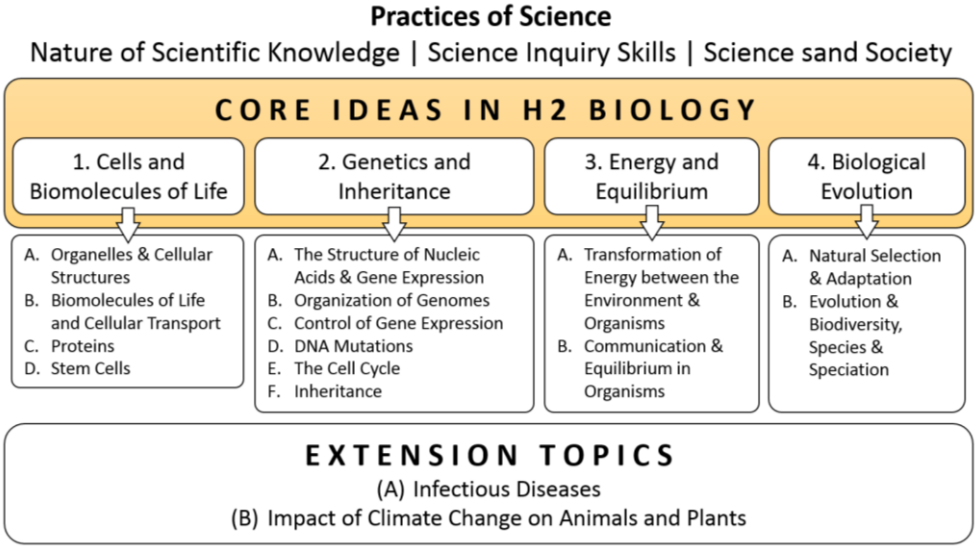
Core Idea 2B

9. Genetics & Inheritance (VI)

Organization & Inheritance of Viral Genomes



SYLLABUS OVERVIEW		
No.	**Overarching Idea**	**Topics**
1	**Core Idea 1** The Cell and Biomolecules of Life	Cell – The Basic Unit of Life
2		Biomolecules of Life and Cellular Transport
3	**Core Idea 3** Energy and Equilibrium	Transformation of Energy – Photosynthesis and Cellular Respiration
4	**Core Idea 2** Genetics and Inheritance	Genetics and Inheritance (I) – The Cell Cycle
5		Genetics and Inheritance (II) – DNA Replication and Gene Expression
6		Genetics and Inheritance (III) – DNA Mutations and their Consequences
7		Genetics and Inheritance (IV) – Molecular Techniques in DNA Analysis
8		Genetics and Inheritance (V) – Organization of Genome & Control of Gene Expression in Eukaryotes *[Includes Core Idea 1D: Stem Cells]*
9		Genetics and Inheritance (VI) – Organization and Inheritance of Viral Genomes
10		Genetics and Inheritance (VII) – Organization of Genome & Control of Gene Expression in Prokaryotes
11		Genetics and Inheritance (VIII) - Inheritance
12	**Core Idea 3** Energy and Equilibrium	Communication and Equilibrium in Multicellular Organisms
13	**Core Idea 4** Biological Evolution	Biological Evolution
14	**Extension Topic A** Infectious Diseases	Immunity and Infectious Diseases
15	**Extension Topic B** Impact of Climate Change on Animals & Plants	Climate Change – Causes and Impacts on Animals and Plants

NARRATIVE

An understanding of *Genetics and Inheritance* that would help make sense of the transition from molecular to organismal level. *Genetics and Inheritance* provides the molecular basis to the understanding of how variations in populations arise and this is important in the study of biological evolution. At the cellular level, expression of genes involves cellular structures such as the nucleus, endoplasmic reticulum and ribosome. Many essential products of gene expression are enzymes involved in biochemical pathways which control physiological functions. As such, mutation of genes may give rise to dysfunctional proteins which in turn could result in diseases. Sickle cell anemia and cancer are raised as examples of a monogenic and a multi-genic disease respectively.

The following questions should help students frame their learning:

- How does the genetic make-up of an organism influence its appearance, behavior and survival?
- How can we ensure continuity of human as a species?

Heritable information, in the form of DNA (and in some cases RNA), provides for continuity of life

Genetic information is stored in an organism's DNA; expression of genes results in the synthesis of functional products, such as rRNA, tRNA and proteins. These products play a role in intra- and extra-cellular biochemical pathways and influence the physiological processes in organisms.

Genomes contain heritable information necessary for continuity of life at all levels: cell, organism and system. This information is stored and passed on to subsequent generations via DNA. Reproduction can occur at the cellular or organismal level; each progeny needs to receive heritable genetic information from its parents.

An understanding of how eukaryotic, prokaryotic and viral genomes are organised has implications on how gene expression in organisms is controlled. Unlike prokaryotes and eukaryotes, the genome of viruses varies greatly; they can be DNA or RNA in nature, single or double-stranded, depending on the type of virus. Viruses undergo different reproductive cycles: some bacteriophages, e.g. T4 phage, reproduce via lytic cycle while others, e.g. lambda phage, reproduce via lytic and/or lysogenic cycles; animal viruses, such as influenza virus and HIV, reproduce through other mechanisms. Again, unlike their prokaryotes or eukaryotes counterparts, viruses do not photosynthesize or respire, and they require host cells (bacteria, plants or animals) to reproduce. As such, debate ensues as to whether viruses are considered living or non-living.

LEARNING OUTCOMES

Core Idea 2B: Organization of Genomes
In contrast to eukaryotic and prokaryotic genomes, the viral genome varies according to the type of virus; the genome may be DNA or RNA in nature and single or double-stranded. For RNA viruses, they may possess either positive-sense RNA (i.e. identical to viral mRNA and thus can be immediately translated) or negative-sense RNA (i.e. complementary to viral mRNA and thus must be converted to positive-sense RNA by RNA polymerase before translation).

Candidates should be able to:

a) Describe the structure and organization of **viral**, prokaryotic and eukaryotic genomes (including DNA/RNA, single-/double-stranded, number of nucleotides, packing of DNA, linearity/circularity and presence/absence of introns)

b) Describe how the genomes of viruses are inherited through outlining the reproductive cycles of:
- **i)** Bacteriophages that reproduce via lytic cycle only, e.g. T4 phage;
- **ii)** Bacteriophages that reproduce via lytic and lysogenic cycles, e.g. lambda phage;
- **iii)** enveloped viruses, e.g. influenza; and
- **iv)** retroviruses, e.g. HIV

c) Describe how variation in viral genomes arises, including antigenic shift and antigenic drift.

LECTURE OUTLINE

1. Overview of viruses
- 1.1 Characteristics of viruses
- 1.2 General features of viral reproductive cycle

2. Structure and Organization of Viral Genome
- 2.1 Structure of Viral Genome
- 2.2 Organisation of Viral Genome

3. Bacterial Viruses (Bacteriophages)
- 3.1 T4 bacteriophage
  - 3.1.1 Structure
  - 3.1.2 Reproductive cycle (lytic)
- 3.2 Lambda bacteriophage
  - 3.2.1 Structure
  - 3.2.2 Reproductive cycle (lytic and lysogenic)

4. Animal Viruses
- 4.1 Influenza Viruses
  - 4.1.1 Structure
  - 4.1.2 Reproductive cycle
- 4.2 Human Immunodeficiency Virus (HIV)
  - 4.2.1 Structure
  - 4.2.2 Reproductive cycle
- 4.3 Treatment of viral diseases
  - 4.3.1 How viral infections cause disease
  - 4.3.2 Overview of treatment strategies

5. Variation in viral genome (e.g. influenza virus)
- 5.1 Antigenic shift
- 5.2 Antigenic drift

TEXTBOOK REFERENCES

Biology, Campbell and Reece, 9th Edition, *pgs 427 - 441*

INTERNET ANIMATIONS

1. Entry of Virus into Host Cell	2. Mechanism for Releasing Enveloped Viruses	3. *T4 phage reproductive cycle*	4. *Lambda phage reproductive cycle*
5. *Influenza virus reproductive cycle*	6. *HIV reproductive cycle*	7. *HIV treatment (protease and reverse transcriptase inhibitors)*	8. *Antigenic drift*
9. *Antigenic shift*			

1. Introduction

1.1 Characteristics of Viruses

Key concept 1:
Viruses are the simplest biological systems. They are infectious particles consisting of 1) nucleic acid, 2) capsid, and 3) in some cases, a viral envelope. (Fig 1.1a)

1. **Nucleic acid** (viral genome) (details in Section 2.1)

2. **Capsid** (protein coat)
   - It is a protein coat, built from a large number of protein subunits called **capsomeres.**
   - There are many capsid shapes (eg. helical, icosahedral, complex) (Fig. 1.1b).
   - The viral nucleic acid plus its surrounding protein capsid is known as a **nucleocapsid**.
   - Functions of the capsid:
     i. **Encloses the viral genome** and protects it from digestion by enzymes.
     ii. Aids in the **attachment to and penetration of the host cell**.
     iii. **Carries viral enzymes** involved in viral replication.

3. **Viral envelope** (only in some viruses i.e. enveloped viruses)
   - Consists of a **phospholipid bilayer** (derived from the **host's plasma membrane** during budding) which surrounds the capsid.
   - Some contain **glycoproteins** that project from the viral envelope as spikes. These glycoproteins are **encoded by** the **viral genome.** Examples of enveloped viruses with glycoproteins are influenza viruses and HIV.
   - Functions
     i. **Glycoproteins** on the viral envelope are **complementary in shape to** and can therefore bind to the **receptor proteins** on the host cell membrane. This determines the **specific host range** (i.e. specific cell types or species/organisms that a virus can infect). Some viruses have broad host ranges (E.g. West nile virus) while some viruses have narrow host ranges (E.g. HIV).

     ii. The viral envelope facilitates the **entry** of viruses into host cells by *either* **direct fusion** with the host cell membrane (Fig. 1.1c), or through **receptor-mediated endocytosis (RME)** (Fig. 1.1d)**.**

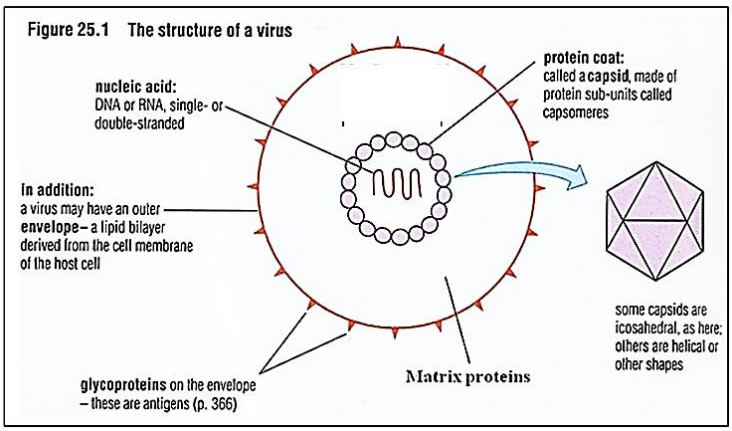


Fig. 1.1a: General structure of a virus.

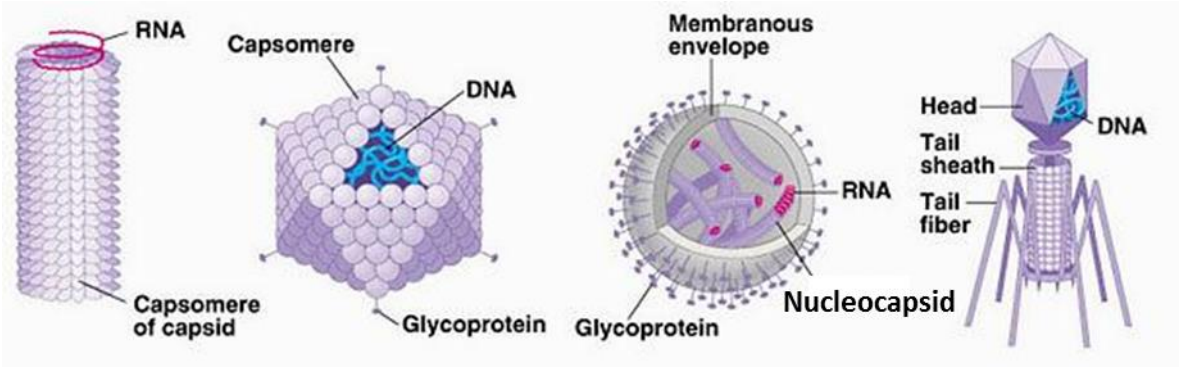


Fig. 1.1b: (From left to right) Tobacco moscaic virus with a helical capsid, Adenovirus with a icosahedral capsid, Influenza viruses with an envelope studded with glycoprotein spikes, Bacteriophage T4 with a complex capsid consisting of an icosahedral head and a tail apparatus.

4. Viruses range from about **20 nm to 400 nm** (Fig. 1.1c) in length.

- The tiniest viruses are only 20nm in diameter, smaller than a ribosome.
- They can only be observed under the electron microscope (not light microscope).
- They can pass through the small pores of filters (that are able to retain bacteria).

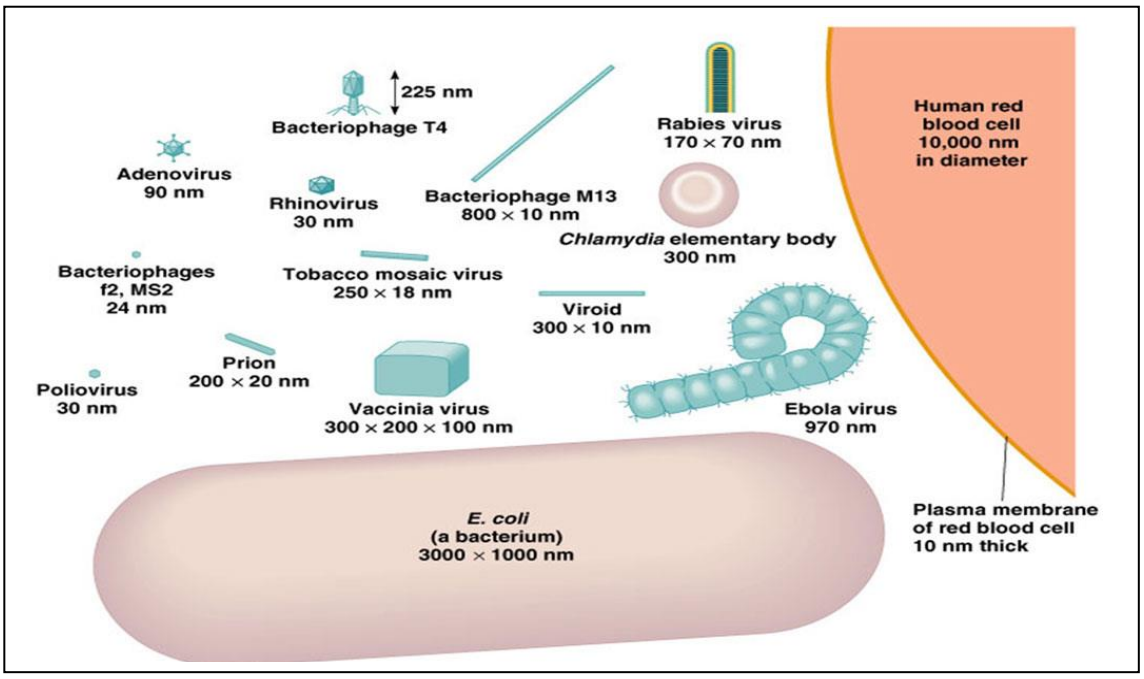


Fig. 1.1c: Relative sizes of microorganisms.

Key concept 2:
Viruses exhibit both living and non-living characteristics.

- **Living characteristics**
  To be defined as living organism, a species must possess genetic material (DNA or RNA), and be capable of reproducing itself.

  - Viruses possess **genetic material** (either DNA or RNA, which may be single-stranded or double-stranded).

  - Viruses are **capable of reproducing** themselves **within host cells**.

- **Non-living characteristics**
  If a living organism is defined as a cellular structure which is capable of reproducing independently, then viruses are non-living organisms.

  - Viruses do not possess cellular structures or organelles.

  - Viruses **lack** the **metabolic enzymes and organelles** required for DNA replication and protein synthesis. They need to exploit the metabolic machinery of **permissive host cells** (cells in which a virus is able to replicate) for **reproduction**. Metabolic machinery exploited includes nucleotides, enzymes, ribosomes, tRNAs, amino acids, ATP etc.

- Hence all viruses are simply called **"obligate intracellular parasites".** Obligate parasites are parasites that can only reproduce within a host. Other examples of obligate parasites include some bacteria (eg. Chlamydia) and protozoa (eg. Plasmodium).

Key concept 3:
Each virus has a specific host range.

- Some viruses have a broad host range (i.e. can infect many species) e.g. Influenza virus, while others have a narrower host range e.g. Variola virus which causes Smallpox (FYI only).

- To be able to infect a host cell, the virus particle has to first bind to the host cell membrane before entering the host cell (Fig. 1.1d, 1.1e).

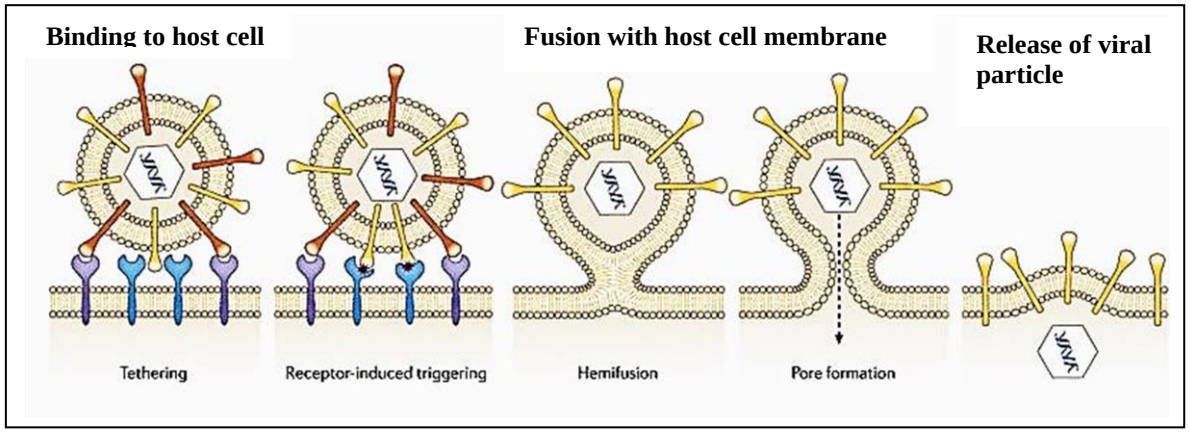


Fig. 1.1d: Enveloped virus entering host cell by direct fusion (e.g. HIV).

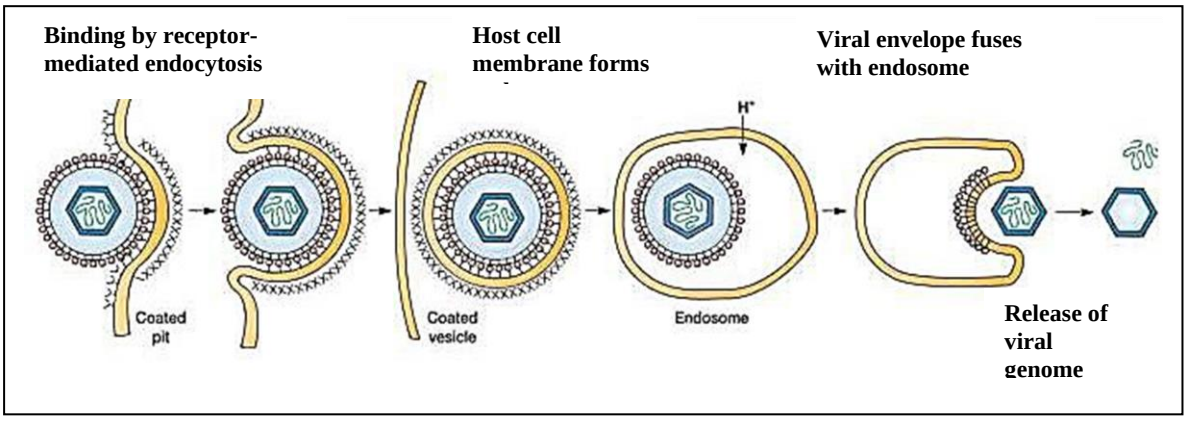


Fig. 1.1e: Enveloped virus entering host cell by RME (e.g. Influenza virus, but note that depicted virus is not representative of Influenza virus structure).

Think: Why do viruses infect only specific host ranges?

……

……

1.2 General features of viral reproductive cycle (Fig. 1.1f)

- *Recall Key Concept 2*: Viruses are non-living and are **obligate intracellular parasites** as they can only reproduce in host cells. They **lack metabolic enzymes** (e.g. DNA-dependent RNA polymerases) **and organelles** (e.g. ribosomes) for protein synthesis.

Key concept 4:
Viruses complete their reproductive cycle in four major steps: (1) Attachment, (2) Entry, (3) Synthesis, and (4) Assembly and release.

a) Attachment/Adsorption phase:

1. **Proteins/glycoproteins** on viral capsid/outer envelope have **shapes complementary** to **specific receptors** on the host cell membrane and **bind** to them.

b) Penetration/Entry phase:

For animal viruses:

2. The viruses then enter the host cell either via **direct fusion** between the viral envelope and host cell surface membrane or **receptor-mediated endocytosis**.

3. **Viral DNA/RNA** and **capsid proteins** are **released** during **un-coating.**

Note: Bacteriophages inject their DNA into host cells.

c) Synthesis phase

4. The virus uses:

(i) **host or viral enzymes** to synthesise **new copies of viral genome** (**replication**).

(ii) **host enzymes and ribosomes** to **express viral genes,** producing **viral proteins.**

d) Assembly and Release phase:

5(i) Viral genome and capsid proteins **self-assemble** to form new viral particles.

5(ii). New viral particles are **released from** the **host cell,** which either **lyses** (bacteria cells only), or remains **intact during budding** of viruses**.**

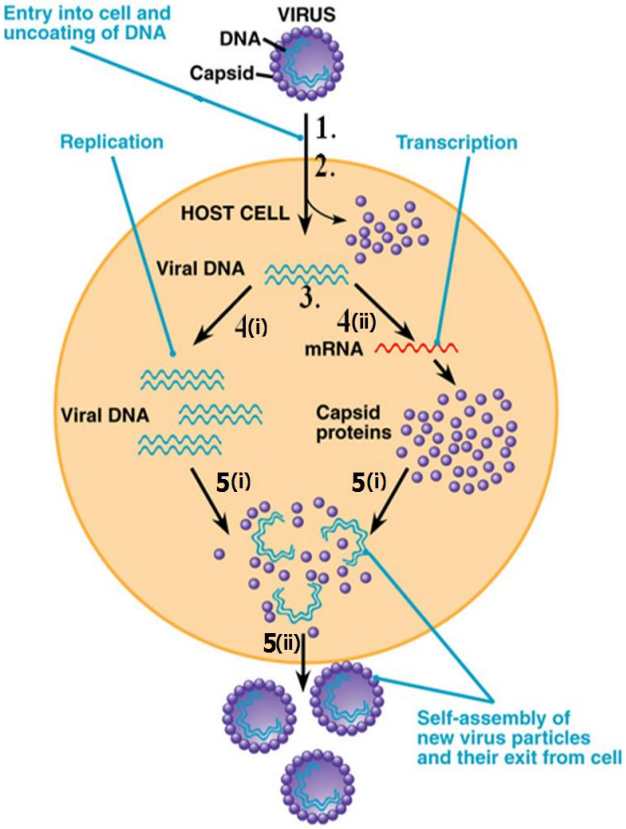


Fig. 1.1f: General viral reproductive cycle.

2. Structure and Organisation of Viral Genome

Candidates should be able to:

a) Describe the structure and organization of viral, ~~prokaryotic and eukaryotic~~ genomes (including DNA/RNA, single-/double-stranded, number of nucleotides, packing of DNA, linearity/circularity and presence/absence of introns)

2.1 Structure of Viral Genome

- Virus genomes range in size from **approximately 1,800 nucleotides** (e.g. ssDNA circoviruses) **to approximately 1.2 million nucleotides** (e.g. dsDNA mimivirus).

- The type of nucleic acid is one major way by which viruses are classified.

    - The **viral genome** comprises either **single-stranded (ss) or double-stranded (ds) DNA or RNA** (but not both).

    - For single-stranded RNA genomes, the strand is labelled either as a **positive (+) strand or negative (-) strand** (Table 1).

Table 1: Classification of single-stranded RNA

Type	Description
Positive (+) strand viral RNA	• Can be considered as **viral mRNA**. • **Directly translated** into **viral proteins**.
Negative (-) strand viral RNA	• Has nucleotide sequence that is **complementary** to that of **viral mRNA / (+) strand viral RNA.** • **Cannot** be directly translated into proteins. • Must be **converted to (+) RNA** by a **viral RNA polymerase** prior to translation.

- The DNA/RNA genome can also be either **linear or circular**.

- The genome may be in **single or multiple copies** (e.g. HIV has 2 identical copies).

- The genome may be **segmented** (i.e. consist of multiple molecules of nucleic acid) (e.g. Influenza virus has 8 segments).

2.2 Organisation of Viral Genome

- Because of its **limited size**, the viral genome carries a few genes:
    - Genes coding for **structural proteins** (components of assembled viral particles) (e.g. capsid proteins, viral glycoproteins, enzymes packaged within viral particles).
    - Genes coding for **non-structural proteins** (proteins that are essential for viral replication inside the host cell, but will not be part of the assembled viral particles).
- Viral genes have coding (**exons**) and non-coding regions (**introns**). Hence **RNA splicing** of the viral pre-mRNA (primary transcript) must occur . This ensures the production of functional viral proteins.
- Genome packaging is a fundamental process in a viral life cycle. There are two main strategies:
    - Many viruses (eg. ssRNA helical tobacco mosaic virus) assemble their capsids spontaneously around the viral genomes (Fig. 2.2a).
    - Some viruses (eg. dsDNA bacteriophages) form protein capsid shells first and then package their genomes into these procapsids (pre-assembled capsid) (Fig. 2.2b). These viruses require a packaging motor protein to translocate the nucleic acids into the capsid, using energy supplied by the hydrolysis of ATP.

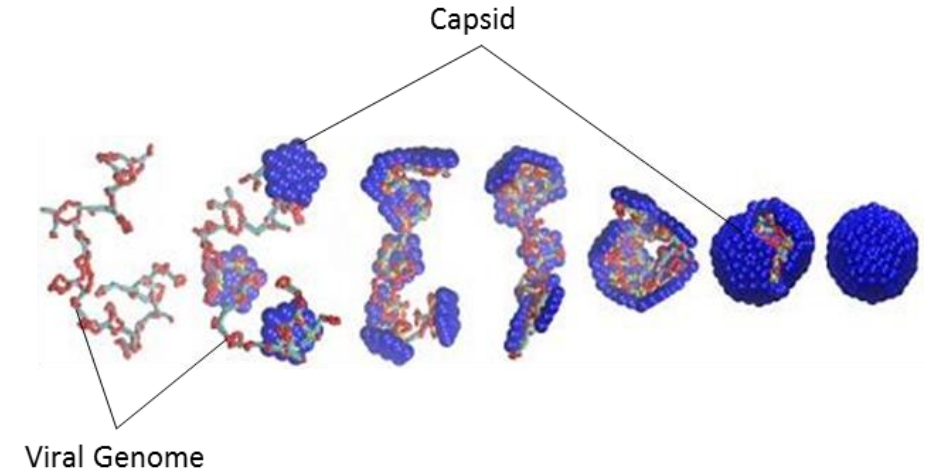


Fig. 2.2a: Computer simulation showing how the capsid (blue) assembles around the viral genome (red).

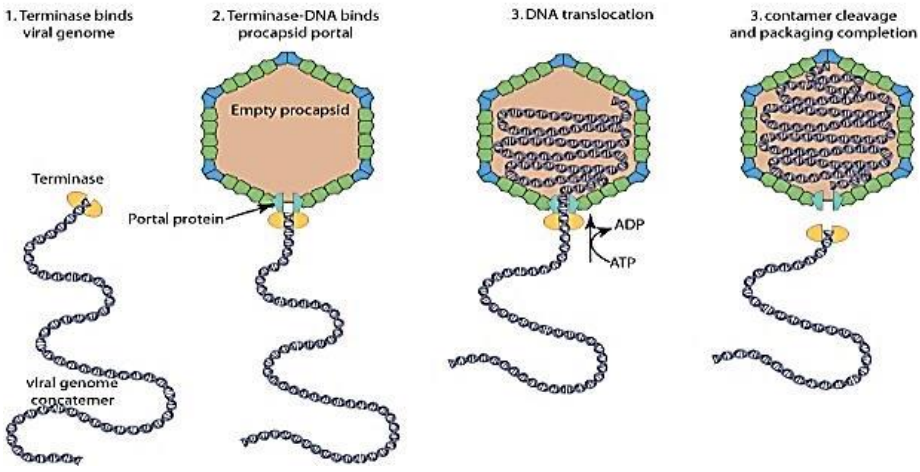


Fig. 2.2b: Packaging of viral genome into procapsids.

3. Bacterial Viruses (Bacteriophages)

- **Bacteriophages** (also known as phages) are **viruses that <u>infect bacteria cells</u>** (Fig. 3) and make use of the machinery of the bacteria to reproduce.

- They are **non-enveloped viruses** and have **double-stranded DNA.**

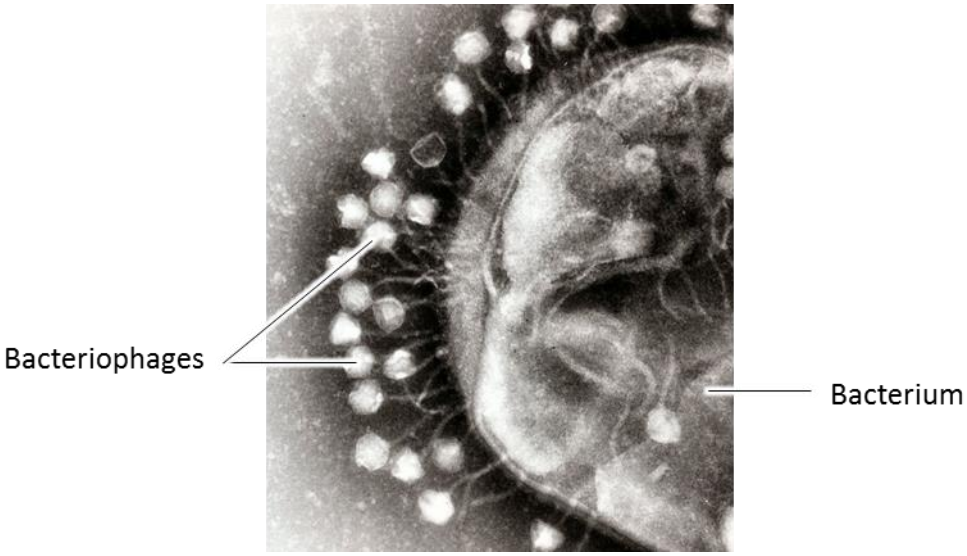


Fig. 3: Electron micrograph of bacteriophages infecting a bacterium.

3.1 T4 Bacteriophage

3.1.1 Structure of T4 Bacteriophage (Fig. 3.1a, 3.1b)

- **Complex virus** with an **icosahedral capsid** attached to a **tail apparatus.**
- The tail apparatus is a **contractile tail**, composed of an **inner core** (allows injection of viral DNA) and an **outer contractile sheath** (contracts during infection of bacteria).
- At the end of the tail is a **baseplate**, with attached **tail fibres** and **tail pins**. The base plate is the **point of attachment** to its **host cells** (i.e. *Escherichia coli*).
- T4 phage genome is a **linear, double-stranded DNA**. Hence, it is a **DNA virus**.

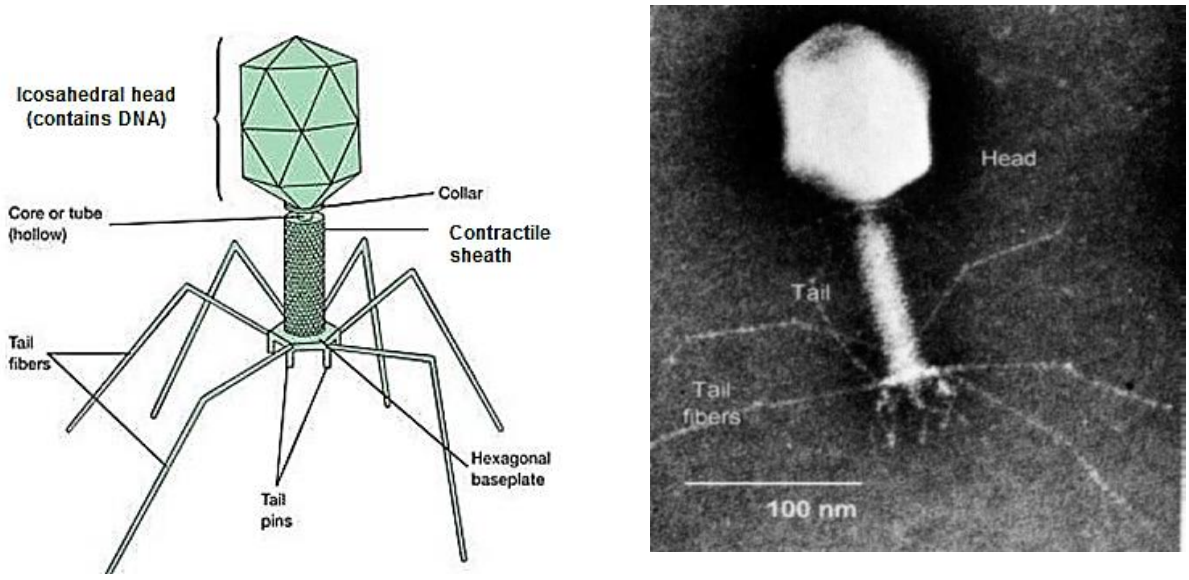


Fig. 3.1a: T4 bacteriophage structure.

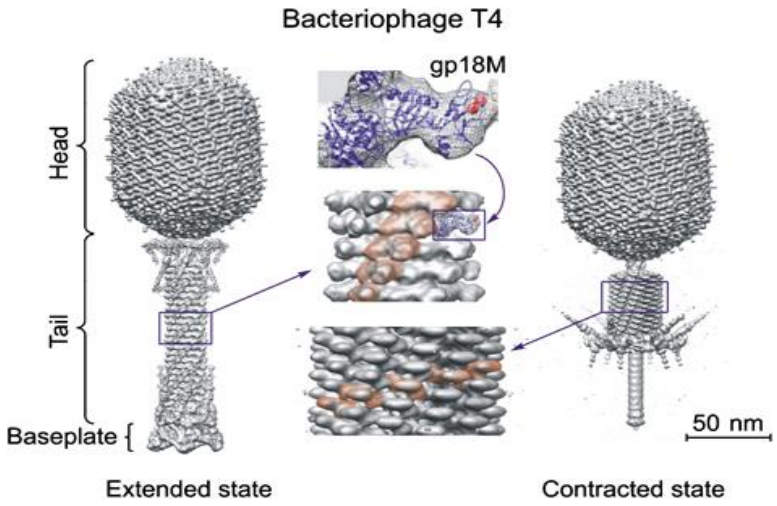


Fig. 3.1b: T4 bacteriophage in extended state (left) and contracted state (right).

3.1.2 Reproductive Cycle of T4 Bacteriophage: Lytic Cycle (Fig. 3.1c)

Candidates should be able to:

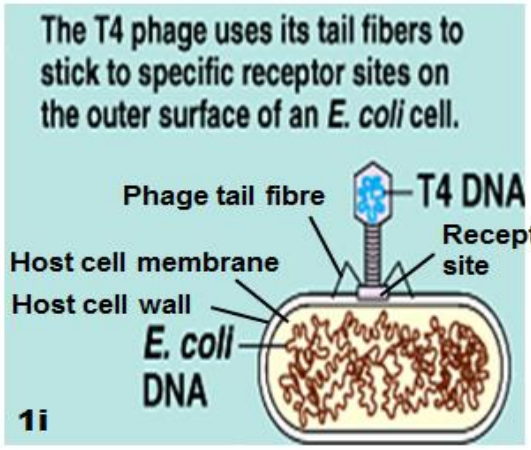
b) Describe how the genomes of viruses are inherited through outlining the reproductive cycles of:

i) Bacteriophages that reproduce via lytic cycle only, e.g. T4 phage

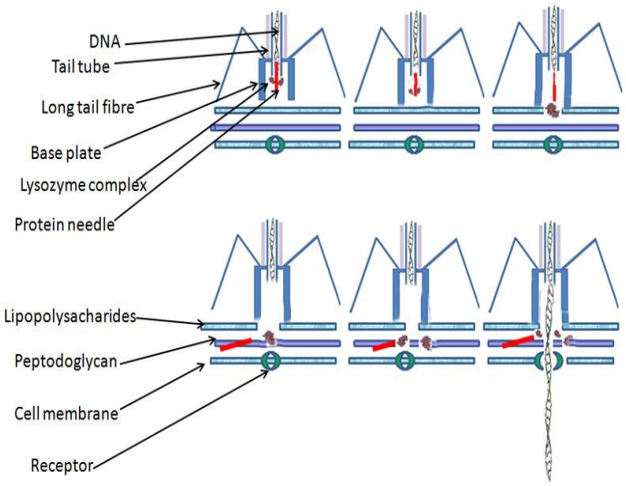
- A phage reproductive cycle that leads to the **death of the host cell** is known as a **lytic cycle**. This cycle typically produces 50-200 progeny (new viruses) in 30-40 minutes.
- A phage that reproduces **only by a lytic cycle** is known as **virulent phage.**
- The lytic cycle is divided into several stages:

1. Adsorption/Attachment Phase

i. **Tail fibres** of phage is **complementary in shape** to the **specific receptor sites** on the **host's cell surface** and bind to them.



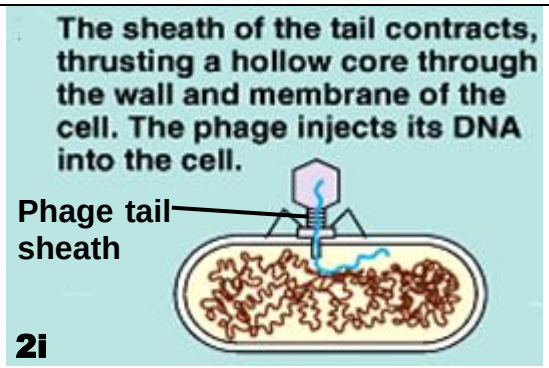
ii. Upon attachment, **lysozymes** are **released** from the tip of base plate to **degrade** a portion of the bacterial **cell wall**. This allows insertion of its tail core.



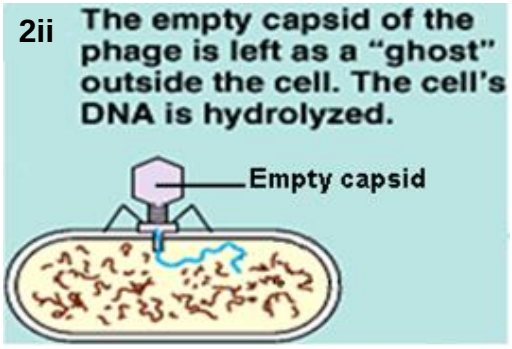
1ii

2. Penetration/Entry Phase

i. **Contractile sheath** of the tail **contracts** and **drives the hollow core through** the **bacterial cell wall and membrane**. This causes the **injection of phage DNA** into the host.



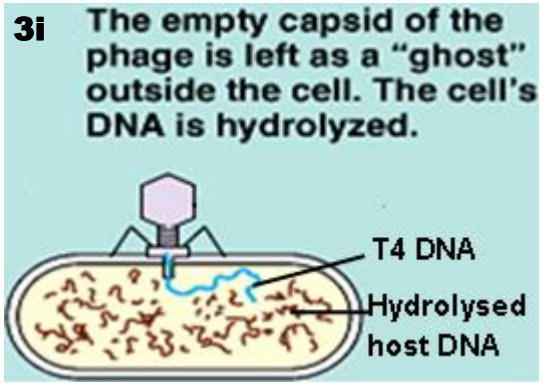
ii. The **empty capsid remains outside** the host cell.



3. Synthesis Phase

i. Synthesis of **early proteins** occur first.

- One of the first phage genes expressed codes for a **phage enzyme (DNase)** that **degrades the host cell's DNA.** This shuts down the synthesis of the bacterium's DNA, RNA, and proteins.
- Other phage genes expressed code for **proteins** that are needed to **replicate the phage DNA** (e.g. virus-specific DNA polymerase).



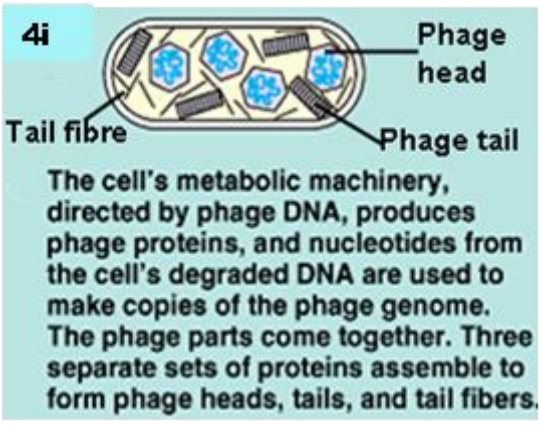
ii. Synthesis of **late proteins** occur next.

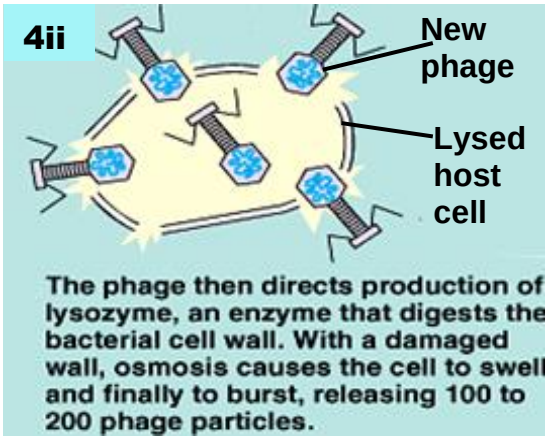
- The newly replicated copies of phage DNA is used for **transcription and translation** to make **structural proteins** (e.g. capsomeres and the various components of the tail).
- **Phage lysozyme** is also made and packaged into the tail of the phage (to allow it to escape from the host cell during the last step).

4. Assembly and Release Phase

i. Once phage proteins are synthesised, they self-assemble to form the capsid components (head, tail, tail fibres). The **phage DNA** is **packaged** into the **capsid** (**encapsidation**) as the head forms.

ii. **Phage lysozymes** are produced, and **digest** the **host's cell wall**. Damaged cell wall enables **entry of water** into the host bacterium cell **via osmosis**, causing it to **swell, lyse** and **release** numerous completed T4 bacteriophages to infect other cells.





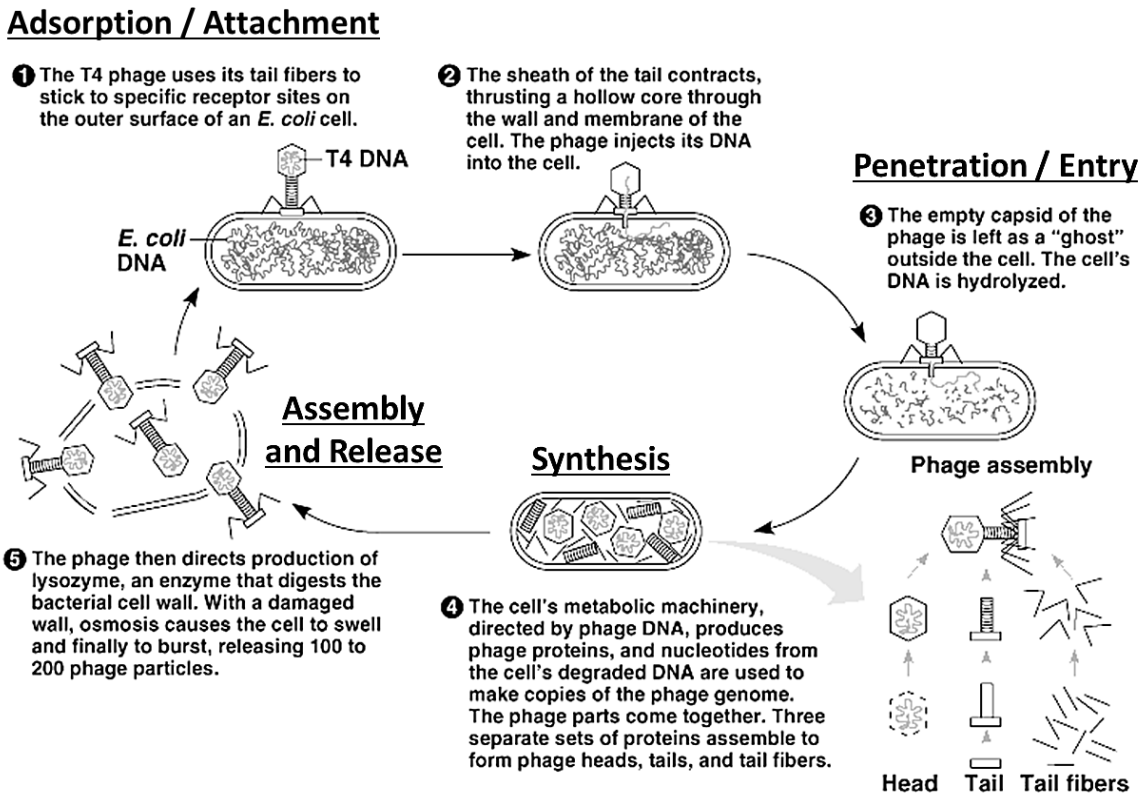


Fig 3.1c: Summary of T4 bacteriophage of the reproductive cycle (Lytic cycle).

3.2 Lambda Bacteriophage

3.2.1 Structure of Lambda Bacteriophage (Fig. 3.2a)

- **Lambda (λ) phage** is a **complex virus** with an **icosahedral capsid** and a **non-contractile tail sheath** consisting of a **single tail fibre.**

- Lambda phage genome is a **linear, double-stranded DNA** which can circularize in the host cell. Hence, it is a **DNA virus**.

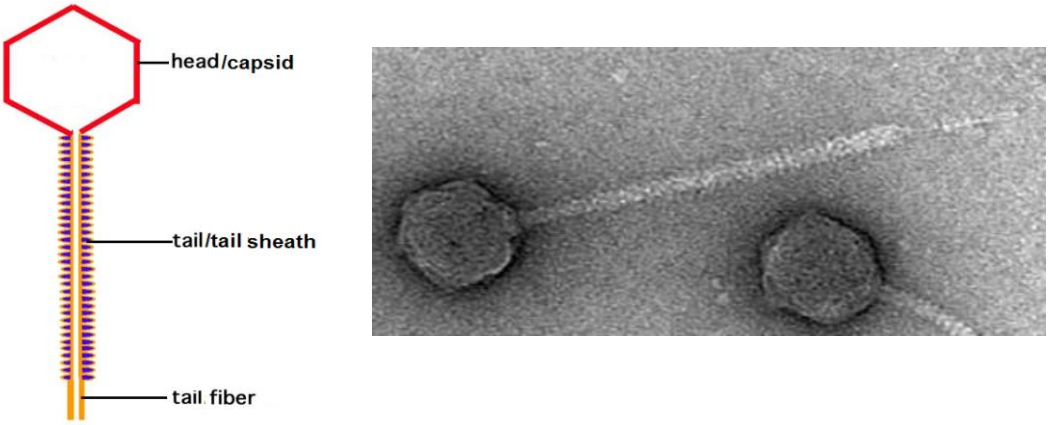
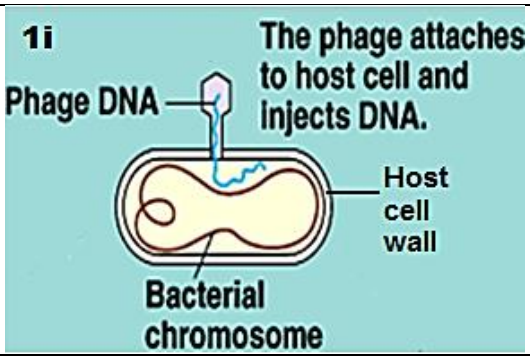
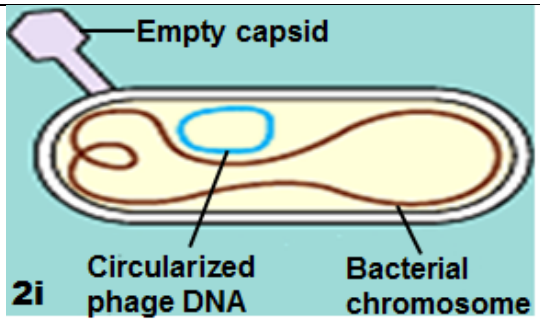


Fig. 3.2a: Schematic diagram (left) and an electron micrograph (right) of a lambda phage.

3.2.2 Reproductive Cycle of Lambda Bacteriophage: Lytic and Lysogenic Cycle (Fig. 3.2b)

Candidates should be able to:
b) Describe how the genomes of viruses are inherited through outlining the reproductive cycles of:
ii) Bacteriophages that reproduce via lytic and lysogenic cycles, e.g. lambda phage

- **Lambda (λ) phage** is a **temperate phage** as it is able to reproduce by **both** modes of reproductive cycles – **lysogenic and lytic cycles**.
- **Lytic** mode of reproduction is similar to that of T4 bacteriophage.
- During the **lysogenic** stage, the virus is **non-virulent** (i.e. does not kill the host cells). The **replication of phage genome** occurs **without destroying** the **host bacterial cells**.
- The lysogenic cycle is divided into several stages:

1. Adsorption/Attachment Phase	
i. **Tail fibre** of lambda (λ) phage has a shape **complementary** to the **specific receptor site** on the **host's cell surface** and binds to it.	
2. Penetration/Entry Phase	
i. The λ phage then **injects** its **DNA** into the **cytosol** of the **host cell**. Within the host, the **phage DNA circularizes**.	

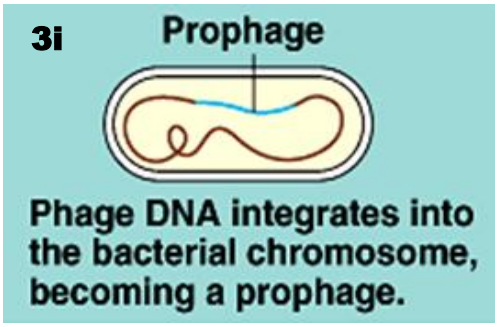
3. Genetic Integration Phase

i. The **circularized DNA integrates** into a **specific site** on the **host bacterial chromosome**. This is done by viral proteins that break both circular DNA molecules and join them to each other.

- At this stage, the **integrated viral DNA** is known as a **prophage**.
- The resulting **host cell containing the prophage** is known as the **lysogen**.

ii. In the prophage stage, **one prophage gene codes for a repressor protein** that **prevents the transcription of the most other prophage genes.** (e.g. genes coding for phage enzymes and proteins that cause cell lysis).

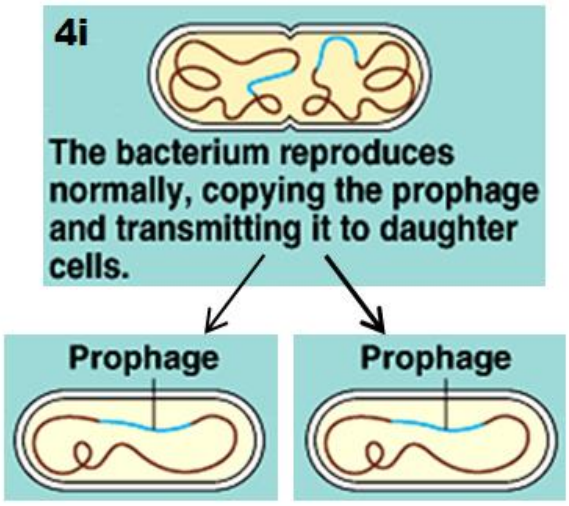
- Thus, the phage genome is mostly silent within the bacterium.



4. Replication Phase (of the phage genome)

i. Every time the **host cell** prepares to divide by **binary fission**, the **phage DNA** is **replicated along with the bacterial chromosome** and is passed on to daughter cells.

- Thus, a single infected cell can quickly give rise to a large population of bacteria carrying the virus in the form of prophages.
- This mechanism enables **viruses to propagate without killing** the **host cells**.



5. Induction Phase

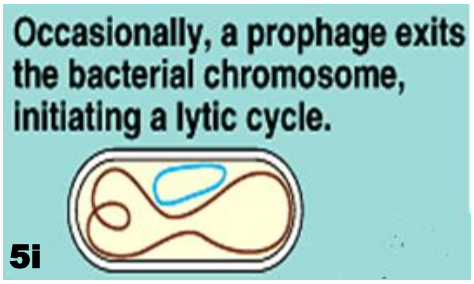
i. A **stressful environmental signal** (e.g. High-energy radiation, presence of certain toxic chemicals, lack of nutrients etc.) can trigger **induction** whereby the virus **switches** its replication mode **from lysogenic to lytic**.

ii. When this occurs, the **prophage is excised** from the host bacterial chromosome.

iii. Certain **proteases** are produced, **hydrolysing the repressor protein.** This allows the other prophage genes to be expressed.

iv. This results in the start of the **lytic cycle** (similar to that of T4 bacteriophage, *Section 3.1.2*).

- The Synthesis phase followed by the Assembly and Release phases would then allow new phage particles to be produced.



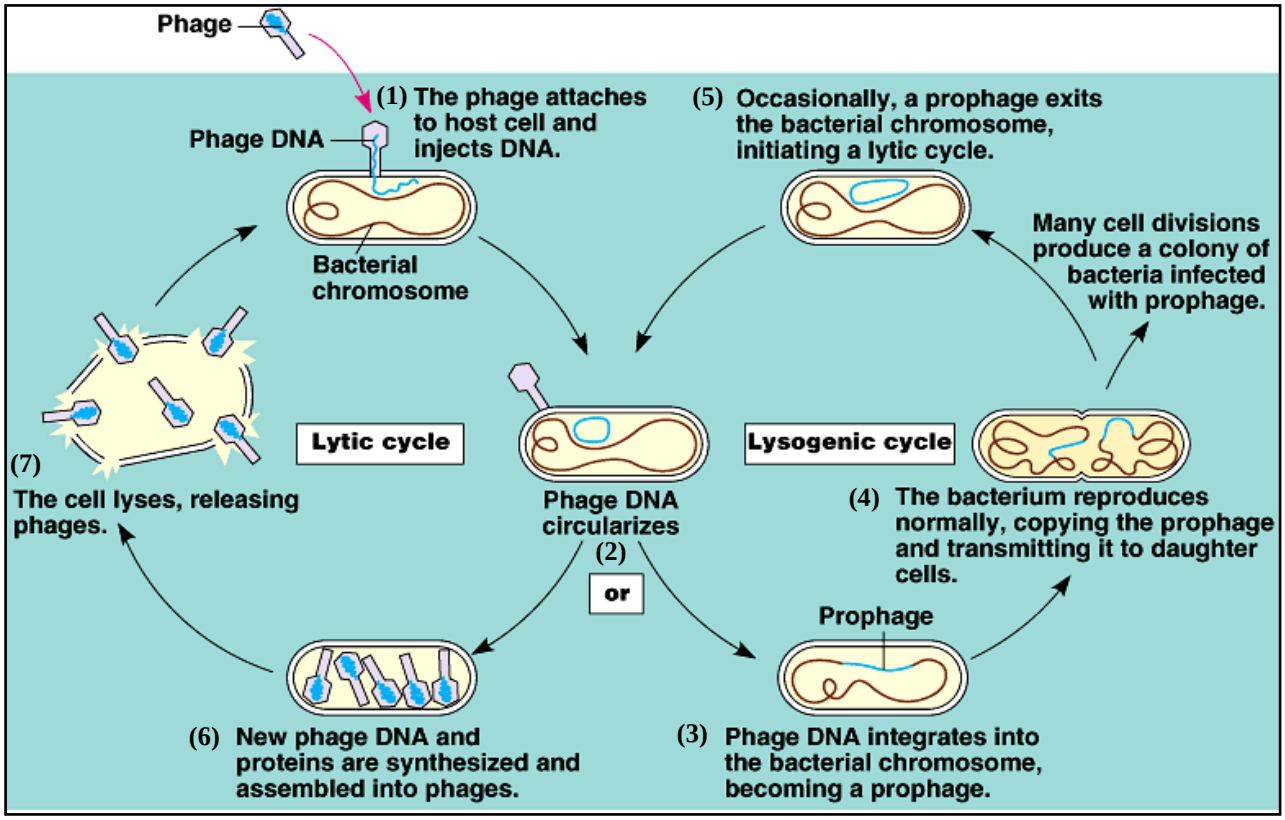


Fig. 3.2b: Replication cycle of the temperate phage: lytic and lysogenic cycle.

Table 2: Comparison between the virulent lytic cycle and a non-virulent lysogenic cycle

Similarities:

Features	
Recognition of host cells	Both involve recognizing and attaching of phages to specific receptor sites on the host's cell surface membrane.
Entry of phage DNA	Phage DNA is injected into the host

Differences:

Features	**Lytic Cycle**	**Lysogenic Cycle**
Effect on host genome	Host cell's DNA is hydrolysed by phage DNase. Phage DNA remains in cytoplasm.	Host cell's DNA is NOT hydrolysed. Phage DNA is integrated into host DNA / chromosome by genetic recombination, forming a prophage.
Replication of phage DNA	Phage DNA exploits host machinery to replicate phage DNA and proteins.	Phage DNA (prophage) replicates when host DNA replicates before host cell divides.
Release of new phages	Phage DNA and proteins assemble to form completed phages. Phage lysozyme weakens host cells wall. Resulting osmosis cause lysis of host to release new phages.	Prophage not released. Remains integrated with host DNA and does not exit host until it enters lytic mode.
Death of host cells	Occurs when cell lyse to release new phages.	Phage genome replicates without destroying host cell.

4. Animal Viruses

4.1 Influenza Viruses

- **Influenza**, commonly known as flu, is an infectious disease affecting mainly **birds and mammals** (eg. humans, pigs, etc)**.**

- Symptoms of disease: Fever, cough and severe muscle aches. Influenza virus can cause severe illness or death of **people at high risk** (e.g. young children, elderly, immunocompromised individuals). This is because:

    - Influenza **viral proteins** trigger the body's **immune response,** causing **inflammation** of the **epithelial linings of the airways.** Inflammation results in symptoms of the disease.

    - In severe cases, lung inflammation may develop into **pneumonia** (lung infection), as the airways are blocked by fluid and there is reduced clearance of infectious agents. This can result in **death.**

- Mode of transmission: They are commonly spread through **aerosols** (i.e. airborne).

- **Target cells**: Influenza viruses infect the **epithelial cells** of the **respiratory system** (e.g. nose, throat, lungs of mammals).

- Types: Influenza A, B, C and D (each with several strains).

    i. **Type A** strains cause severe illness and can infect people, birds, pigs and other animals. They are the only type to have caused **human pandemics** (global disease outbreak).

        - Within this strain, the influenza viruses are further categorized into **subtypes** based on the type of glycoproteins on the viral envelope, namely **haemagglutinin (HA)** and **neuraminidase (NA)**.

        - E.g. Influenza A H1N1 (Swine Flu) or Influenza A H5N1, H7N9 (Avian Flu)

    ii. Type B strains are normally found in humans and cause sporadic small scale outbreaks. These viruses are not classified into subtypes.

    iii. Type C strains cause mild illness in humans and no outbreaks in the population. These viruses are not classified into subtypes.

    iv. Type D strains primarily affect cattle. They are not known to infect or cause illness in people.

4.1.1 Structure of Influenza Virus (-ssRNA, enveloped virus) (Fig. 4.1a – 4.1c)

- A **viral envelope** (derived from the phospholipid bilayer of the plasma membrane of the host cell during budding) surrounds **eight helical nucleocapsids**, each made up of **nucleocapsid proteins associated with viral RNA.** The virus appears spherical in shape.

- The viral envelope has embedded **glycoproteins**.

  i. **Haemagglutinin (HA)**: For **binding** of viruses to **sialic acid / neuraminic acid-containing receptor sites** on the **surface membrane** of **target host cells** (i.e. involved in viral entry).

  ii. **Neuraminidase (NA)** (*aka* sialidase): An **enzyme** that **cleaves sialic acid / neuraminic acid residues** from the host cell surface, allowing the budding viruses to be **released** from infected cells (i.e. involved in viral release).

  ➢ *Note: When viruses gain entry into the host, these surface proteins are considered foreign (i.e. **antigens**) which are recognised by the host's immune system. The host's B lymphocytes (white blood cells) would produce **antibodies which bind to these antigens**.

  ➢ Also, viral antigens such as HA and NA can serve as **targets for antiviral drugs** (e.g. Tamiflu, an inhibitor of NA).

- The **viral genome** consists of **eight segments** of **linear (-) single-stranded RNA** wrapped around **nucleocapsid proteins** (also called nucleoproteins).

- The end of each RNA segment is attached to an **RNA-dependent RNA polymerase.**

  - These viral RNA-dependent RNA polymerases use the **(-) strand RNA as a template** to synthesize the complementary **(+) strand RNA**.

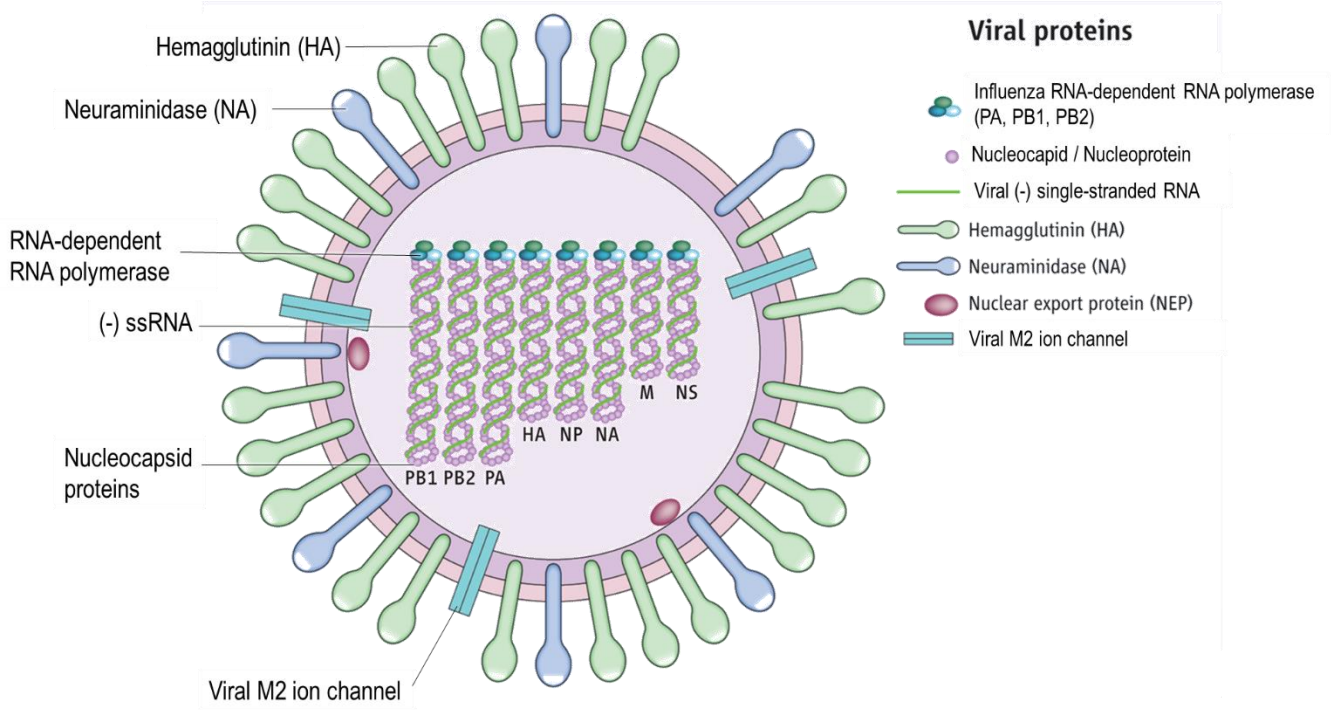


Fig. 4.1a: Generalized structure of an influenza virus.

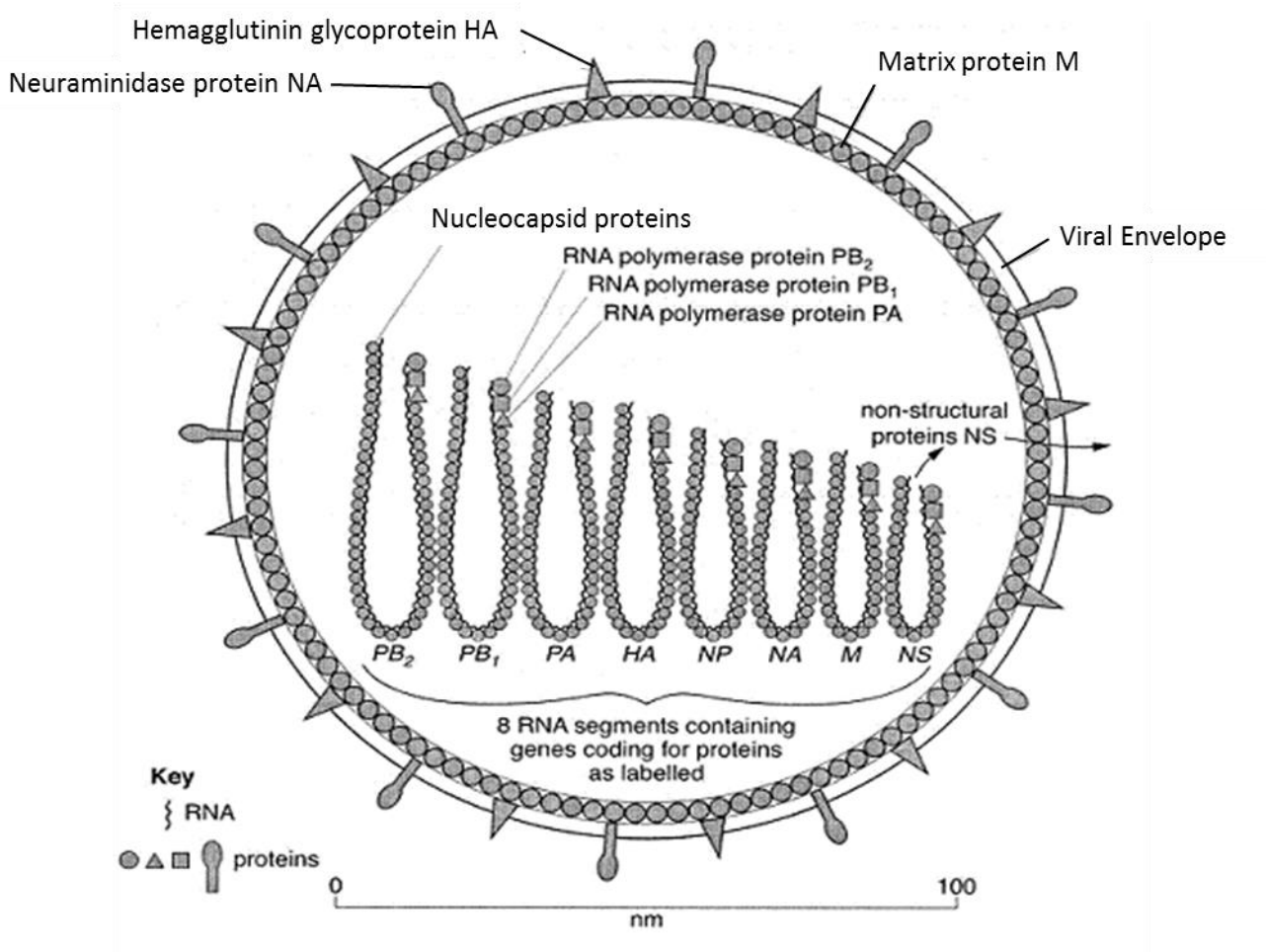


Fig. 4.1b: Detailed structure of the influenza virus.

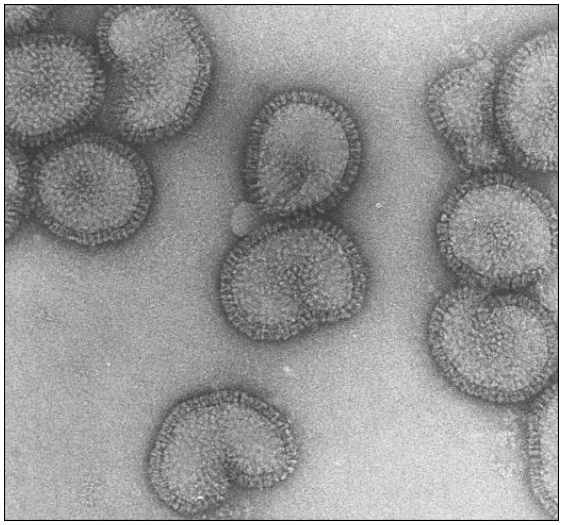


Fig. 4.1c: Electron micrograph of influenza virus.

4.1.2 Reproductive Cycle of Influenza Virus (Fig. 4.1g)

Candidates should be able to:
b) Describe how the genomes of viruses are inherited through outlining the reproductive cycles of:
iii) enveloped viruses, e.g. influenza

1. Attachment/Adsorption

- **Haemagglutinin glycoproteins (HA)** on the **viral envelope** recognize and **bind** to **specific, complementary receptor sites** (containing **sialic acid / neuraminic acid residues**) on the surface membrane of the **host epithelial cells** of the **respiratory system** (Fig. 4.1d).

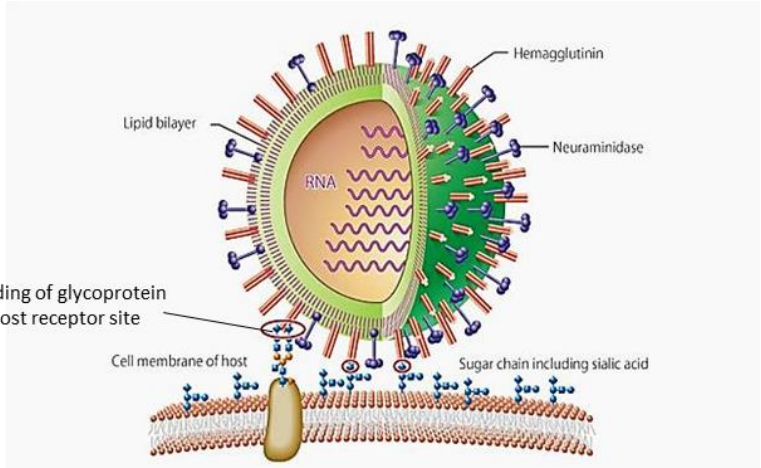


Fig. 4.1d: Glycoproteins on the viral envelope binding to specific complementary receptor proteins on the cell membrane of the host cell.

2. Penetration/Entry (Fig. 4.1e)

- The virus then **enters** the **host cell** via **receptor-mediated endocytosis**, where the host cell membrane forms an **endosome / endocytotic vesicle** around the virus.

- The endosome becomes **acidic**, and this environment triggers a conformational change in haemagglutinin protein, leading to the **fusion** of the **viral envelope** with the **endosomal membrane.**

- The **M2 ion channel** found in the **viral envelope** is important for also acidifying the interior of the virus. This triggers the **release of individual viral nucleocapsids** (from the matrix protein) into the **cytosol**.

- **Cellular enzymes** will then **digest** the viral **nucleocapsid proteins** to release the RNA segments (process is known as uncoating).

- The **viral RNA genome / RNA segments** then migrate to the **nucleus.**

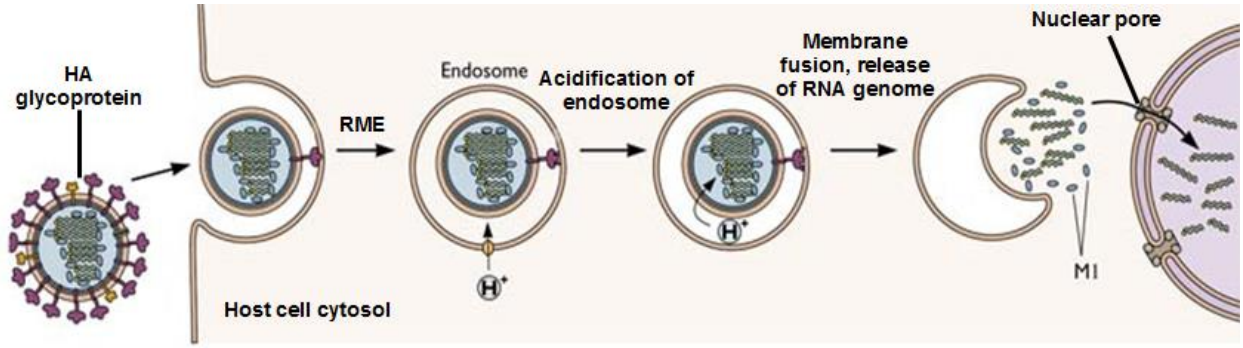


Fig. 4.1e: Influenza virus which enters host cell via receptor-mediated endocytosis (RME).

3. Synthesis (Fig. 4.1f)

- In the host nucleus, the **viral (-) single-stranded RNA** functions as a **template** for making **complementary viral (+) strand RNA**. This process is catalysed by the **viral RNA-dependent RNA polymerase** which is absent in the host cell.

- The **viral (+) strand RNA** (viral mRNA) then acts as a **template for**:

  - **Replication** of **new viral (-) single-stranded RNA genome** within the **nucleus**. This process is also catalysed by **viral RNA-dependent RNA polymerase**.

  - **Translation** into **viral proteins** (e.g. **nucleocapsid proteins / capsomeres** and **envelope glycoproteins**) using host machinery (e.g. **ribosomes**). This happens after the (+) RNA strands translocate out of the nucleus into the host **cytoplasm**.

    - The host's bound ribosomes synthesise the **viral glycoproteins (HA** and **NA)**, which become **part of the membrane** of the **rough endoplasmic reticulum** (**RER**) and **Golgi apparatus (GA)**. In the rER and GA, glycosylation and other biochemical modifications take place.

    - The **Golgi vesicles** with the **embedded glycoproteins** in their **membrane** are then transported to **host plasma membrane**. These vesicles then **fuse** with the host plasma membrane, and the glycoproteins are thus **incorporated** into the host plasma membrane.

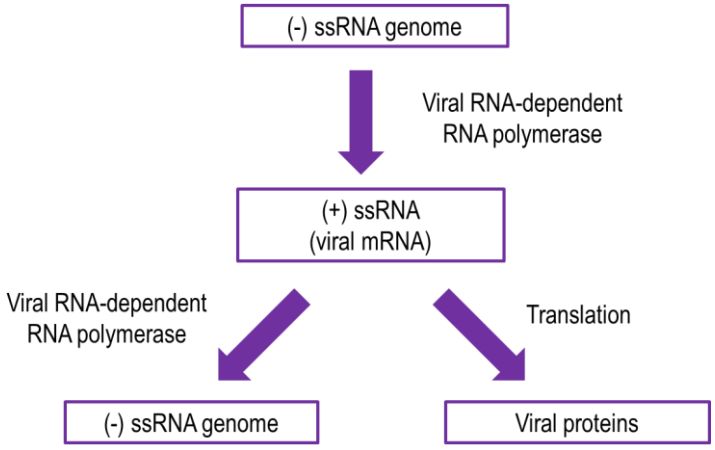


Fig. 4.1f: Summary on the synthesis phase of reproductive cycle of influenza virus

4. Assembly and Release:

- Nucleocapsid proteins and RNA-dependent RNA polymerases produced in the cytoplasm are transported back into the host nucleus.
- In the host **nucleus**, the **nucleocapsid proteins and RNA-dependent RNA polymerases** will associate with **each viral (-) RNA segment** to form **RNA-nucleocapsid protein complexes**. This process is known as **encapsidation**.
- The **newly-assembled RNA-nucleocapsid protein complexes migrate out into the cytoplasm** and then towards the **host cell membrane**, **where** the **glycoproteins HA** and **NA** are **incorporated**.
- As the virus **buds off** *(Reject: "exocytosis")* from the host cell, it is **enclosed by host's plasma membrane** (consisting of the viral glycoproteins), which then forms the **viral envelope.**
- **Neuraminidase** is then able to play the final role in virus budding – **cleaving the sialic acid / neuraminic acid residues** from the host cell surface membrane receptors, thus releasing the new viral particles from the infected host cells.
- Budding **itself does not necessarily kill the host cells** (as opposed to lysis in the lytic cycle of phages), but eventually, the host cell will die due to **depletion of energy and resources.**
- The enveloped viruses are now free to infect other epithelial cells.

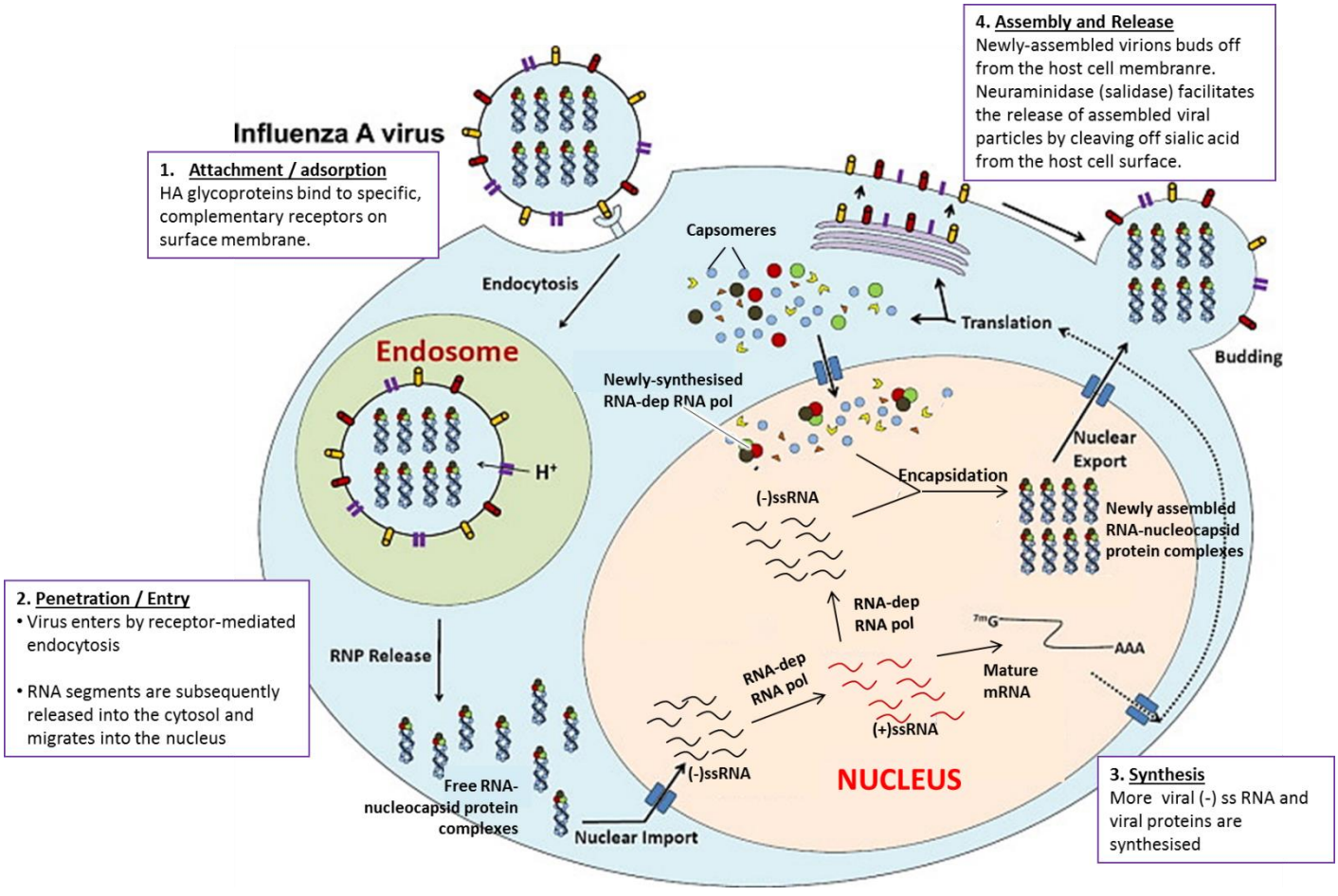


Fig 4.1g: Reproductive cycle of influenza virus.

4.2 Human Immunodeficiency Virus (HIV) (+ssRNA, enveloped virus)

- HIV infection represents the early stages of infection of an individual by HIV and is a progressive disease. As HIV gradually attacks the immune system, a weakened immune system results, leading to **acquired immunodeficiency syndrome (AIDS).**

- Symptoms: **Opportunistic infections** (E.g. pneumonia) caused by other pathogens (e.g. bacteria, other viruses, fungi and parasites), due to a weakened immune system. This is because:

    - Replication of HIV in CD4 / helper T lymphocytes eventually kills the T lymphocytes (e.g. by triggering **apoptosis**). As more HIV particles are released into the blood and more T lymphocytes are infected, **T lymphocytes decrease in number**, thus compromising the immune system.

    - **B lymphocytes** produce antibodies with the help of T lymphocytes. With the decrease in T lymphocytes, **less antibodies** are produced to bind to pathogens (e.g. bacteria) to facilitate their destruction.

    - Note: Random integration of viral DNA into the host genome may also disrupt tumour suppressor genes (e.g. p53 gene), leading to cancer.

- Mode of Transmission:

    - Direct exposure of a person's blood to **body fluids** containing the virus (blood, semen, vaginal secretions) (e.g. sexual contact or contaminated needles).

    - From an infected mother to her baby via breastfeeding or during childbirth.

- Target cells:

    - **CD4 T lymphocytes** (i.e. white blood cells)

    - **Macrophages**

- It is a **retrovirus**:

    - "Retro" means backwards which refers to the reverse direction in which genetic information flows for these viruses (i.e. from RNA to DNA).

    - This is because HIV carries an enzyme called **reverse transcriptase**, which serves to form **double-stranded viral DNA** from **(+) single-stranded RNA viral genome**. It is able to do so as the reverse transcriptase consists of the following activities (Fig. 4.2a):

        i. **RNA-dependent DNA polymerase activity** → forms **single-stranded complementary DNA (cDNA)** from a **(+) single-stranded RNA template.**

        ii. **RNAse activity** → **removes single-stranded RNA** from the viral **RNA-DNA hybrid.**

        iii. **DNA-dependent DNA polymerase** → uses the **single-stranded cDNA** as template to form **double-stranded viral DNA.**

- **Reverse transcription** is **prone to errors** and the enzyme **reverse transcriptase does not proofread.** Hence errors and **new mutations** are introduced during this process. This is one reason why HIV is difficult for the immune system to eliminate (e.g. shape of viral surface proteins (e.g. gp120) is altered, so the antibodies that are made against the earlier strains of HIV can no longer bind).

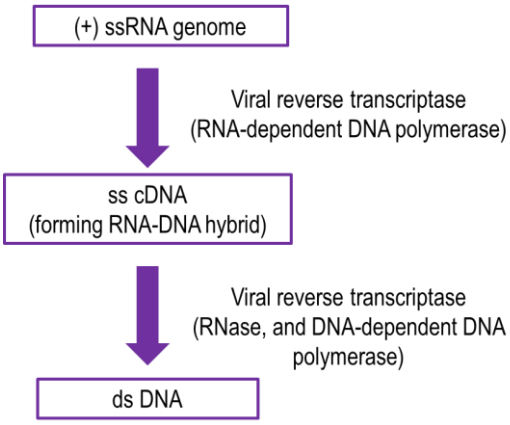


Fig. 4.2a: Synthesis of double-stranded DNA from (+)ssRNA strand using retrovirus reverse transcriptase

4.2.1 Structure of HIV (Fig. 4.2b – 4.2c)

- HIV consists of an **envelope** (derived from the phospholipid bilayer of the plasma membrane of the host cell during budding).
- The envelope has embedded **glycoproteins** (spikes) - **gp120** and **gp41.** Both are involved in **viral entry.**
- The **envelope** surrounds a **cone-shaped capsid**, which in turns encloses:
  i. **Two copies** of **linear, (+) single-stranded RNA** associated with nucleocapsid proteins.
  ii. **Two copies** of **reverse transcriptase.**
  iii. Other viral enzymes, **integrase** and **protease**.

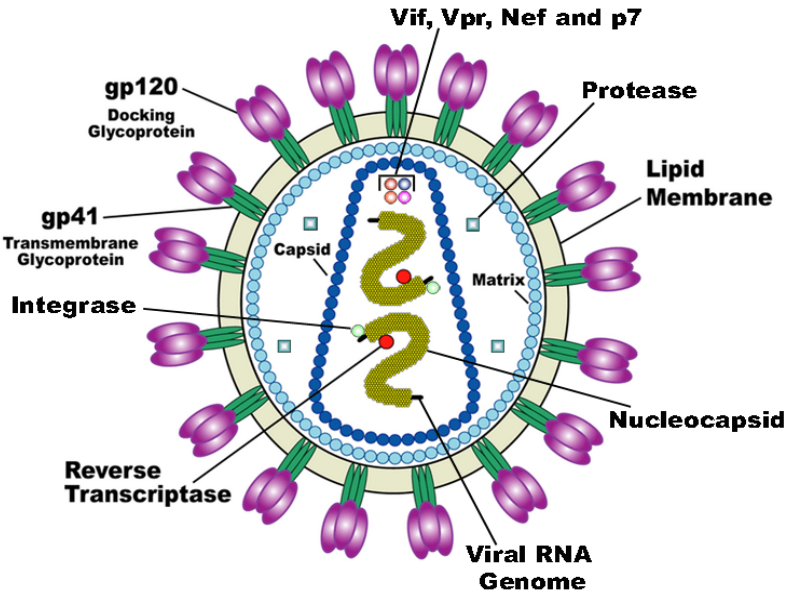


Fig. 4.2b: Diagram of HIV.

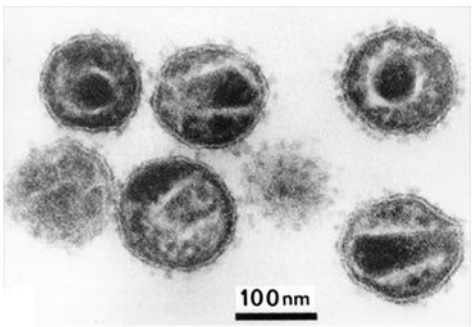


Fig. 4.2c: Electron micrograph of HIV.

4.2.2 Reproductive Cycle of HIV (Fig. 4.2h)

Candidates should be able to:
b) Describe how the genomes of viruses are inherited through outlining the reproductive cycles of:
iv) retroviruses, e.g. HIV

1. **Adsorption/Attachment** (Fig. 4.2d-e)

- Once HIV enters the bloodstream, it circulates throughout the body. However it only infects susceptible host immune cells.
- **Glycoprotein <u>gp120</u>** of HIV **binds specifically** to a **complementary host cell surface <u>receptor protein</u>, <u>CD4</u>** (involved in immune recognition). CD4 is present on the surface membrane of many immune cells such as helper / CD4 T lymphocytes and macrophages.
- HIV entry also requires a **co-receptor** on the host cell membrane, either CCR5 or CXCR4.
  - HIV variants that bind to **CXCR4 co-receptors** infect **helper/CD4 T lymphocytes.**
  - HIV variants that bind to **CCR5 co-receptors** infect **macrophages.**

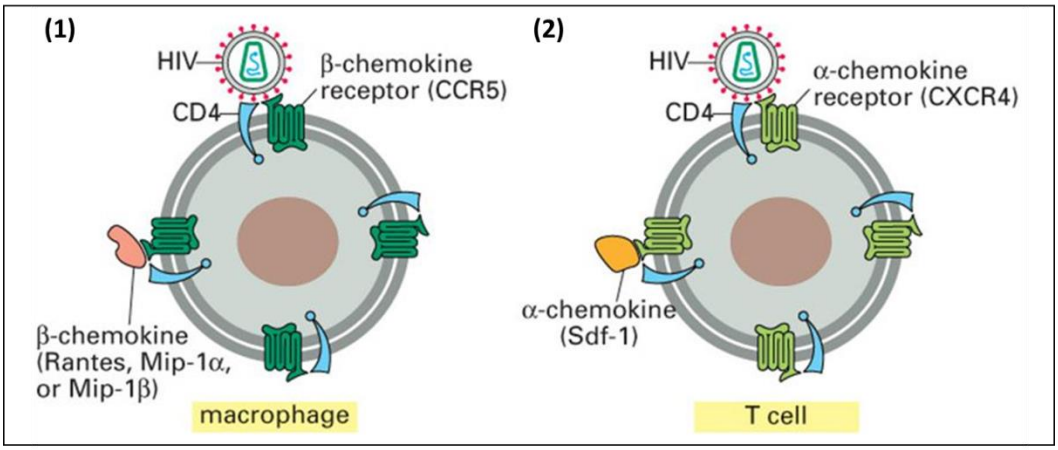


Fig. 4.2d: (1) Binding of HIV to CD4 receptor and CCR5 co-receptor on macrophage. (2) Binding of HIV to CD4 receptor and CXCR4 co-receptor on T lympmphocyte.

- Binding of gp120 to receptors and co-receptors triggers a **conformational change** in the viral envelope protein to **expose** a normally buried **fusion peptide, gp41**. Glycoprotein gp41 mediates the **<u>fusion</u>** between the **viral envelope** and **host cell surface membrane**.
- After fusion, the cone-shaped capsid is separated from the envelope.

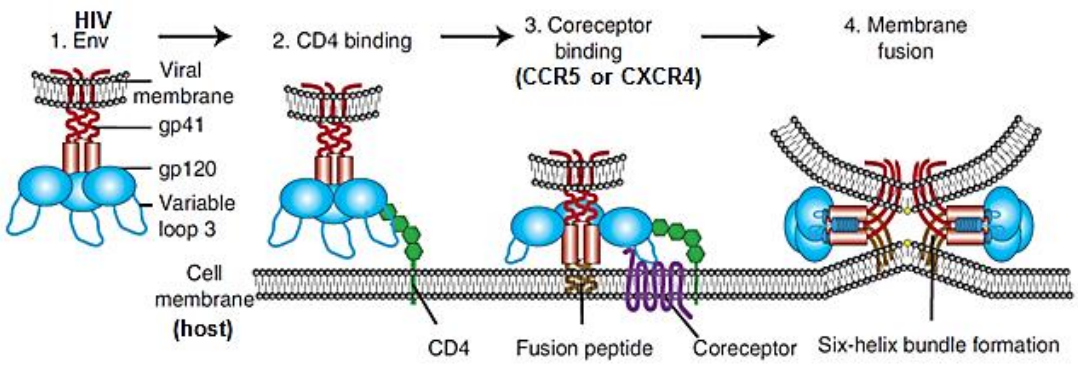


Fig. 4.2e: HIV enters host cell via fusion between the viral envelope and the host cell surface membrane.

2. **Penetration/Entry**

- Once inside the host cell, **the capsid proteins** are **digested** by **cellular enzymes,** causing **viral RNA** and **viral enzymes** to be **released**. This process is called **uncoating.**

- In the **cytoplasm**, reverse transcription occurs, catalysed by viral **reverse transcriptase**.

  - The viral **(+) single-stranded RNA (ssRNA)** is used as the **template** to synthesize a **complementary single-stranded DNA (cDNA)** by **RNA-dependent DNA polymerase**.

  - The **ssRNA** is then **removed** from the RNA-DNA hybrid by **RNase**.

  - The **single-stranded cDNA** is then used as a **template** to synthesize a **linear double-stranded DNA** by **DNA-dependent DNA polymerase**.

3. **Integration**

- The newly formed **double-stranded DNA** migrates to the **nucleus** and **integrates into** the **host genome**. This process is catalysed by the viral **integrase**. The viral double-stranded DNA becomes a **permanent** part of the host cell genome.

- Once integrated, the viral DNA is known as a **provirus**.

- The host CD4 T lymphocytes can be activated to undergo cell division ("clonal expansion"). This enables the provirus to be **replicated** along with the host cellular DNA.

- The provirus can remain **latent / dormant** (i.e. undetected by the immune system as it does not assemble into infectious viral particles) within a cell for a long period of time. This is why AIDS patients typically show clinical symptoms only after a long latency period of 8-10 years.

4. **Synthesis and assembly**

- When the **host CD4 T lymphocytes** are **activated** (stimulated during an immune response), the **integrated proviral DNA** is **transcribed** by **host DNA-dependent RNA polymerases** into **viral mRNA** molecules within the nucleus of the host cell.

- The viral (+)mRNA formed serves as:

  i. **new viral genome** (to be incorporated into new viruses), which will then associate with nucleocapsid proteins.

  ii. **template** for **translation** (by host ribosomes on rough ER) into **viral polyproteins** (i.e. a large protein that is cleaved into smaller proteins with different functions).

Note: **HIV mRNA** is **polycistronic** (i.e. one mRNA → many proteins) (Fig. 4.2f).

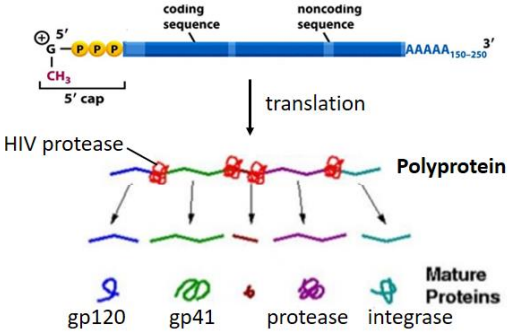


Fig. 4.2f: HIV mRNA is polycistronic.

- The **viral polyproteins** are then **cleaved** by **<u>HIV protease</u>** to form **functional viral proteins** including:

  - Structural proteins (e.g. capsid proteins, envelope glycoproteins, viral enzymes)
  - Non-structural proteins

- Once the viral **glycoproteins <u>gp120</u>** and **<u>gp41</u>** are biochemically modified in the **rER** and **GA**, they are **transported** by **Golgi vesicles** to the **plasma membrane** of the host cell. When membrane of Golgi vesicle **fuses** with the host cell plasma membrane, these **glycoproteins** are **incorporated** into the latter.

- The **two linear (+) single-stranded RNA genome, two reverse transcriptase molecules**, **HIV protease** and **integrase enzymes** are **encapsidated** by the **capsid proteins / capsomeres.**

5. **Release**

- The newly assembled **cone-shaped capsid and its contents will migrate** to the **host cell plasma membrane**, **where the viral glycoproteins gp120 and gp41 are incorporated**, and **<u>bud off</u>** to form new viruses.

- Viruses take away part of the **host cell plasma membrane** (containing gp120 and gp41) to **form** the **viral envelopes**.

- Budding itself **does not necessarily kill the host cell**, but eventually, the host cell will die due to **depletion of energy and resources.**

- The new viral particles are ready to infect other cells.

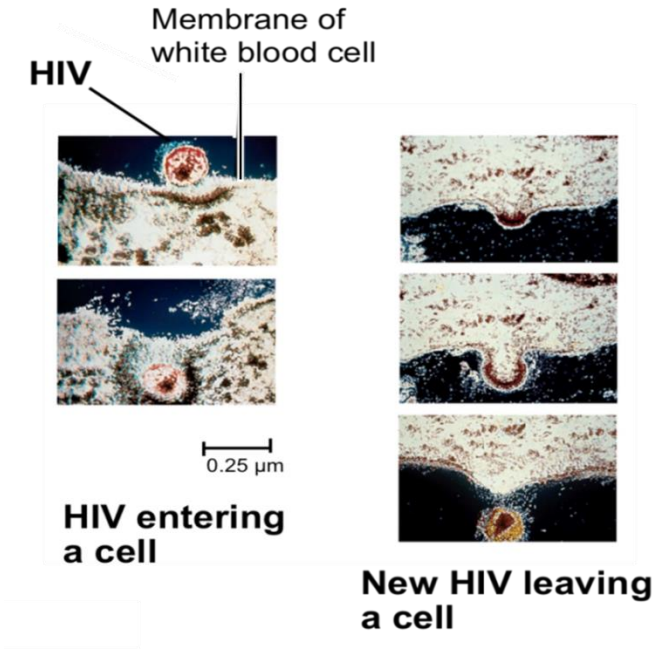


Fig. 4.2g: Electron micrograph of HIV infecting a white blood cell.

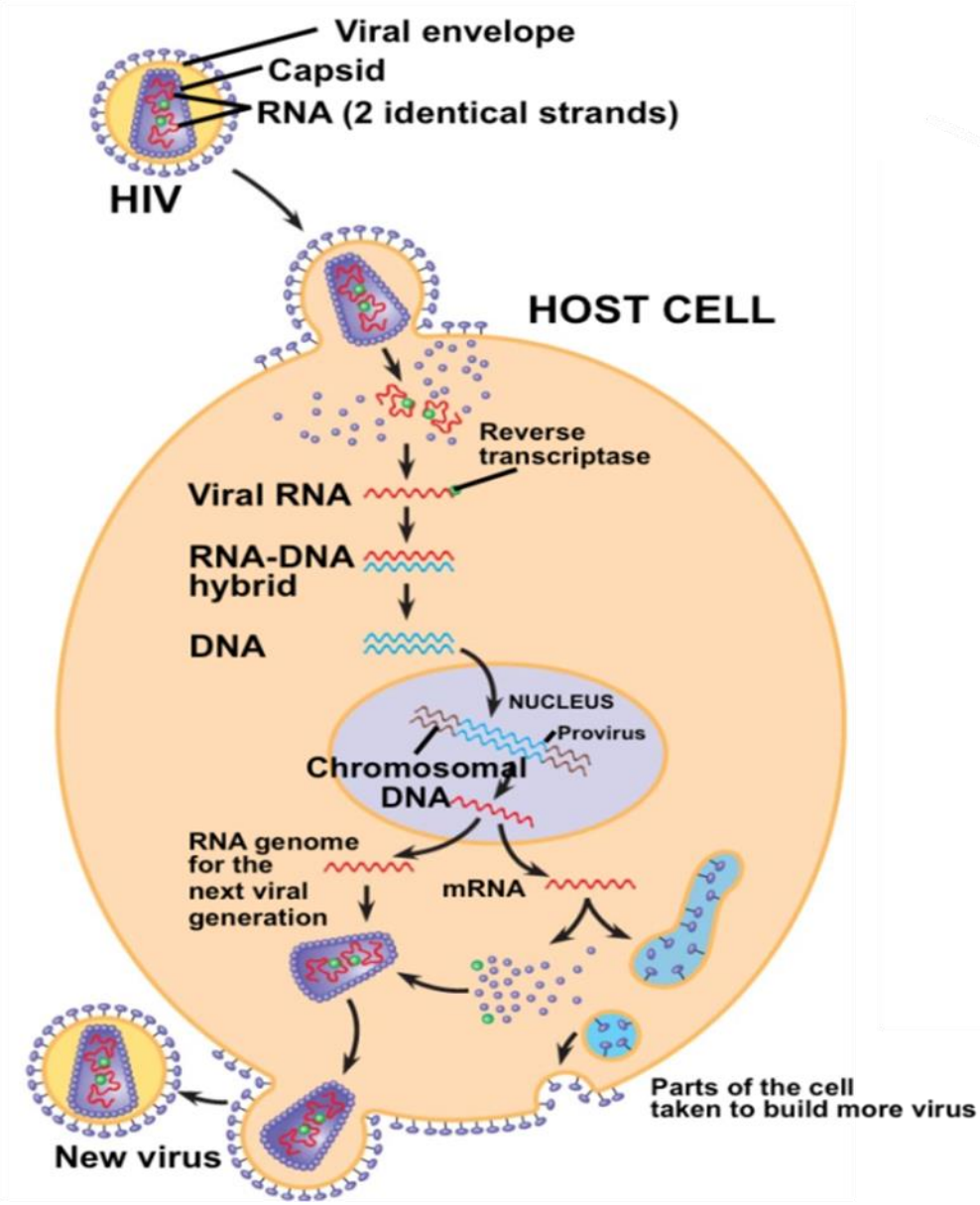


Fig 4.2h: Annotated summary of the reproductive cycle of the HIV

4.3 Treatment of viral diseases

4.3.1 How viral infections cause disease

(Details to be covered under the Topic: Immunity and Infectious Diseases)

Key Concept 5:
Viral infections cause diseases in the host by disrupting host tissues and functions.

- Viruses cause disease in different ways:

  1. Direct cell damage and death may result from:

     - Inhibition of normal host cell functions (DNA/RNA/protein synthesis) **depletes** the **host cell** of **cellular materials** (e.g. amino acids, nucleotides) essential for normal functions of the cell. This may cause structural or functional defects in the infected host cells.

     - Some **viral gene products** are **toxic**, causing cell injury directly. For example, the viral NSP4 protein of rotaviruses causes gastroenteritis and diarrhea in the host.

  2. Indirect cell damage may result from:

     - **Attachment** of **viral proteins / glycoproteins** (i.e. antigens) to the infected host cell surface membrane. This may result in an **immune response** as the infected host cell may be recognised as **foreign**, and are thus destroyed by the body's immune defences. Many of the temporary symptoms associated with viral infections, such as fever and aches, are a result of the body's efforts at defending itself against infections.

     - **Integration of viral genome** may result in certain types of human **cancer** (e.g. due to insertion of an oncogene or disruption of a tumour suppressor gene). For example, there are strong evidences showing the close association between Hepatitis B and C (HBV and HCV) and liver cancer, and Human papillomavirus (HPV) with cervical cancer.

- The **extent of damage** a virus causes depends partly on the ability of the **infected tissue** to **regenerate** by cell division.

  - People **usually recover** completely from colds because the epithelium of the respiratory tract can efficiently repair itself.

  - However, damage inflicted by poliovirus to mature nerve cells is **permanent** because these cells do not divide and usually cannot be replaced.

4.3.2 Overview of treatment strategies

Key Concept 6:
Treatment of viral diseases targets the reproductive cycle of the virus.

- Viruses are non-living and therefore viral diseases **cannot be treated** with **antibiotics** that kill bacteria (e.g. tetracycline, which inhibits bacterial ribosomes).

- Instead, **antiviral drugs** targeting the **replication cycle** of the virus are administered. The aim is to suppress the replication so as to reduce the number of virus particles in the blood (viral load).

- Examples of antiviral drugs include:

i. **Vaccines**
   - **Harmless versions** of a **specific virus** (e.g. weakened virus, heat-killed virus, subunit of a virus, inactivated toxins produced by virus).

   - They act as an **antigen** which stimulates an **immune response** (i.e. **antibody production** against the antigen). This will constitute **future defence,** as when the body encounters the actual virus in future, the immune system will recognise and eliminate the virus quickly (Fig. 4.3a) *(Refer to topic: Immunity and Infectious Diseases).*

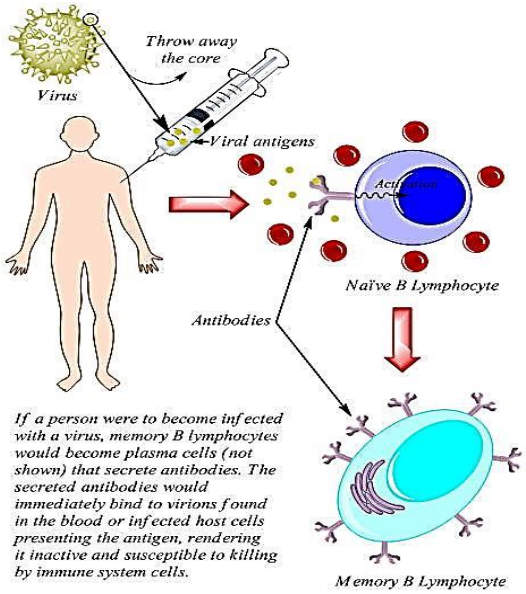


Fig. 4.3a: Mechanism of action of vaccines.

ii. **Nucleotide mimics/analogues** (Fig. 4.3b)
   - **Inhibit viral DNA polymerases / RNA polymerases / reverse transcriptases.**

   - These **prevent replication of viral genome** and **synthesis of viral proteins**.

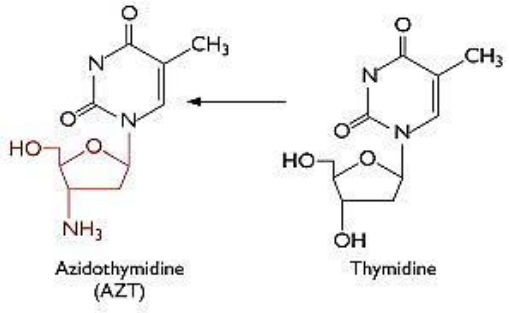


Fig. 4.3b: Azidothymidine (AZT) is used to curb HIV replication. It is a thymidine analogue that works by interfering with the synthesis of viral DNA by viral reverse transcriptase.

iii. **<u>Protein inhibitors</u>** (Fig. 4.3c – 4.3d)

- Viral **glycoprotein inhibitors** → prevent entry (e.g. Enfuvirtide inhibits **HIV gp41**, hence prevents fusion/entry of virus) or release (e.g. Oseltamivir/Tamiflu inhibits **neuraminidase** of the **influenza virus**, hence prevents new viral particles from being released from the host cell)

- Viral **ion channel inhibitor** (e.g. Amantadine inhibits **influenza M2 channel protein**, hence prevents uncoating of the virus to release the viral genome)

- Viral **enzyme inhibitor** (e.g. Ritonavir inhibits **HIV protease**, hence prevents the production of functional viral proteins; Raltegravir inhibits **HIV integrase**, hence prevents the integration of viral DNA into the host genome.)

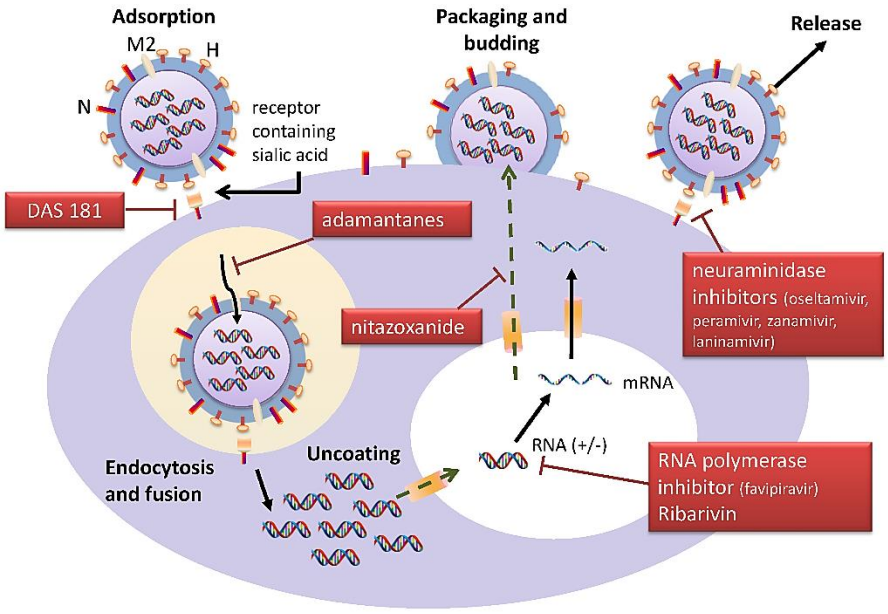


Fig. 4.3c: Treatment options for influenza.

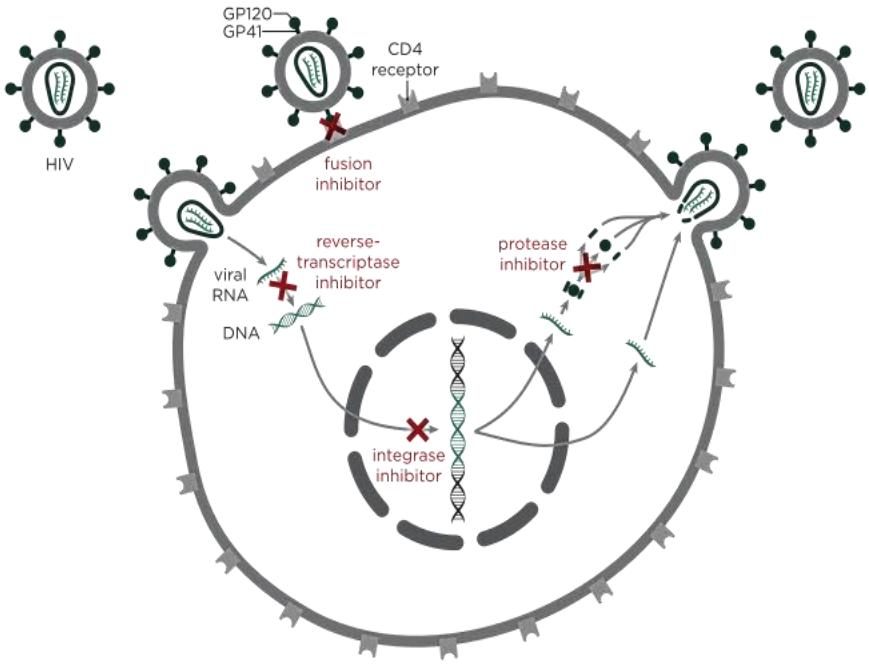


Fig. 4.3d: Antiviral therapy options to suppress HIV replication. Usually the HIV treatment consists of antiviral drug "cocktails" comprising of at least three antiviral drugs (usually a combination of two nucleoside mimics and a protease inhibitor). As HIV genome mutates very quickly, taking more than one drug helps to prevent drug resistance, allowing the drugs to be used for a longer time.

5. Variation in viral genome

Candidates should be able to:
c) Describe how variation in viral genomes arises, including antigenic shift and antigenic drift.

- Viral diseases may lead to an **epidemic** (a disease occurring in an unusually high number of individuals in a population at the same time – e.g. SARS) or a **pandemic** (a worldwide epidemic – e.g. Influenza).

- This is because viral genomes can exhibit **genetic variation, thus altering viral structure**. For example, a new Influenza A subtype occasionally emerges, causing a flu pandemic as the human population has little to no immunity against it.

- The viral genome changes due to two mechanisms:
  - Antigenic drift
  - Antigenic shift

  Note: "Antigenic" refers to antigens (proteins on the viral surface) that cause the host immune system to respond.

5.1 Antigenic Drift (Fig. 5.1a)

- It is a **gradual** process (i.e. occurs over a longer period of time).

- It involves **minor mutations** to the **genes encoding the viral surface glycoproteins** (e.g. influenza HA and NA which are involved in attachment and release of virus from host cells respectively).

- One or more amino acids are changed, hence the **shape of the glycoproteins** (antigens) are **slightly modified**. This makes it different from previous strains, hence it is necessary to reformulate the flu vaccine every year.

5.2 Antigenic Shift (Fig. 5.1b)

- Antigenic shift can **only** occur in viruses with **segmented genomes**, with genes found on each distinct segment (e.g. influenza virus).

- It is a **sudden** process.

- It involves a **major change to the viral surface glycoproteins** (e.g. influenza HA and NA which are involved in attachment and release of virus from host cells respectively). This is not caused by a gene mutation but by a genetic exchange process. Entirely novel antigens are created.

- Process:

  - **More than one strain of virus infects the same host cell** (i.e. co-infection) - this is possible as some species (e.g. pig – the "mixing vessel") are capable of being infected by different types of the virus. HA and NA from different strains of virus would be incorporated in the viral envelope of the new virion (surface antigens).

  - **Genetic reassortment** occurs (i.e. segmented viral genome from different strains of virus are mixed together) during the process of viral replication.

- The progeny virus has **segments of genome from different strains of parental viruses**. Hence, the progeny virus will have a **mixture of the surface antigens of the different strains of parental viruses**, forming a **new subtype**.

- E.g. If a human H3N2 influenza virus and an avian H7N3 influenza virus infect the same host cell, genetic reassortment can occur. The progeny virus can contain H7 from the avian virus and N2 gene from the human virus, making a subtype H7N2 that is different from the two original viruses. The new subtype may have pandemic potential (Fig. 5.1c).

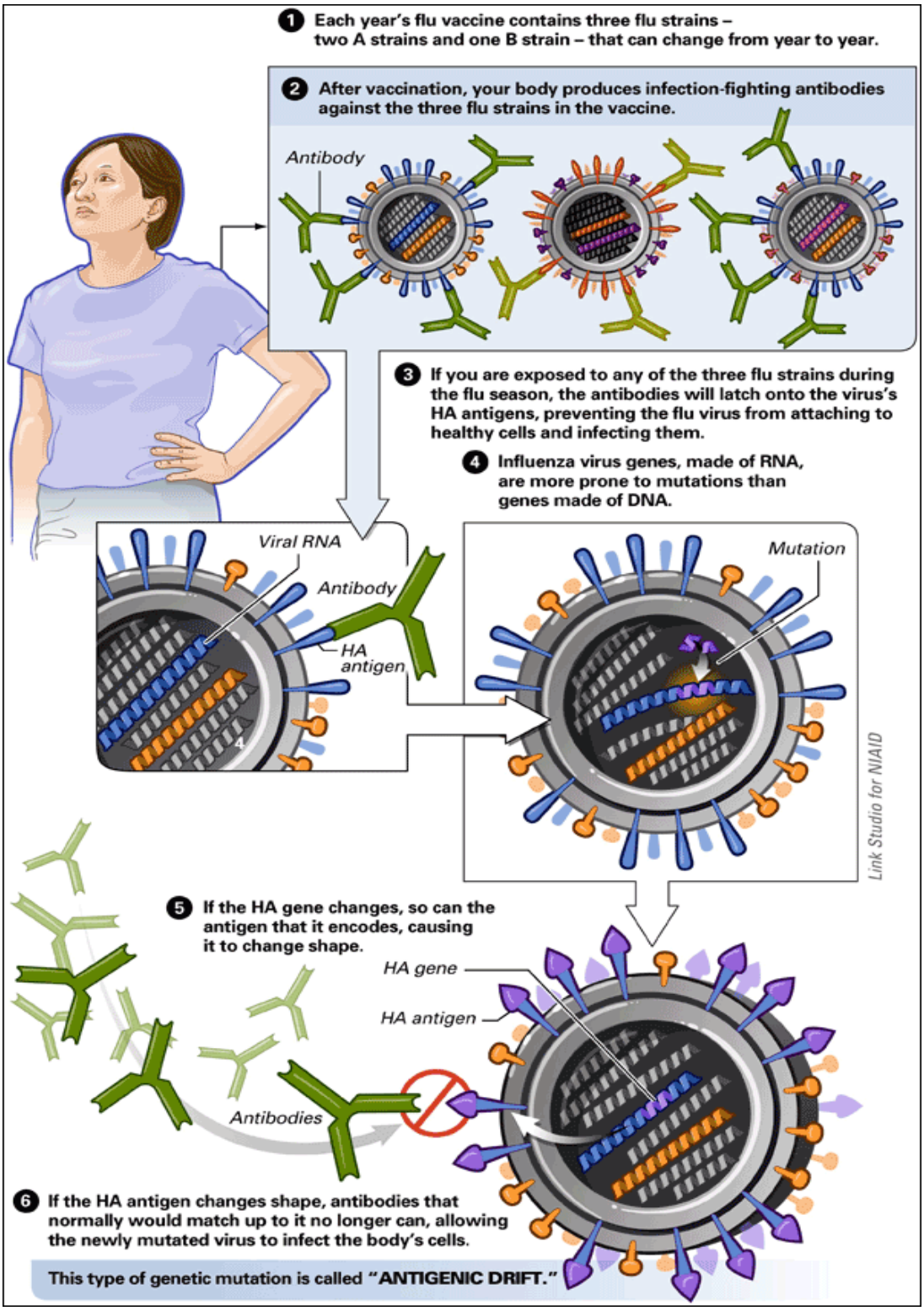


Fig. 5.1a: Antigenic drift involves genetic mutation.

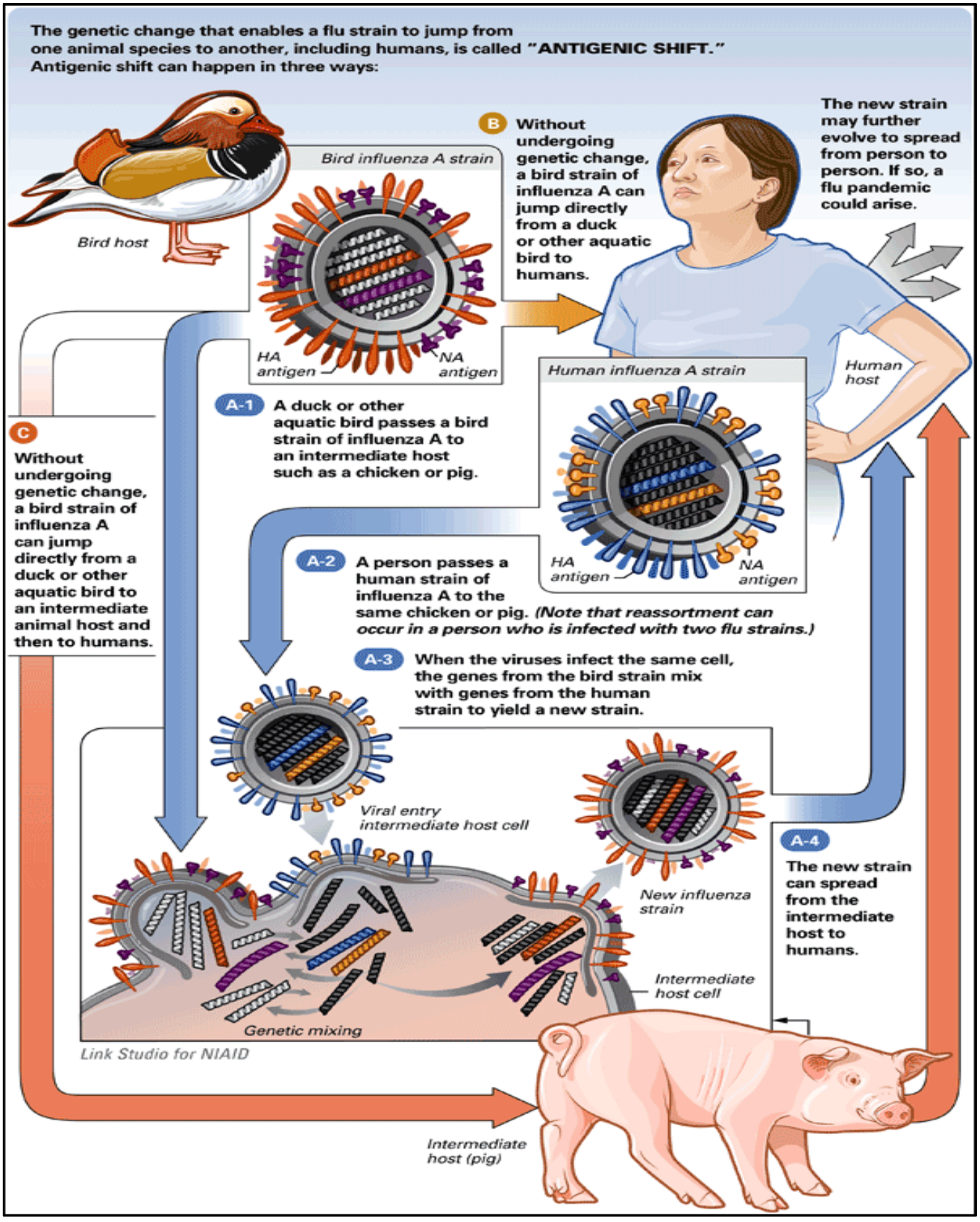


Fig. 5.1b: Antigenic shift involves genetic reassortment.

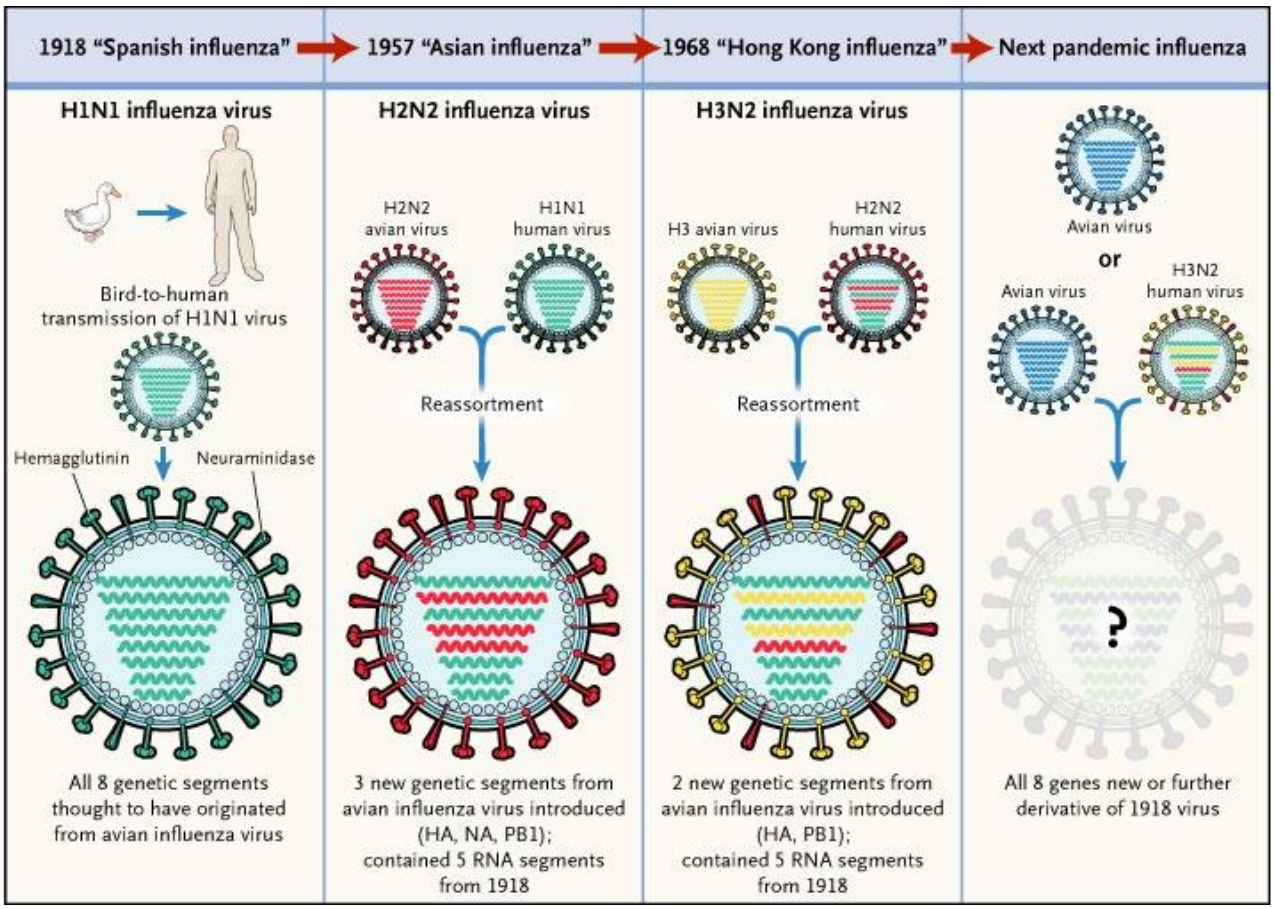


Fig. 5.1c: How antigenic shift in influenza virus can lead to pandemics.

Checklist

(Use the questions below to check your understanding)

1. *How are viruses classified?*

2. *Describe the structure and organization of the genome of:*

i) T4 bacteriophage
ii) Lambda bacteriophage
iii) Influenza virus
iv) HIV

3. *Describe the reproductive cycle of:*

i) T4 bactriophage
ii) Lambda bacteriophage
iii) Influenza virus
iv) HIV

4. *Name two enveloped viruses and describe how they adsorb on the host cells.*

5. *State how different variety of influenza viruses arise. Describe the process/es.*

6. *State how different variety of HIV arise. Describe the process/es.*

Summary Table – Comparison between Bacteriophages, Influenza Virus and HIV

Type of Virus	T4 Bacteriophage (Lytic Cycle)	Lambda Phage (Lysogenic cycle)	Influenza Virus	HIV
Viral genome:	Linear Double-stranded DNA	Linear double-stranded DNA	Segmented linear single stranded (-) RNA	2 Linear single-stranded (+) RNA
Capsid:	Icosahedral	Icosahedral	Helical	Cone-shaped
Type:	Complex virus (with contractile tails)	Complex virus (with non -contractile tail)	Enveloped (with glycoprotein spikes HA and NA)	Enveloped (with glycoprotein spikes gp41 and gp120)
Host:	Bacteria (*E. coli*)	Bacteria (*E. coli*)	Animal: Respiratory epithelial Cells	Animal: CD4 T-Cells, macrophages
(i)Attachment and Penetration:	Tail fibres attach to complementary receptor sites on outer surface of cell wall	Tail fibre attach to complementary receptor site on outer surface of cell wall	Viral HA glycoproteins recognize and bind to specific sialic-acid containing receptor molecules on surface membrane of host. Enter by _____	Viral gp120 glycoprotein recognizes complementary CD4 receptor protein on T-cells or macrophages. Enter by _____
(ii) Synthesis of viral genome	Nil (because viral genome is dsDNA)	Nil (because viral genome is dsDNA)	In the nucleus of host: (-)ssRNA is used as a template to synthesise (+)ssRNA (mRNA) by _____	In the cytoplasm of host: (+)ssRNA is used as a template to synthesise cDNA and then dsDNA by _____
(ii)Any Integration of viral genome into host genome?	No integration of viral genome	Integrated into host cell genome as prophage (lysogenic cycle).	No integration of viral genome	dsDNA is integrated into host cell. Forms _____.
Type of Virus	T4 Bacteriophage (Lytic Cycle)	Lambda Phage (Lysogenic cycle)	Influenza Virus	HIV
(iv)Replication of viral genome: & synthesis of viral proteins	Host cell machinery used to replicate and transcribe phage DNA, then to synthesize viral proteins during translation.	Lysogenic: Prophage replicates as bacterial cell undergoes binary fission. Lytic: When induced, prophage is excised from bacterial DNA. Host cell machinery used to replicate and transcribe the excised phage DNA, then synthesize viral proteins during translation.	(-) viral ssRNA genome replicated using (+) viral ssRNA (mRNA) as template Viral mRNA is used as a template for translation to synthesize viral proteins.	Proviral DNA is replicated as T-cell replicates. (+) Viral ssRNA genome is transcribed from the integrated proviral DNA. Viral mRNA is used as a template for translation to synthesize viral proteins.
Host cell Genome – *What happens?*	DNA of host cell is degraded	Lysogenic: DNA of host cell is not degraded. Lytic: DNA of host cell is degraded.	DNA of host cell is not degraded	DNA of host cell is not degraded.
Release:	Lysis of host cell. Causes death of host cell	Lysogenic: No release Lytic: Host cell lysed to release viral particles.	Bud off from epithelial cell.	Bud off from T-cell.

= End of lecture notes =