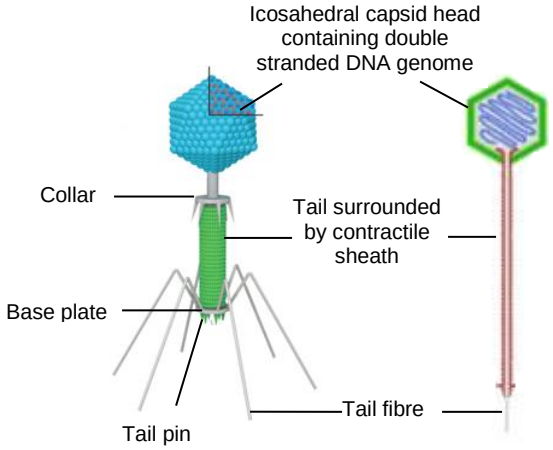
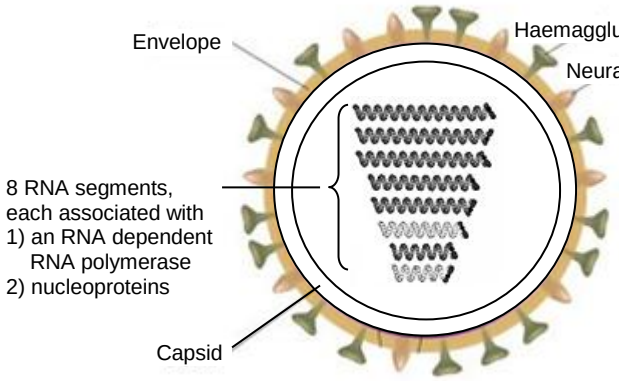
- **Are viruses are considered living or non-living?** Living as they contain **genetic material**. However, non-living because they have **no cellular organization** and only show characteristics of living things when in host cell.
  Characteristics of living things include1) metabolic activity 2) cellular organization 3) ability to reproduce and grow in numbers 4) ability to respond to stimuli and adapt to environment
- **Why are viruses obligate parasites?** This is because viruses, like obligate parasites, **depend on host cells to complete their life cycle**.

Structure of Viruses

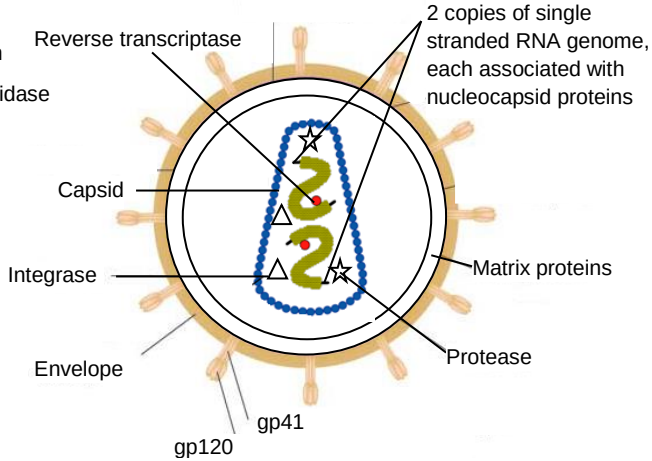
Size: 10-300nm	**Bacteriophages**		**Animal Viruses**	
			Enveloped	
	T4 phage	Lambda phage	Influenza	Human Immunodeficiency Virus (HIV)
Genome ▪ Nucleic acid that codes for synthesis of viral components and enzymes for viral replication & assembly ▪ Can be either DNA/RNA, single/double-stranded	▪ Double-stranded DNA		▪ **(-) strand RNA** →viral genome is **complementary to viral mRNA** ▪ **<u>8 different</u>** segments **of single stranded RNA** associated with **nucleoproteins** ▪ Each RNA segment is packed with 3 polymerase proteins which come together to form an **RNA-dependent RNA polymerase** enzyme complex which replicates and transcribes the viral genome in the host cell	▪ **(+) strand RNA** →viral genome has the **same sequence as viral mRNA** ▪ **<u>2 identical</u> copies** of **single stranded RNA** bound to **nucleocapsid proteins**
Capsid ▪ Protein coat that surrounds and protects viral genome ▪ Comprise subunits called capsomeres	▪ Icosahedral capsid head		▪ Present.	▪ Present, conical shaped Enzymes reverse transcriptase, integrase and protease found in capsid
Envelope ▪ Phospholipid bilayer surrounding the nucleocapsid ▪ Derived from host cell membrane ▪ Embedded with viral glycoproteins involved in host cell recognition	▪ Absent		▪ Glycoproteins embedded in envelope: haemagglutinin (80%) & neuraminidase (20%)	▪ Glycoprotein embedded in envelope: gp41 gp120 is attached to gp41



T4 phage **Lambda phage**



Influenza Virus



Human Immunodeficiency Virus

Antigenic Drift and Antigenic Shift

Antigenic Drift : When the influenza virus replicates in its host cell, mutations frequently occur due to the **poor proofreading mechanism** of the **viral RNA-dependent RNA polymerase** and the **fast replication rate of the virus**. Over time, there is an **accumulation of mutations in the viral genome.** Sometimes, these mutations produce viruses with **<u>modified** surface antigens</u>** (e.g. glycoproteins such as haemagglutinin or neuraminidase) with **different conformation**. If these viruses infect a host that does not have the antibodies that recognise these modified surface antigens, the host becomes susceptibleto the virus.

Antigenic Shift: When a **bird strain** of influenza A and **human strain** of influenza A infect a **single cell** of an **intermediate host** (e.g.a **pig**), **genetic reassortment** can occur. Thus when new viruses are assembled in the host cell, a **new combinations of RNA segments** can come together. Sometimes, genetic reassortment produces viruses with **<u>new** surface antigens</u>** (e.g. glycoproteins such as haemagglutinin or neuraminidase). If these viruses infect a **human host** the host becomes susceptibleto the virus, as the host will not have the antibodies that recognise these **<u>new** surface antigens</u>**,

Virus Life Cycle

Stages	Bacteriophage		Enveloped animal viruses	
	T4 phage (Lytic phage)	**Lambda phage (Temperate phage)**	**Influenza**	**HIV**
1. Attachment Virus recognises and attaches to host cell	▪ **Attachment sites** on tail fibres **adsorbs** to **complementary receptor sites** on bacterial surface (e.g. *E.coli*)		Enveloped viruses use viral glycoproteins to bind to specific receptor molecules on host cell. ▪ **Hemagglutinin binds to complementary sialic acid receptor** on host cell (e.g. **epithelial cells in respiratory tract**) membrane	▪ **gp120 binds to complementary CD4 receptors** on **T helper cells or (macrophages)** with the help of a co-receptor.
2. Penetration Viral genome introduced into host cell	▪ Bacteriophage releases **lysozyme** which **digests bacterial cell wall** ▪ This allows the **release of molecules** from the bacterium which triggers a change in shape of the proteins in the base plate which causes the **contraction of tail sheath** which will drive the **hollow core tube** through **cell wall** ▪ When the tip of the hollow core tube **reaches the plasma membrane**, **phage DNA is injected** into the bacterial cell ▪ The empty capsid remains outside		Release of capsid into host cell cytosol ▪ Virus enters host cell by **endocytosis** (the process involves ***invagination*** of membrane) ▪ Endocytic vesicle fuses with **lysosome** → which lowers the pH → causes viral envelope to fuse with lipid bilayer of vesicle → nucleocapsid is released into cytosol	▪ With the help of **gp41**, **the viral envelope fuses with host cell membrane** → nucleocapsid is released into cytosol (NB: HIV can also enter by endocytosis)
			Degradation of capsid to release viral genome (uncoating) Capsid degraded by cellular enzymes and the 8 viral RNA segments that are released into cytosol **enter the nucleus**	Capsid degraded by cellular enzymes→ the 2 viral RNA strands and enzymes are released into the **cytosol**
3. Replication Synthesis of viral components & viral genome replication	▪ **Host cell macromolecular synthesizing machinery** is used to synthesise phage proteins ▪ **Early phage proteins**: degrade host DNA ▪ Phage DNA synthesized using host cell nucleotides and early proteins ▪ **Late phage proteins**: are phage enzymes and structural components	▪ **Linear** phage **DNA circularizes** and **inserted** into **host cell genome** by enzyme **integrase** ▪ The integrated phage DNA is known as a **prophage** ▪ Expression of phage genes is repressed by phage **repressor proteins**. Hence new phages are not synthesized ▪ Prophage replicates along with bacterial chromosome ▪ During **spontaneous induction, cellular proteases** are activated. They destroy the repressor proteins ▪ The prophage is then excised from the bacterial genome ▪ The replication phase of lytic cycle then occurs.(see left)	▪ Viral **RNA-dependent RNA polymerase** uses viral genome as a template to synthesise mRNA ▪ mRNA 1. **enters cytosol** →translated into **viral structural components** (Capsid proteins are made in the cytosol. Envelope glycoproteins are made in the RER & eventually are embedded in host cell membrane) 2. can also **act as template** for synthesis of **new viral RNA genome** in the nucleus. Viral RNA genome then exits nucleus.	▪ **Reverse transcriptase** makes DNA strand using viral RNA as template to form a DNA-RNA hybrid. The RNA is then degraded and the 2nd DNA strand is made → double-stranded DNA molecule produced ▪ Viral DNA **enters nucleus** → inserted into host cell genome by **integrase** → Viral DNA known as **provirus** →can remain **latent** for a long time ▪ Upon **activation**, viral DNA transcribed to viral RNA which **enters cytosol** ▪ Viral RNA can either act as mRNA and be translated into proteins or become part of the genome of the new virions ▪ mRNA 1. is translated to **viral polyproteins** 2. is translated into envelope glycoproteins gp120 and gp 41 in the RER and eventually are embedded in the host cell surface membrane.
4. **Maturation** Assembly of complete viruses	▪ Phage DNA and capsid assemble into a DNA-filled head ▪ Head, tail and tail fibers assembled independently & join in a specific sequence.		▪ Capsid proteins associate with host cell membrane where viral glycoproteins are inserted. ▪ Nucleoproteins associate with the RNA genome and then interact with capsid proteins that have associated with the glycoproteins embedded on the plasma membrane. ▪ This initiates the budding process.	**For HIV, maturation is completed only after release of virus.** ▪ The viral RNA genome and polyprotein assembles at the cell surface membrane where viral glycoproteins have been inserted.
5. **Release**	▪ Phage **lysozyme** synthesised within the cell breaks down the bacterial cell wall ▪ Bacterial cell membrane lyses and release the newly formed virions		▪ Newly formed viruses bud off by ***evagination***, acquiring host cell membrane with embedded viral glycoproteins ▪ **Neuraminidase facilitates the release** of the new virions from the host cell membrane by cleaving sialic acid from the host cell receptor.	▪ Newly formed viruses bud off by ***evagination***, acquiring host cell membrane with embedded viral glycoproteins ▪ Viral **protease** cleaves polyproteins, forming viral enzymes and proteins. ▪ The viral RNA genome and enzymes are then encapsulated by a protein coat to form a **capsid** ▪ The mature HIV virus (virion) is now able to infect neighbouring cells.

Influenza Life Cycle

(1) **Hemagglutinin** recognizes & binds to **sialic acid** receptor on host membrane

(2a) Virus enters host cell by **endocytosis** (which involves ***invagination*** of membrane)

(2b) Endocytic vesicle fuses with **lysosome** → which lowers the pH → causes viral envelope to fuse with lipid bilayer of vesicle → nucleocapsid is released into cytosol

(2c) Capsid degraded by cellular enzymes and viral RNA **enters nucleus**

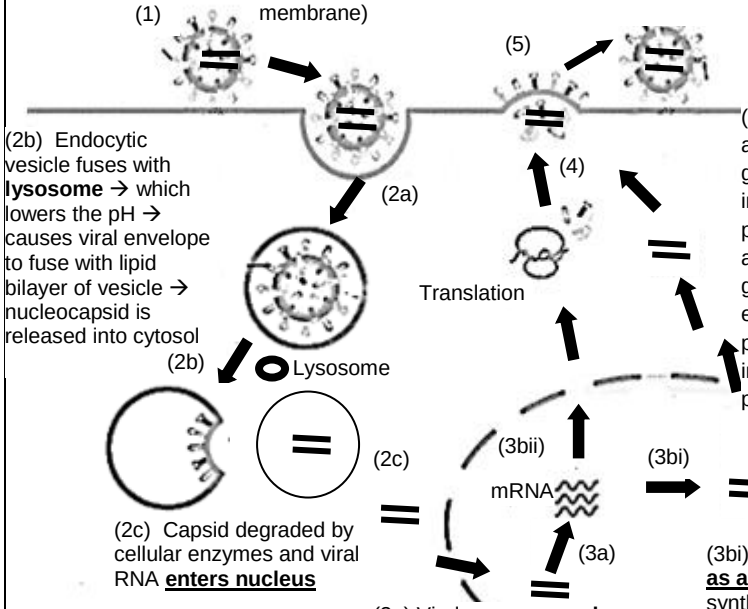
Note:
Only 2 out of the 8 RNA segments are shown due to space constraints in the diagram)

(3a) Viral genome **used as a template** for **mRNA** synthesis by **RNA-dependent RNA polymerase.**
(3bii)mRNA then **enters cytosol** → translated into **viral structural components** (Capsid proteins are made in the cytosol. Envelope glycoproteins are made in the RER & are eventually embedded in host cell membrane)

(3bi) **mRNA** can **used as a template** for synthesis of **new viral RNA genome** in the nucleus

(4) Nucleoproteins associate with the RNA genome and then interact with capsid proteins that have associated with the glycoproteins embedded on the plasma membrane. This initiates the budding process.

(5) Newly formed viruses bud off by ***evagination***, acquiring host cell membrane with embedded viral glycoproteins. **Neuraminidase facilitates the release** of the new virions from the host cell membrane. Host cell may or may not be lysed.



HIV Life Cycle

(1) **gp120 binds to CD4 receptors** on T lymphocytes (or macrophages) with the help of a co-receptor.

(2a) With the help of **gp41**, **the viral envelope fuses with host cell membrane** → nucleocapsid is released into cytosol

(2b) Capsid degraded → viral RNA and enzymes released into **cytosol**

(3a) **Reverse transcriptase** makes DNA strand using viral RNA as template → RNA degraded → 2nd DNA strand made → double-stranded DNA molecule (ds DNA) produced

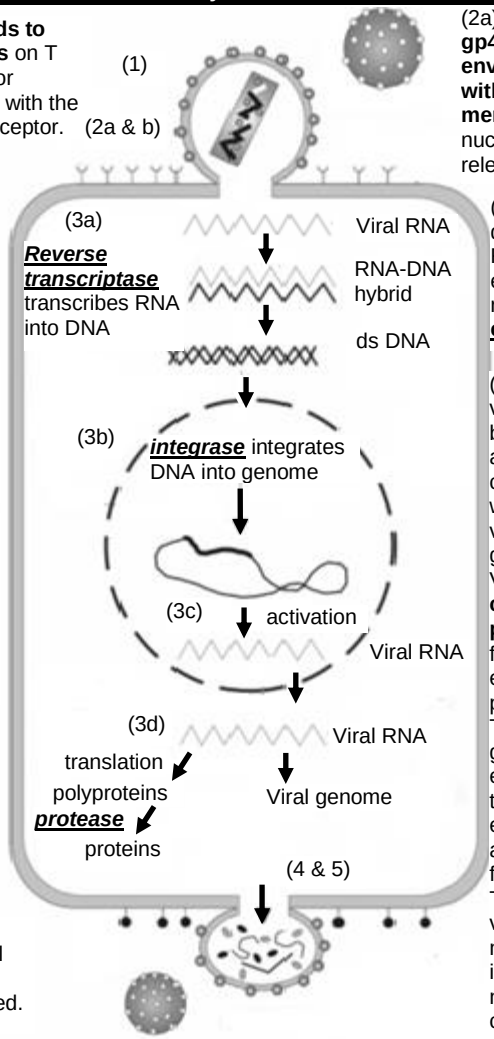
(3b) Viral DNA **enters nucleus** → inserted into host cell genome by **integrase** → Viral DNA known as **provirus** →can remain **latent** for a long time

(3c) Upon **activation**, viral DNA is transcribed to viral RNA which **enters cytosol** Viral RNA can either act as mRNA and be translated into proteins or become part of the genome of the new virions.

(3d) mRNA is translated to
1. **viral polyproteins**
2. envelope glycoproteins gp120 and gp 41 in the RER which eventually are embedded in the host cell surface membrane.

(4) Viral RNA genome and polyprotein assemble at the cell surface membrane where viral glycoproteins have been inserted.

(5) Newly formed viruses bud off by ***evagination***, acquiring host cell membrane with embedded viral glycoproteins. Viral **protease cleaves polyproteins**, forming viral enzymes and proteins. The viral RNA genome and enzymes are then encapsulated by a protein coat to form a **capsid.** The mature HIV virus (virion) is now able to infect neighbouring cells.



Pathogenecity of Influenza

When influenza will bind to sialic acid receptors on epithelial cells of respiratory tract
↓
Influenza replicates within it and then buds off. Infected epithelial cells eventually lyse
↓
The build up of dead epithelial cells results in inflammation and symptoms of influenza appear
→runny nose & scratchy throat
↓
The epithelial layer weakens and the individual is more susceptible to bacterial infections like pneumonia

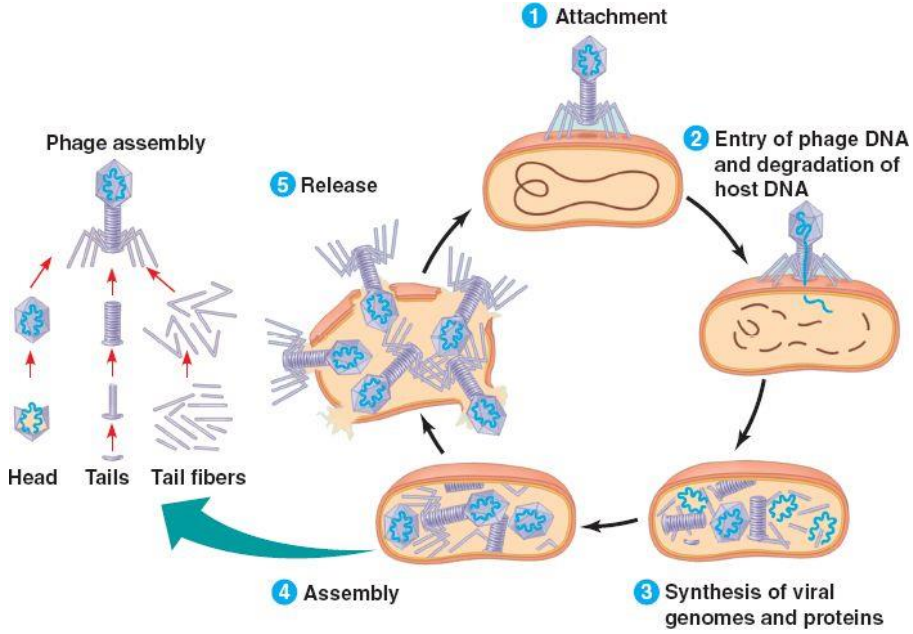
- Treatment:1) antibiotics for bacterial infections
  2) antiviral drugs which target viral enzymes i.e enzyme inhibitors
  e.g:Tamiflu for some strains of influenza

Pathogenecity of HIV

When HIV binds to CD4 receptor on a T helper cell, a type of T lymphocyte
↓
HIV replicates within it and then buds off. Infected T helper cells eventually lyse.
↓
With fewer T helper cells, the immune system is depressed & individuals are more susceptible to opportunistic infections. When infections become unmanageable→AIDS → death

- Virus able to avoid detection by immune system as it mutates at a high rate during replication →surface proteins altered →prevent recognition & elimination by immune system
- Treatment: drug cocktail that targets (1) enzymes(RIP) i.e. enzyme inhibitors
  (2) glycoproteins (gp120) i.e. entry inhibitors

Life Cycle of Lytic Phage (e.g. T4)



Life Cycle of Temperate Phage (e.g. Lambda)