
◉ Sheet ○ Slides

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# Antivirals

Not all viral infections can be treated. In this lecture, we will discuss the treatment of Herpes simplex virus (1, 2) -HSV- , Cytomegalovirus, respiratory syncytia virus, influenza virus, hepatitis, and, to lesser extent, HIV.

The head of a pin can hold five hundred million rhinoviruses (cause of the common cold). One sneeze can generate an aerosol of cold viruses suspended in the atmosphere for a quarter of an hour, and these viruses are able to infect thousands of people.

Revision of the common infection pathway of any virus (in most of the cases)

1) Adsorption: the virus links to the receptor on the cell.
2) Penetration.
3) Uncoating.
4) Synthesis: in this step, the viruses use the cell machinery to produce new viruses (cell hijacking). Viral enzymes are used; such as DNA and RNA polymerases, reverse transcriptase, and RNA dependent DNA polymerase. RNA polymerase is used for the transcription of proteins. Some viruses integrate their genome into the cell DNA (using integrase), like HIV. After that, the genome is packed in the capsule.
6) Release.

In pharmacology, we want to intervene in these steps, using a drug, to inhibit one of the processes. For example, we can inhibit the adsorption, penetration, uncoating, release and the proteases (which are cutting enzymes). Note that different viral infections are treated with different drugs.

**Viruses are either:**

A- DNA viruses, such as:
1- Varicella-zoster virus (causes shingles).
2- Herpes simplex 1 (causes herpes labialis (oral herpes), genital herpes, & herpes encephalitis). This virus is very common orally, and genitally in women.
3-Epstin Bar virus (linked to Burkitt lymphoma and nasopharyngeal carcinoma).
4-Cytomegalovirus causes viral Pneumonia which is lethal. It infects only immunocompromised patients (such as cancer patients).

B- Or RNA viruses, such as:
1-HIV 2-Rhinovirus. 3-Hepatitis A+C. ( Hepatitis B is DNA virus.)
4-Influenza A+B+C.

# Antimetabolites

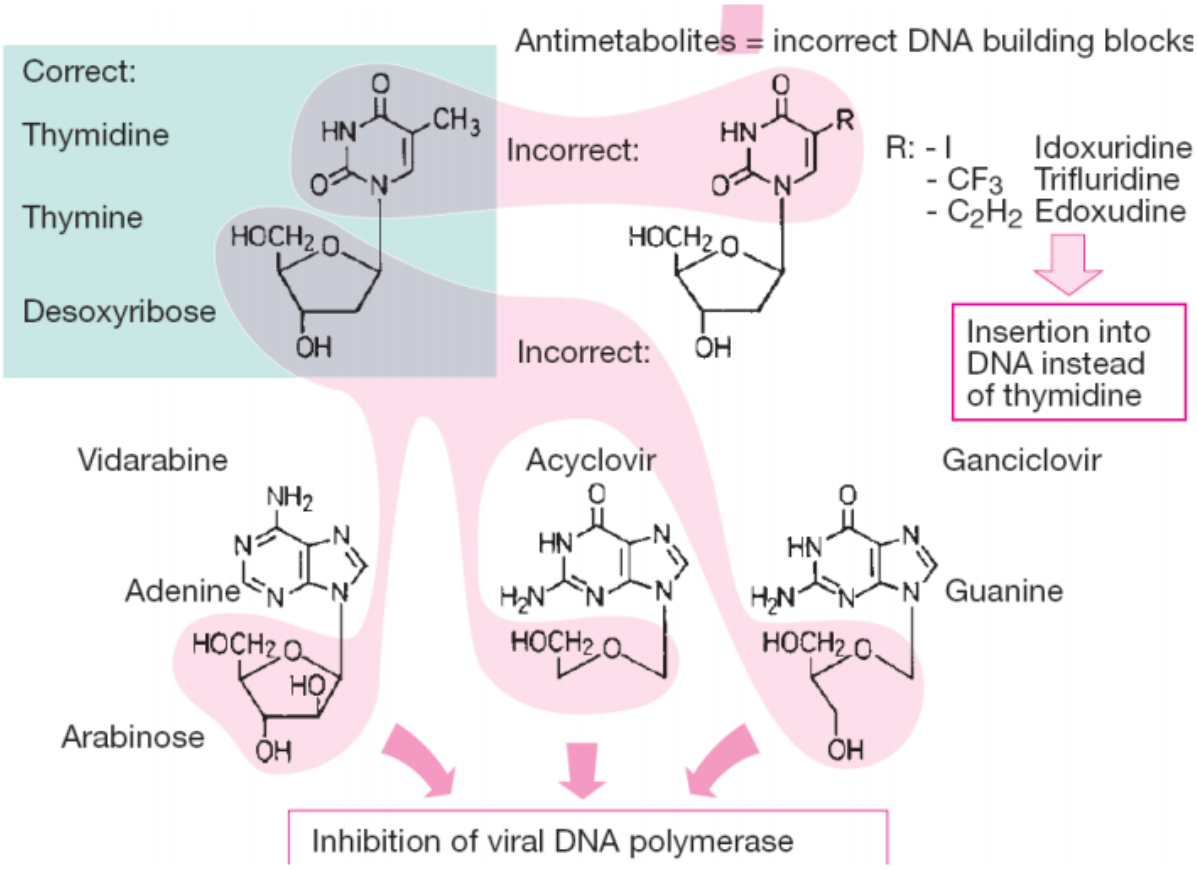
In the 1980s, the idea of viral infection treatment was complex. And because the viruses are intracellular pathogens, we had to kill all dividing cells, infected or not, by antimetabolite drugs which are similar to chemotherapeutic drugs, with very bad side effects. With the progress of time pharmacists made beautiful antimetabolite drug which is *Acyclovir*.

## Acyclovir

This drug is the most commonly used drug to treat viral infections caused by herpes viruses. It is an antimetabolite antiviral, which means that it inhibits the synthesis of DNA. It resembles nucleosides structure; they look like T or G (notice the structure in the slides).

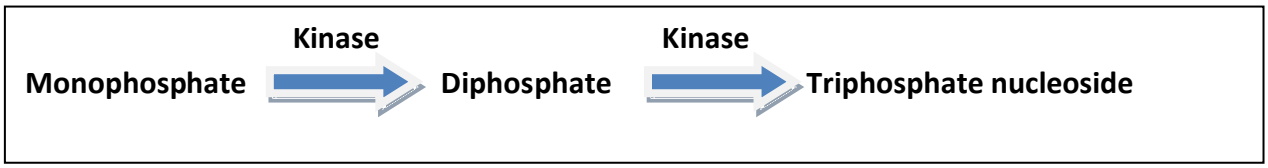
The Antimetabolites (like Acyclovir), act as false nucleosides; when incorporated within the viral DNA, the block the continuation of replication, blocking transcription, so the virus cannot replicate anymore and this is called **chain termination**.

- What happens actually is that viral polymerase thinks that this is a true nucleoside; so it incorporates into the DNA and stops the transcription because it is not an actual nucleotide.



What is so special about acyclovir? SELECTIVITY.

Before Acyclovir, we had a problem with selectivity. The virus gets in the cell and hijacks its machinery, the only solution to get rid of the virus is to kill it, and the problem is that if the drug is not selective, it is going to kill replicating cells as well. Most of the antimetabolite drugs are **nucleoside-like**, to become **nucleotide-like** and interfere with the viral DNA, three phosphate groups have to be added to these structures by the enzyme **kinase**.




To appreciate the importance of acyclovir, we are going to compare it with older antivirals.

| **Other antivirals** (slide #6 in antiviral file) not to be memorized. Ex: **Vidarabine** | **Acyclovir**<br>Targeted therapy |
|---|---|
| Old generations depend on the **cellular Thymidine kinase** of the host; it will inhibit the viral DNA polymerase and the human DNA polymerase specially in replicating cells (such as bone marrow). | Acyclovir is only recognized by the **viral Thymidine kinase**; acyclovir is only activated (1$^{st}$ step of phosphorylation) in infected cells and does not affect the replication of normal cells.<br>* Acyclovir is 30 folds more potent against viral enzymes than against host enzymes. |
| Toxic to replicating cells of the host causing bone marrow suppression (very bad) | Not toxic |
| No longer used | Very commonly used |

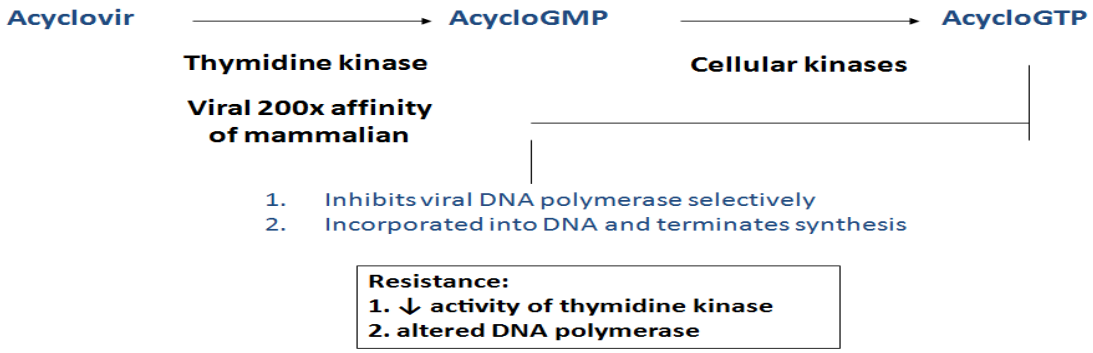
Note: this kinase's selectivity is only observed in the kinase that mediates the **initial phosphorylation step** which turns the X nucleoside into an X-monophosphate. The remaining two steps are mediated by cellular kinases in both acyclovir and the other group of antivirals.

Acyclovir is active against: Herpes simplex, Varicella-zoster, and 1/2 activity against Cytomegalovirus. It is rapidly broken down in cells. It is orally active and relatively non-toxic systemically.

**Q**: Is there a resistance against acyclovir? Yes, but not very common. The resistance against acyclovir develops in two ways:

1) Decreasing the activity of viral kinases.
2) Altering DNA polymerase.

RNA viruses are more prone to mutations than DNA viruses.




Clinical cases:

Remember: Acyclovir is used to treat : Herpes simplex infections (genital herpes, labialis -cold sores- and herpes encephalitis).

A patient had herpes labialis infection and went to the doctor, and the doctor refused to give him a drug, why??
To prescribe an active treatment against viral infections, you have to treat the patient from the beginning, before the spread of the virus throughout the body (the spreading takes 36 hours after the manifestation of symptoms). If the doctor gives a DNA synthesis inhibitor, the virus may have already been spread and the drug will not be active.

If the doctor may decide to prescribe a drug in case of HSV which makes mouth labialis the viral spread; and that may happen in severe cases to decrease the severity of labialis and the duration of infection. In this case, the duration would be decreased by one day (normally labialis takes 7 days).
Usually we treat labialis by giving **Acyclovir** (200 mg 5 times a day or 400mg 3 times a day) for seven days to reduce the duration by one day, in addition to the reduction of the severity. Therefore, treatment is not necessary but if in severe cases.

The usage of antiviral drugs does not really cure the infection. It usually reduces the duration of the infection by 1-2 days and the severity of infection.

In genital herpes cases (very common in the west), which are usually severe, oral acyclovir shortens the duration of symptoms by approximately 2 days from 6 days to 4 day , the one and half day is critical because genital herpes is severe.

In the treatment of encephalitis IV Acyclovir is given.

The treatment of chickenpox in immunocompromised patients and pregnant woman is acyclovir (200 mg  5 times a day or 400mg 3 times a day) for seven days. Also, Acyclovir is the drug of choice to decrease the duration and severity of Varicella-zoster which causes shingles.

What does this mean?

It means that in the treatment of viral infection we deal with the situation differently. We are going to prescribe the drugs while knowing that drugs are not magical and will not cure patients instantly. Usually, genital herpes will take time (6 days) depending on the infection and its sight. We will tell the patient that this drug will only *shorten the duration of symptoms* by 2 days. This is the bottom line of the treatment. So, if my patient has a recurrent genital herpes, the herpes treatment is only going to benefit by 2 days.

**The acyclovir is used prophylactically** with patients who have been treated with radiotherapy, because they are in danger of infection by reactivation of latent viruses. But remember we do not give a whole dose in prophylaxis; instead, we give half of dose (200mg twice a day or three times a days).

A research done on our population found that 85- 90% of us have a latent HSV (herpes simplex virus) in the mouth. So when the patient gets immunocompromised, stressed, exposed to sun...etc, patients will become susceptible toward latent viruses (recurrence), thus infected, so we need to give them prophylactic acyclovir. Recurrence of HSV is to have oral or genital herpes infection more than 4 times a year.

Acyclovir is post treatment suppression in patients with frequent recurrences of genital herpes. Genital herpes is a big problem for ladies. In post treatment suppression the lady has recurrence; we give acyclovir for 7 days. Because the viral load will increase after finish of treatment, we continue giving acyclovir as post treatment suppression in order to decrease viral load. So, after the 7-day treatment, half of the dose is given twice daily for 1, 2, 3... years (usually for 6 months).

Prophylaxis vs. post treatment suppression:

Prophylactic treatment is given before the manifestation of the disease; whereas post treatment suppression is applied after the disease manifestation.

Topical acyclovir cream is substantially less effective than oral therapy for primary HSV infection. It is of no benefit in treating recurrent genital herpes and labialis.

Acyclovir adverse effects:

1- Generally, it causes nausea, vomiting, and diarrhea. Also, it can induce headache but after 3 days will hide.

2- When acyclovir is administered IV, it causes Renal insufficiency and neurologic toxicity. So, acyclovir is not given as a rapid infusion or bolus dose. Such side effect is more pronounced with patients with dehydration and preexisting renal impairment. Adequate hydration (using normal saline, 1-2 liters daily) which accelerates the excretion of the drug outside the body, a slower rate of infusion, and dosing based on renal function may reduce the renal toxicity of drugs.

The absorption of acyclovir is poor in GI tract. Linking it with ester link makes it more absorbable. Such development is applied in valaciclovir. So we can decrease the dose and frequency of administration (twice a day instead of four times a day).

## Ganciclovir

Ganciclovir is a very close brother to the acyclovir (notice the structural differences). The modification on acyclovir structure decreases its selectivity (affects the side effects) and makes ganciclovir more specific for cytomegalovirus.

Ganciclovir is active against all Herpes viruses including CMV (100 time than acyclovir), and has Low oral bioavailability, so it is given I.V. Ganciclovir is the drug of choice against CMV infections; including retinitis, pneumonia and colitis.

Ganciclovir adverse effects:

*Bone marrow suppression (leukopenia 40%, thrombocytopenia 20%) and CNS effects (headache, behavioral, psychosis, coma, cnvulsions).

*1/3 of patients have to stop because of adverse effects.
With cancer patients (for example in King Hussein cancer center), CMV is treated with acyclovir IV. After that, if the patient does not respond, we give him Ganciclovir. That is done because of the bad side effects of ganciclovir which are similar to cancer chemotherapeutic drugs.

Sometimes, patient with Herps (I, II, Varicella, CMV) infection, is not responding after being heavily treated acyclovir and ganciclovir, why?

These patients are infected with resistant viruses. So, we have to change the strategy, from antimetabolite drugs (mimicking the nucleoside, getting phosphorylated and getting incorporated into the DNA; thus inhibiting the elongation of the DNA); to a direct DNA polymerase inhibitor by foscarnet.

## Foscarnet

Foscarnet is an inorganic pyrophosphate analog. It is a direct inhibitor of DNA polymerase without an activation by viral Thymidine kinase (the same target for acyclovir, however Foscarnet works from a different angle), and reverse Transcriptase (which converts RNA into DNA), that's why the drug is approved for HIV patients {the problem with HIV is its integrase activity}.

The drug is active against Herpes (I, II, Varicella, CMV) including those resistant to acyclovir and ganciclovir.

What does this mean?

(1) It can be used instead of ganciclovir to treat CMV retinitis and other CMV infections.

(2) It can be used to treat H. simplex resistant to Acyclovir.

(3) HIV

Q: Is the drug approved as a safe drug?
Absolutely NO, nephrotoxicity is a common side effect (25%).

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Now, we will talk about RNA viruses and how to treat them.

### 1- Influenza A&B:

Influenza viruses are continually changing their antigen (glycoprotein), so every year will appear new species of Influenza viruses and new vaccines.

Notice that RNA viruses (such as influenza virus) can develop resistance frequently.

Influenza vaccine:

This vaccine can protect us from some strains of the virus (such as H1N1), and can help in decreasing the influenza severity and incidence (questionable). But this does not mean that it covers all strains; because mutations on the virus are being developed, so the developed vaccine covers the strains the have already been developed, but does not cover what is going to be developed in the future.

We treat influenza with four drugs:

A: Attachment inhibitor:

**1-Rimantadine**
**2. Amantadine**

These inhibit the release of the viral material out of the endosome.

Rimantadine and Amantadine are not used anymore, so forget about them. They have lost their susceptibility thus their approval. All (H1N1 viruses) are resistant to those drugs.

B: Neuraminidase inhibitors: (release inhibitors)

**1. Oseltamivir**
**2. Zanamivir**

Oseltamivir and Zanamivir Both are inhibitors of viral neuraminidase.
Viral neuraminidase catalyzes cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids, a process necessary for release of virus from host cell surfaces. Neuraminidase inhibitors thus prevent release of virions from infected cell. "If you stop this neuraminidase-catalyzed cutting, you will stop the spread of the virus."

When you look up these drugs you will find out that these drugs are useful for combating influenza infections:

| | |
|---|---|
| **zanamivir: by <u>inhalation</u>** | **oseltamivir: <u>orally</u>** |

Because these drugs inhibit virus spread, they are administered as soon as symptoms appear. It is crucial to be within 48 hours because the virus replication is highest between 24-72 hours after onset of illness. When a 5-day course of therapy is initiated within 36-48 hours after the onset of symptoms, the duration of the illness is decreased by 1-2 days compared with patients taking placebo. So we only decrease the duration of infection rather than actually killing the virus and treating the symptoms, so we must be sure that the benefit is more than the risk , the risk here being the development of resistance; so we should not overuse these drugs.

DO NOT FORGET TO STUDY THE DOCTOR'S SLIDES.

“Doctors?" said Ron, looking startled. "Those Muggle nutters that cut people up?”