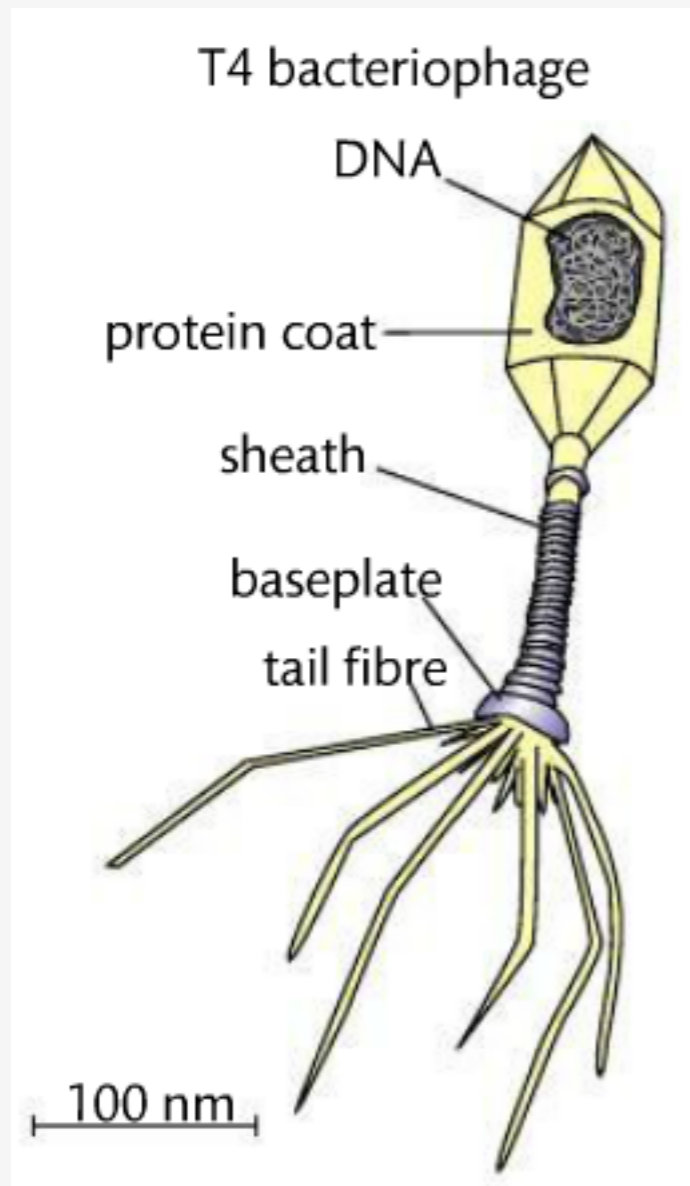




Option D: Medicinal Chemistry

Part D.5

D.5 Antiviral Medications

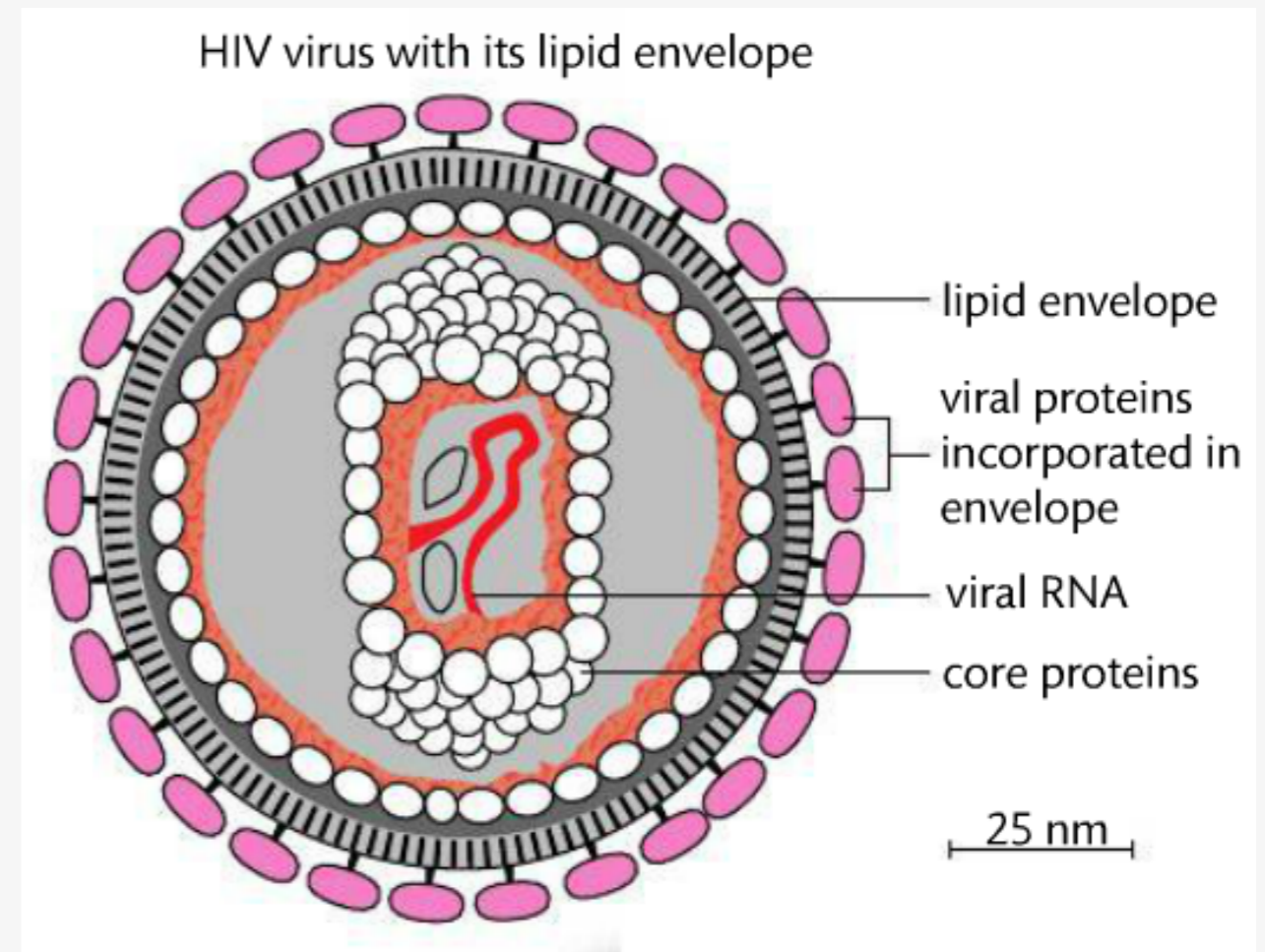


- ▶ Virus - parasite that takes over the host cell to reproduce
- ▶ only has protein and nucleic acid (either DNA or RNA)
- ▶ very small - submicroscopic
- ▶ hijackers - takes over host cell, the cell dies and releases thousands of viral particles

D.5 Antiviral Medications

Terminology

- ▶ **antibodies** - produced in response to viral infections
- ▶ **immune response** - action by the antibodies against a virus
- ▶ **immunity** - protection against repeated infections with the same virus



D.5 Antiviral Medications

Flare-ups

- ▶ when a virus lays dormant in your system and reappears at a different time
- ▶ chicken pox virus as a child leads to shingles as an adult
- ▶ herpes cause cold sores



SARS virus - from china in 2002

D.5 Antiviral Medications

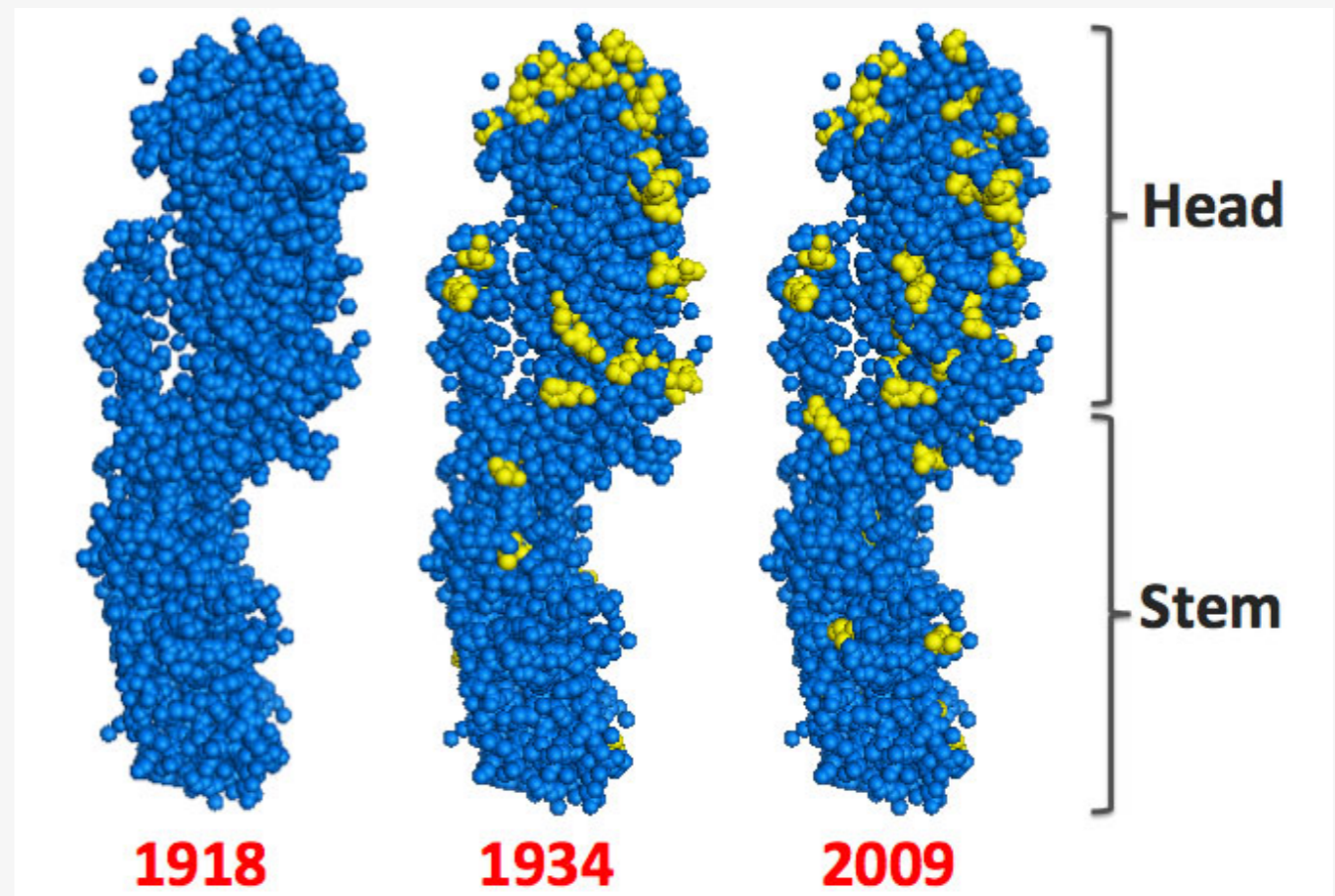
Treating Viruses

- ▶ Antibiotics don't work because there is little for the drug to target - ie. cell wall
- ▶ multiply and mutate rapidly - changing its reaction to drugs
- ▶ Vaccines - prophylactic treatment to prevent viral infections
 - ▶ Work by stimulating the body into an immune response and creating immunity (polio, measles, small pox)

D.5 Antiviral Medications

When vaccines don't work...

- ▶ Considering vaccines target a specific virus, if the structure changes (mutates), there is now a new strain that needs to be vaccinated against
- ▶ New flu vaccines are created each year to try and "target" the most prevalent flu strain (varied effectiveness)



D.5 Antiviral Medications

Antivirals

- ▶ main strategy to treat viral infections
- ▶ interfere in some way with the viral life cycle
- ▶ Example - Amantadine: cage-like structure that causes changes in the cell membrane that prevents entry of the virus into the host cell (a "bouncer")

D.5 Antiviral Medications

Influenza

- ▶ Common disease that most experience at some point
- ▶ dangerous to elderly and those with compromised immune systems
- ▶ approximately 500,000 people die each year from the flu
- ▶ constant fears of global outbreak (or **pandemic**)
- ▶ In 1918, a flu pandemic started that lasted 2 years and killed 20 million people - started as a harmless flu and mutated to a virulent strain - 'The Spanish Flu'

D.5 Antiviral Medications

Influenza

- ▶ Two main types of flu virus, Influenza A and B
- ▶ Spherical Viruses and have RNA in their genetic material
- ▶ Two key proteins:
 - ▶ **Hemagglutinin (H)** - glycoprotein that enables the flu virus to 'dock' with the host cells prior to entering
 - ▶ **Neuraminidase (N)** - an enzyme that catalyzes a cleavage reaction which allows particles to escape the host cell and spread infection

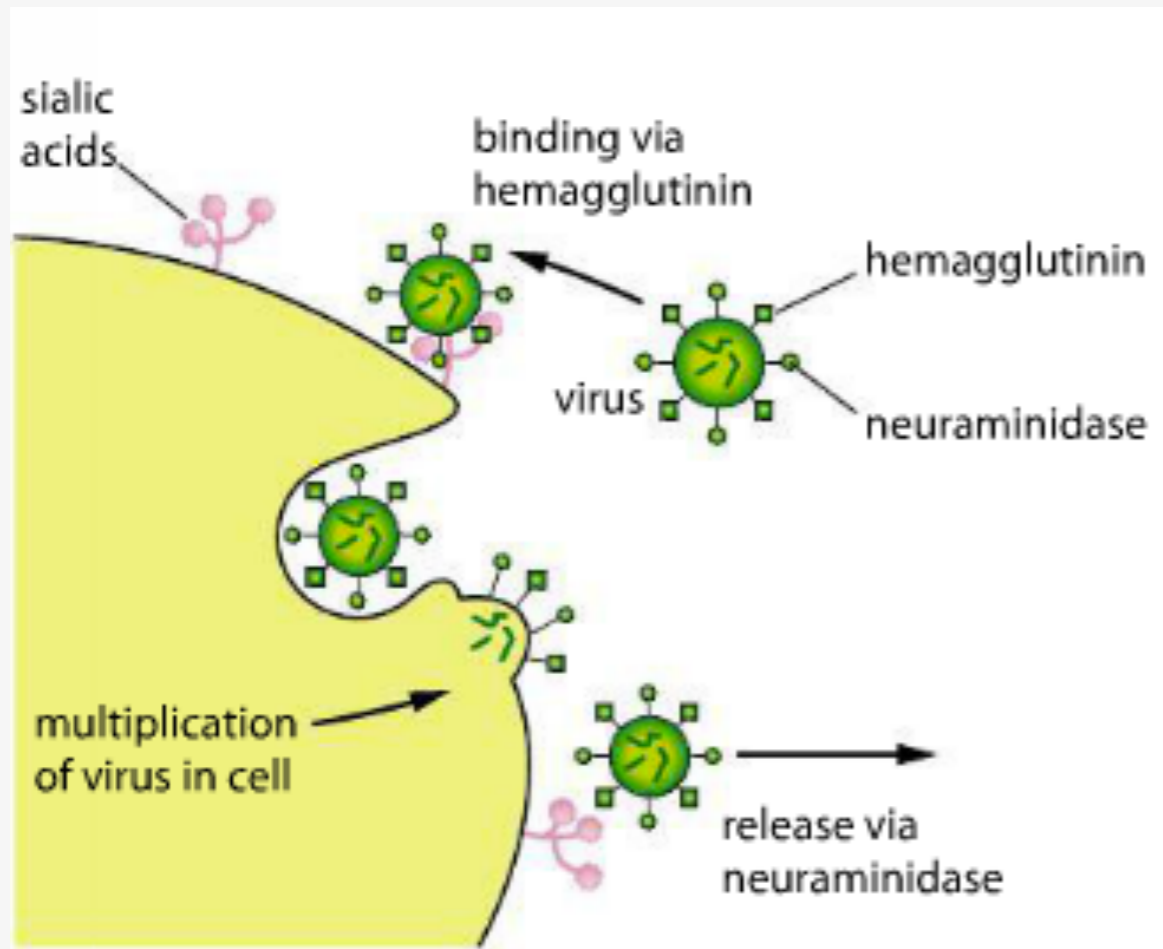
D.5 Antiviral Medications

Familiar Viruses

- ▶ H1N1
 - ▶ Strain of Influenza A that circled the globe in 2009
 - ▶ People had little natural immunity
 - ▶ WHO declared it a pandemic and lifted the alert in 2010
 - ▶ 250,000 people are believed to have died, mostly in Africa and South-East Asia

D.5 Antiviral Medications

Structure of the Virus

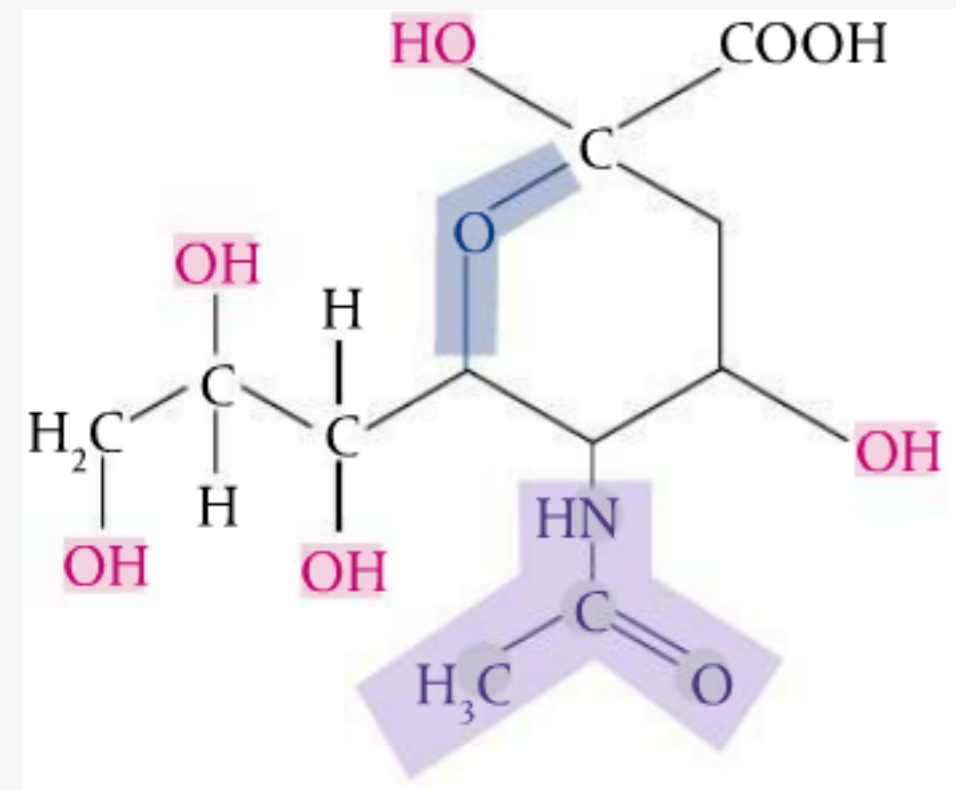


- ▶ Neuraminidase (N) seems to be better target for drug design
- ▶ N binds to the sialic acid (the substrate) at the *active site* - catalyst
- ▶ Researchers needed to design something that would inhibit the binding of the enzyme
- ▶ X-Ray crystallography found the structure of the N including the binding to the active site

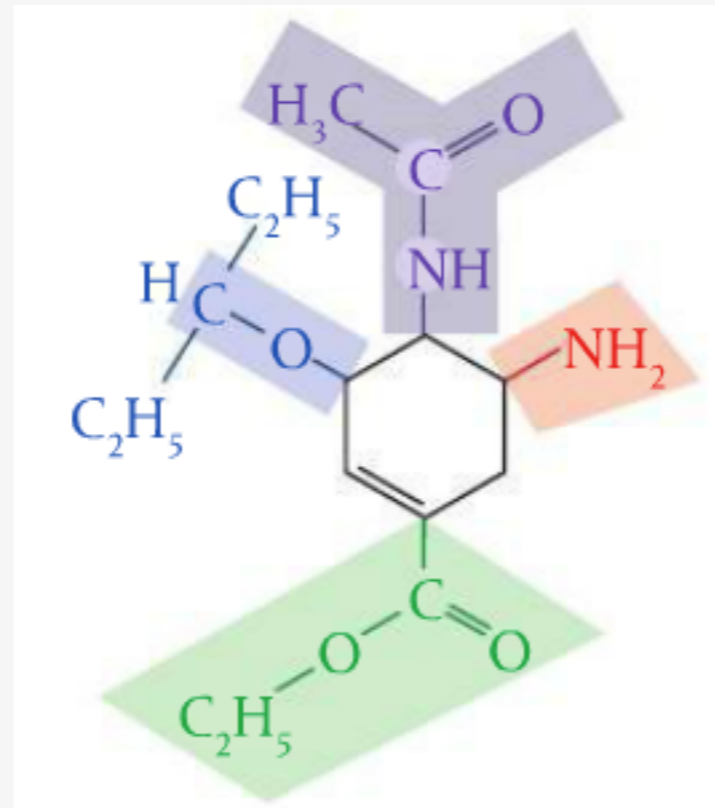
D.5 Antiviral Medications

Neuraminidase Inhibitors

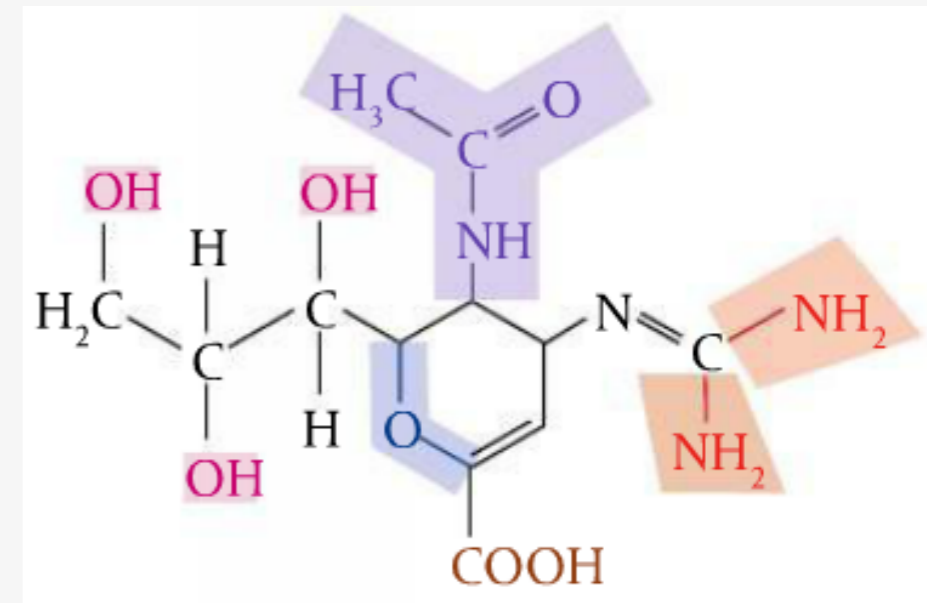
- ▶ First designed by a team in Australia (2000)
- ▶ Zanamivir (Relenza) & oseltamivir (Tamiflu)



Sialic Acid



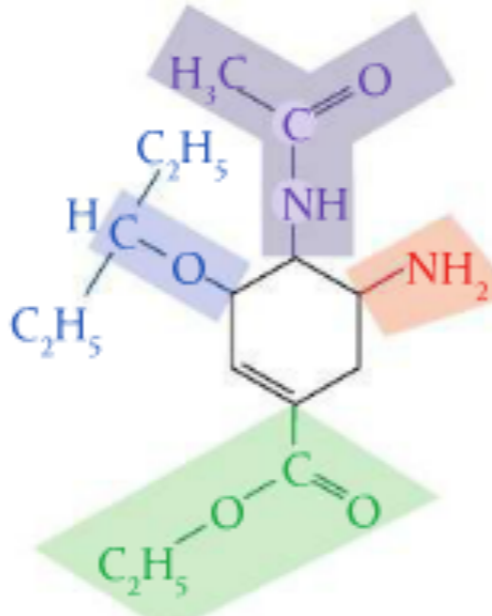
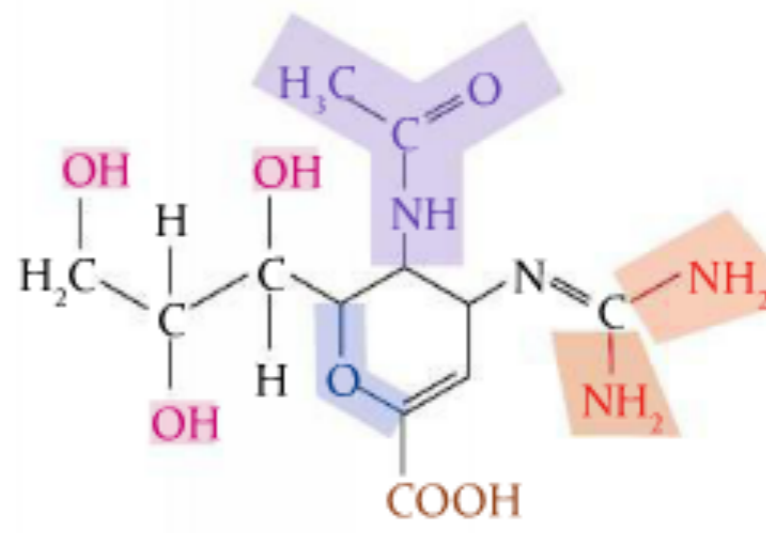
Tamiflu



Relenza

D.5 Antiviral Medications

Table 37 - data booklet

	Oseltamivir (Tamiflu)	Zanamivir (Relenza)
structure	 <p>The structure of Oseltamivir (Tamiflu) features a cyclohexene ring. It is substituted with an alkenyl ether group (blue), a primary amino group (orange), a carboxamide group (purple), and an ester group (green).</p>	 <p>The structure of Zanamivir (Relenza) features a cyclohexene ring. It is substituted with an alkenyl ether group (blue), a primary amino group (orange), a carboxylic acid group (brown), and three hydroxyl groups (pink).</p>
functional groups	alkenyl ether primary amino carboxamide ester	alkenyl ether primary amino carboxamide carboxylic acid hydroxyl (3)
drug action	neuraminidase inhibitor	neuraminidase inhibitor
administration	orally	inhalation
resistance to drug	some rare strains of flu virus have shown resistance	no resistance reported
counter-effects	nausea, vomiting	possible asthma

D.5 Antiviral Medications

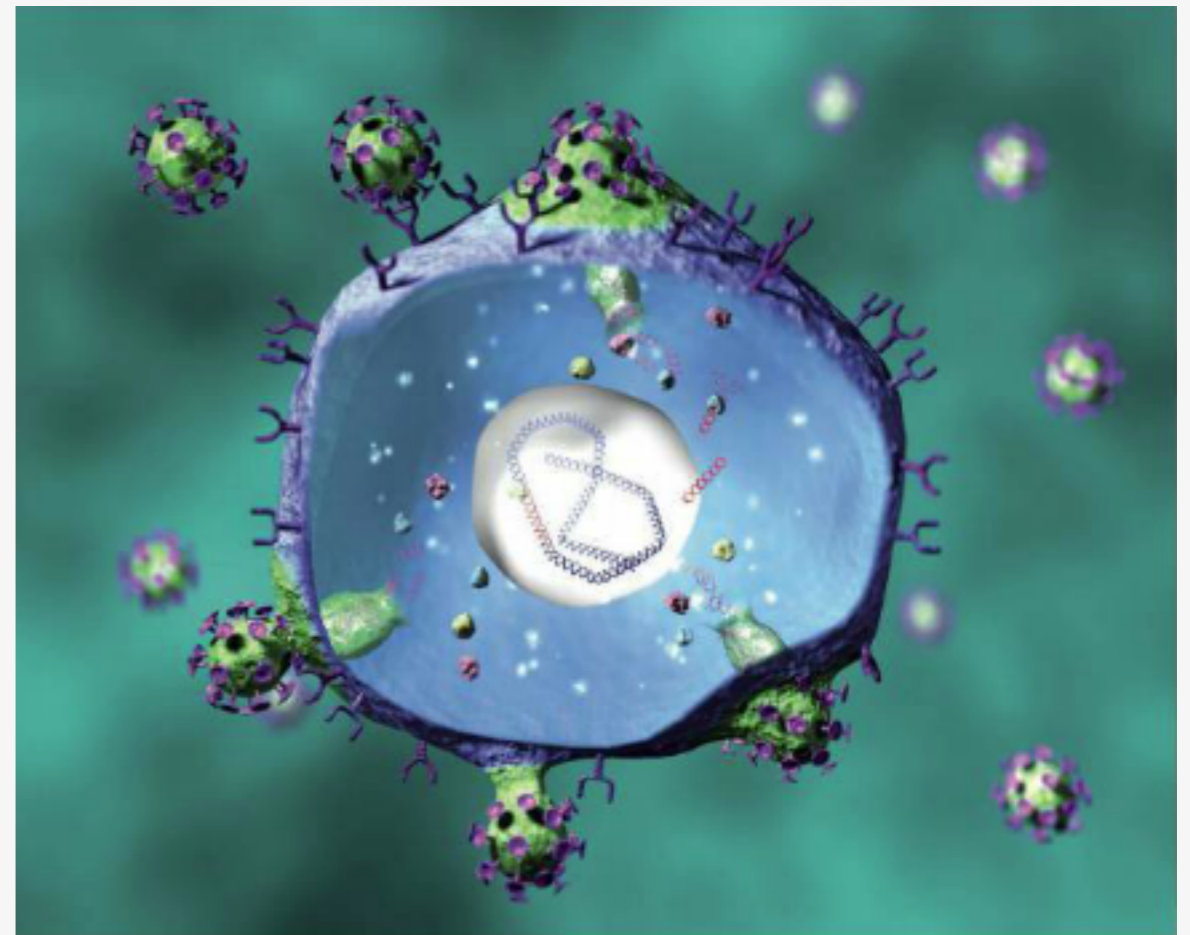
AIDS - A Viral Pandemic

- ▶ Acquired Immune Deficiency Syndrome (AIDS) - caused by Human immunodeficiency virus (HIV)
- ▶ transmitted from person to person through body fluids
- ▶ disease is characterized by a failure of the immune system
- ▶ body falls prey to opportunistic infections such as pneumonia and forms of cancer
- ▶ Infects white blood cells known as CD4⁺ T Cells

D.5 Antiviral Medications

Fight against HIV

- ▶ Reasons why HIV is more challenging than other viruses to defeat:
 - ▶ destroys the T Cells
 - ▶ mutates rapidly (even within the patient)
 - ▶ often lies dormant in host cells - nothing for immune system to respond to



D.5 Antiviral Medications

Antiretroviral Drugs (ARVs)

- ▶ HIV is considered a retrovirus because its genetic material is RNA and the enzyme *reverse transcriptase* controls the synthesis of DNA from the RNA
- ▶ ARVs can give long lasting suppression (becomes a chronic disease instead of a deadly one)
- ▶ Target and interrupt the following stages of the life cycle:
 - ▶ binding and fusion of the virus to the receptor on the CD4 cell membrane
 - ▶ reverse transcription of viral RNA to DNA in the host cell
 - ▶ integration of viral DNA into the host chromosome
 - ▶ release of new viral particles by budding from the host cell

D.5 Antiviral Medications

ARVs

- ▶ Inhibitors of the viral enzyme reverse transcriptase are the most widespread
 - ▶ First ARV drug to be approved- AZT - zidovudine
 - ▶ best results occur when a combination of ARVs are used
- ▶ Combo treatments include two different reverse transcriptase inhibitors plus a third drug - available as a single pill
- ▶ Most combo treatments can cost \$12,000 per patient per year
- ▶ Must be sustained throughout the patients life