Microbiology

◉ Sheet ○ Slides

Number : 6

Done by : Tala Ashour

Corrected by: Noor Isbeih

Subject: Virology

Doctor: Antiviral drugs 1

00/00/0000

.....

Antiviral Drugs

Review

- All DNA viruses replicate in the nucleus except for "pox virus".
- All RNA viruses replicate in the cytoplasm except for "HIV, influenza" viruses.
- The most antigenic parts of the virus are the spikes and glycoproteins.
- Viruses are obligate intracellular parasites.
- They do not have a metabolic machinery of their own they use the host enzymes.
- Degree of dependence on the host cell differs within virus's types, i.e. DNA viruses are more dependent on the host that RNA viruses (remember RNA viruses have their own replication enzymes).

Most multiplications takes place before diagnosis is made, most of the time especially in acute infections, such as Respiratory Tract Infection ,once the virus enter into the body, it has a short incubation period "one to five days" and once the virus enter it starts to replicate. And the virus is introduced and replicated before even the signs and symptoms appear so for certain viral infections the person is contagious before even knowing that he has the infection such as Measles and Mumps viruses which are common among children.

Because the virus is being replicated and produced and shed into the secretions and the patient without being aware will transmit the disease to others through contacting without knowing that he's infected.

1-Many antiviral drugs are purine and pyridine analogs.

- Purine analogs meaning they mimic or they have a structure which is similar to -A, G- nucleotides, Pyridine analogs have a structure similar to T, C nucleotides.
- These drugs work on newly formed replicating viruses.
- They replace the original nucleotides therefore preventing further addition of nucleotides after that point, so the replication process will stop.

2-Many antiviral drugs are pro-drugs

- In the inactive form of the drug
- In order for this drug to be activated it requires certain enzymes,
- Whether a cellular or viral enzymes in order to phosphorylate or activate the drug.

Is that good or bad?

- If it needs activation by a viral enzyme it will work only on the cells that were infected with the virus.
- The drug is given systematically, but it will only be active in the cells which are infected with the virus because inside those cells we have availability of the viral enzymes that will activate the drug
- The advantages of this is minimization of the side effects

If the drug is activated by cellular enzymes it will work on several cells thus increasing the side effects and cause harm to the body.

- But before the government give license to the drug they measure the degree of harm it cause to patients, usually the benefit of using the drug outweighs the harm it cause
- ”Remember benefit/harm ratio"

- Most of the time, although the drug is activated by cellular enzymes it has higher affinity toward the viral nucleic acid more than cellular nucleic acid.

Antiviral drugs inhibit active replication:

So the viral replication resumes after drug removal, it only affects the actively replicating or newly produced viruses, so the virus that has replicated is not going to be affected, (they affect the viruses that will be formed after the drug is taken).

- So they don’t work on latent viruses.

Review about Latency:

- Human papilloma virus and Herpes virus are examples on latent viruses.
- HIV and Rabies viruses have long incubation period and they are not latent viruses, (some references considers HIV as latent virus but for sure it doesn't achieve the latency meaning).
- In the Herpes family we have 8 genera, human herpes virus from 1 to 8.
- More specific naming Herpes simplex virus 1, Herpes simplex virus 2, Herpes varicella-zoster virus, Epstein-barr virus, cytomegalovirus.
- Those five correspond to human herpes virus from 1 to 5 accordingly.
- Human herpes virus 6 and 7 (no common name).
- Human herpes virus 8: Kaposi sarcoma-associated virus (Kaposi sarcoma is a dermatological lesion seen in AIDS patients).

- Varicella-zoster virus associated with chicken-pox in during childhood(الجدري المائي).

- 7-10 days the child recover completely but the virus never exits the body.

Latent viruses are associated with two phases of illness:

1-Acute phase of illness: the patient becomes symptomatic then after recovery the virus goes and seeks a place to hide usually in dorsal root ganglia. It hides and stays dormant خامل but it is not being completely cleared from the infected body.

- Hides in a form of circular extrachromosomal DNA, and it doesn't integrate with the host genome.

2-Latent phase of illness

Conditions of latency: presence of the full genome or a part of the genome in the dormant cells, production only of very early proteins. "Some references may say transcription of very early enzymes other say production".

- So we said that antiviral drugs don't affect latent viruses, because they are non-replicating viruses.

Let's talk a little bit more about **chicken Pox**:

They remain dormant in the dorsal cell ganglia, they become active again at any suppression of the immune system (AIDS, immuno-suppressants drugs) also at old age will reactivate the cells from their sleep.

The primary infection caused by herpes virus is asymptomatic, and as the reactivation occurs the symptoms appear.

- Ex: herpes fever blisters (stress ---immunosuppression----reactivation---- symptoms).
- Reactivation factors of herpes fever blisters: stress, fever, UV light.
- Varicella-zoster virus needs a huge drop in immunity in order to reactivate (seen in elderly).

Two theories of reactivation:

1-At the latent phase the virus is continuously replicating but at very slow rate and once the cell becomes unable to cope with the amount of virus it releases the virus.

2-metabolic changes occur within the cell which lead to reactivate these latent virus therefore replication occurs and the virus is released into the peripheral nerves then goes to the skin.

- From the thoracic nerves (mainly) to the dermatomes (nerve endings in the skin).

- In addition to the antiviral drugs the immune system plays an important role and it's essential for the eradication and the clearance of the virus from the body. (They work side by side).
- So the antiviral drugs play an **additive role or a synergistic role** in addition to the immune system.
- We **don't** give antiviral drugs for influenza, common cold and gastroenteritis. Symptomatic treatment will be given (like vitamin c, etc).
- In case of chronic infections such as (HIV, Hepatitis B, and C infection) we give antiviral drugs in order to elongate the incubation period.
- Hepatitis B (85% acute infections / 15% chronic).
- Hepatitis C (15% acute infections / 85% chronic).

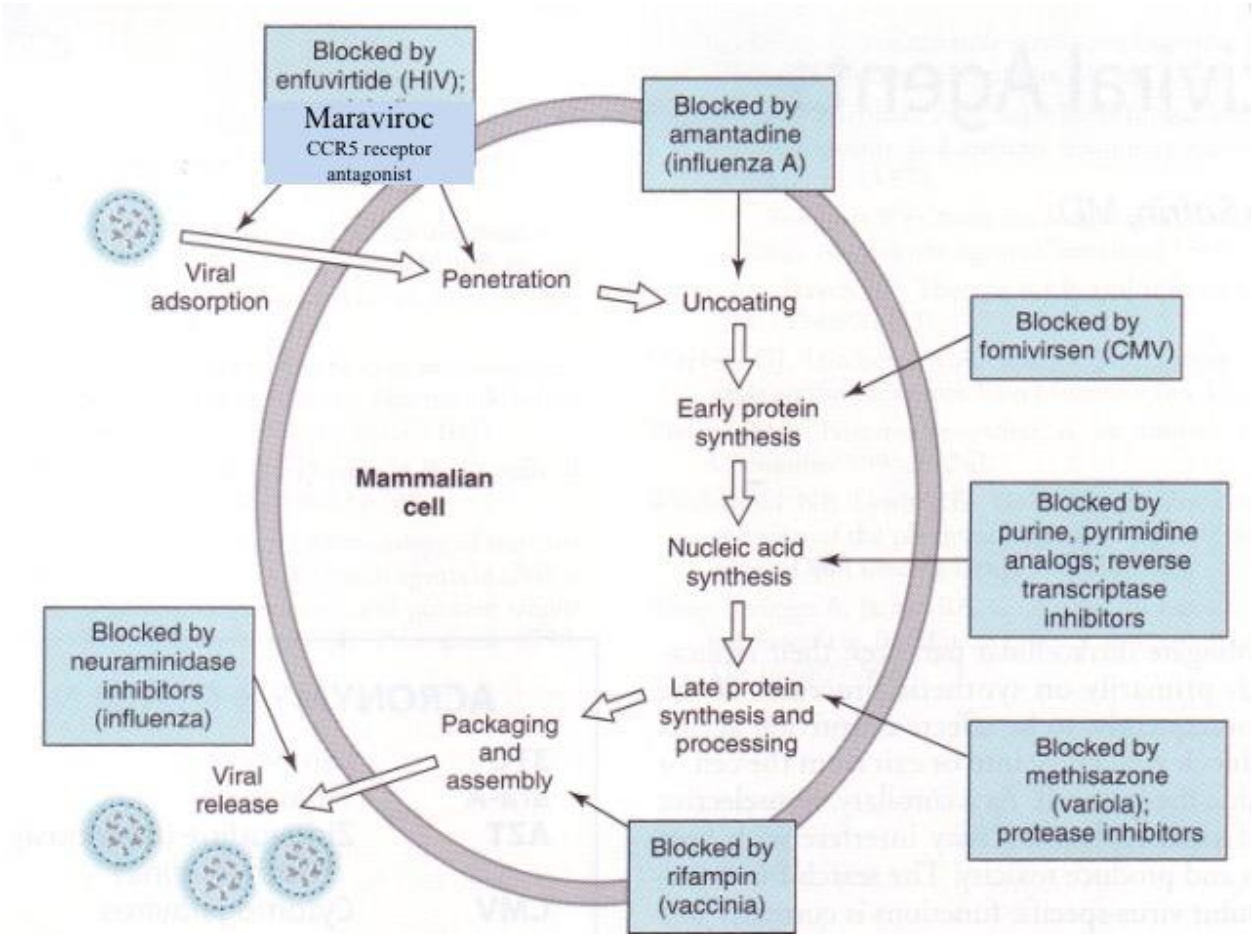
- Notice that AIDS differ from HIV infection. (AIDS means complete collapse of the immune system i.e.CD4 count below 200).

- Clinical efficacy depends on: achieving an inhibitory concentration at the site of infection "infected cells" just like the antibiotics.
- Antivirals need to have a good conc. In order to prevent the replication of the virus otherwise if you have some optimum conc. This would lead to compensatory mutation which will lead to a resistance to the antiviral drugs from the virus "just like the bacteria".

Antiviral drugs and stages of viral replication:

Cell entry, attachment, Penetration, Uncoating, Transcription, translation, Assembly, and release.

We have antiviral drugs that could target these different steps of replication.



1-Viral adsorption: enfuvirtide, Fuzeon, for HIV, Maraviroc also Target the CCR5 receptor antagonist.
"We said that in HIV we need receptors and co-receptors" So the first one blocks the receptor the second one block the co-receptor.

2- Uncoating step: the dis-assembly of the capsid and the release of the genetic material into the cytoplasm, it's inhibited by. • Amantadine / Rimantadine In the case of influenza A.

3- Early proteins synthesis: "Fomivirsen "cytomegalovirus.

4- Nucleic acid synthesis: blocked by -purine-pyrimidine analogs and reverse transcriptase inhibitors.

5-late proteins synthesis
6- Assembly
7-Release: we have neuraminidase inhibitors such as Oseltamivir "Tamiflu" for "influenza A and B".

- Remember neuraminidase is one of influenza glycoproteins.

Antiviral agents by virus:

• Anti-herpesvirus

- Acyclovir / Valacyclovir.

• Famciclovir / Penciclovir.
• Ganciclovir / Cidofovir.
• foscarnet.
• Trifluridine / idoxuridine / Vidarabine.
• Once activated they all become Acyclovir.
The difference is in the bioavailability. If u need a 10mg of Acyclovir you might need 2mg of Valacyclovir or Ganciclovir •
Valacyclovir become exactly the same as Acyclovir.
Famciclovir become exactly Penciclovir
So the dose is reduced according to differences in bioavailability.

Acyclovir & related compounds:

• Valacyclovir is a prodrug of Acyclovir with better bioavailability.

• Famciclovir is hydrolyzed to Penciclovir and has greatest bioavailability

• Penciclovir is used only topically whereas Famciclovir can be administered orally.

- Acyclovir (and its derivatives) are the drugs of choice for herpesvirus (1 and 2 and 3) "can be given iv, topical, orally"

- Ganciclovir is the drug of choice for cytomegalovirus

- Acyclovir is activated by the viral enzymes, thymidine kinase is present in both herpes simplex and chicken pox>>the drug of choice is Acyclovir

The analog inhibits viral DNA-polymerase

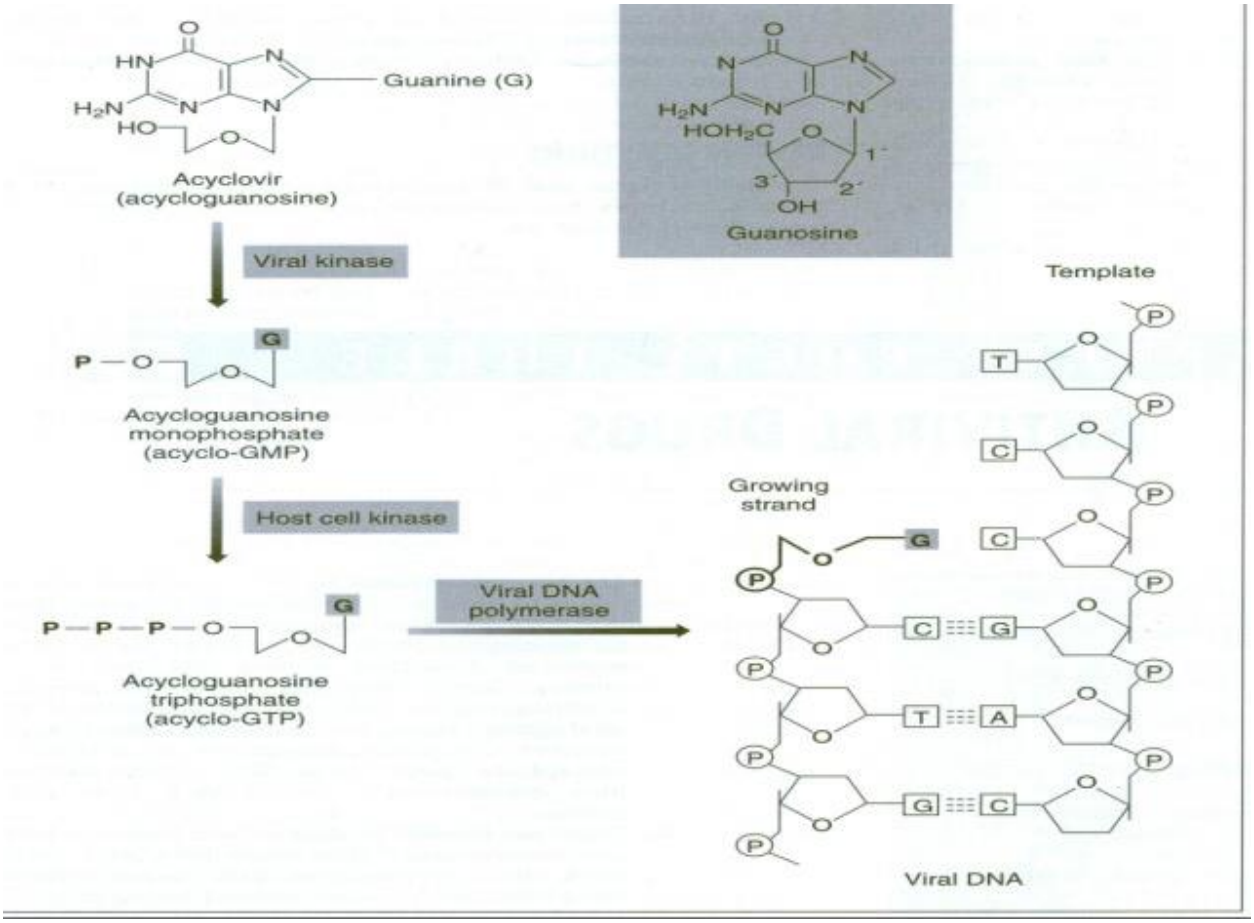
• Incorporation of acyclovir triphosphate into the growing viral DNA chain

• Only actively replicating viruses are inhibited

Ul97 enzyme for cytomegalovirus this enzyme is the one that phosphorylate the Ganciclovir into the active form

• Acyclovir, Valacyclovir, Ganciclovir, Famciclovir, Penciclovir all are guanine nucleoside analogs.

So they mimic guanine "G" Let's talk more about this, since they mimic guanine, when the virus is replicating and the G turn comes they will replace G and get inserted into the genome, this will inhibit further nucleotides from being added to The chain.



The acyclovir >>acycloguanosine>>mono-phosphate acycloguanosine "by the action of the viral kinase">>triphosphate form>>inserted by viral polymerases >>inhibition, Acyclovir is thus selectively activated in cells infected with herpes virus.

• Uninfected cells **do not** phosphorylate acyclovir.

The characteristic mechanism of action of the enzyme "thymidine-kinase" has been developed by scientists to kill tumor cells ,they inject DNA which expresses thymidine kinase so inside these tumor cells there is going to be thymidine kinase then they treat with Ganciclovir, acyclovir so these cells once the drug reach These cells it's going to be active and it's going to stop the replication. It reduces the cancerous mass

Acyclovir: HSV-1, HSV-2, VZV, Shingles "the after latency active form of chicken pox, mostly seen among old people >50”
Ganciclovir / Cidofovir: CMV
Famciclovir: Herpes genitalis and shingles
Foscarnet: HSV, VZV, CMV, HIV
Penciclovir: Herpes labialis
Trifluridine: herpetic keratoconjunctivitis

Pharmacokinetics of Acyclovir:

- Oral bioavailability ~ 20-30%
- Distribution in all body tissues including CNS
- Renal excretion: > 80%
- Half-lives: 2-5 hours
- Administration: Topical, IV, oral

Topical: in case of blusters like those around the mouth. Acyclovir given to shorten the length of the lesion. (Herpes labialis)
Oral: shingles need to be treated with acyclovir orally and we need a strong pain killer because most of the time the reactivation of VZV is associated with pain "replicate in the nerves"
IV: herpes meningitis, in Encephalitis.

Therapeutic uses:

Acyclovir is the drug of choice for:
- HSV Genital infections
- HSV encephalitis.
- HSV infections in immunocompromised patient

Ganciclovir is the drug of choice for:
- CMV retinitis in immunocompromised patient "usually the CMV is seen more in immunocompromised, in immunocompetent they might be asymptomatic"

- This is one of the features of the latent viruses you might be infected with herpesvirus, even the recurrence sore fever, herpes megalis, fever blister most of the time it's the recurrence infection not the first time of infection, so when you see the case it could be the second time of infection. "Not the primary infection,

you have been infected previously most of the time the primary infection is asymptomatic and the infection encountering is the reactivation of the virus"

• This reoccurrence is not only associated with defective immune system, there are other triggering factors like exposure to the sun, chemicals

• In CMV we usually talk about immunocompromised patients due to immune suppression therapy and HIV patient's . this is the time where the immune system collapse and all these latent viruses might become re-activated

• So CMV is rarely seen as an infection, can be seen in immunocompetent patient very rarely but more associated with immunocompromised

• Prevention of CMV disease in transplant patients

Cidofovir:

• It is approved for the treatment of CMV retinitis in immunocompromised patients and Adenovirus infections

When we talk about adenovirus we should consider that there is no specific treatment for adenoviral infection, but they found that treating "especially those in military new" have more frequent lower respiratory tract infections with adeno virus so when we treat them with Cidofovir they would benefit from it Also in vaccination for adenoviral infections for the rest of people there is no vaccine But for early military soldiers this treatment is beneficial.
So they made them a vaccine for this group of patients only

• It is a nucleotide analog of cytosine – no phosphorylation required. "This means that this drug is not a pro-drug" so it's going to have effect on viral infected and non-viral infected cells

• It inhibits viral DNA synthesis
• Available for IV, intravitreal injections, topical
• Nephrotoxicity is a major disadvantage. •

- **Vidarabine is a nucleoside analog. (Adenosine**)

Respiratory viral infections:

1-Influenza –
• Amantadine / Rimantadine "Inhibitors of the uncoating>>don't need enzyme, work in influenza A"

• Oseltamivir "Tamiflu _trade name" Zanamivir
(Neuraminidase inhibitors)

Influenza A, B

The reason why the drugs are different:
Influenza -A has two types of glycoproteins HA" hemagglutinin" attachment, NA "neuraminidase" in the release of the virus, and the attachment

NA it keeps the virus attached to the host cell where the virus is replicated, then a bond is cleaved to set the virus for release if we treat with na-inhibitors you will inhibit the release of the virus, so by this mechanism the virus is inhibited

Amantadine and Rimantadine work specifically on the uncoating step in m-proteins which unique for Influenza -A and not present in Influenza -B

2-RSV (respiratory syncytial virus).

- Treated with Ribavirin
- Bronchiolitis – pneumonia in infant "in age below 6 month"
- The age group 2-6 months.
- The name came because of the ability of the virus to cause syncytia “multinucleated giant cells"

How does the syncytia occur?

- One of the cytopathic effects in pathogenesis

What is the mechanism?

The enveloped viruses once they enter the cell, the envelope fuses with membrane of the host cell and becomes a part of the membrane once the virus enters its going to leave a part of the envelope which has glycoproteins, the cells are close to each other so the neighboring cell will identify this cell because of their receptors and fusion occur ... If more than one cell is infected with the virus you will get a large cell with many nuclei

- RSV is capable of syncytia formation

Inclusion bodies:

- Either cytoplasmic or in the nucleus
- These are remnants of viral replication and they represent the structural proteins "Capsid, spikes"
- The inclusion contain the remnants of the capsid "leftovers" either in the nucleus or the cytoplasm it depends on the type of the virus, if it replicate inside the nucleus we will have inclusion bodies inside the nucleus."
- We have exceptions, CMV replicates in the nucleus but it has both cytoplasmic and nucleic inclusion bodies”

The drug	The virus	Mechanism
enfuvirtide, Fuzeon, Maraviroc	HIV	Target ccr5 ,adsorption
.• Amantadine / Rimantadine	Influenza A	uncoating
fomivirsen	cytomegalovirus	Early synthesis
-purine-pyrimidine analogs and reverse transcriptase inhibitors		Nucleic acid synthesis

Oseltamivir "Tamiflu_trade name" Zanamivir (Neuraminidase inhibitors)	Influenza A,B	release
Ganciclovir	Cytomegalovirus	
Acyclovir **Cidofovir**	Chicken pox CMV, adenovirus "military"	