Retroviruses

A family of Retroviruses distinguished by three characteristics:
(1) genetic information in ribonucleic acid (RNA);
(2) virions possess the enzyme reverse transcriptase; and
(3) virion morphology consists of two proteinaceous structures, a dense core and an envelope that surrounds the core.

The genome is composed of two identical molecules of single-stranded RNA, which are similar in structure and function to cellular messenger RNA.
Deoxyribonucleic acid (DNA) is not present in the virions of retroviruses.

A **retrovirus** is an RNA virus that replicates in a host cell through the process of reverse transcription. First it uses its own reverse transcriptase enzyme to produce DNA from its RNA genome, the reverse of the usual pattern, thus *retro* (backwards). This new DNA is then incorporated into the host's genome by an integrase enzyme. The cell then treats the viral DNA as part of its own instructions, making the proteins required to assemble new copies of the virus. Retroviruses are enveloped viruses that belong to the viral family *Retroviridae*.

HIV-1 and **HIV-2**, the agents that cause **AIDS**, are retroviruses.

A special variant of retroviruses are endogenous retroviruses which are integrated into the genome of the host and inherited across generations.

The virus itself stores its nucleic acid in the form of a mRNA (including the 5'cap and 3'PolyA inside the virion) genome and serves as a means of delivery of that genome into cells it targets as an obligate parasite, and constitutes the infection. Once in the host's cell, the RNA strands undergo reverse transcription in the cytoplasm and are integrated into the host's genome, at which point the retroviral DNA is referred to as a provirus. It is difficult to detect the virus until it has infected the host.

When a retrovirus DNA is integrated into the host cell's genome, it becomes a provirus. the information contained in a retroviral gene is used to generate the corresponding protein via the sequence: RNA → DNA → RNA → protein.

Structure

Virions of retroviruses consist of enveloped particles about 100 nm in diameter. The virions also contain two identical single-stranded RNA molecules 7-10 kilobases (kb) in length.

A typical, "minimal" retrovirus consists of:

- an outer **envelope** which was derived from the plasma membrane of its host
- many copies of an **envelope protein** embedded in the lipid bilayer of its envelope
- a **capsid**; a protein shell containing
- two molecules of **RNA** and

- molecules of the enzyme **reverse transcriptase**

The main virion components are:

Envelope: composed of lipids (obtained from the host plasma membrane during budding process) as well as glycoprotein encoded by the env gene.

RNA: consists of a dimer RNA. The RNA genome also has terminal noncoding regions, which are important in replication, and internal regions that encode virion proteins for gene expression.

The 5' end includes four regions, which are R, U5, PBS, and L.

The 3' end includes 3 regions, which are PPT (polypurine tract), U3, and R.

Proteins: consisting of **gag** proteins, protease (**PR**), **pol** proteins and **env** proteins.

Gag proteins are major components of the viral capsid, which are about 2000-4000 copies per virion.

Protease (PR) is expressed differently in different viruses. It functions in proteolytic cleavages during virion maturation to make mature gag and pol proteins.

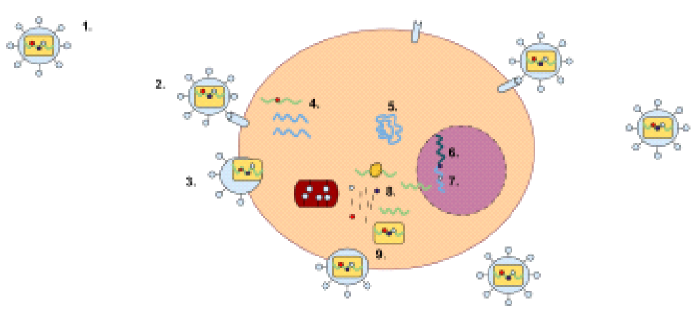
Pol proteins are responsible for synthesis of viral DNA and integration into host DNA after infection.

env proteins play a role in association and entry of virion into the host cell. The env gene serves three distinct functions: enabling the retrovirus to enter/exit host cells through endosomal membrane trafficking, protection from the extracellular environment via the lipid bilayer, and the ability to enter cells. The ability of the retrovirus to bind to its target host cell using specific cell-surface receptors is given by the surface component (SU) of the env, while the ability of the retrovirus to enter the cell via membrane fusion is imparted by the membrane-anchored trans-membrane component (TM). Thus the env protein enables the retrovirus to be infectious.

Multiplication / Replecation

Infection of a host cell requires that the cell have a surface protein (CD4 and CCR5 molecules) that can serve as a **receptor for the envelope protein** of the retrovirus.

All the proteins in the virus particle are encoded by its own genes.



A retrovirus has a membrane that contains glycoproteins, which are able to bind to a

receptor protein on a host cell. Within the cell there are two strands of RNA that have three enzymes, protease, reverse transcriptase, and integrase
(1). The first step of replication is the binding of the glycoprotein to the receptor protein
(2). Once these have been bound the cell membrane degrades and becomes part of the host cell, and the RNA strands and enzymes go into the cell
(3). Within the cell, reverse transcriptase creates a complementary strand of DNA from the retrovirus RNA and the RNA is degraded, this strand of DNA is known as cDNA
(4). The cDNA is then replicated, and the two strands form a weak bond and go into the nucleus
(5). Once in the nucleus, the DNA is integrated into the host cells DNA with the help of integrase
(6). This cell can either stay dormant, or RNA may be synthesized from the DNA and used to create the proteins for a new retrovirus
(7). Ribosome units are used to transcribe the mRNA of the virus into the amino acid sequences which can be made into proteins in the Rough Endoplasmic Reticulum. This step will also make viral enzymes and capsid proteins
(8). Viral RNA will be made in the nucleus. These pieces are then gathered together and are pinched off of the cell membrane as a new retrovirus
(9). The retroviral genome also contains a **packaging signal** sequence ("**P**") which is needed for the newly-synthesized RNA molecules to be incorporated in fresh virus particles.

Transmission

- Cell-to-cell
- Fluids
- Airborne, like the Jaagsiekte sheep retrovirus

Genes

Retrovirus genomes commonly contain these three open reading frames that encode for proteins that can be found in the mature virus:

- *group-specific antigen* (gag) codes for core and structural proteins of the virus;
- *polymerase* (pol) codes for reverse transcriptase, protease and integrase; and,
- *envelope* (env) codes for the retroviral coat proteins.

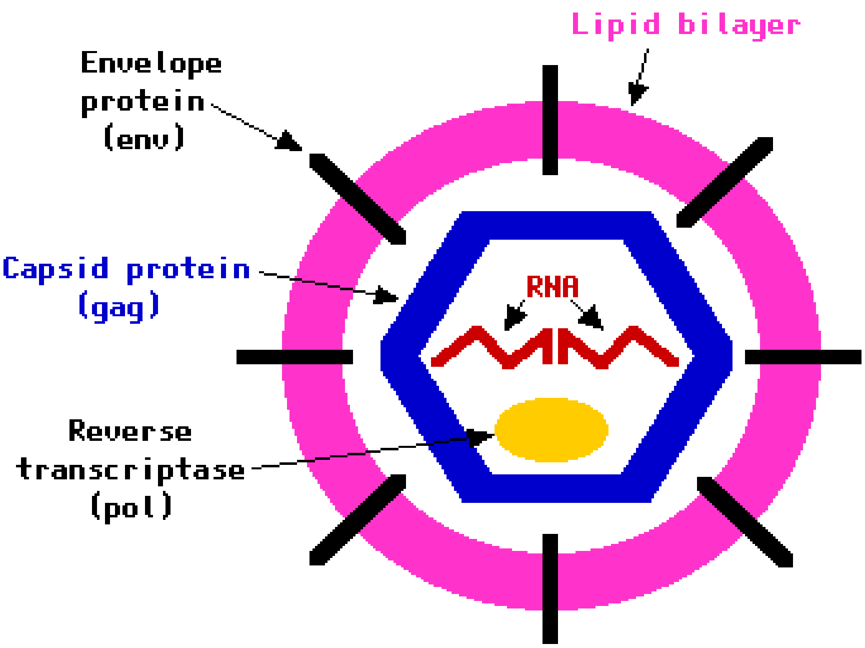
  The genome of retroviruses is flanked at each end by repeated sequences ("**R**") that enable the DNA copy of the genome to be inserted into the DNA of the host and act as enhancers, causing the host nucleus to transcribe the DNA copies of the retroviral genome at a rapid rate.

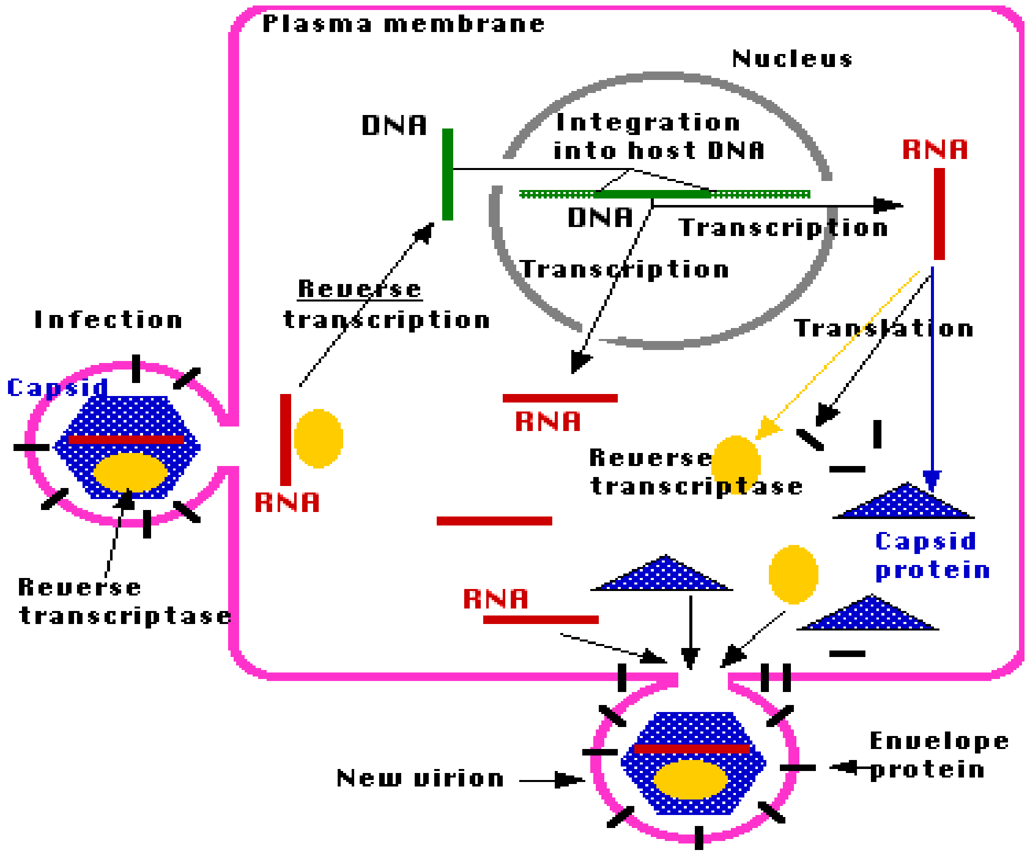
Treatment

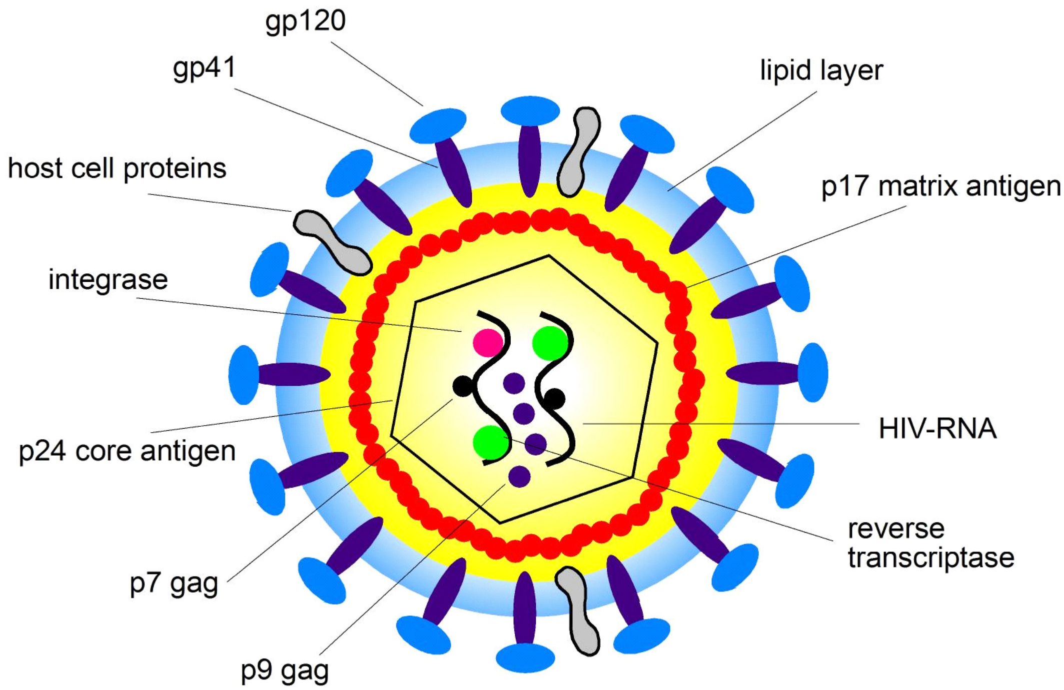
Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV. Different classes of antiretroviral drugs act on different stages of the HIV life cycle. Combination of several (typically three or four) antiretroviral drugs is known as

highly active anti-retroviral therapy (HAART).

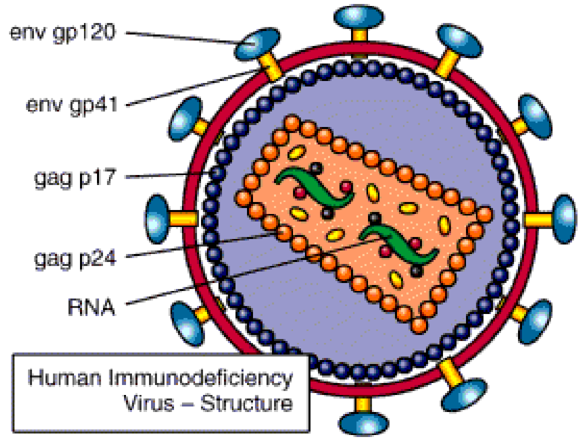
Importance : Retroviruses are proving to be valuable research tools in molecular biology and have been used successfully in gene delivery systems.

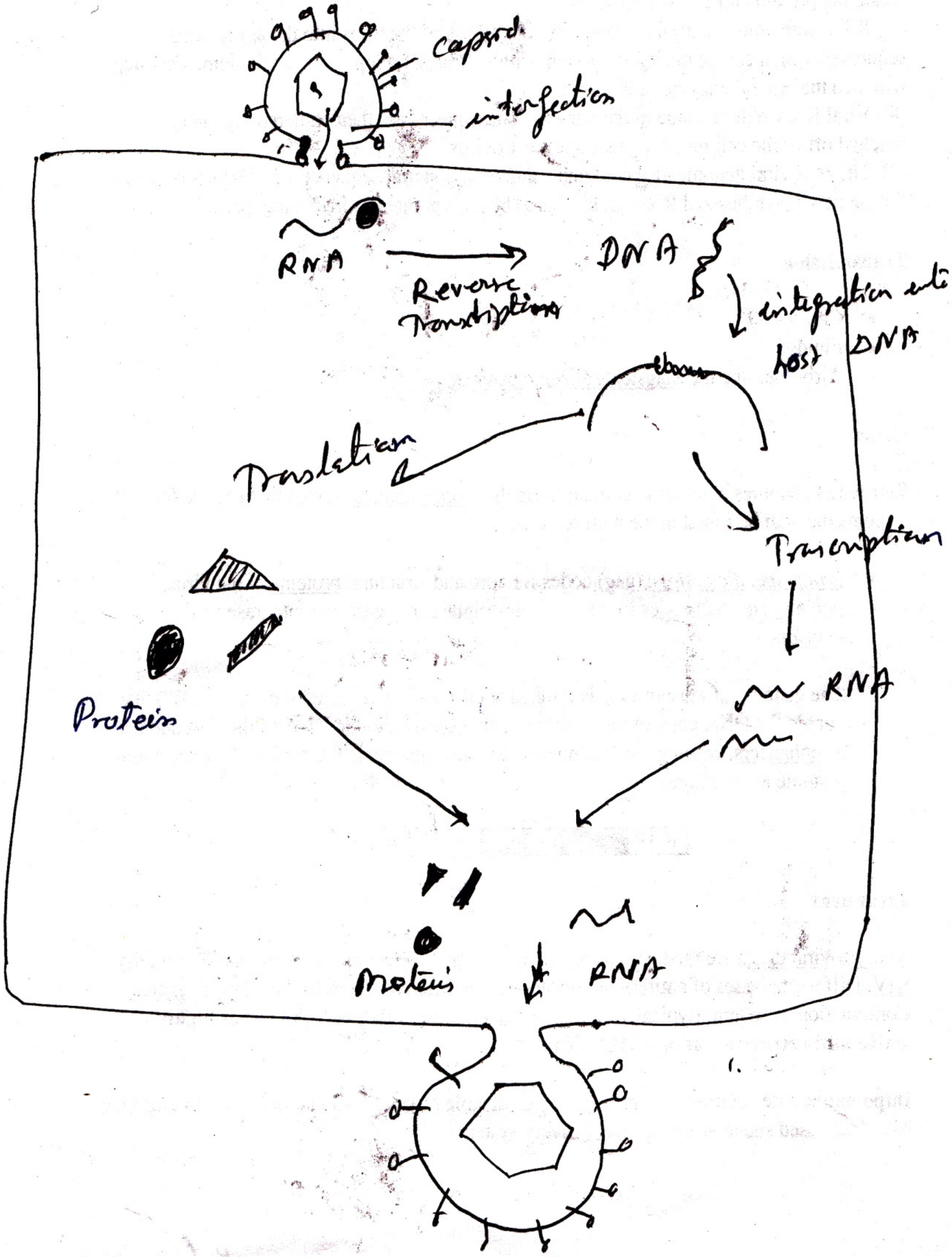



Plasma membrane
Nucleus
DNA
Integration
into host DNA
RNA
DNA
Transcription
Transcription
Reverse
transcription
Infection
Translation
Capsid
RNA
RNA
Reverse
transcriptase
Capsid
protein
Reverse
transcriptase
RNA
Envelope
protein
New virion


gp120
gp41
lipid layer
host cell proteins
p17 matrix antigen
integrase
HIV-RNA
p24 core antigen
reverse
transcriptase
p7 gag
p9 gag

HIV Virus


env gp120
env gp41
gag p17
gag p24
RNA
Human Immunodeficiency
Virus – Structure



Replication of Retrovirus.