



◉Sheet ○Slides

number : 22

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Notes written in boxes are for your information and aren't included in the exam

**Revision:**

We have started in taking about antiviral drugs , the problem in viral infections is the hijacking of the cell by viruses and using it as a machine for protein synthesis .

We have 2 types of viruses : DNA & RNA viruses

We have talked about 4 DNA viruses and their drug : *Herpes simplex ,Varicella zoster, chickenpox and Cytomegalovirus* . all these viruses are treated by **Acyclovir**.

- in the first 1980s ,we were using **Virdarabine** drug which is like a chemotheraputic agents instead of Acyclovir , it causes killing of normal and infected cells .

- but Acyclovir only targets viral cells because of its high affinity towards the viral thymidine kinase more than its affinity towards human thymidine kinase.

Sometimes, a patient with Herps (I, II, Varicella, CMV) infection, is not responding after being heavily treated acyclovir and ganciclovir .So we give him **Foscarnet** which is direct inhibitor of DNA polymerase without an activation by viral Thymidine kinase and we give it IV .

End of DNA viruses .

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we will start talking about RNA viruses that are composed of 4 types: *Influenza A & B , Respiratory suncytial virus (RSV) , HIV and hepatitis c*.

## ➢ Influenza

Influenza is an RNA virus. we have 4 drugs to treat this virus:

- 2 of them are Attachment Inhibitors. The primary antiviral mechanism of **Amantadine** and **Rimantadine** (Attachment Inhibitors ) is to block the viral membrane matrix protein, which function as an ion channel that is required for the fusion of the viral membrane with the cell membrane .
  these drugs " بنمسكهم و برنميهم بالزبالة " , because we already have resistance against them.
- Others 2 drugs are Neuraminidase inhibitors :
  1. **Oseltamivir** (**Tamiflu** is the trade name ) administered orally ( tablets ).
  2. **Zanamivir** ( **Relenza** is the trade name ) administered by inhalation ( sprayer ).

- ( Viral Neuraminidase: is an important enzyme for releasing of virus from the cell after being replicated, acting by catalyzing cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids ) .
- Neuraminidase inhibitors thus prevent releasing of virions from infected cell .

Early administration for These 2 drugs is crucial because replication of influenza virus peaks at 24–72 hours after the onset of illness ( after this period, viruses will be spread out). Anyway the replication is contentious but the "peak" had already occurred .

What is the outcome of this drug ?

When a 5-day course of therapy ( twice a day) is initiated within 36–48 hours after the onset of symptoms, the duration of illness is decreased by 1–2 days compared with those on placebo (placebo is ineffectual treatment for a disease, like suger pills for example . = دواء وهمي ) . 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 nowadays being in the development of resistance so we shouldn't overuse these drug .

- Influenza usually occurs for 5-7 days .

Oseltamivir is really prohibited to be used by WHO , because we don't have a drug for viral influenza except it and his "twin" :Zanamivir . So we keep it away from misuse and abuse , in order not to become resistant from the viruses . So it is highly regulated by the "United Nations" to be used in 3 cases only :

1. Infant less than 2 years with severe influenza infection .
2. Geriatric ( over 65years patient) with severe /complicated influenza infection.
3. Diabetes patient with low immunity and infected by influenza ( we add here all immune compromised / immunosuppressant patients who have severe influenza infection ).

The last drug resort in treating H1N1 (swine flu) were: **Oseltamivir and Zanamivir**.

In Complicated influenza infections - that involving the lower respiratory tract (like pneumonia) - we are allowed to use Oseltamivir ( life threatening cases ).

High regulation of Oseltamivir is virtually depending on the awareness of doctors (to use it in life threatening cases only ) , not depending on putting it in locker ( like for morphine )

Severity is diminished, and the incidence of secondary complications in children and adults decreases, this is why we use this drug .

Toxicities ( not large in reality) :

- Exacerbation of reactive airway disease by zanamivir ( causes irritation for patients who have asthma , emphysema and bronchitis because it is inhaled) .
- Nausea and vomiting for oseltamivir ( not common or clear side effects ) .

Prophylaxis of influenza by oseltamivir is neede in 2 cases :

- for respiratory physicians ( who are susceptible for influenza infection from patients) especially in when it is epidemic (rapid spread of infectious disease in a short period in a given population ) .
- For immuno-compromising people who live or in contact with another person - who has full/normal immunity - and is infected with influenza .

In treatment we use oseltamivir twice a day - 75 mg ,But in prophylaxis we use it one daily only (Once-daily prophylaxis is 70–90% effective in preventing disease after exposure)

**Peramivir** is used for influenza as oseltamivir & zanamivir , but it is administrated Intravenously IV .

Extra : in the pandemic situation of H1N1 , patients were with coma and weren't be able to take oral drugs ( as oseltamivir ) so there was a "conditional license" to use Peramivir IV, for only 6 months . After that it entered in "clinical trial" until it was approved to be used in 2015 .

Influenza is a very serious infection .It may be lethal in immune comprised patients! .

## ➢ Retroviral agents , HIV or AIDS virus .

HIV is different in life cycle from the other viruses .

- Firstly attachment then it transform from RNA to DNA virus by reverse transcriptase enzyme , then it will be integrated in the DNA of the B memory cells ( unfortunately, we don't have any drug to inhibit this integration) and this person becomes a HIV carrier ( carries this DNA ) or HIV infected ( usually after 10 years of incubation period ) .

- After that , the DNA of HIV virus undergoes expression to synthesis proteins . These proteins are connected together and separated by proteases then they are packed and released .
- AIDS is targeted in all the infection steps fusion, transcription integration, cleavage, release. So many drugs are available; anti-fusion, anti-release, anti-integrase, anti-transcription drugs, anti-packaging and budding .Yet we can't treat it , we only cover it and prolong the patient's life at most 10-15 years .
- The main problem in this AIDS virus is that it is a RNA virus that easily is mutated and becomes resistant .

To treat them we must use **highly active antiretroviral therapeutics (HAARTs)** that must by a combination of drugs - not a single drug - ( same as in cancer treatment , we treat the problem by drugs ).

So we give (antimetabolite + protease inhibitor + non antimetabolite drug + sometimes with integrase inhibitor) .

But if we give only one drug , HIV will immediately develop a mutation then will become resistant ( enough to know how quickly it becomes resistant , that if the patient has forgotten to take protease for 3 doses - approximately 3 days - resistance will arise !! ) .

AIDS is called the *acquired immune deficiency disease* but in reality its origin was *gay related autoimmune deficiency disease* ( now 60% of AIDS infected people are gays! ).

**HAART for AIDS patients :**

1- Antimetabolite **Zidovudin** ( memorize this name ) which is Azidothymidine (AZT) in scientific name that inhibits reverse transcriptase . Because it is a non selective antimetabolite , Zidovudin is toxic to bone marrow.

2- Non-nucleoside or Non-competitive reverse transcriptase inhibitor ( or its non antimetabolite RT inhibitor) which is **Nevirapine**

** بغض النظر عن الأسماء المذكورة بالسلايد بس احفظوا ال Nevirapine .

- Acts as foscarnet that binds directly to polymerase and produce inhibition and here this drug goes directly to Reverse transcriptase and producing inhibition .
- Combination therapy with AZT (resistant mutants rapidly emerge, little use in monotherapy) .

- If we have a pregnant women infected with AIDS , and we want to prevent the transmission to its baby ( vertical transmission) we were using Zidovudin (Remember: it is antimetabolite and makes bone marrow suppression so the prescription of it depends on Benefit/Risk Ratio ) until we discovered Nevirapine which was a Good blocker of mother to child transmission (perinatal - breast feeding) so a Single dose of it at delivery reducing HIV transmission by 50% with a Single dose to baby by 72 hours . Unfortunately, Nevirapine now isn't recommended to be used because we a have a resistance for it , so we came back to use Zidovudin ( which is used before the delivery of baby by 4 to 5 months to reduce the rate of vertical (mother to-newborn) transmission of HIV by up to 23% ) .
- Here we have a bizarre side effect ( depending on the dose) which is RASH .

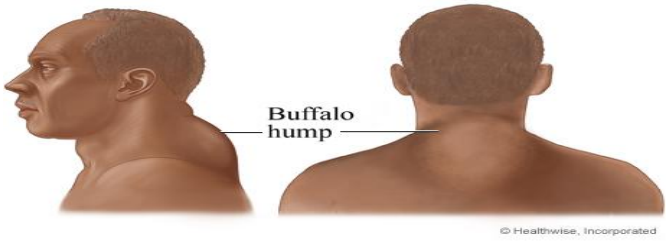
Rash is very common in patients ( a maculopapular eruption) that occurs in up to 20% of patients , usually in the first 4–6 weeks of therapy.

Although typically mild and self-limited, rash is dose limiting in about 7% of patients (7% of patients can't complete taking this drug because rash is so severe ).

Women appear to have an increased incidence of rash.( generally, being a woman mean increased incidence in most side effects !).

The problem with these drugs NNRTI or nevirapine is they develop a rash in 20% of patients, so to reduce this problem we start with a low dose and increase it with a time as the patient's body adjusts/tolerates to it (**escalation or accelaration** of the dose) . over 14 days providing better tolerance and less rash , sometimes the rash can be strong and severe .

3- Protease Inhibitors: have side effects because Protease tends to be interact and inhibit cytochrome P450 (mostly CYP3A4 and CYPA5 ) so you need to be very careful and think very well before prescribing other drugs ,very serious problems can happen , and another bizarre side effect called buffalo hump .



- **"New targets " ( in slides ) aren't required , like integrase inhibitor .**

These combinations are very effective; however, the problem of these complicated regimens is COMPLIANCE. And the components of HAART MUST be taken at different times. Compliance (meaning the patients won't take these drugs because of their side effects so you need to explain to the patient that this is the only way and that he needs to take these drugs as planned). Because if the drugs ( PI) aren't taken for 1-2 days, resistance will develop causing more problems. very fast manipulation causing the resistance.

non-compliance with protease inhibitor therapy is a serious concern as the new virus that emerges is resistant to the inhibitor being taken and also resistant to other protease inhibitors." If the patient develops resistance against one protease inhibitor, it will develop against all other protease inhibitors and those therapies won't work ".

## ➢ Hepatitis C Virus

| It is called :The Egyptian disease ( Pandemic, found in more than 35% of Egyptians) |
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- Hepatitis A Virus , maybe treated or not ( depending on the patient's situation) sometimes it take 6 months to be cured without drugs .
- Hepatitis B is a dormant virus that causes cirrhosis in the liver and cancers . Only 25% of patients are given drugs , because no symptoms are clear .

To treat Hepatitis C Virus we give 2 Anti-Hepatitis C Virus Agents :

- **Ribavirin** : It is a nucleotide-like drug ( antimetabolite that inhibits DNA synthesis ).

- **Interferon-alpha** (pegylated)

  - With Interferon-alpha , we use a new strategy in treatment based on : enhancing the immunity of the patient to attack the virus ( triggering antiviral immunity) .
  - Interferon mechanism of action:

1. binds to cell surface receptors
2. induces expression of translation inhibitory protein (TIP) .
3. TIP binds to ribosome, inhibits host expression of viral proteins

The end result of treatment: expression of viral protein is inhibited

(الدكتور ما رح يشرح عن الالية لانو مش ماخدين Immunology ) .

Interferon will be administrated parenterally ( injection ) with **polyethylene gylcol (PEG)** ( as in giving bezathine with pinicillin )

Normal Interferon must be taken daily but Pegylated interferon is taken weekly (for 4 weeks ) to trigger the immune system to attack these viruses .

Interferon and Ribavirin are taken for 24 week / 6 months .

Not included :

There are new combination of drugs that is found in western world ( not in Jordan ) because it is very expensive drug ( 75000$ for the whole coarse ) . This drug is very cheap in Egypt and India because hepatitis c is pandemic there ( 500$ only).

These new drugs such as ( **sofosbuvir and elbasvir** ) target special proteins which are present only in Hepatitis C . **sofosbuvir targets NS5B protein.**

In reality we have 7 genotypes of hepatitis c , that aren't treated by the same drug .So sofosbuvir for example treats all genotypes 1-6 but doesn't treat type 7 . This situation is a good example to understand personalized medicine . Also , personalized medicine includes virus to target which gene is present in the virus and prescribes the drugs .

*A smile only takes a moment , but the memory behind that smile*

*sometimes last Forever.*

لما توصلوا لهون ادعولي ☺

*The end*