Viral replication

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Basic Structure of Viruses

- **Components**
  - **Genetic Material:** DNA or RNA (not both)
  - **Protein Coat (Capsid):** Protects genetic material
  - **Envelope (in some viruses):** Lipid membrane derived from host cell
- **Shapes and Sizes**
  - Helical, icosahedral, complex structures
- **Examples**
  - Enveloped Viruses: HIV, Influenza virus
  - Non-Enveloped Viruses: Adenovirus, Poliovirus

Viral Classification

- **Based on Genetic Material**
  - DNA Viruses
  - RNA Viruses
- **Based on Replication Strategy**
  - Baltimore Classification (detailed later)

Overview of Viral Replication Steps

- **General Steps:**
  1. Attachment (Adsorption)
  2. Penetration (Entry)
  3. Uncoating
  4. Synthesis (Replication and Protein Production)
  5. Assembly (Maturation)
  6. Release (Egress)

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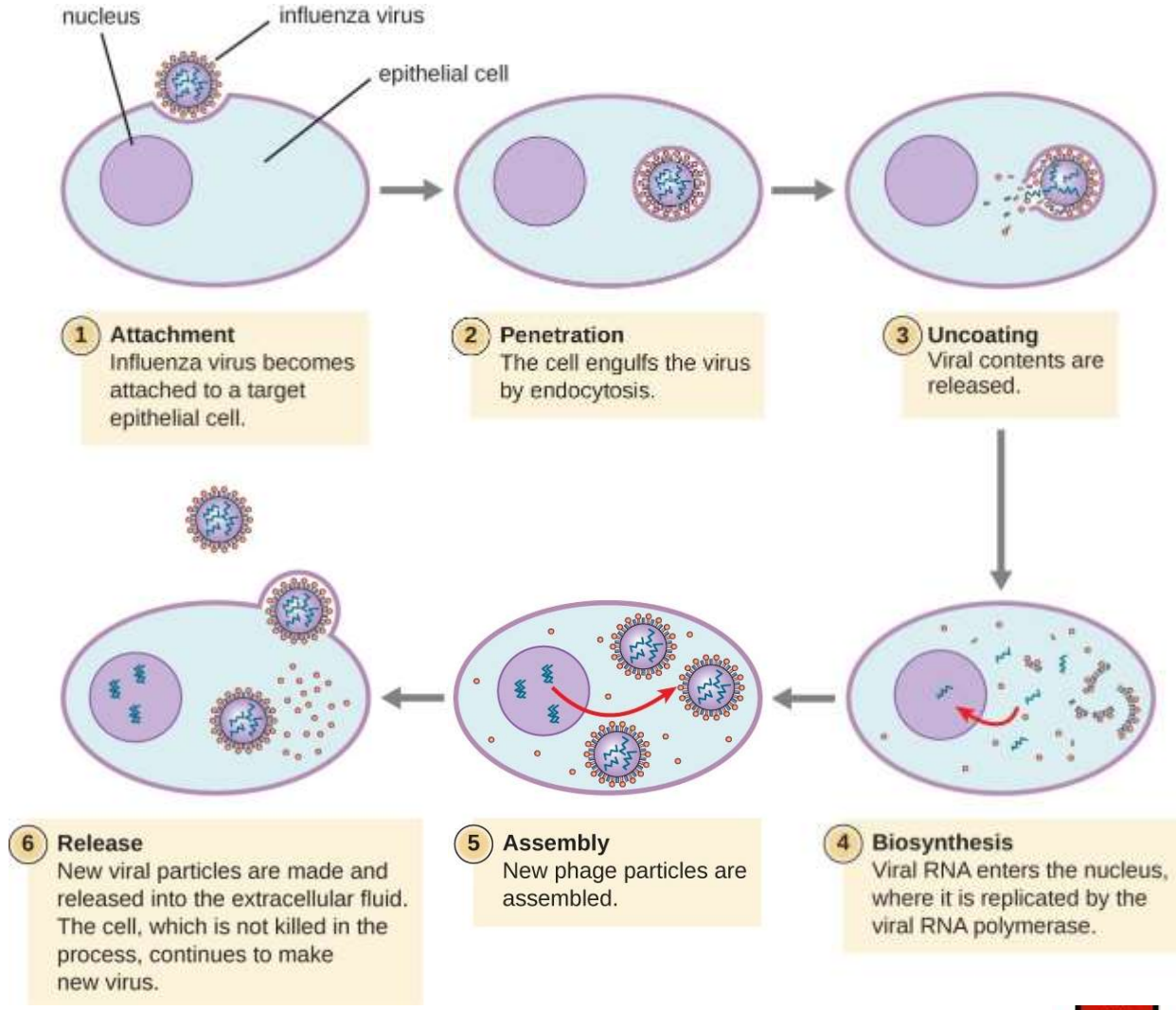
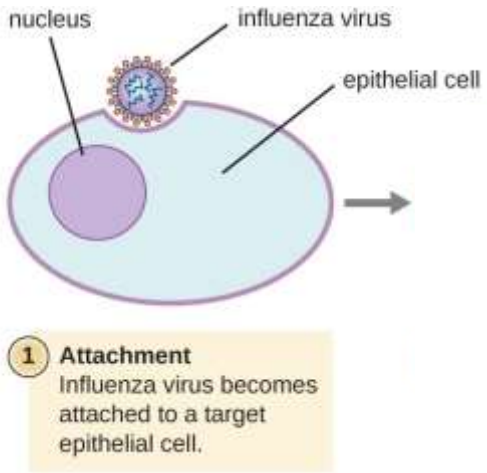


Viral Replication Steps
Step 1 - Attachment (Adsorption)

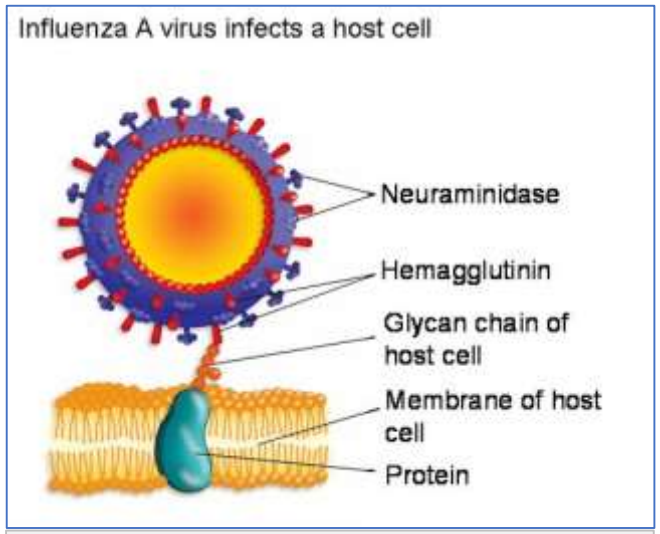
- **Mechanism:**
  - Viral surface proteins (ligands) bind to specific receptors on the host cell membrane.
  - The receptors on cells are protein or carbohydrate or lipid components of the cell surface.
- **Specificity:**
  - Determines host range and tissue tropism.
  - Cells without the appropriate receptors are not susceptible to the virus.
- **Examples:**
  - **HIV:** gp120 binds to CD4 receptors on T-helper cells.
  - **Influenza Virus:** Hemagglutinin binds to sialic acid residues on respiratory epithelial cells.



Viral Replication Steps

Step 1 - Attachment (Adsorption) - Examples

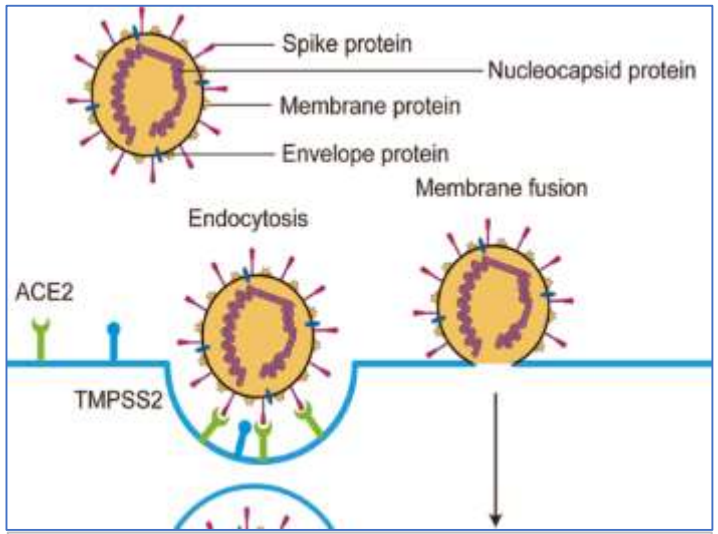
Influenza virus



Hemagglutinin (HA): attaches to sialic acid-containing receptors on respiratory epithelial cells

Neuraminidase (NA): cleaves newly formed virions off the sialic acid-containing receptor, allowing the virus to exit cells

COVID-19

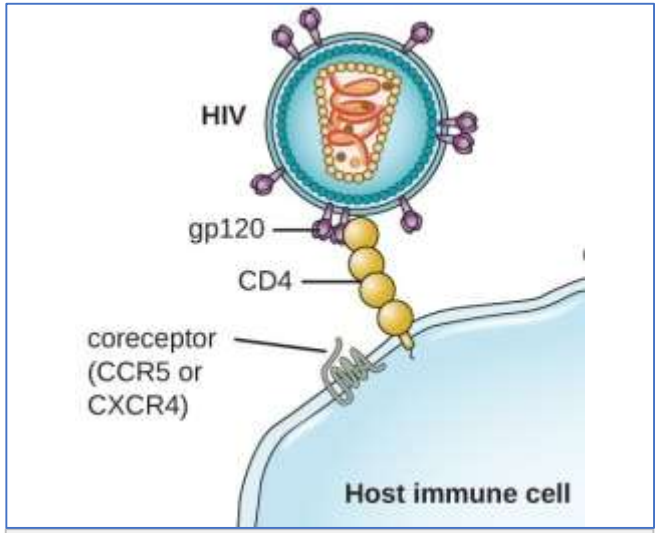


The spike protein binds to the membrane protein angiotensin-converting enzyme 2 (ACE2).

Transmembrane protease serine 2 (TMPRSS2) activates the spike protein.

Membrane fusion and uncoating of the viral RNA occur.

HIV

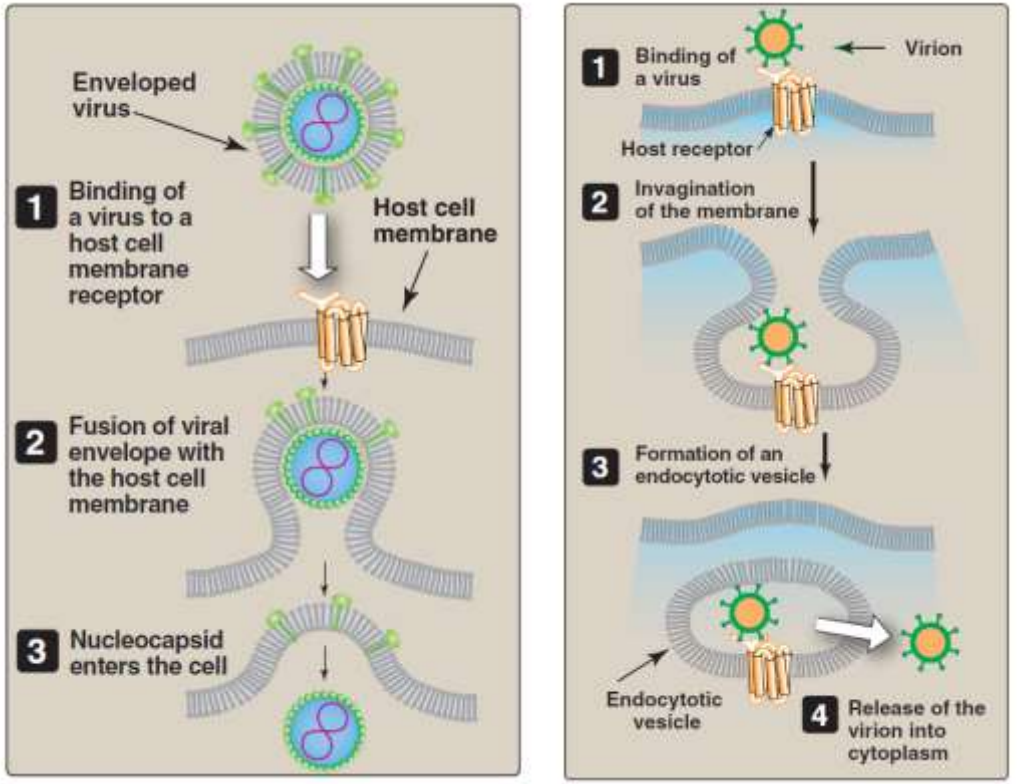


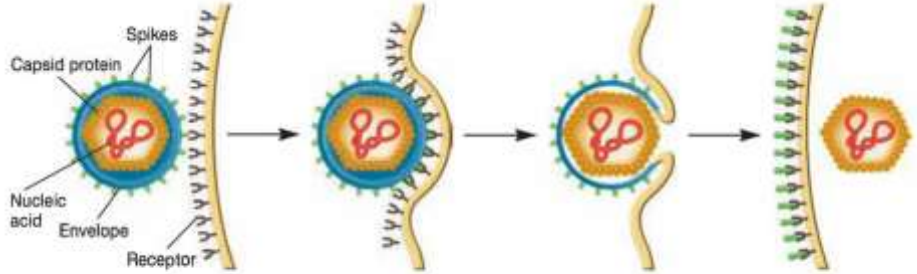
The joining ligand of HIV is **gp120** which binds to the most common cellular receptors glycoproteins (CD4).

Viral Replication Steps
Step 2 - Penetration (Entry)

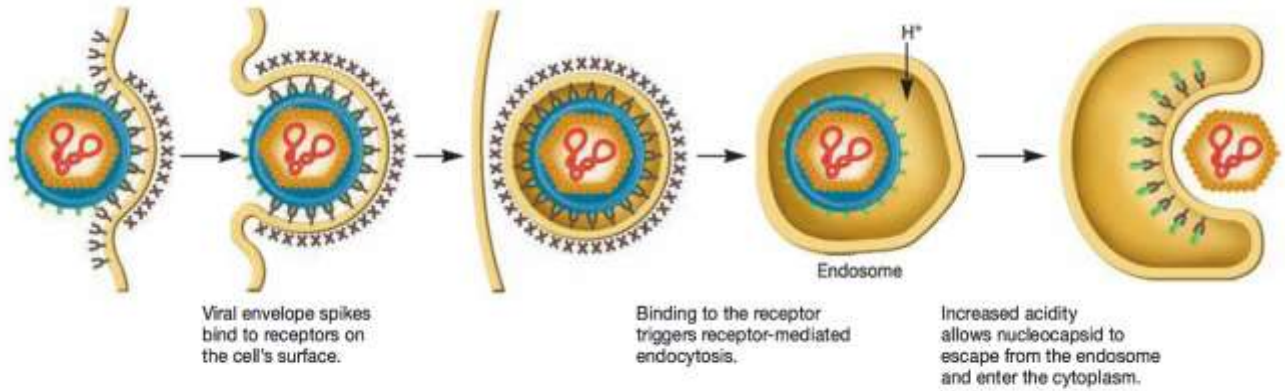
Mechanisms:

- **Direct Fusion (Enveloped Viruses):**
  - Viral envelope fuses with the plasma membrane of the cell.
  - The end result of this process is that the nucleocapsid is free in the cytoplasm, whereas the viral membrane remains associated with the plasma membrane of the host cell.
  - Example: HIV entering T-cells.
- **Receptor-mediated endocytosis (Enveloped and Non-Enveloped Viruses):**
  - The cell membrane invaginates, enclosing the virion in an endocytotic vesicle (endosome).
  - Clathrin-mediated endocytosis:e.g. Adenoviridae/ Caveolin mediated endocytosis: e.g. Papillomaviridae / Macropinocytosis: e.g Picornaviridae / Non-clathrin, non-caveolin mediated endocytosis
  - Example: Adenovirus (Clathrin-mediated endocytosis).

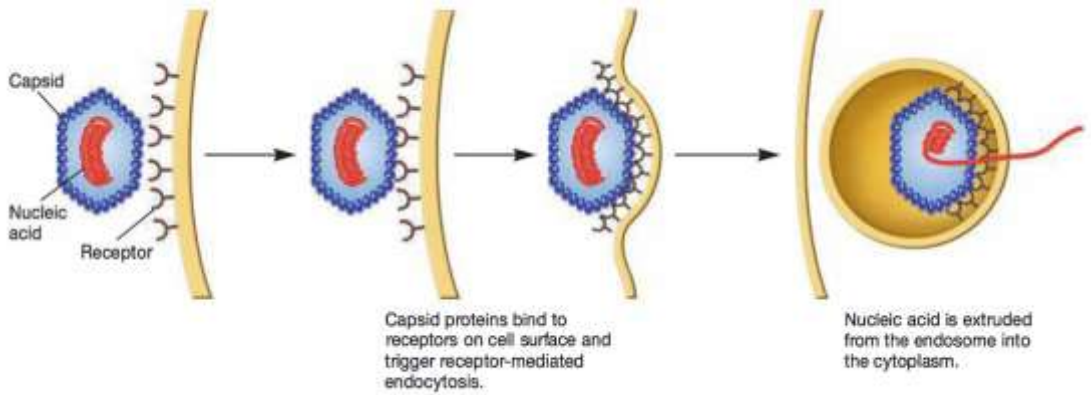




(a) Entry of enveloped virus by fusing with plasma membrane



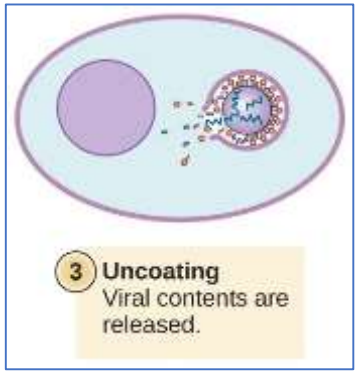
(b) Entry of enveloped virus by endocytosis



(c) Entry of nonenveloped virus by endocytosis

Viral Replication Steps
Step 3 - Uncoating

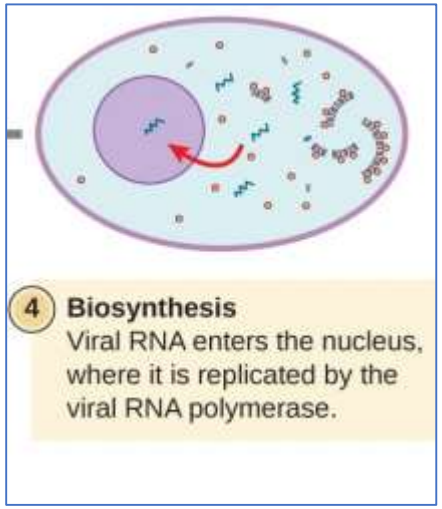
- **Definition:**
  - Refers to the separation of the capsid from the viral genome. It results in the loss of virion infectivity.
- **Mechanisms:**
  - Lysosomal Enzymes: degrade the proteins of the viral capsid.
  - Conformational Changes: Triggered by pH shifts.
- **Examples:**
  - Influenza Virus: Uncoating facilitated by M2 ion channel in acidic endosome.



Viral Replication Steps

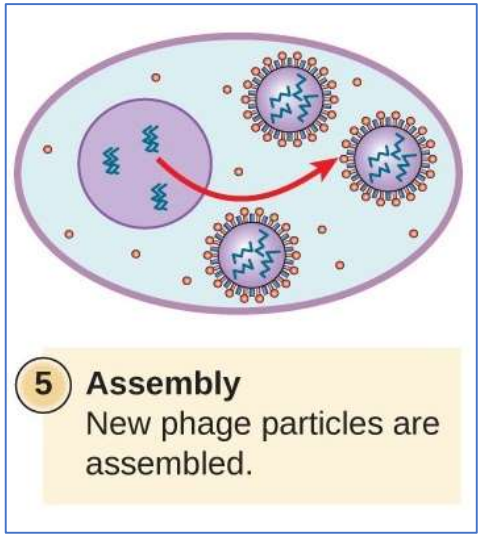
Step 4 –Synthesis: Replication and Protein Production

- Once uncoating has taken place, synthesis of viral nucleic acid starts.
- The site of production of nucleic acid also varies between viruses.
  - Most of the DNA viruses except Pox and Herpes replicate in nucleus.
  - All RNA viruses replicate in cytoplasm except Orthomyxoviruses and Retroviruses, which for certain stages of replication get into the nucleus of the cell
- How different viruses with different genome replicate?
  Baltimore Classification



Viral Replication Steps
Step 5 – Assembly (Maturation)

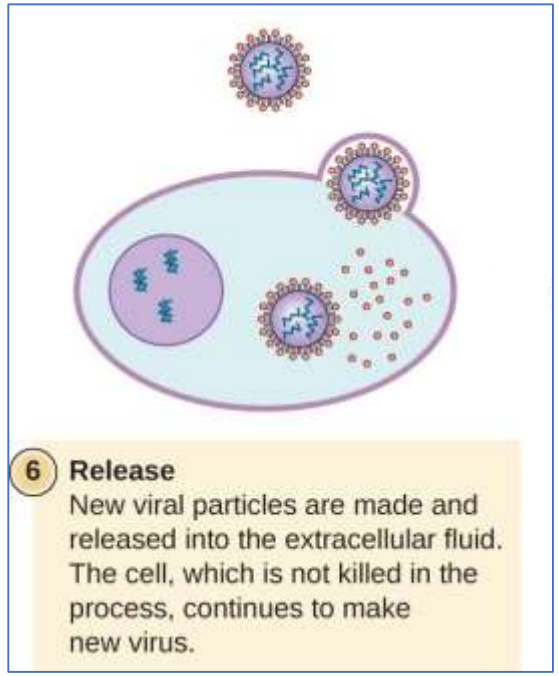
- **Process:**
  - Assembly of viral genome and proteins into new virions.
- **Locations:**
  - Assembly of nucleocapsids generally takes place in the host cell compartment where the viral nucleic acid replication occurs (that is, in the cytoplasm for most RNA viruses and in the nucleus for most DNA viruses).
    - For DNA viruses, this requires that capsid proteins be transported from their site of synthesis (cytoplasm) to the nucleus.



Viral Replication Steps

Step 6 –Release

- Release is a simple process – the cell breaks and releases the virus.
- Enveloped viruses acquire the lipid membrane as the virus buds out through the cell membrane.



Negative vs. Positive Sense Strand of DNA and RNA

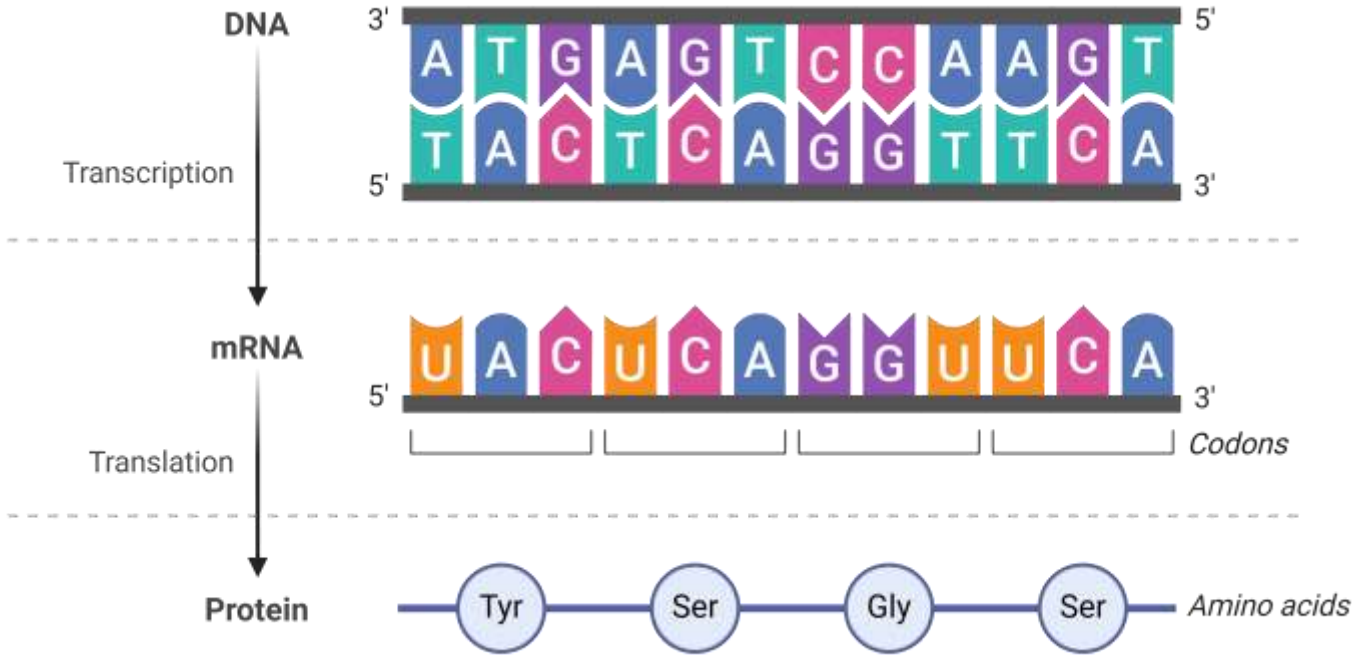
DNA

Negative-sense

Positive-sense

- Negative DNA strand was used to make mRNA (+ssRNA)
- mRNA can then be translated to make proteins

Negative vs. Positive Sense Strand of DNA and RNA

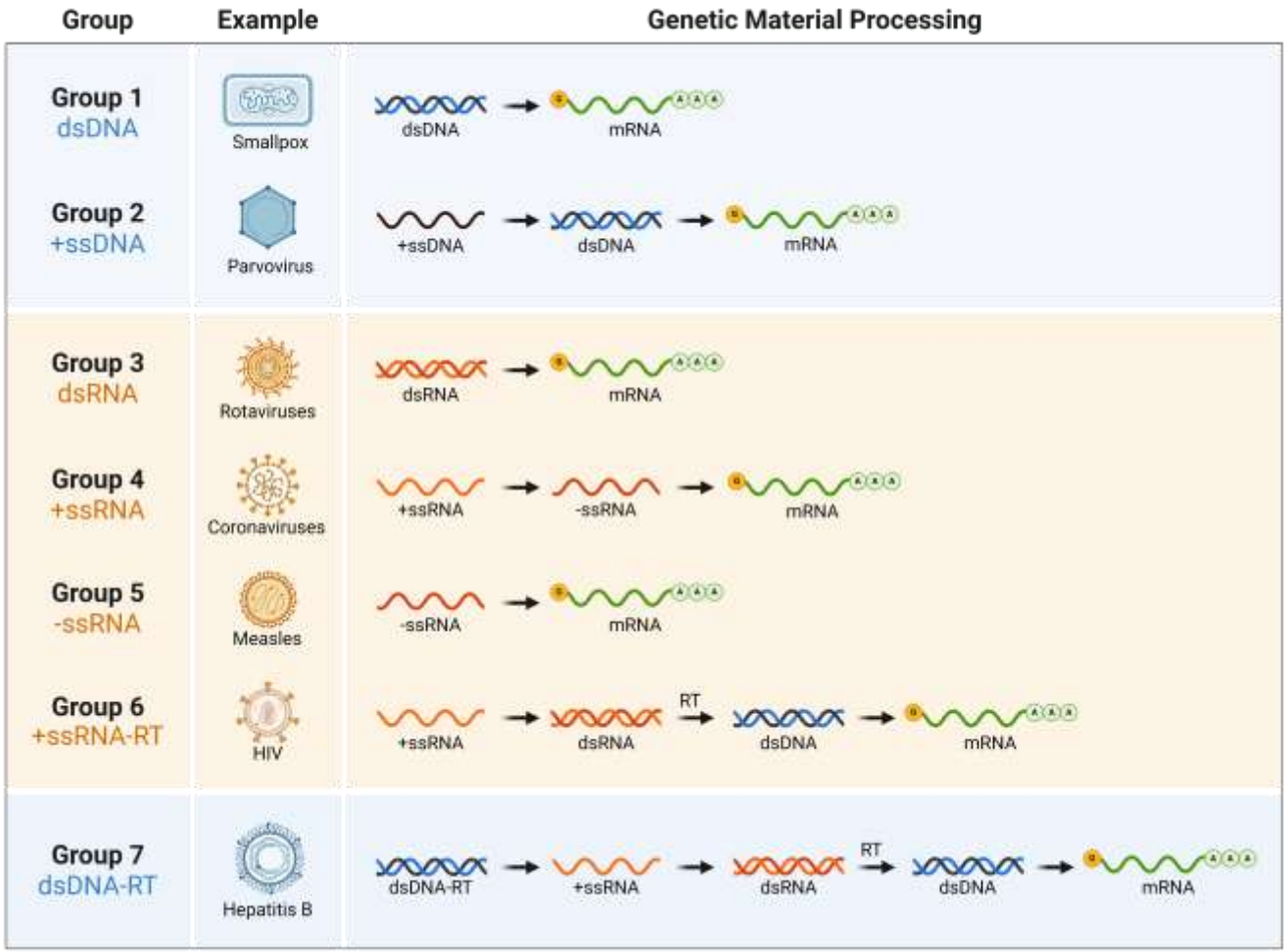


Viral replication = Protein synthesis + copying genetic material

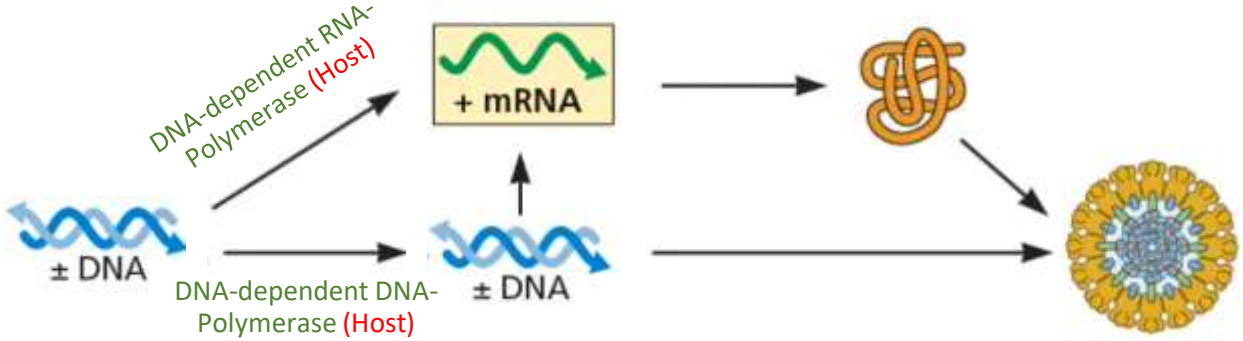
BUT

It's not as simple—or as romantic—as it might seem. Viruses have their own complex dance with life!

Baltimore Classification

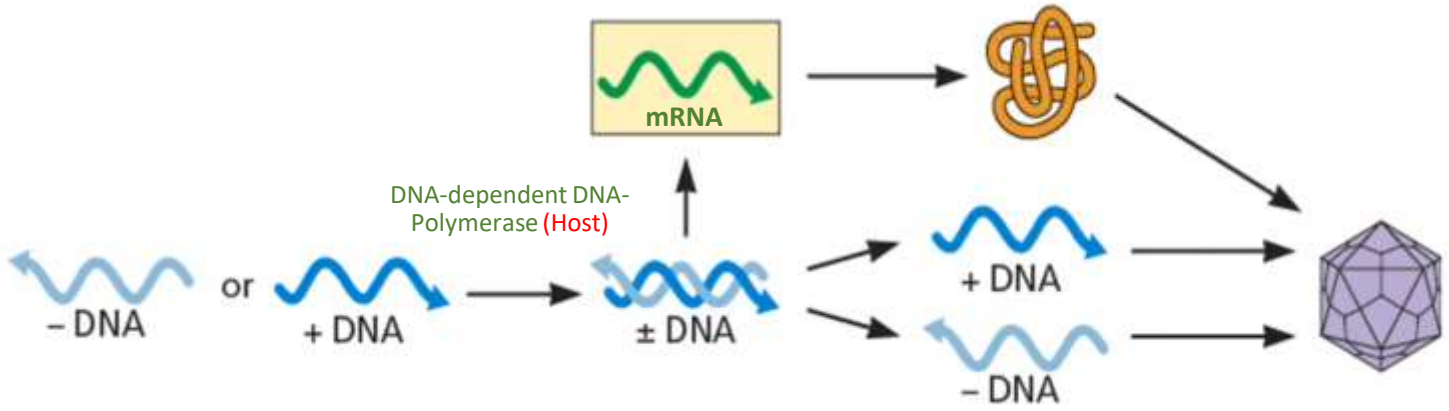


Group 1: Replication of dsDNA Virus



- The replication of dsDNA viruses is a straight-forward.
- They use the cell's replication machinery to transcribe their genome into mRNA immediately.
- Host enzymes for mRNA synthesis and DNA replication are available in nucleus hence, it needs to enter the nucleus.
- **Example:** papillomaviruses, polyomaviruses, adenoviruses and herpesviruses.

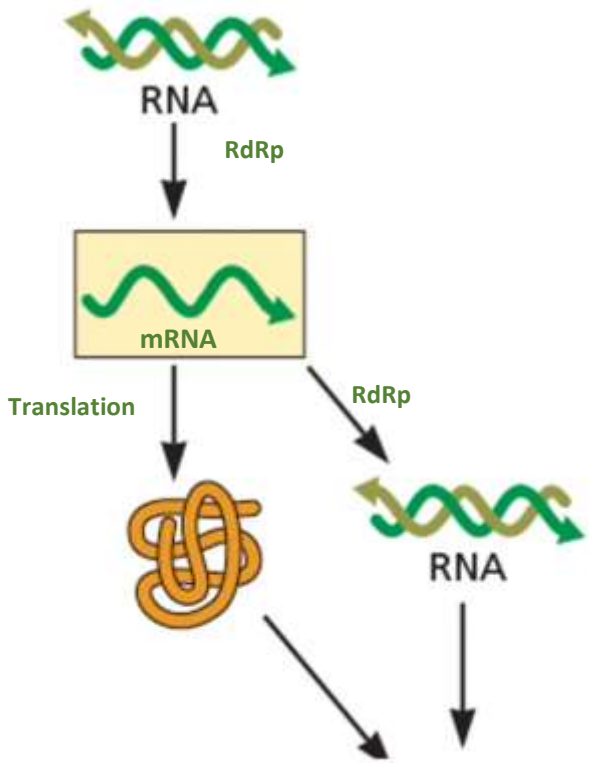
Group 2: Replication of ssDNA Virus



- This can be used to both manufacture viral proteins and as a template for viral genome copies.
- For the minus-strand DNA viruses, the genome can be used directly to produce mRNA but a complementary copy will still need to be made, to serve as a template for viral genome copies.

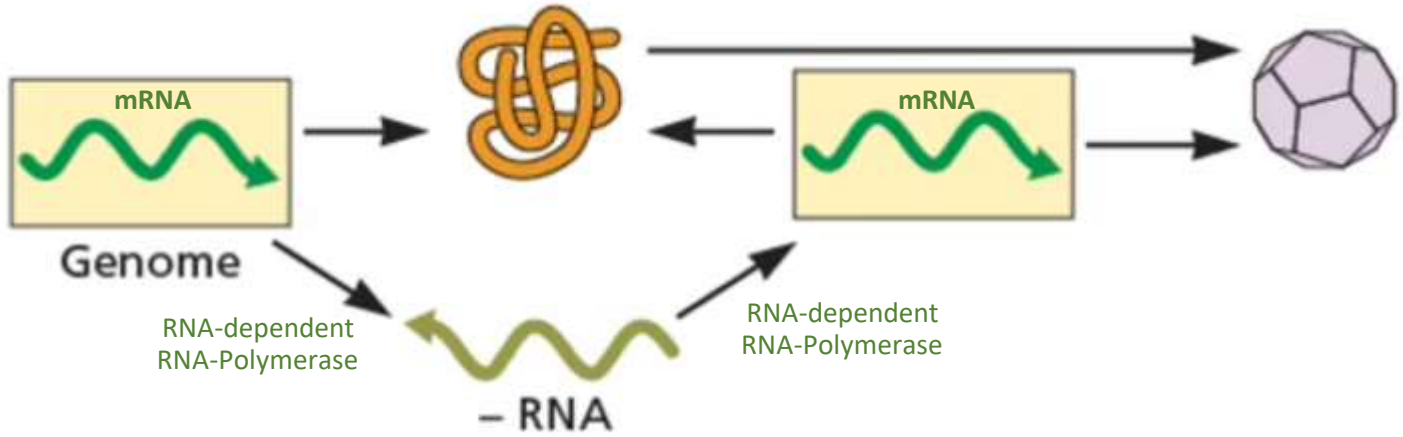
Group 3: Replication of dsRNA Virus

- Double-stranded RNA viruses infect bacteria, fungi, plants, and animals, such as the rotavirus that causes diarrheal illness in humans.
- The viral RNA-dependent RNA polymerase acts as both a **transcriptase** to transcribe mRNA, as well as a **replicase** to replicate the RNA genome.
- Prokaryotic and eukaryotic cells do not carry **RdRp**.



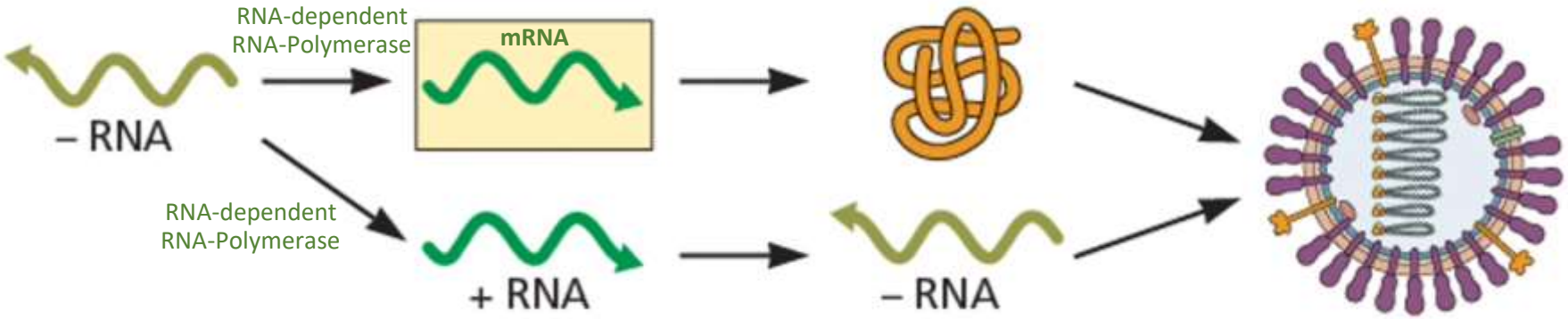
After entering the host body, the viral RNA-dependent RNA polymerase (RdRp) transcribed the dsRNA genome into mRNA, later this transcribed mRNA is used for the translation or replication.

Group 4: Replication of (+) ssRNA Virus



- Viruses with plus-strand RNA, such as poliovirus, can use their genome directly as mRNA with translation by the host ribosome occurring as soon as the viral genome gains entry into the cell.
- One of the viral genes expressed yields an RNA-dependent RNA-polymerase (or RNA replicase), which creates minus-strand RNA from the plus-strand genome.
- The minus-strand RNA can be used as a template for more plus-strand RNA, which can be used as mRNA or as genomes for the newly forming viruses.

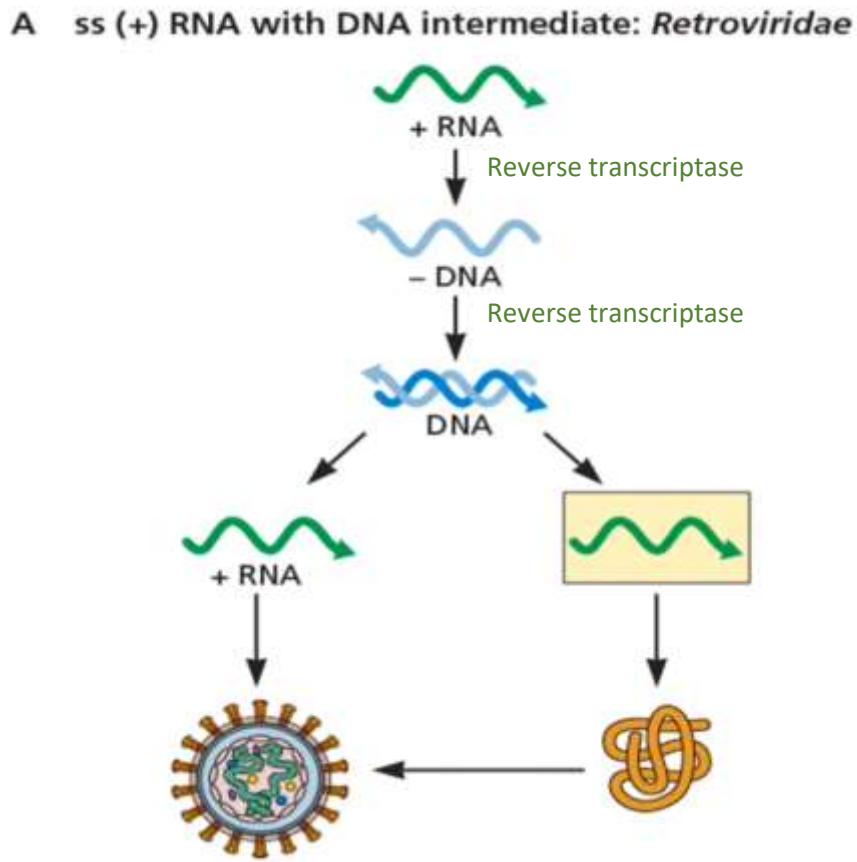
Group 5: Replication of (-) ssRNA Virus

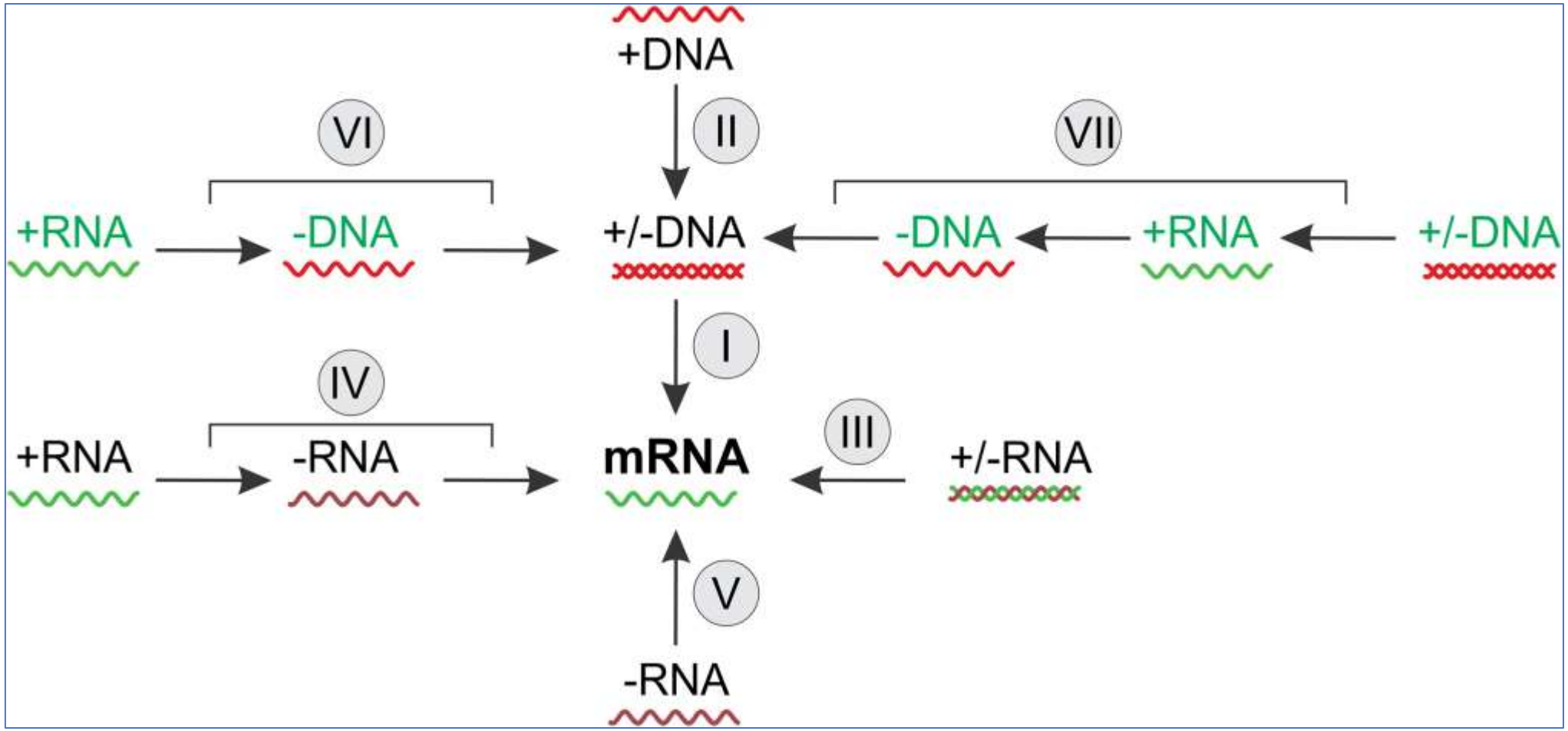


- Minus-strand RNA viruses include many members notable for humans, such as influenza virus, rabies virus, and Ebola virus.
- Since the genome of minus-strand RNA viruses cannot be used directly as mRNA, the virus must carry an RNA-dependent RNA-polymerase within its capsid.
- Upon entrance into the host cell, the plus-strand RNAs generated by the polymerase are used as mRNA for protein production.
- When viral genomes are needed the plus-strand RNAs are used as templates to make minus-strand RNA.

Group 6: Replication of (+) ssRNA-RT Virus (dsDNA intermediate)

- Despite the fact that the retroviral genome is composed of +ssRNA, it is not used as mRNA. Instead, the virus uses its reverse transcriptase to synthesize a piece of ssDNA complementary to the viral genome. The reverse transcriptase also possesses **ribonuclease** activity, which is used to degrade the RNA strand of the RNA-DNA hybrid. Lastly, the reverse transcriptase is used as a DNA polymerase to make a complimentary copy to the ssDNA, yielding a dsDNA molecule.
- **Example:** Human immunodeficiency virus (HIV)




+DNA
VI
II
VII
+RNA
-DNA
+/-DNA
-DNA
+RNA
+/-DNA
I
IV
+RNA
-RNA
mRNA
III
+/-RNA
V
-RNA