 and gp41, as well as HLA (human leukocyte antigens) membrane proteins taken from host cells. (HLA proteins are signals that protect the viral particle from the immune system, which ordinarily searches out and destroys foreign invaders.) Lining the inside of the envelope are hundreds of copies of the matrix protein p17. Two copies of the RNA genome are contained in a bullet-shape capsid composed of the core protein p24. The nucleocapsid protein p7 coats the RNA genome. Enzymes associated with viral genome are reverse transcriptase (RT), integrase, and protease.

HIV Infection: An Overview

In the reproductive cycle of HIV (**Figure 2**), the infective process begins when the virus binds to a host cell. Binding, which occurs between viral surface glycoproteins and specific plasma membrane receptors, initiates a fusion process between host cell membrane and viral membrane. Subsequently, the viral capsid is released into the cytoplasm and the viral reverse transcriptase catalyzes the synthesis of DNA strands complementary to two copies of the viral ssRNA. This enzymatic activity also catalyzes the conversion of the single-stranded DNA into a double-stranded molecule. The double-stranded DNA version of the viral genome is then translocated into the nucleus, where it integrates into a host chromosome. The integrated proviral genome, acting like a prophage, is replicated each time the cell undergoes DNA synthesis. The mRNA transcripts produced when the viral genome is transcribed direct the synthesis of numerous copies of viral proteins. New virus, created as copies of the viral RNA genome are packaged with viral proteins, is released from the host cell by a "budding" process.

HIV Structure

HIV (diameter = 120 nm) is an enveloped virus (i.e., its external surface, called an envelope, is derived from the plasma membrane of a host cell). The principal component of the HIV envelope is the glycoprotein *Env*, a complex of three gp120/gp41 heterodimers. (The numbers indicate the size of the protein. For example, gp120 is a glycoprotein with a mass of 120 kDa.) The overall structure of the Env trimer, also called the gp160 spike, consists of a cap composed of three gp120 molecules. These are noncovalently linked to a stem, composed of three gp41 molecules, that anchors Env into the viral envelope. Env is a fusion machine that enables HIV to attach to and fuse with target cells.

HIV contains a cylindrical core within its capsid. Inside the core are two copies of its ssRNA genome. The RNA molecules are coated with a nucleocapsid protein p7, essential for vRNA translation and packaging. The bullet-shape core itself is composed of the core protein p24. Copies of the matrix protein p17 form the inner lining of the viral envelope. The core also contains several enzymes: reverse transcriptase (RT), integrase, and protease. The RT has RNA-directed DNA polymerase activity, which converts the viral ssRNA into a ssDNA and DNA-directed DNA polymerase activity, which converts the viral ssDNA into dsDNA. The RT subsequently degrades the viral ssRNA. Later, when new viral particles are being assembled, the protease cleaves newly synthesized polypeptides to create the protein components of infectious HIV.

The HIV Infection Cycle

The first step in viral entry into target cells is the high-affinity binding of gp120 with the CD4 receptor, a glycoprotein on the surface of target cells, most notably the T-4 helper lymphocytes. T-4 helper cells play a critical role in regulating the activities of other immune system cells. T-cell infection requires the interaction of the gpl20-CD4 complex with a chemokine receptor, which acts as a co-receptor. (The immune system chemotactic agents called chemokines stimulate T cells by binding to receptors on the T-cell plasma membrane.) In the early stages of infection, the co-

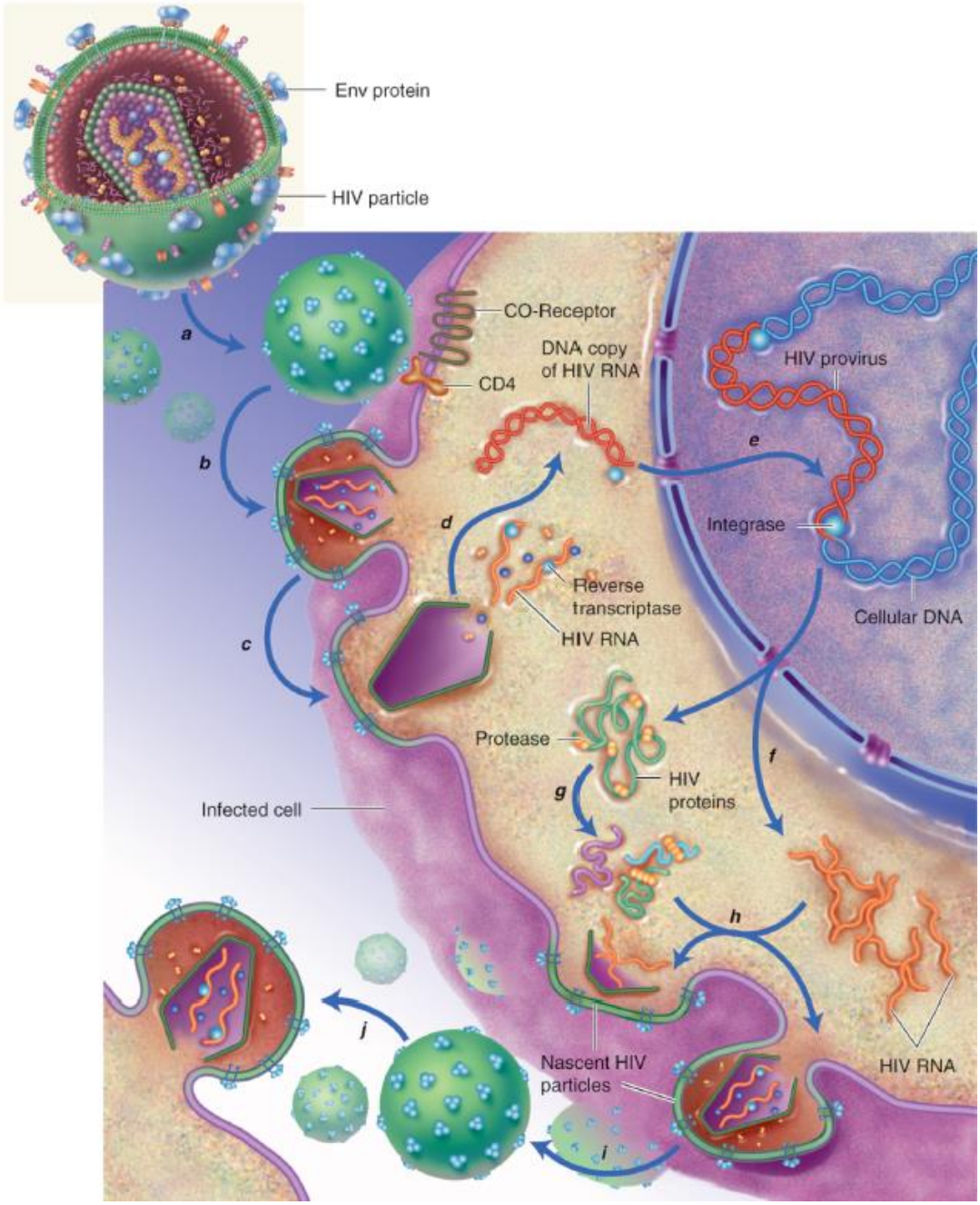

FIGURE 2

Reproductive Cycle of HIV, a Retrovirus

After the viral particle binds to surface receptors on the host cell (a), its envelope fuses with the cell's plasma membrane (b), thus releasing the capsid and its contents (vRNA and several viral enzymes) into the cytoplasm (c). The viral enzyme reverse transcriptase catalyzes the synthesis of a DNA strand complementary to the vRNA (d) and then proceeds to form a second DNA strand that is complementary to the first. Subsequently the double-stranded viral DNA (vDNA) transfers to the nucleus, where it integrates itself into a host chromosome with the aid of a viral integrase (e). The provirus (the integrated viral genome) is replicated every time the cell synthesizes new DNA. Transcription of viral DNA results in the formation of two types of RNA transcript: RNA molecules that function as the viral genome (f) and molecules that code for the synthesis of viral protein (e.g., reverse transcriptase, capsid proteins, envelope proteins, and viral integrase) (g). The protein molecules are combined with the vRNA genome during the creation of new virus (h) that buds from the surface of the host cell (i) and then proceeds to infect other cells (j).

receptor CCR5 (or less often CXCR4) helps HIV enter T cells; other cells that are known to be infected by HIV include some intestinal and nervous system cells. Recent evidence suggests that humans with two copies of a gene for a variant of the CCR5 receptor, CCR5-Δ32, are resistant to HIV infection. CCR5-Δ32 apparently provides protection against plague and smallpox as well, but for all three diseases, the portion of the population that benefits is relatively small.

The binding of gp120 to the CD4 receptor and the co-receptor causes a conformational change in the Env complex that converts it into a fusion-active state with the exposure of the gp41 fusion protein. Gp41 then proceeds to insert itself into the target cell plasma membrane. Further conformational changes in gp41 cause the viral and cell membranes to be pulled close enough for fusion to take place. Once the viral envelope has fused with the cell's plasma membrane, HIV's RNA and enzymes (RT, integrase, and protease) are injected into the cytoplasm and then transported via microtubules into the nucleus. Along the way, RT catalyzes the synthesis of double-stranded vDNA using vRNA as a template. After the vDNA is integrated into a host cell chromosome, proviral DNA remains latent until the specific infected T cell is activated in an immune response. The proviral DNA then directs the cell to synthesize viral components. Newly synthesized viruses bud from the infected cell.

Within 30 minutes of an active infection in a cell, the expression of 500 cellular genes has been suppressed and 200 have been activated. Within hours, host cell mRNA has largely been replaced by viral mRNA. The virus has crippled the cell's capacity to generate energy and repair virally inflicted DNA damage.

Cell death is triggered by several mechanisms that include the following:

1. A virus activates the genes that induce apoptosis, a normal cell mechanism by which cells respond to external signals such as those that occur in developmental processes.
2. The simultaneous budding of numerous viral particles from the cell membrane may tear the membrane and cause leakages that cannot be repaired, or the massive release of new virus from a cell may so deplete the cell that it disintegrates.
3. The binding of cell surface gpl20 molecules to CD4 receptors on nearby healthy cells leads to the formation of large, nonfunctional multinucleated cell masses called *syncytia*.

HIV Infection and AIDS

HIV infection occurs because of direct exposure of an individual's bloodstream to the body fluids of an infected person. Most HIV is transmitted through sexual contact, blood transfusions, and perinatal transmission from mother to child. Once HIV has entered the body, it infects cells that bear the CD4 antigen on their plasma membranes.

HIV infection progresses through several stages, which may vary considerably in length among individuals. Initial symptoms, which usually occur soon after the initial exposure to the virus and last for several weeks, include fever, lethargy, headache and other neurological complaints, diarrhea, and lymph node

enlargement. (Antibodies to HIV are detectable during this period.) Exaggerated versions of these symptoms, referred to as the AIDS-related complex, may often recur. Eventually, the immune system becomes so compromised that the individual becomes susceptible to serious opportunistic diseases and is said to have developed AIDS. The time required for the development of AIDS may vary from 2 years to 8 or 10 years. For reasons that are not understood, a few patients do not develop AIDS even after 15 years of HIV infection. (It has recently been suggested that some of these individuals are infected with attenuated HIV variants.) Among the most common AIDS-related diseases are *Pneumocystis carinii* pneumonia, cryptococcal meningitis (inflammation of membranes that cover the brain and spinal cord), toxoplasmosis (brain lesions, heart and kidney damage, and fetal abnormalities), cytomegalovirus infections (pneumonia, kidney and liver damage, and blindness), and tuberculosis. HIV infection is also associated with several types of cancer, the most common of which is a rare skin cancer called Kaposi's sarcoma.

There is no cure for AIDS. Treatment seeks to suppress symptoms (e.g., antibiotics for the infections) and to slow viral reproduction. Mortality rates have decreased since 1995 because of the introduction of a treatment protocol called highly active antiretroviral therapy that consists of combinations of drugs from the following categories: (1) entry (fusion) inhibitors (maraviroc and enfuvirtide), (2) nucleoside reverse transcriptase inhibitors (e.g., azidothymidine, also called zidovudine or AZT, and abacavir), (3) nonnucleoside reverse transcriptase inhibitors (NNRTIs: e.g., efavirenz and rilpivirine), (4) protease inhibitors (e.g., indinavir and lopinavir), and (5) integrase inhibitors (raltegravir and elvitegravir).

The development of an AIDS vaccine is problematic because the viral genome mutates frequently (i.e., its surface antigens become altered).

SUMMARY: HIV infection disrupts cell function. By suppressing some cellular genes and activating others, the HIV genome directs the host cell to produce new HIV particles that proceed to infect other cells.