"Antiviral Drugs Chemotherapy"

Vaccines have to date occupied the central position in attempts to control virus infections. Vaccines are relatively cheap, safe and the immunity is often lifelong. However, some viruses and for some reasons are not fully amenable to this approach such as Influenza, Herpesviruses, retroviruses and rhinoviruses. So, there is a need for antiviral drugs active against viruses for which vaccines are not available or not highly effective because of a multiplicity of serotypes (e.g. rhinoviruses) or constantly changing virus (e.g. Influenza and HIV).

However development and use of drugs chemotherapy very difficult and little because:

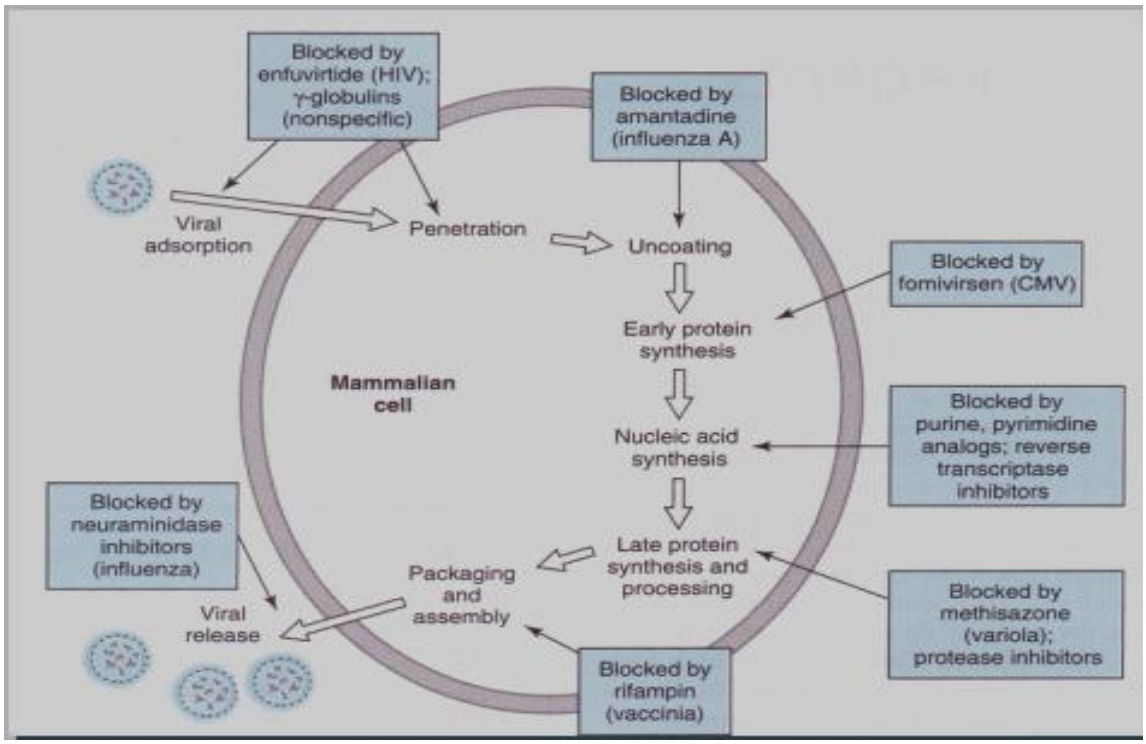
- The viruses are obligate intracellular parasites so it's difficulty to induce selective toxicity against viruses.
- Multiplicity of serotypes and this mean the emergency of drugs resistant by viral mutant.
- Latent infection, some viruses are latent in the cells e.g. HSV.
- Drugs are relatively ineffective because most multiplication of virus take place before diagnosis is made and many cycle of replication occur during I.P. when the health of patient in well.

We need antiviral drugs:

- Against viruses to which vaccine are not available
- To reduce of morbidity and economic loss due to viral infection
- Treatment of immunocompromised patients.

Antiviral drugs targeted the following stages in viral replication:

- Cell entry (attachment and penetration)
- Uncoating
- Transcription of viral genome
- Translation
- Assembly of virion components
- Release



"Antiviral drugs targeted stages of viral replication"

Chemical structure of antiviral drugs:

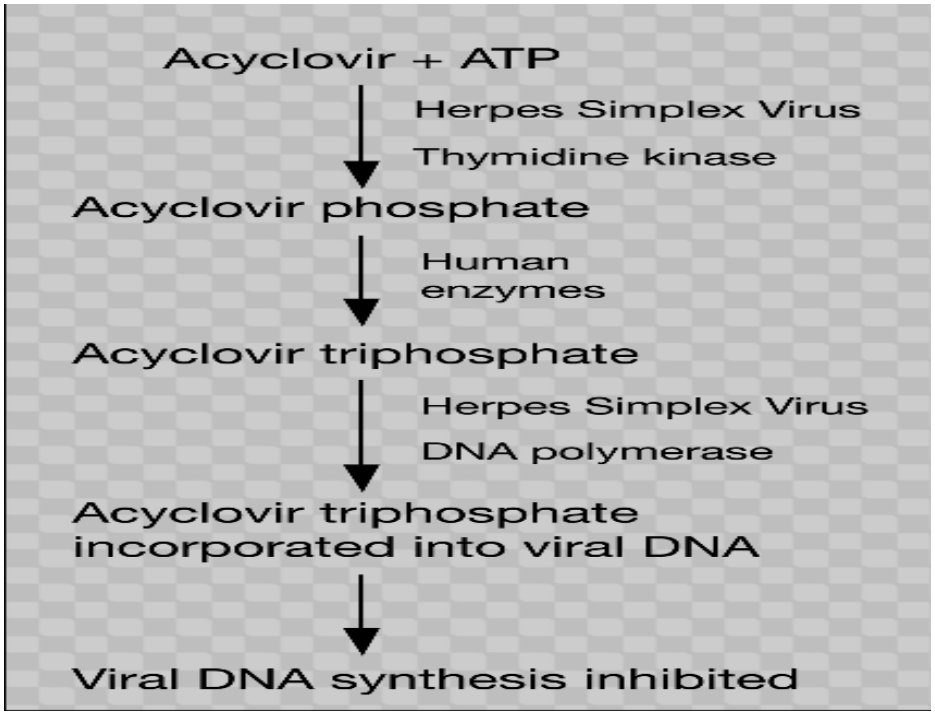
A. Nucleoside Analogue:

Particularly include acyclovir (against HSV) and AZT (against HIV), (Nucleoside analogue… Nucleoside "sugar nitrogen base") , use topically in treatment of eye herpetic lesion, intravenously effect against HSV-1 encephalitis and oral administered for treatment of genital herpes and herpetic lesion in immunocompromised patients…. (but not against latent infection in ganglia).

1- Acyclovir:

Mode of action:

Acyclovir is name as Acycloquanosin or Zovirax, it's converted by viral thymidine kinase to acyclovir monophosphate which is converted by host cell kinases to acyclovir triphosphate (ACV- TP) . ACV-TP act as competitively inhibits and inactivates HSV- specific DNA polymerase preventing viral DNA synthesis without effecting the normal cellular processes.



"Mode of action of Acyclovir"

Microbiology:

Acyclovir is active against most species in the herpesvirus family:

- Herpes simplex virus type 1 (HSV1)
- Herpes simplex virus type 2 (HSV2)
- Varicella zoster virus (VZV)
- Epstein – Bar virus (EBV)
- Cytomegalovirus (CMV)

2-Ganciclovir:

Mode of action:

Act against Cytomegalovirus , name as (Methyl quinine derivatives) inhibition of viral DNA polymerase by the same mechanism of Acyclovir but CMV not have thymidine kinase so directly acting upon by cellular kinase inhibit viral DNA polymerase.

3-Idoxuridine:

Mode of action:

Used topically in treatment of keratoconjunctivitis due to HSV. It's not use systemically because it's effect against cellular DNA so too toxic. Name as (IDU, IUDR). It is halogenated pyrimidine so incorporated into viral and cellular DNA after phosphorylation by cellular kinase mis matching bairing of quinine.

4-Vidarabine:

Mode of action:

Name as arabinofuranosyladenine (Ara-A). It's purine analogue like action of acyclovir, effect against VZV, CMV, and HSV. Used topically.

5-Trifluridine:

Mode of action:

Name as trifluorothymidine (TFT). It is an anti- herpesvirus antiviral drug used primarily on the eye topically for herpes keratitis. It's fluorinated pyrimidine nucleoside incorporated into viral DNA replication CF3 group added to the uracil components blocks base pairing.

6-Ribavirine:

Mode of action:

Effective against DNA and RNA viruses, nucleoside analogue act against synthesis of viral mRNA. Use in treatment of Syncytial respiratory virus (RSV) and influenza virus and giving I.V for treatment of Lassa fever.

7-Zidovudine:

Mode of action:

Invention in 1987 as first anti virus drug for treatment of HIV orally. Act against HIV, EBV and HBV. Named as (AZT, Qzido thymidine or Retrovir). It's thymidine analogue use against retroviruses because it's reverse transcription inhibitor. **Mode of action**: Zidovudine phosphorylated by cellular kinase form zidovudine triphosphate which incorporated into viral DNA proviral and inhibit the action of viral reverse transcriptase block viral synthesis.

8-Dianosin:

Invented in 1991. Name as Dideoxyinosin (DDI), inhibit HIV reverse transcriptase and blocking synthesis of provirral DNA.

9-Zaicilabine:

Invented in 1992. Reverse transcriptase inhibitor. Act against (Hepatitis B virus) HBV.

10-Stavudin:

Invented in 1984. Name as (duT). Act against HIV.

11-Lamivudin:

Invented in 1995. Reverse transcriptase inhibitor. Act against HIV and HBV.

B-Nucleotide Analogue:

Cidofavire:

Mode of action:

Invented in 1996. Act against CMV. Inhibit provirral DNA polymerase so terminate growing of DNA chain.

C-Non nucleoside reverse transcriptase inhibitors:

Nevirapin:

Mode of action:

Invented in 1996. Act against HIV. Bind directly to reverse transcriptase enzyme.

D-Protease inhibitors:

1-Indinavire……. HIV 1996

2-Ritonavire…….HIV 1996

3-Saquinavire….. HIV 1995

Mode of action:

They inhibit protease required at late stage of replication to cleavage structural protein to form mature viruses.

Other types of antiviral agents:

Foscarent: it's a structural mimic of the anion pyrophosphate that selectively inhibits the pyrophosphate binding site on viral DNA polymerases at concentration do not affect human DNA polymerases. Action against HSV, CMV, EBV, HBV and Retro viruses.

Methisazone: it's inhibit protein synthesis of pox viruses by blocking translation of late mRNA.

Interferons:

Are a group of host coded proteins made and releases by host cells in response to presence of pathogens such as viruses, bacteria, parasites and tumor cells. In a typical scenario a virus- infected cell will release interferons causing nearby cells to heighten their anti- viral defenses. IFNs belong to the large class of proteins known as cytokines. Interferons are named for their ability to "interfere" with viral replication.

Types of Interferons:

- **Interferon type I:** present in humans are IFN-α (produce by leukocyte and induced by DS (RNA) viruses and IFN-β (produced by fibroblast and induced by DS (DNA) viruses.
- **Interferon type II:** class of IFN-γ (produced by lymphocytes and induced by mitogens)
- **Interferon type III:** signal through a receptor complex consisting of IL10R2 and IFNR1. It is important in some type of virus infection.

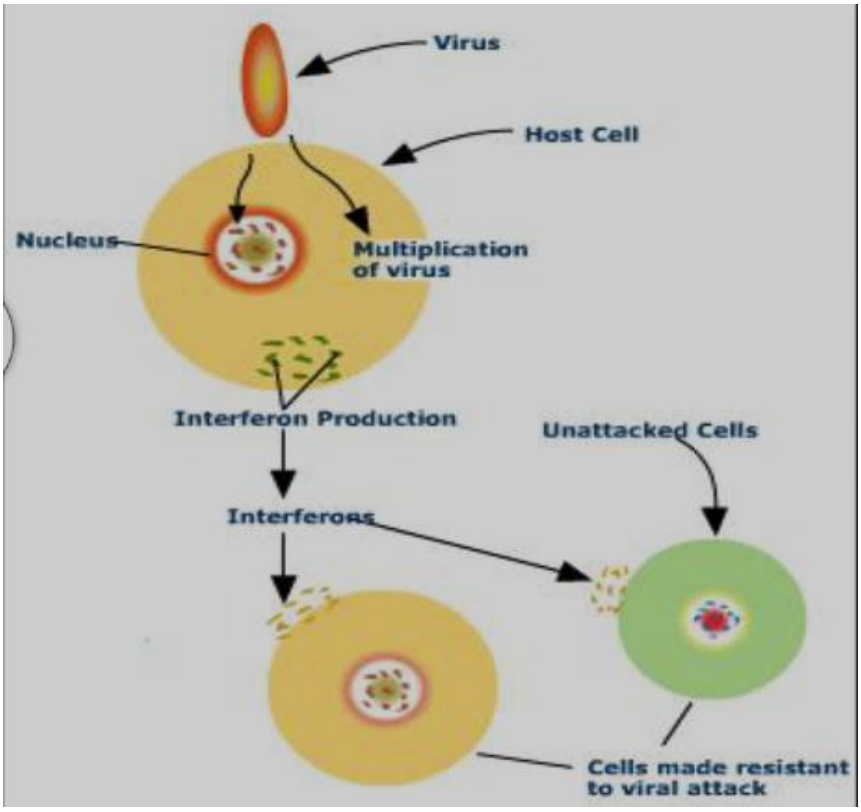
Inducers of interferon synthesis:

1. RNA viruses stronger than DNA viruses.
2. DS RNA
3. Bacterial endotoxins and mitogens.

Mode of action:

It's host specific not viral species specific, play important role in defense against viral infections:

- Viral infection induce production of interferon from the host cell
- Interferon bind to uninfected cells and stimulate these cell to produce of enzyme or protein (antiviral protein) these including:
  - Protein kinase (ds RNA dependent phosphorylation of inactivation of cellular inhibition factor leading to inhibition of protein synthesis).
  - Oligonucleotide synthesis (activation of cellular endonuclease leading to viral mRNA degradation).
  - Cellular endokinase.
- These antiviral protein blocking translation of mRNA to viral protein



"Role of Interferon in viral infection"

Interferons resistant:

Some of viruses counteract interferons activity through:

- Production of specific viral protein blocking activation of protein kinase e.g. Adenovirus and Herpesviruses.
- Neutralization of IFN-γ receptors
- Activation cellular inhibitor of protein kinase e.g. Influenza viruses and polio v.