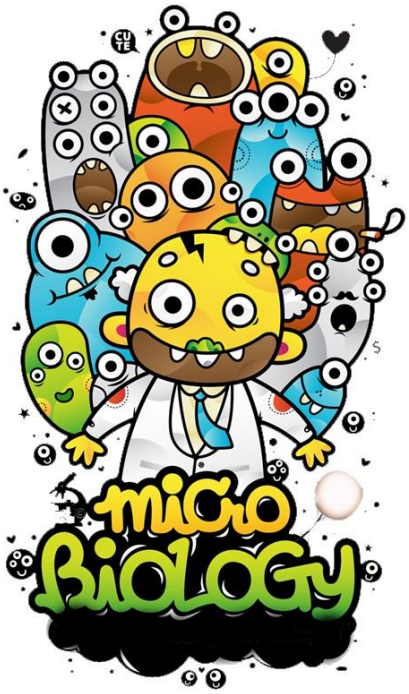

Subject: Antiviral drugs

Lecture No.: 7

Done by: Doaa Kotkot

Corrected by: Mariam Hassoneh

This is the last sheet for Dr.ashraf's material so please study it with some love, and make sure to keep the slides beside you while you're studying this sheet because they're all included and **it only contains additional notes U.U !**

Good luck to all of you ")

^ Slide 4

- Purine (A & G) or Pyrimidine (C & T) analogs :

Most anti-viral drugs belong to this type. Once this type of anti-viral drugs; which acts on genome replication step; is inserted in the viral genome instead of the actual nucleotides in the elongating genome of the replicating virus, it'll lead to viral replication inhibition.

^ Slide 5

- Ex : herpes viruses; when they are latent, the antiviral drugs won't be effective against them.

- We give the antiviral drugs to aid (help , boost) the immune system and not as a substituent for it.

- Inhibitory concentration MUST be enough to cure , which means enough concentration of the drug must be administrated to reach the proper efficacy (to be effective) .

^ Slide6

Antiviral drugs work on different stages of viral replication (each drug acts on a specific stage of viral replication).

^ Slide7

- Anti-viral Drugs target stages of viral replication to block them and so block viral replication .

- Examples :

1. Enfuvirtide and Maraviroc : Both target HIV adsorption or penetration.

2. Amantadine : Targets Influenza A uncoating.

3. Fomivirsen : Targets CMV (Cytomegalo virus فيروس مضخم للخلايا) early protein synthesis.

4. Purine, pyrimidine analogs : Target nucleic acid synthesis by blockage of genome replication as previously mentioned.

5. Methisazone (variola) : Targets late protein synthesis.

Ex: In case of HIV; which is synthesized as a poly protein then further cleaved by proteases to enter assembly step , if poly protein cleavage into individual proteins is inhibited , this will prevent assembly of new viruses .

6. Rifampin (vaccinia) : Targets packaging and assembly.

7. Neuraminidase inhibitors : Target Influenza release.

* Note: The hemagglutinin (primary function of it is attachment to receptors on target cells) and neuraminidase (acts in release step by cleaving the bond between host cell receptors and sialic acid) glycoproteins are important in the ability of the virus to cause influenza; HA has a role in adsorption and NA has a role in release stage . If we inhibited release , we would decrease the viral load.

- Antiviral drugs are grouped into:

1. Anti-Herpes virus drugs (slide 8)

^ Slides 9 - 14

* Note: The Herpes family of viruses includes 8 different viruses that affect human beings.

The viruses are known by numbers as human herpes virus 1 through 8 (HHV1 - HHV8) , and can also be known as HSV (Herpes Simplex Virus).

1. HSV1(above the waist infections) : It is typically the cause of cold sores around the mouth (Herpes labialis).

2. HSV2 (Below the waist) : It typically causes genital herpes.

3. HSV3 (varicella zoster) : Causes chickenpox. It can also cause a recurrent virus infection of the skin, which is called herpes zoster or shingles.

* This is an example of latency; during childhood the patient have chickenpox, then the virus inters the latent phase and lies dormant in

the body and causes nothing. During adulthood and drop in the immune system, it will be reactivated again and cause shingles.

4. HSV4 (Epstein-Barr virus)

5. HSV5 is the official name of cytomegalovirus (CMV)

6. HSV6

7. HSV7

8. HSV8 (Kaposi's sarcoma-associated herpes virus).

*Remember ،it's a DNA virus.

a. Acyclovir / Valacyclovir

- Acyclovir is activated by a viral enzyme (viral specific enzyme called thymidine kinase).

- What's the difference between acyclovir and valacyclovir ?!

There’s actually NO DIFFERENCE between them because once they’re phosphorylated (activated) by thymidine kinase , they become the same . The difference is in bioavailability; valacyclovir has a higher bioavailability than acyclovir , so the dosage of valacyclovir must be less than that for acyclovir, because the effective conc. of the drug is going to be the same if we started with 10ml acyclovir OR 5ml valacyclovir for example (not clinically actual) .

b. Famciclovir / Penciclovir

have the same concept above.

c. Gancyclovir / Cidofovir : the drug of choice for CMV .

* Note: CMV has the enzyme UL97 which will activate the prodrug Gancyclovir.

- What does (Guanine nucleoside analogs) mean ?? They are inserted instead of guanine but have a different structure than it, so they prevent further polymerase reading, preventing by that further addition of nucleotides after this point and so prevent virus replication.

- If the antiviral drug ;which is a prodrug; was activated by a viral enzyme, it will be more specific than if it was activated by a cellular enzyme , so less side effects on other non- infected cells.

^ Slide15

* Numbers aren't important :P

- Acyclovir is administered :

1. Orally : for cold sore or fever blister which is caused by HSV-1 , and mostly it's a reactivation not a primary infection.

2. Topically : for shingles . Actually the drug is taken by two routes; orally, and topically (for the rash).

3. IV : for meningitis or encephalitis which are caused by HSV. In these cases, you should have high suspicion that the cause is Herpes virus , so you need to treat the patient immediately with acyclovir.

^ Slide 17

- When we talk about HSV infections such as in shingles, can the patient get out of this round of reactivation without giving him antiviral drugs ? Or it is a must to give him antiviral drugs ?

In other words , if we didn't give the patient any antiviral drug, would we cause harm to him ??

It's not necessary to give antiviral drugs to cure; because the patient will draw out after a short period (5-10 days) , but if we give it, **symptoms length will be shortened** . On the other hand, if we are talking about HSV meningitis or encephalitis; an inflammation of the brain matter which leads to its liquefaction and causes death in most cases; it's a must to give the patient antiviral drugs .

- CMV virus is a member of HSV family and most infections by it are seen in immune compromised patients. Suppose the patient got infected with CMV virus which can lie dormant inside the body , and had a chronic illness or was taking immune suppressing drugs (such as in transplant patient), in case the patient's health deteriorated , you should think of reactivation of that virus and prescribe Ganciclovir to aid the immune system.

^ Slide18

- Cidofovir is not specific for adenovirus since actually there is no specific anti- viral drug to treat adenovirus, but they found improvement in patients who had respiratory tract infection by Adenovirus when treated with Cidofovir though it's not a routine.

- Cidofovir is not a prodrug which means :

1. No phosphorylation required.
2. It doesn't need to be activated by either viral or cellular enzyme so it can affect both; infected and non-infected cells , and so the risk of side effects is higher.
   * Note : Always before approving any drug, they do the necessary trials and experiments on it, and it must have more inhibition role on viral genome than that on cellular genome to be approved.

^ Slide21 not included =)

^ Slide23

When we say that oral bioavailability of a drug 10-20% , this means that the drug can be given orally but the amount at the site of action is going to be very low , then we should give a high dose, but as a result we may increase the side effects on the patient , SO it would be better to find an alternative route to be given in inhibitory conc. without the need of increasing the dose.

2. Anti-viral drugs used to treat respiratory infections.

a. Anti - Influenza drugs (slide 25)

- If you want to administer the antiviral drug for infections with short period like influenza (5 to 7 day illness) , you should take it at the early stages of the infection (day 1 or 2) in order to shorten illness duration and symptoms .

WHY ???

Here’s a thing to always keep in mind, it is not a routine to treat influenza with anti- viral drugs (check it in real life if you wish!) . Recovering influenza is mostly by bed rest, Vitamin C that exists in lemons and oranges and usually known to boost immunity, antipyretic

drugs (Analgesics like paracetamol) , drugs for sneezing and coughing and rhinorrhea (runny nose) , and so , it's actually a SYMPTOMATIC treatment .

Another reason is because anti-viral drugs are mostly expensive (25 – 30 JD) compared to price of drugs used routinely, so it's really a waste to use if not urgently required !

1. Amantadine / Rimantadine

^ Slides 26 , 27

- What do we mean by prevention?

Prevention comes in cases of :

1. Pandemic spread (swine flu)

2. Household infections; when most members of the family are sick , the few remaining have a high chance to get infected, so we give antiviral drugs as prophylactic treatments.

- Which step of viral replication do they target ?

Uncoating ; they prevent uncoating of the virus and release of RNA segments into the cytoplasm to start early protein synthesis .

*Remember: there are three types of human influenza; A,B & C (Type C causes mild infection and most of the time it's subclinical).

- Amantadine and Rimantadine are used only against Influenza A because they target M protein (a capsid protein) which is unique for Influenza A .

^ Slide 28

- The resistance for Amantadine and Rimantadine is v.high nowadays. It differs from one population to another, in certain populations it's up to 90% resistant.

^ Slides 29 – 31

2. Oseltamivir / Zanamavir

- used for both A & B influenza viruses.

- Which step of viral replication do they target?

Release , by inhibiting neuraminidase , the virus sticks to the cell and is never released.

b. Anti – Respiratory syncytial (RSV) drugs

^ Slides 32 – 34

Causes lower respiratory tract infections in infants aged below two years (5, 6 months up to a year , year and half to 2 years) and causes bronchiolitis and bronchopneumonia (this is well observed in pediatrics' hospital admissions in winter) .

The drug of choice is Ribavirin; which is given by aerosol (mixture of gas and liquid particles) in nebulizers (تبخيرة) .

3. Anti – Hepatitis drugs (Slide 35)

- In treatment of Hepatitis B , Lamivudine is first given , if resistance existed then give entecavir which is a new generation of anti- Hepatitis B drugs .

- In treatment of Hepatitis C , Ribavirin is given with a type of interferons called **Pegylated interferons** (a new form of interferons which is structurally modified to slow down the virus release).

* Remember : interferons are signal proteins released by microbe – infected cells to **interfere** microbe's replication by increasing other cells' defense against infection (more info in slide 50) .

- Sofosbuvir is a new drug used for Hepatitis C treatment (in combination with the previous 2) , its main problem that it's really expensive (1000$ / 1 pill / 1 day in a 12- week course) but cases that gone out of the disease due to it indicated promising results .

4. Anti- retroviral drugs

^ Slides 37- 39

- When you hear HAART (Highly active antiretroviral therapy) you should always remember HIV.

- In combination of drugs or cocktail drug, each drug acts at different stage of viral replication in order to give the maximal effect (Maximal

efficacy) .This will make the treatment more effective and can minimize viral resistance.

* A thing to keep in mind , Why is it a must to always give HIV treatment as a combination ?? Because **all HIV drugs are prone to drug resistance !!**

- Drugs target different HIV replication stages :

1. Adsorption or penetration inhibitors (as mentioned in page 1 , slide 7)

2. Reverse transcriptase inhibitors : They inhibit change of RNA to dsDNA .

3. Integrase inhibitors : They inhibit insertion of the viral genome into the DNA of the host cell.

4. Protease inhibitors (as mentioned in page 2 , slide 7)

Once we treat the patient during incubation period, this will hold back the development of AIDS , that means instead of having the disease after 20 years, he may have it after 30 for example; because here we're helping the immune system to decrease the viral load and to keep on holding the disease back. So without treatment, **the immune system will collapse earlier.**

- Antiviral drugs which act as CCR5 receptor antagonist are associated with more side effects; because all host cells express CCR5 receptor so it's not specific.

* AGAIN : there are many drugs that act on both; viruses and host cells but as you know in order for the drug to be approved, it must have an effect on the virus higher than that on our cells.

^ Slide40

- Not to be memorized but you must be able to distinguish between different stages' inhibitors , like between transcriptase inhibitors and protease inhibitors and so on.

^ Slide 49

- Once the patient has become an AIDS patient, this means the immune system has collapsed, and the chance of multiple bacterial and viral infections (opportunistic diseases) is VERY HIGH !

5. Interferons (Slides 50,51)

^ Slide 52

- The mechanism indicates the main action of interferons which is inhibition of translation and so inhibition of protein synthesis.

FIN :D

"Welcome every morning with a smile. Look on the new day as another special gift from your Creator, another golden opportunity."