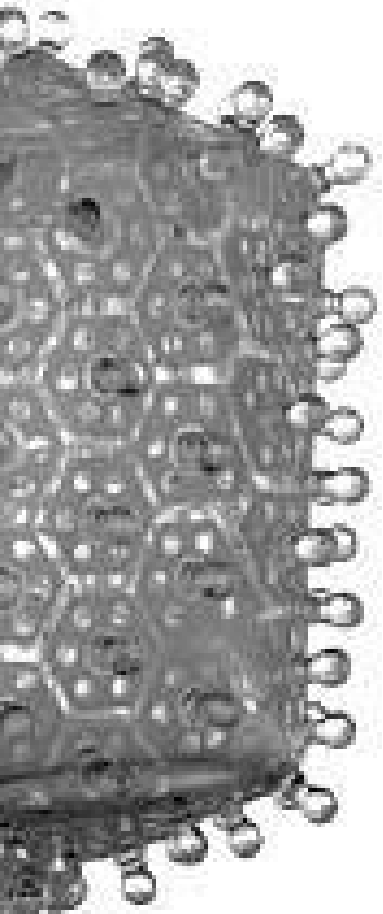

Microbiology

Lecture No:..36 (11-viro)

Dr Name:..Dr. Hamed.....

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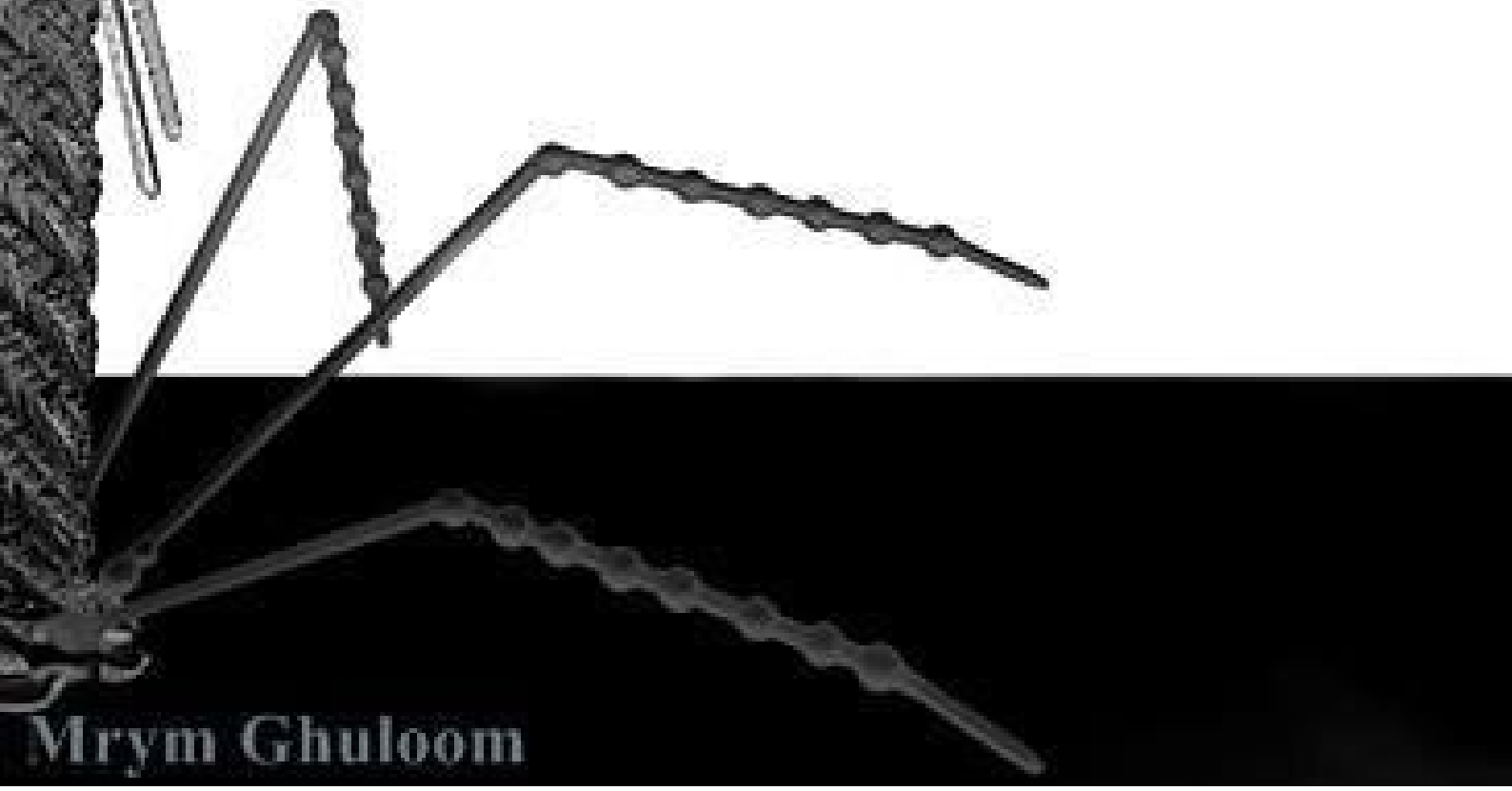
Sheet ■ Slide □



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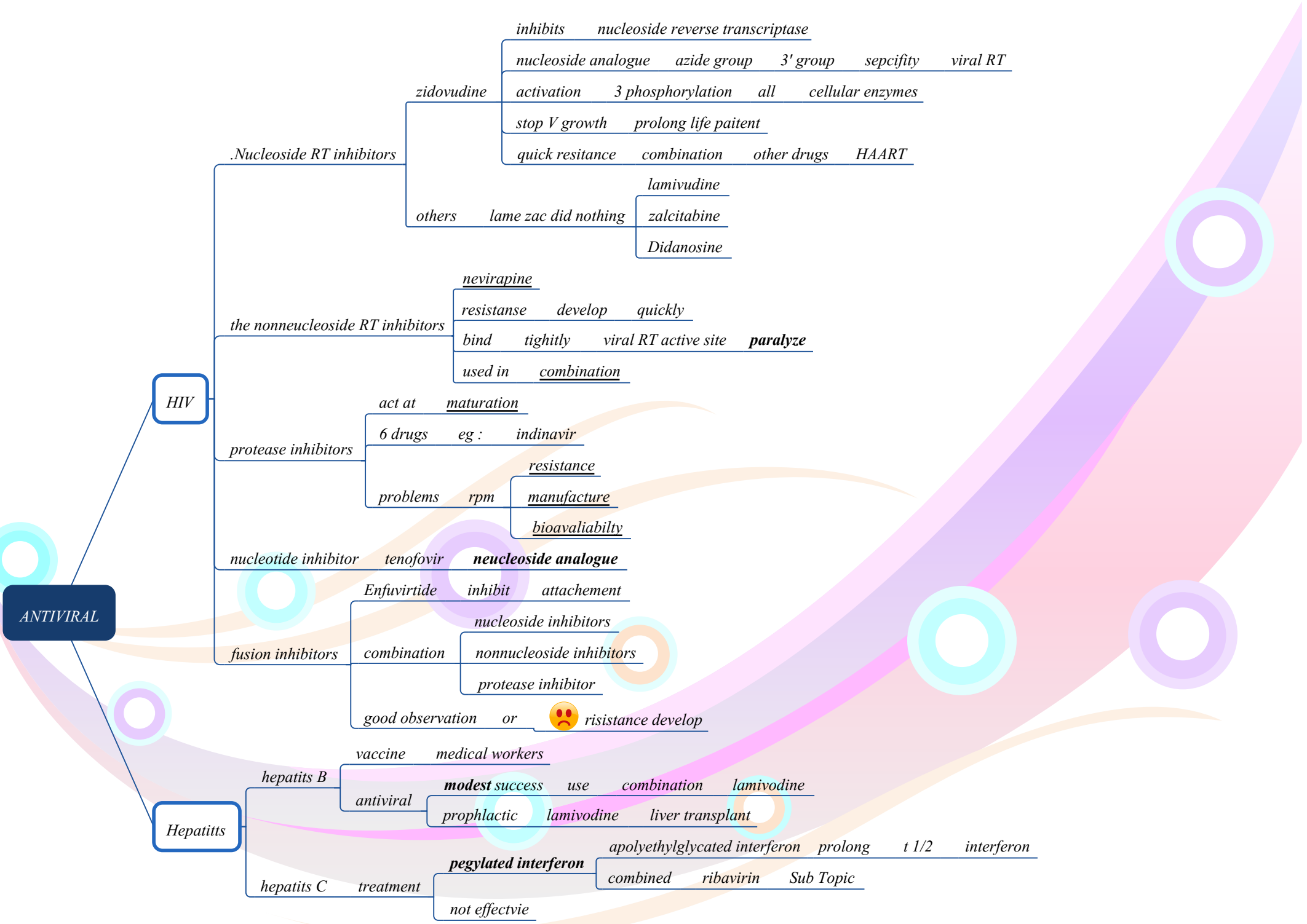
ANTIVIRAL
HIV
.Nucleoside RT inhibitors
zidovudine
inhibits nucleoside reverse transcriptase
nucleoside analogue azide group 3' group sepcifity viral RT
activation 3 phosphorylation all cellular enzymes
stop V growth prolong life paitent
quick resitance combination other drugs HAART
others lame zac did nothing
lamivudine
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Didanosine
the nonneucleoside RT inhibitors
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resistanse develop quickly
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Hepatitts
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vaccine medical workers
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modest success use combination lamivodine
prophlactic lamivodine liver transplant
hepatits C treatment
pegylated interferon
apolyethylglycated interferon prolong t 1/2 interferon
combined ribavirin Sub Topic
not effectvie

Antiviral drugs

Just before you start reading the sheet go ahead and give the mind map a shot and see how great it is , I bet you will finish this lecture in an instant ☺

Today we will talk about about the treatment of two viruses : the HIV" human immunodeficiency virus" , which is from the retrovirus family , and hepatitis B and C .

Treatment of HIV virus :

We have five categories of antivirals that we use for the HIV. The first category is:

1 .Nucleoside RT inhibitors "NRTI"

The first example for this category is zidovudine "AZT" (AZT means azidothymidine, and it is another name of zidovudine.

it's a nucleoside analogue and it inhibits the enzyme reverse transcriptase, it acts like ACV "acyclovir" which is used to treat herpes. So this drug will be triphosphorylated to become active and it's an inhibitor for the reverse transcriptase *by inhibiting the chain elongation*, how?

This drug is a nucleoside analogue that has an *azide group* at the 3' end instead of having a hydroxyl group. So ,the RT will add azidovudine to the chain and then it comes to add another nucleotide , it will not find the OH group to add on it , and that's how termination of the elongation of the chain occurs . This drug has specificity for the viral reverse transcriptase and it doesn't affect the DNA polymerase so its specific in its actions. The phosphorylation here happens by cellular enzymes, ***unlike the acyclovir*** which its first phosphorylation step happens by viral enzyme (thymidine kinase)and the last two happen by cellular enzymes.

Written by M.aladawi

The other antivirals in this group basically act in the same way. Clinically we can use this drug to treat HIV and to prevent it . This drug will stop the growth of the virus and keep the viral load under specific level (threshold) of copies , so it will prolong the life of the patient.

-Resistance may develop quickly for this antiviral, and sine the virus develops resistant quickly for it , either *you use another drug, or you combine this drug with another one.*

- In treating the HIV patient we stop the treatment in order to give the immune system a chance to rebound as the immune system may keep the viral load under control , and that what is called the ***interrupted therapy.***

✓ Other nucleoside analogues : ddi (Didanosine), ddC (Zalcitabine), and 3TC (Lamivudine)

*You will see that lamivudine is used to treat hepatitis B

*** A Note from the writer : Mnemonic for these 3 drugs: " **lame zac did** nothing _ picture that doctor zac didn't treat you cause the virus developed resistance, so you need other drug {those three " ☺ " }

* you have to use combination therapy , which is abbreviated HAART "highly active antiretroviral therapy" .

The other category is:

2. **The nonneucleoside RT inhibitors NNRTI**

e.g.: nevirapine, they inhibit the reverse transcriptase .

-Drug resistance develop quickly upon treatment.

- these antivirals have different mechanism of action , they will tightly bind to the viral RT active site and distort it, they will **paralyze** the reverse transcriptase instead of deceiving it like zidovudine, so it acts **directly** not

like zidovudine that acts as an analogue, and you have to use it in .combination with nucleoside and protease inhibitors

The third category is the:

3. **Protease inhibitors**

they act at the *maturation* stage . if you remember when HIV is about to leave the cell ,in order to mature and become infectious , it has to cleave the late proteins and this is done by proteases, so HIV will reform itself and become infectious . The protease inhibitor will inhibit this protease ,so it will inhibit the virus from becoming infectious .

We have six drugs that inhibit the HIV protease e.g. : indinavir .

Some problems regarding the HIV protease inhibitors :

1- expensive to manufacture . 2-the drug resistance easily develops . 3- the patient has to take so many tablets (7 to 10 tablets) . 4 – poor bioavailability .

*** A Note from the writer: mnemonic for it problems: " RBM _ means rounds per minutes, this virus is speedy resistant"

The forth category is the

4. **Nucleotide RT inhibitor**

e.g.: tenofovir . they will target the RT just like the **nucleoside analogue**. They can be used instead of NRTI

The last category is the

5. **Fusion inhibitors**:

e.g. : **Enfuvirtide (fuzeon).**As we took in the targets of antivirals that it inhibits the fusion of HIV to the cell .The Enfuvirtide will inhibit the glycoprotein 41 which is important for the virus fusion .

Combination chemotherapy (HAART)

We use nucleoside inhibitors "e.g. zidovudine " , nonnucleoside inhibitors plus the protease inhibitor. In this combination the patient consumes 15 tablet a day ,so the compliance is a problem and it is little in the HIV patients , so you must keep an eye on these HIV patients , otherwise any default will lead to the development of resistance shortly . - Many AIDS patients have benefited from drugs combinations

Treatment is monitored as we said in the previous lecture , using ***molecular technique*** to detect the load (how many copies you have) , usually the target is to decrease the load to 50 copies and that is undetectable in the blood . the sample is taken from serum and you detect the level of the virus in order to tell that your combination therapy is working and reducing the load or not .

****

Hepatitis C & B

Hepatitis C as well as B spread through blood , so the health workers are susceptible for these two viruses .we have a vaccine for hepatitis B , so if you're vaccinated , you will be in the safe side , but this vaccine isn't given to all people " only medical workers " . {News flash: after finishing 3rd year you will be vaccinated from hepatitis B ☺ "easy for me to say ☹ "}. This vaccine is taken in 3 doses.

Hepatitis C treatment

-Persistent infection can lead to chronic liver disease and the virus is the leading cause for liver transplantation in developed nations. Maybe the cause is that the drug addicts share the syringes they take the drug by , sharing the virus too.

- There is a treatment but the efficiency is not that high, we use **pegylated interferon** which is a **polyethylene glycol** interferon and the propose of

the glycosylation is to prolong the half life of the interferon . This p**egylated interferon** in combination with **Ribavirin** is the best treatment available for this moment.

Hepatitis B

Regardless having a vaccine, we have 400 million chronic carriers of this virus which can develop liver cirrhosis, hepatocellular carcinoma and liver failure.

*** A Note from the writer :

" man those diseases are lethal take him to the CHC "community health center "*** It's just a mnemonic for you ☺

*Theses carriers are either unvaccinated or unresponsive , **so what's the difference ?**

Unvaccinated , they haven't got the vaccine , but unresponsive are given the vaccine but the titer of the antibodies have not reached the desired levels . Doctors who are not responsive are asked to choose specialties away from blood.

-The antiviral for this virus has **a modest** success (success depends on the region used in and the patient status) . However, we have a combination of interferon with lamivudine.

As the book says ,we use them **separately**; first we use the interferon and if the patient didn't respond , go and try lamivudine , and that's what you suppose to know . But in reality , they are used together as a combination. The lamivudine is a nucleoside analogue as we mentioned in the HIV , and it will inhibit the RT { reverse transcriptase } and stop the replication of hepatitis B , but **why does lamivudine acts on " hepatitis B " although it is not a retrovirus ?**

If you remember, the hepatitis B genome is partially circular (i.e. one circle is complete while the other is not and must be completed for the virus to be infectious and replicates its genome to many copies) . To complete the other strand , the virus carries its own REVERSE TRANSCRIPTASE☺ which can be inhibited by lamivudine .

And lamivudine can be used prophylactically in people who undergo liver transplantation .

-Relapses الانتكاس can occur due to discontinue therapy Or with monotherapy , that's why we must use combination therapy.

-A second nucleoside analogue is adefovir, which also can be used for
- chronic hepatitis B patients .

-The treatment with IFN is effective in 20-30% of patients ,however effectiveness will increase if you use combination therapy .

NOTE: interferons are not required from the book and the doctor said study from his slides , they are enough.