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Antiviral drugs

1-Viruses are obligate intracellular parasites, they absolutely require living host cells in order to multiply and thus cannot be cultured outside their hosts.

2-Comprise a core genome that contain a single type of nucleic acid, either DNA or RNA.

3-Contain a protein coat (capsid) (sometimes itself enclosed by an envelope of lipids, proteins, and carbohydrates) that surrounds the nucleic acid.

4-It is lack both a cell wall and a cell membrane

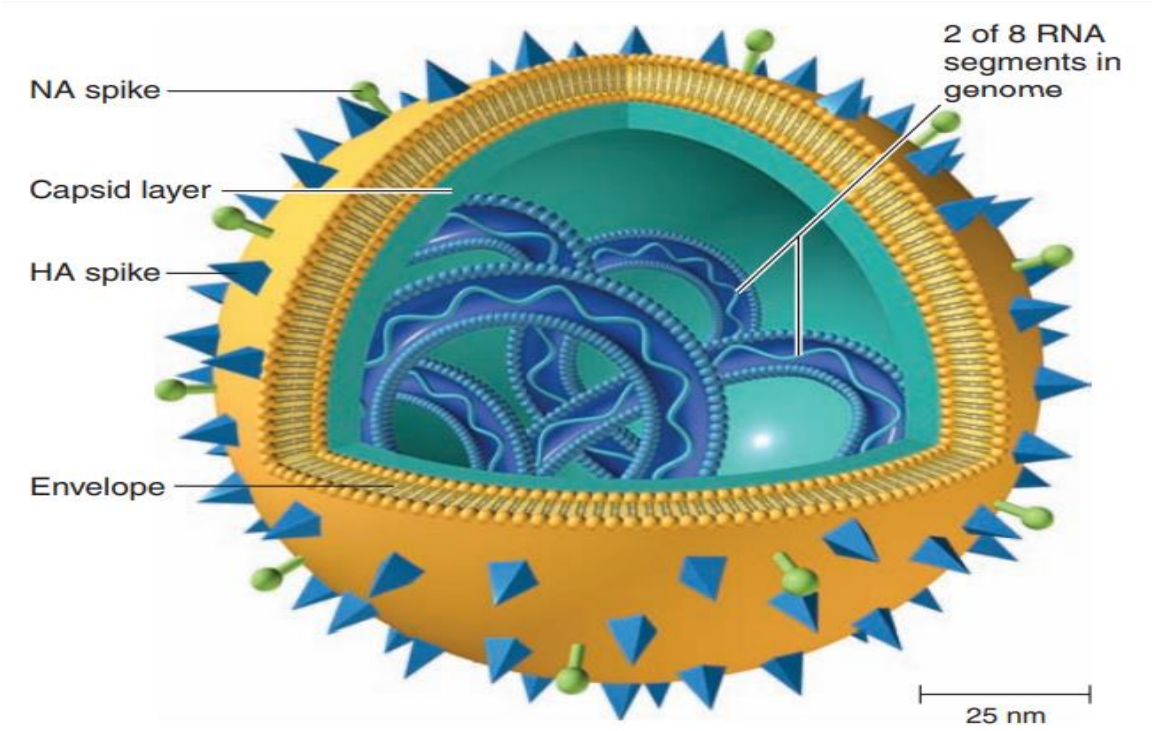


Figure Detailed structure of the influenza virus. The virus is composed of a protein coat (capsid) that is covered by a lipid bilayer (envelope) and two types of spikes. The genome is composed of eight segments of RNA:

Viral replication consists of several steps

(1) Attachment of the virus to receptors on the host cell surface.

(2) Entry of the virus through the host cell membrane.

(3) Uncoating of viral nucleic acid.

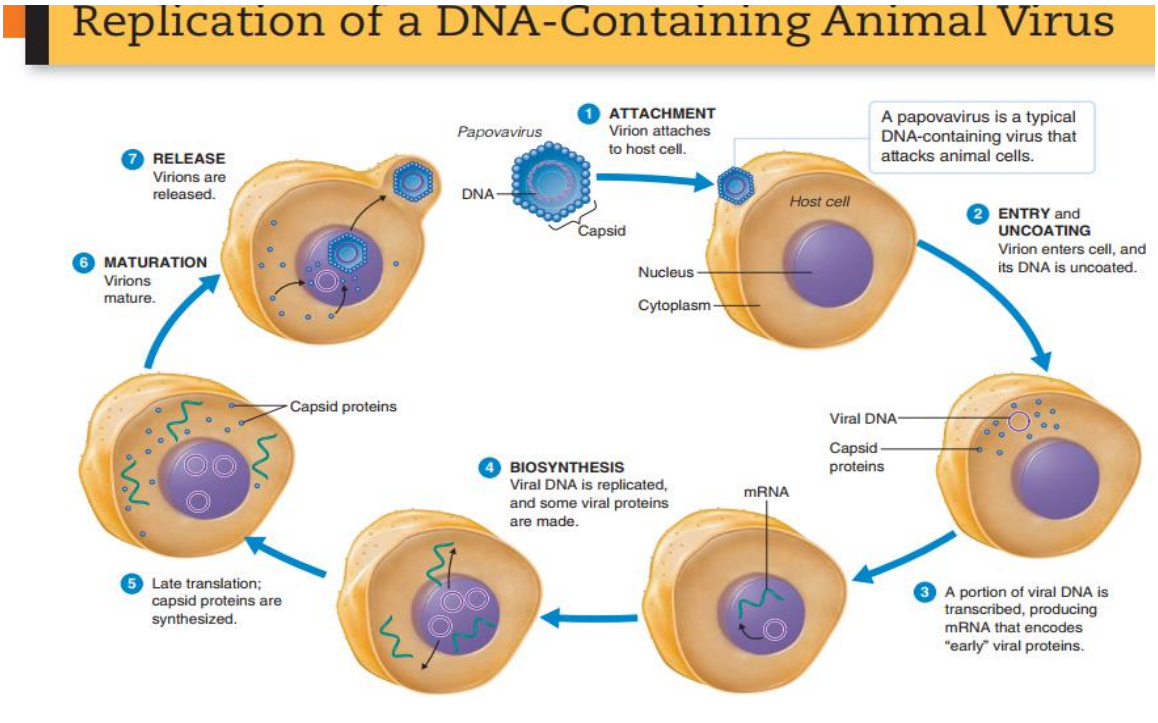
(4) Synthesis of early RNA or DNA.

(5) Synthesis of late, structural proteins.

(6) Assembly (maturation) of viral particles .

(7) Release from the cell.

Note:Antiviral agents can potentially target any of these steps



Viral replication in animals generally follows these steps: attachment, entry, uncoating, biosynthesis of nucleic acids and proteins, maturation, and release.

Knowledge of viral replication phases is important for drug development strategies, and for understanding disease pathology.

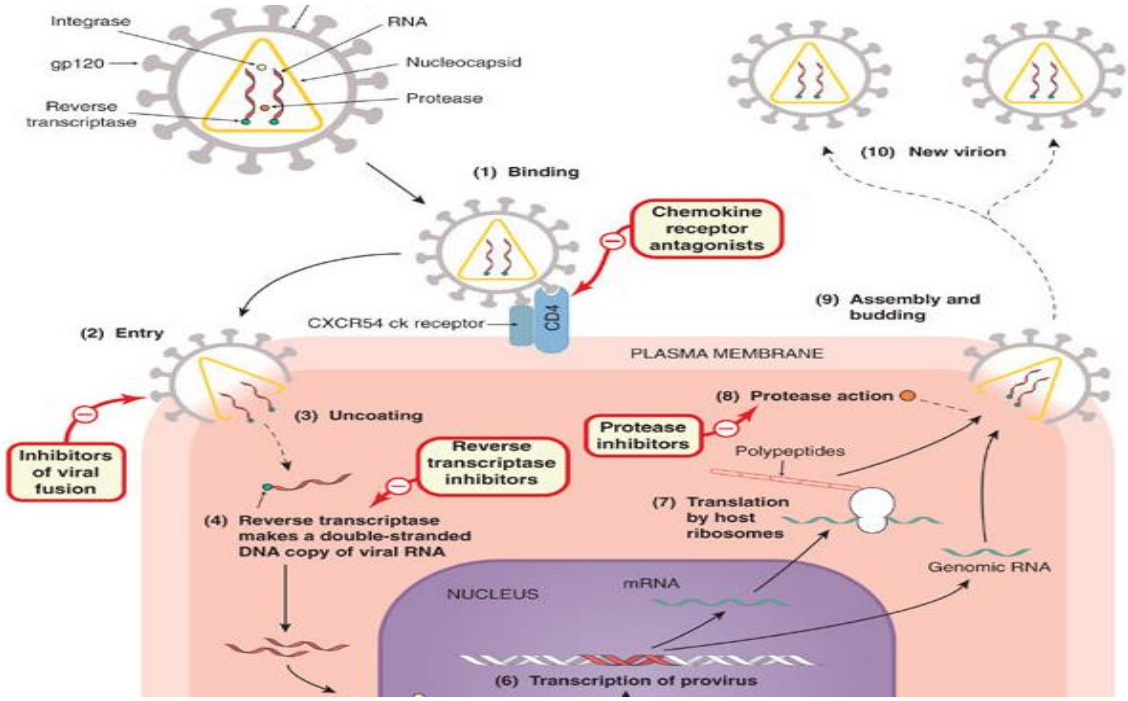


Figure: Schematic diagram of infection of a CD4⁺ T cell by an HIV virus

General mechanismes of action of antiviral drugs

a-Interference with viral cell binding

b-Interruption of virus uncoating

c- Interfere with viral nucleic acid synthesis. Such drugs generally are nucleic acid analogues that interfere with RNA and DNA production .

The objective of antiviral activity

a-Eradicate the virus while minimally impacting the host

b-Prevent further viral invasion

There are key differences between the principles of antiviral therapy as compared to antibacterial therapy.

Because viruses use host cellular for replication, it is difficult to achieve selective action against viral replication Thus,nonselective inhibitors of virus replication may interfere with host cell function and result in toxicity

e.g:Cytarabine

Cytarbine (antiviral) is not very selective in their activity.

As a result, side effects of these drugs have limited the clinical utility of parenterally administered formulations in veterinary species

why timing is critical to successful antiviral therapy, with early therapy resulting in optimal efficacy?

Because the initial phases of viral infection are often asymptomatic, treatment is often delayed until the infection is well established

Note: Antiviral drugs can only have virostatic actions, limiting replication until the host's immune system eliminates the viral infection

1-Famciclovir

Antiviral drug is a synthetic purine analogue (acyclic nucleoside analogue).

Mechanism of action

1-Famciclovir (acyclic nucleoside analogue) requires three phosphorylation steps for activation.

2-It is converted first to the monophosphate derivative by the virus-specified thymidine kinase

3- Then to the di- and triphosphate compounds by host cell enzymes (guanylate cyclase).

4-Famciclovir triphosphate

A-Inhibits viral DNA synthesis by inhibits viral DNA polymerase

B- Incorporotion into viral DNA —thus inhibiting viral DNA chain elongation and chain termination

5-It is considered virostatic .

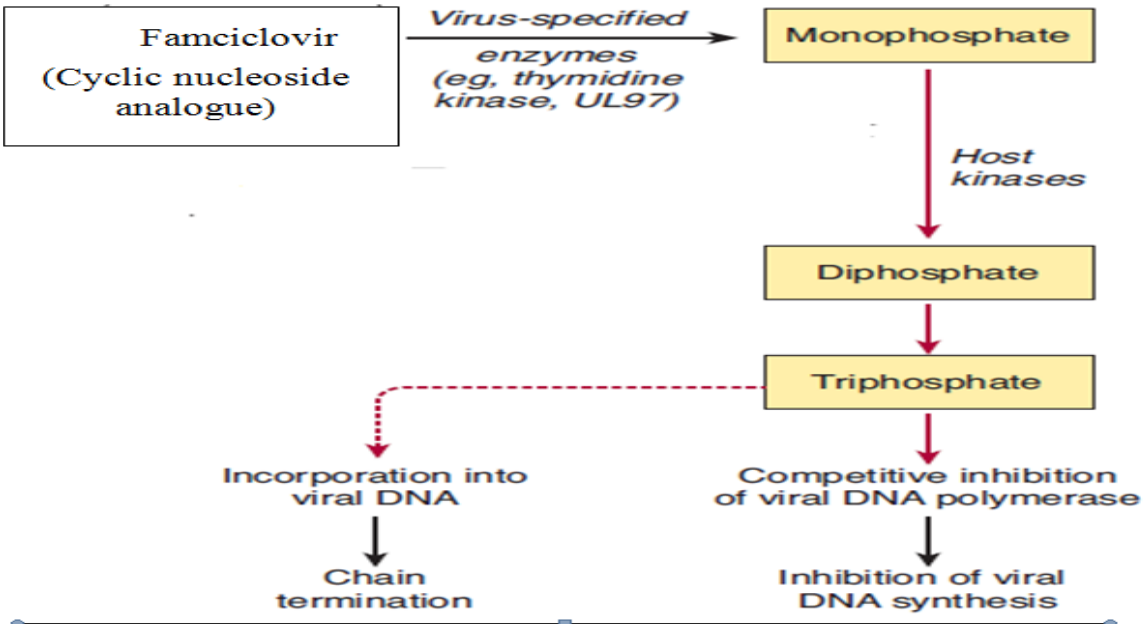


Figure :Mechanism of action of famciclovir

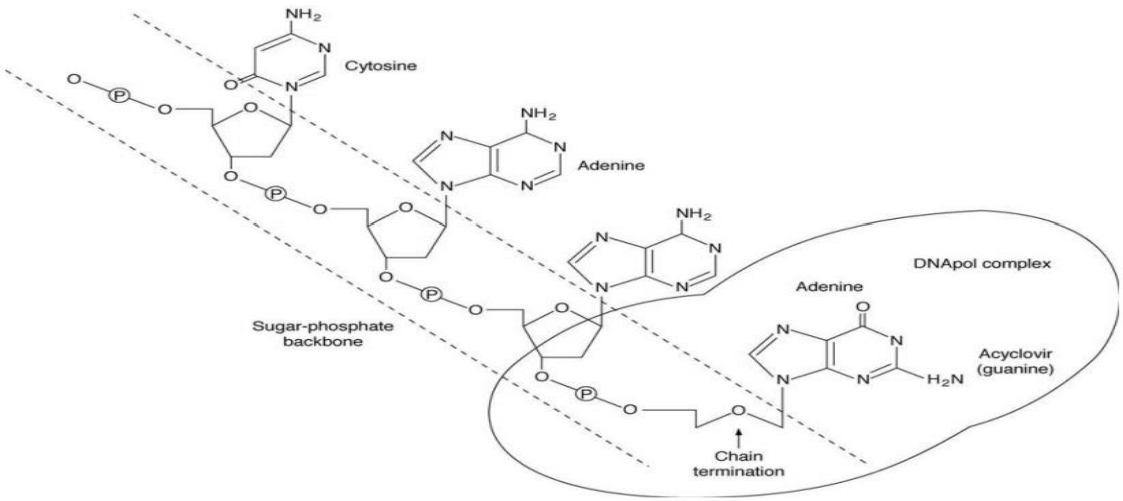


FIGURE 6.1 The mechanism of action of acyclovir. (A) activation and (B) Inhibition of DNA synthesis and chain termination.

Clinical uses :

Used in cats with ocular (conjunctivitis) or upper respiratory (rhinosinusitis) and dermatitis associated with feline herpes (FHV-1).

Its efficacy was studied using an oral dose of 90 mg/kg every 8 hours

Adverse effects

Adverse effects observed from famciclovir in cats include mild anemia

Why dverse effect of famciclovir is mild

Because famciclovir is requires the viral kinase for initial phosphorylation .Thus, famciclovir has selectively toxicity to viral which the active metabolite accumulates—only in infected cells in compared with host cell .

2-Zidovudine (AZT) Antiretroviral

Chemically, zidovudine is an analogue of thymidine.

Mechanism of action

1-Acts to inhibit the viral enzyme reverse transcriptase that prevents conversion of viral RNA into DNA.

2- This causes a virustatic effect in retroviruses

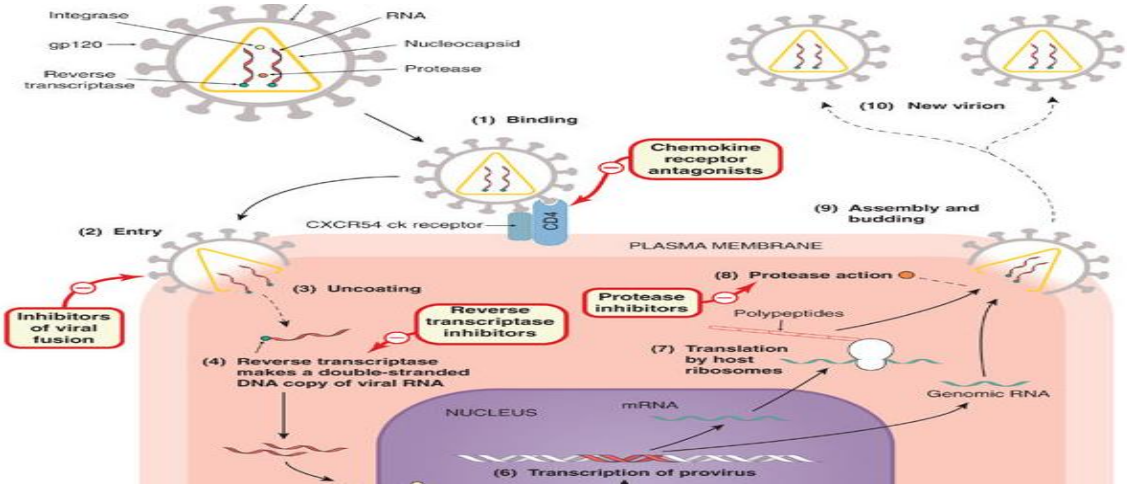


Figure: Schematic diagram of infection of a $CD4^+$ T cell by an HIV virus

Clinical uses

In veterinary medicine, zidovudine may be useful for treating Feline immunodeficiency virus (FIV).

Thus,zidovudine can

1-Reduce the viral load in infected cats

2- Improve clinical signs

In cats, doses of 25 mg/kg q12h IV or PO produced drug concentrations in the effective range to inhibit the virus.

Advers effects and side effects Zidovudine include

1- Gastrointestinal disturbances (e.g. nausea, vomiting, abdominal pain).

2- Blood disorders (sometimes anaemia or neutropenia)

3- CNS effects (e.g. insomnia, dizziness, headache).

3-Oseltamivir Phosphate (Neuraminidase Inhibitor)

Oseltamivir Phosphate antiviral for:

1-influenza A&B viruses;(Viral respiratory tract infections) .

2-May be effective for parvovirus infections in dogs .

Note:

Immunization against influenza A is the preferred approach.

However, antiviral agents are used when patients are allergic to the vaccine .

Note

Oseltamivir phosphate is an ester prodrug that is converted by hepatic esterases to its active metabolite, oseltamivir carboxylate.

Mechanism of action oseltamivir phosphate

1-Oseltamivir carboxylate competitively inhibits a specific neuraminidase enzyme that is (influenza virus) required for entery into host cell, replication and release of virus from infected cells .

2-Thus Oseltamivir prevent the release of newly formed virus and their spread from cell to cell .

Clinical Use

Oseltamivir used for strains of equine influenza A virus (EIV)

which administered at a dose rate of 5 mg/kg twice daily for 5 days cause **attenuation (decrease)** of the following clinical signs :

1 -Viral shedding,

2-Fever .

3-Secondary bacterial pneumonia.

Note :

Unlike the antiherpetic (Famciclovir) and antiretroviral (Zidovudine) drugs discussed above, oseltamivir does not act by directly inhibiting viral replication.

Instead, oseltamivir is a competitive inhibitor of the enzyme neuraminidase, which influenza viruses use as part of the process of budding of the replicative viral particles from infected cells.

Side effects

Not reported when oseltamivir was administered to horses

4-Interferon

Interferon are a family of naturally occurring inducible glycoproteins synthesised by immune system of mammalian cell in response to viral infections

Now generally produced commercially using recombinant DNA technology that interfere with the ability of viruses to infect cells.

Interferon are potent cytokines that possess

1- Antiviral .

2-Immunomodulating .

3-Anticancer properties

There are at least three types, α, β, and γ, involved in regulation and modulation of immune reactions.

Mechanism of action

Interferon alfa appears to function by

1-Induction of intracellular signals .

2-Binding to specific cell membrane receptors,

3-Resulting in inhibition of viral penetration, translation, transcription, protein processing, maturation .

Clinical uses

1-Treatment of hepatitis B and C .

2- Cancers such as hairy cell .

3-Leukemia

Adverse effects:

1- The principal dose-limiting toxicities are bone marrow suppression including granulocytopenia .

2-Neurotoxicity characterized by behavioral disturbances; severe fatigue and weight loss