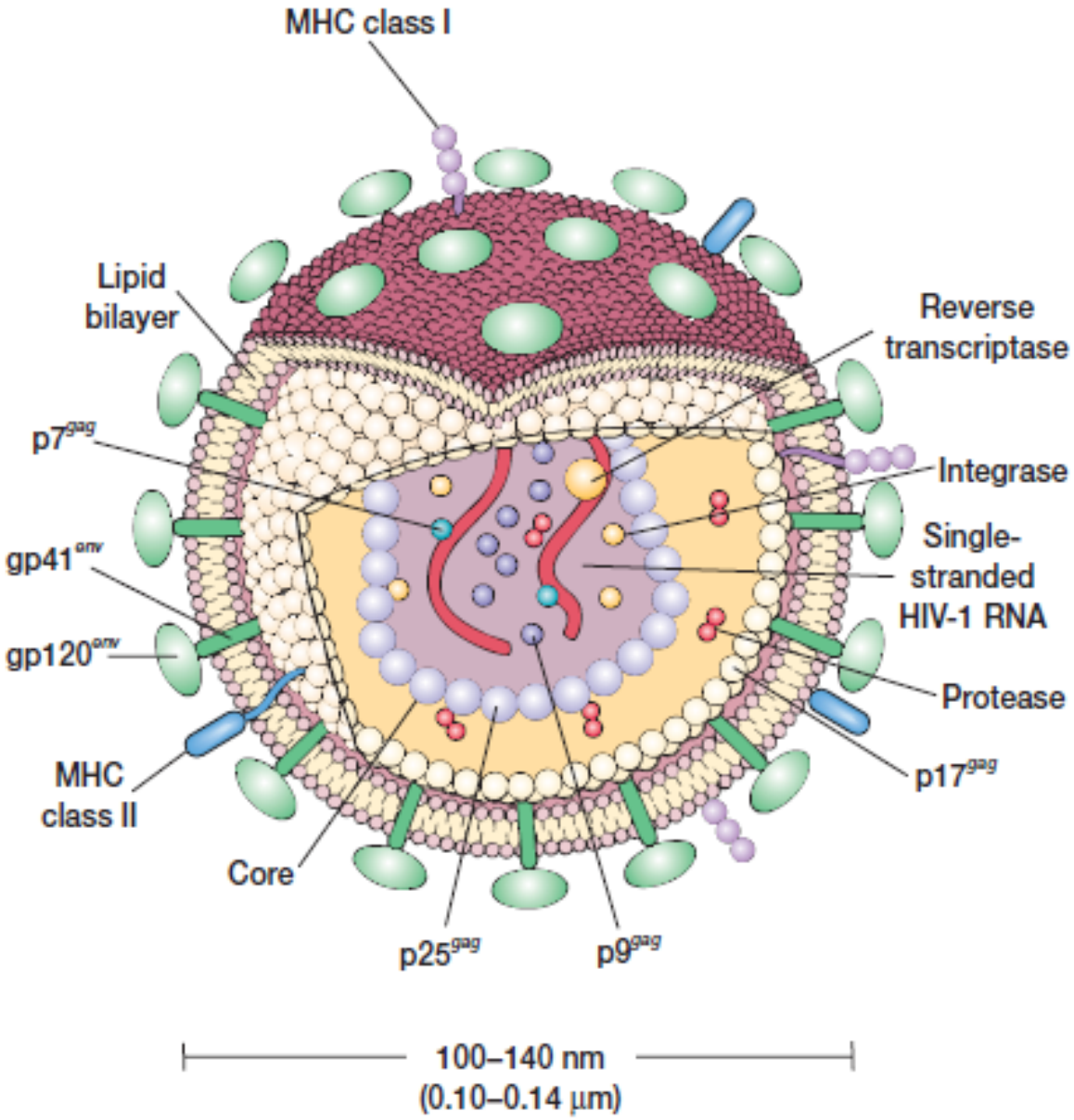
Acquired Immune Deficiency Syndrome (AIDS)

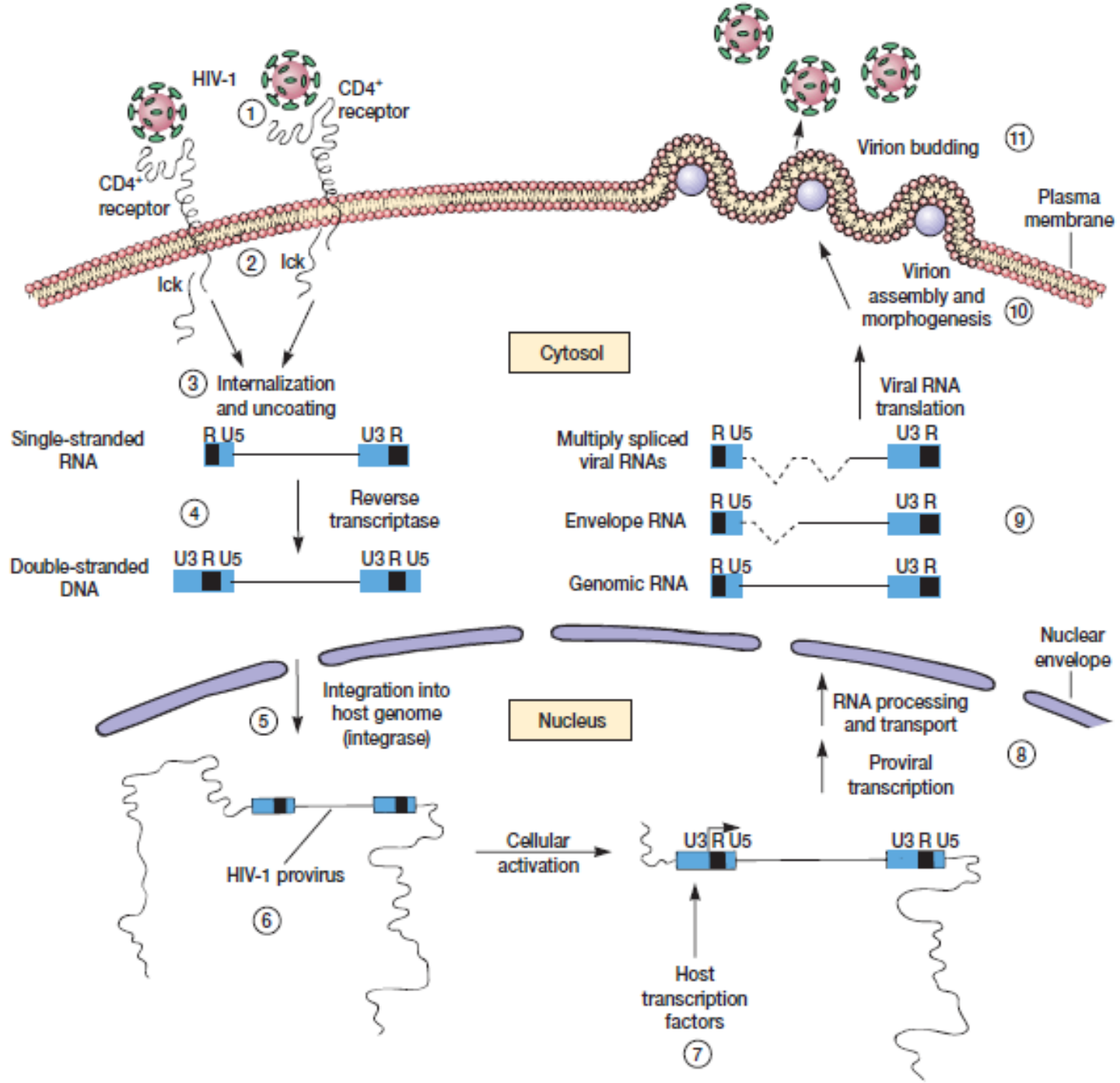
AIDs

- First described in 1981 AIDS is the result of an infection by the human immunodeficiency virus (HIV), a lentivirus within the family Retroviridae.
- Simian immunodeficiency viruses (SIVs) related to HIV-1 and HIV-2, the strains primarily responsible for AIDS, have been isolated from African primates.
- HIV-1 is an enveloped lentivirus and a member of the family Retroviridae with a cylindrical core inside its capsid.
- Inside core contains two copies of its plus single-stranded RNA genome and several enzymes.
- Thus far 10 virus-specific proteins have been discovered.
- One of them, the gp120 envelope protein, participates in HIV-1 attachment to CD4 cells (T-helper cells).
- The AIDS virus is acquired by direct exposure of a person's bloodstream to body fluids (blood, semen, vaginal secretions) containing the virus, through sexual contact, or perinatally from an infected mother to her fetus.


MHC class I
Lipid bilayer
Reverse transcriptase
p7gag
Integrase
gp41env
Single-stranded HIV-1 RNA
gp120env
Protease
MHC class II
p17gag
Core
p25gag
p9gag
100–140 nm
(0.10–0.14 μm)

- Once inside the body, the virus gp120 envelope protein binds to the CD4 glycoprotein plasma membrane receptor on CD4 T cells, macrophages, dendritic cells, and monocytes.
- Recent evidence shows that the virus requires a co-receptor (CCR5 (CC-CKR-5) chemokine receptor protein) in addition to the CD4 receptor.
- A second chemokine co-receptor, called CXCR-4 or fusin, is T cell–tropic and used by an HIV strain that is active at later stages of the infection. This strain induces the formation of syncytia.
- Individuals with two defective copies of the *CCR5 gene* do not seem to get AIDS; apparently the virus cannot infect their T cells.
- People with one good copy of the *CCR5* gene do get AIDS but survive several years longer than those with no mutation.

- Entry into the host cell begins when the envelope fuses with the plasma membrane, and the virus releases its core and two RNA strands into the cytoplasm.
- Inside the infected cell, the core protein remains associated with the RNA as it is copied into a single strand of DNA by the RNA/DNA-dependent DNA polymerase activity of the reverse transcriptase enzyme.
- The RNA is next degraded by another reverse transcriptase component, ribonuclease H, and the DNA strand is duplicated to form a double-stranded DNA copy of the original RNA genome.
- A complex of the double-stranded DNA (the provirus) and the integrase enzyme moves into the nucleus and integrated into the cell's DNA catalyzed by the integrase.
- The integrated provirus can remain latent, giving no sign of its presence.
- Alternatively the provirus can force the cell to synthesize viral mRNA.
- Some of the RNA is translated to produce viral proteins by the cell's own ribosomes.
- Viral proteins and the complete HIV-1 RNA genome are then assembled into new virions that bud from the infected host cell .
- Eventually the host cell lyses.


HIV-1
CD4+ receptor
1
CD4+ receptor
2
Lck
Lck
Virion budding
11
Plasma membrane
Virion assembly and morphogenesis
10
Cytosol
3
Internalization and uncoating
Viral RNA translation
Single-stranded RNA
R U5
U3 R
Multiply spliced viral RNAs
R U5
U3 R
4
Reverse transcriptase
Envelope RNA
R U5
U3 R
9
Double-stranded DNA
U3 R U5
U3 R U5
Genomic RNA
R U5
U3 R
Nuclear envelope
Integration into host genome (integrase)
5
Nucleus
RNA processing and transport
8
Proviral transcription
HIV-1 provirus
6
Cellular activation
U3 R U5
U3 R U5
Host transcription factors
7

AIDS pathogenesis

- The precise mechanism of AIDS pathogenesis still is not known, and many hypotheses exist.
- Many believe that AIDS is caused primarily by depletion of T cells and disruption of their function, although the exact mechanisms are unclear.
- The cytopathic effect may be due to the disruption of plasma membrane permeability and function by excessive virus budding.
- Free gp120 proteins may bind to CD4 proteins on uninfected cells, making them targets for attack by immune system cells.
- Infected cells do fuse with other cells to form large, multinucleate syncytia that eventually die, and this may contribute greatly to cell destruction.
- Possibly, insertion of the provirus DNA into the cell's genome and the transposition of the integrated provirus disrupt cell function and destroy the host T cell.

Antivirals

- The antivirals currently approved for use in HIV disease are of three types.

(1) Most reverse transcriptase inhibitors are nucleoside analogues that inhibit the enzyme reverse transcriptase as it synthesizes DNA.

- Examples include AZT or zidovudine (Retrovir), didanosine (Videx), ddC or zalcitabine (HIVID), stavudine (Zerit), and lamivudine or 3TC (Epivir).

(2) The nonnucleoside inhibitors of reverse transcriptase include delavirdine (Rescriptor) and nevirapine (Viramune).

(3) The protease inhibitors work by blocking the activity of the HIV protease and thus interfere with virion assembly.

- Examples include indinavir (Crixivan), ritonavir (Norvir), nelfinavir (Viracept), and saquinavir (Invirase).

- Another avenue of current research is the development of a vaccine that can:
- (1) stimulate the production of neutralizing antibodies which can bind to the virus envelope and prevent it from entering host cells, and
- (2) promote the destruction of those cells already infected with the virus.
- The production of an effective vaccine, if possible, is not yet in sight.
- One difficulty is that the envelope proteins of the virus continually change their antigenic properties.