Microbiology

◉ Sheet ○ Slides

Number : 7

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Subject: Anti-viral drugs 2

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27/12/2015

بسم الله الرحمن الرحيم

***In this sheet we will complete the influenza drugs topic then we will move to complete antiviral drugs slide.**

***Everything in the slide is included here**.

Influenza drugs

#What are the benefits of antiviral drugs?

-When used for treatment "treatment for immunocompromized patients", antiviral drugs can lessen symptoms and shorten the time you are sick by 1 or 2 days. They also can prevent serious flu complications, like pneumonia. For people with a high risk medical condition, treatment with an antiviral drug can mean the difference between having milder illness instead of very serious illness that could result in a hospital stay.

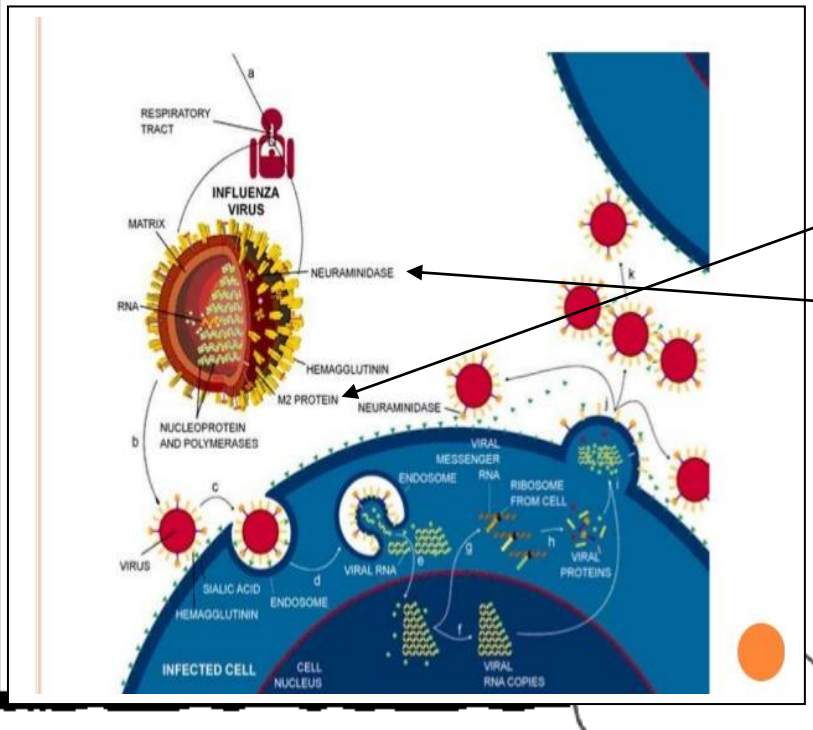
-Antiviral drugs may be used prophylactically to prevent action of some viruses such as influenza A. "for example it can be given to nursing home residents if there is an outbreak of influenza A"

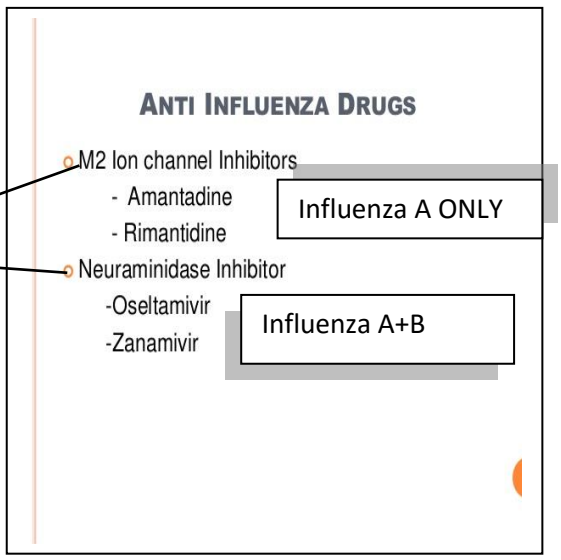
Remember!

- Influenza is caused by RNA viruses.

-Influenza viruses make up of 3 genera:

*influenza A "with M2 protein" *influenza B * influenza C "associated with very mild illness"





An acute viral infection

It is characterized by a rapid onset of disease, a relatively brief period of symptoms, and resolution within days without the need of using anti viral drugs.

A Chronic infection

- The term ‘chronic infection’ refers to an infection that has been going for more than 6 months.
- The term refers specifically to the duration of infection, not to the severity of the disease.
- Treatment with anti-viral drugs must be taken once diagnosed the infection like: hepatitis B,C /HIV viruses and so on.

  (e.g. treatment of patients infected with HIV virus with antiviral drugs>>you prolong the incubation period of the virus "decrease the route of the virus">>preventing the patient to undergo AIDs status "prolapsed of immune system and died is expected"

Amantadine " A man to dine look for picture mnemonic in MRS PAGE 322"

Introduction

- Classification
  - antiviral
    - blocks viral uncoating
      - amantadine
- Drugs
  - amandatine
  - rimantadine

Mechanism

- Action
  - prevent viral uncoating
    - by inhibiting the viral membrane M2 protein channel.

Uses

- Influenza A
  - NOT influenza B
  - used for both prophylaxis and treatment
- Parkinson's disease" taken in pharmacology lecture"

Pharmacokinetics of Amantadine

- Oral bioavailability ~ 50-90% "so given orally"

Pharmacology

- Amandatine crosses the blood-brain barrier(BBB)
- Rimantadine does NOT cross the blood-brain barrier(BBB)

Oseltamivir/ Zanamavir (Neuraminidase inhibitors):

• Do not interfere with immune response to influenza A vaccine. • Can be used for both prophylaxis and acute treatment.

• Oseltamivir is orally administered

. • Zanamavir is given intranasal. • Risk of bronchospasm with zanamavir

when influenza drugs are prescribed ?H1NI

#How often do you take them?

we don't usually use anti-influenza drugs but in" treatment +prophylaxis" as we treat influenza symptoms (fever,cough,..) that associated with fatigue "bed rest".

7.1 Ribavirin

} Ribavirin is a guanosine analog.

} Requires phosphorylation to mono-, di- and triphosphate to be active.

} Triphosphate Inhibits RNA polymerase and depletes cellular stores of guanine (inhibit IMDH)

} Decrease synthesis of mRNA 5' cap (interfere with guanylation and methylation of nucleic acid base)

*explanation of these 2 points are not mention in the lecture to understand them only I will discuss them below.

Antiviral spectrum :

RIBA virion mnemonic:

RSV: "respiratory syncytial virus" ,,**R**NA viruses are susceptible.
Influenza **B**, Parainfluenza,…hepatitis **C** PATIENTS.
Arenaviruses (e.g. lassa fever)

Aerosol inhalation treatment of ribavirin.

*extra note:aerosol is a substance enclosed under pressure and able to be released as a fine spray.

***R**SV: "respiratory syncytial virus":-is so-named because it cause respiratory infection as (acute bronchiolitis , bronchial pneumonia in infants:2-6months and symptoms are mild resulting with formation of **seroconversion** :" **seroconversion** is the time period during which a specific antibody develops and becomes detectable in the blood against antigen">>providing immunity.

-RSV is the number one cause pneumonia in young children especially infants less than 6 months of age also it might infect children below than 2 years .

-RSVs contain F-protein that causes formation of multi-nucleated giant cells(syncytial cell).

Spectrum is : RNA viruses are susceptible, including influenza, parainfluenza viruses, RSV, Lassa virus

So Ribavirin is an alternative drug for:

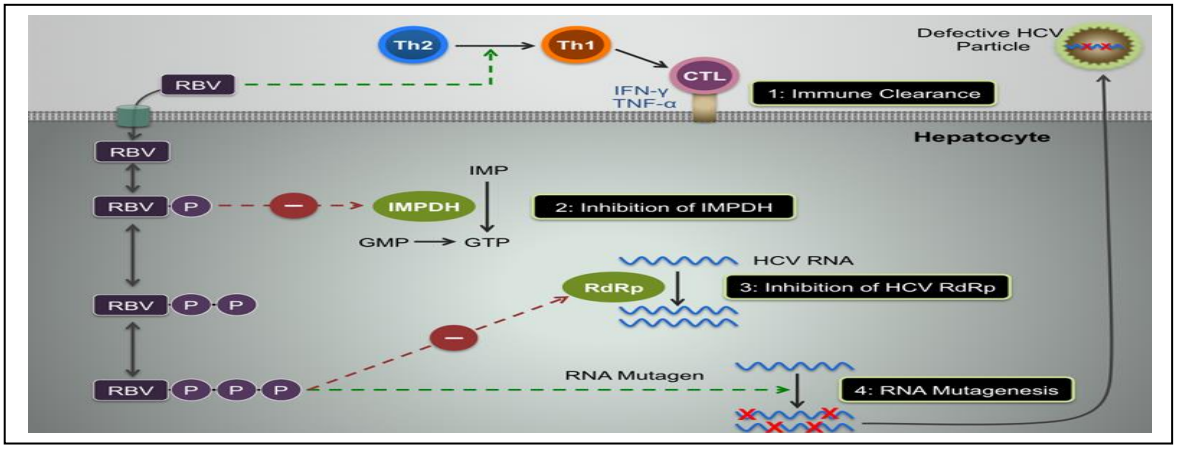
*Extra note :lassa virus is an arenavirus that causes Lassa hemorrhagic fever, a type of viral hemorrhagic fever (VHF)

• Influenza, parainfluenza, measles virus infection in immunocompromised patients

Explanation of the last 2 points:"very helpful to read them"

*Ribavirin 5'-monophosphate inhibits cellular inosine monophosphate dehydrogenase(IMDH), thereby depleting intracellular pools of GTP.[29]

It(IMDH) catalyzes the rate-limiting reaction of *de novo* GTP biosynthesis.



*Ribavirin is **a guanosine** ribonucleoside **analog** that displays broad-spectrum anti-viral activity and is currently used for the treatment of some viral infections. Ribavirin has recently been proposed to also be a **mimic of the 7-methyl guanosine cap found at the 5′ end of mRNAs** **So**:

} Decrease synthesis of mRNA 5′ cap (interfere with guanylation and methylation of nucleic acid base"prevent adding of more viral nucleotides">>causing chain termination of viral genom.

So,

Ribavirin

Introduction

- Classification
  - antiviral
- Drugs
  - ribavirin

Mechanism

- Action
  - inhibits production of guanine nucleotides
    - via competitive inhibition of IMP dehydrogenase
  - prevents capping of viral mRNA.

• Distribution in all body tissues, except CNS

Uses

- Chronic hepatitis C
- RSV
- Given orally, IV, and as aerosol/inhalation in RVS." RSV bronchiolitis and pneumonia in hospitalized children (given by aerosol)"

Adverse effects

- Avoid in pregnancy
- Hemolytic anemia/jaundice

7.2-Hepatic Viral infections :

HBV: hepatitis B virus.

Mnemonic -'ILA EnT'

→ **I**nterferon alpha with Ribavirin for Hepatitis **C**."INTERFERON WILL BE DISSCUSED LATER IN THIS SHHET"

→ **L**amivudine (3T**C**)>>**C**ytosine analog-HBV.

→ **A**defovir

→ **Ent**ecavir– **G**uanosine analog – HBV –for lamivudine resistance strains cytosine."firstly you give lamivudine,if resistant then given entecavire"

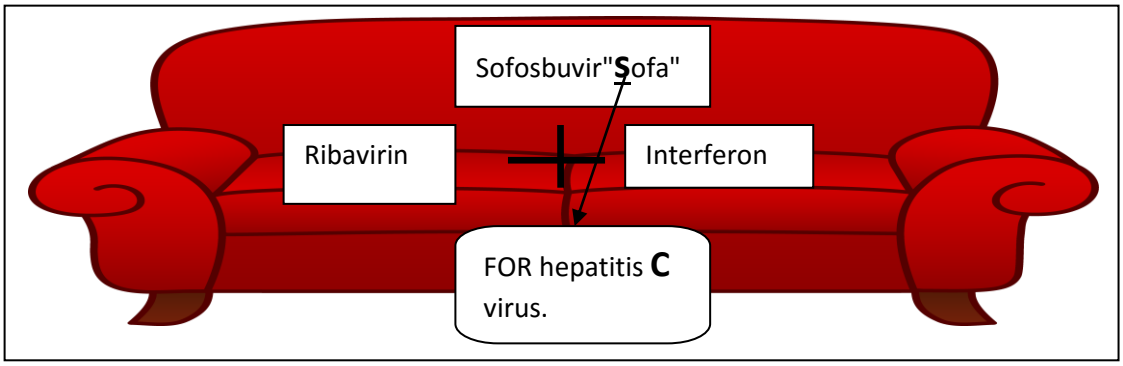
→ **T**enofovir

C-analog

G-analog

For H**B**V

• Sofosbuvir "Sofa"- nucleotide analog used in combination with other drugs (Ribavirin and Interferon) for the treatment of hepatitis C virus (HCV) infection. Course of 12 weeks **cost 84,000$.**



Note:

*Hepatitis A B C D E,,,

B+C>>CHRONIC INFECTION once they are diagnosed, starting of anti-viral treatment is must(IT'S A ROUTINE).*B:15% *C:85%.

A,D,E,,,,,:ACUTE INFECTION"SELF-LIMMITING anti-viral drugs are not a routine".

*for HBV+HCV:

If I give these 3 drugs together , 90-95% treatment of the cases I will expect that they will block the viral replication:

1) Ribavirin 2) Lamivudine 3)Entecavire

-Sofosbuvir may also be given as one tablet a day but it's very expensive.

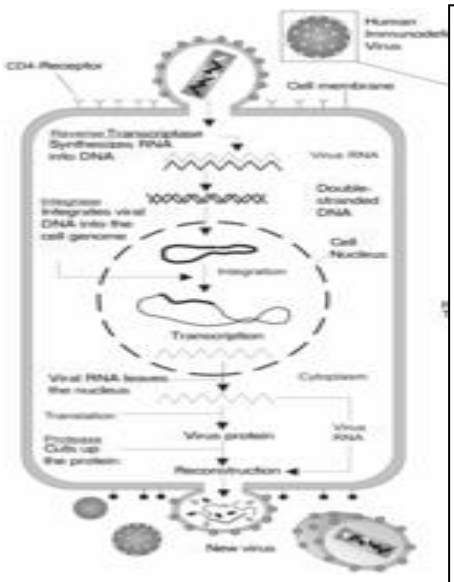
If I give these 2 drugs together, 60-65% treatment of the cases I will expect:

1)Interferon 2)Ribavirin.

*Note:" Like antibiotics for bacteria, specific antivirals are used for specific viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; ***instead they inhibit their development.***

7.3 Anti-retroviral drugs(ARV)

(The human immunodeficiency virus "HIV")



Remembering the HIV replication:"you can watch this tutorial animation"

1.Once RNA "diploid RNA:2 copies of RNA" is released into the cytoplasm of the host cell ,reverse transcriptase make a DNA copy of the viral RNA genome.

2.As a DNA being formed, reverse transcriptase degrades the RNA strand.

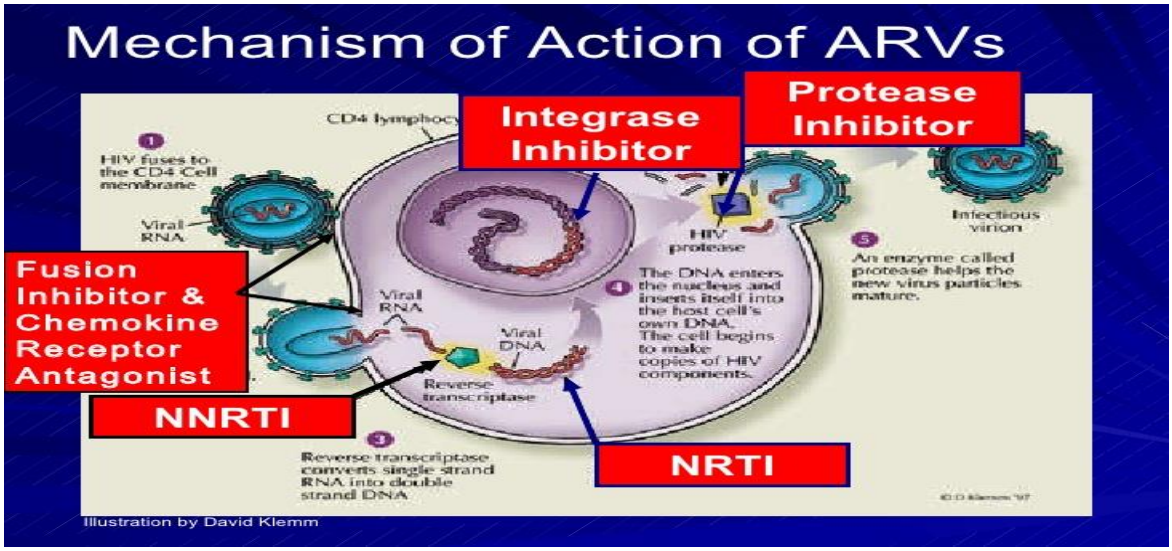
3.A complementary DNA strand is then added by reverse transcriptase, and the end of the resulting double-stranded DNA moved to the nucleus and inserted into the host-cell chromosome by the viral **integrase enzyme**. "the integral viral DNA is now referred to as **proviral DNA**.

4-THEN transcription and translation of mRNA yielding viral enzymes and structural proteins ."some of the functional proteins are formed from the cleavage of **a long poly-protein** by the enzyme protease.

5-Finally, the viron released by budding.

*AIDs are caused by HIV which is ***an enveloped virus.***

*Enveloped virus>>entry to the host cell by fusion>>envelope left as a part of the host cell:"envelope is derived from the host membrane ,with viral glycoproteins such as gp41 and gp120 inserted into the membrane as the virus leave the host.



***Each step of the virus replication has certain drug that target this replication step:"you don't have to memorize the names of drugs here as the doctor will mention in the exam the name of drug and its group"**

1) **FU**sion inhibitors – En**FU**virtide "FUzeon"

- inhibiting viral **En**try"block the interaction of glycoprotein and receptors": Inhibit viral fusion, preventing viral replication

- Many forms of HIV, the virus that causes AIDS, initially use CCR5"cellular receptors" to enter and infect host cells so you may think if we block them we block the virus entry but it's not a true that the drug doesn't act on our cells but on the virus :

*The exact function of CCR5 is still unknown.

*Effect of blocking these receptors are still under investigation.

– Newest class of antiretroviral drugs .

– Used in combination"**FUZE** with other drugs" with other drugs active against HIV .

*side effects are not included.

*slide 38 "Entry inhibitor" wasn't mentioned by the doctor.

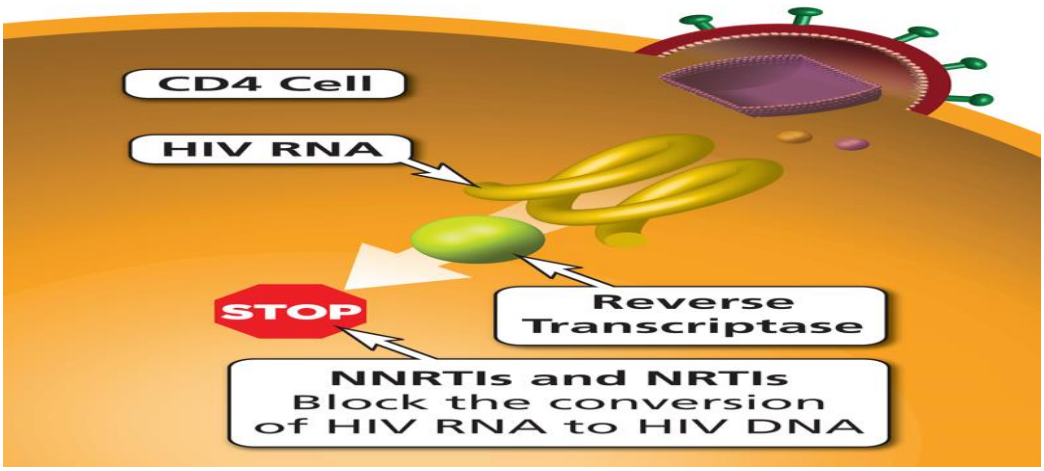
2)In**TEGRA**se inhibitors – Ral**TEGRA**vir

" • RalTEGRAvir • ElviTEGRAvir • DoluTEGRAvir and • MK-2048"

Inhibits HIV genome integration into host cell chromosome by inhibiting HIV integrase enzyme.

3) Reverse transcriptase inhibitors (RTIs)

-HIV uses its reverse transcriptase enzyme to convert single stranded RNA into double stranded DNA :



– Blocking the activity of the enzyme reverse transcriptase, preventing production of new viral DNA:

*Nucleoside/Nucleotide reverse transcriptase inhibitors and Non-nucleoside reverse transcriptase inhibitors block this process.

When HIV infects a cell, reverse transcriptase copies the viral single stranded RNA genome into a double-stranded viral DNA. The viral DNA is then integrated into the host chromosomal DNA, which then allows host cellular processes, such as transcription and translation to reproduce the virus. RTIs block reverse transcriptase's enzymatic function and prevent completion of synthesis of the double-stranded viral DNA, thus preventing HIV from multiplying.

1) NRTIs

NRTIs:

Nucleoside/Nucleotide.

1- Nucleoside Analogs:

*Analog to thymidine,cytosine,adenine, guanine,,,

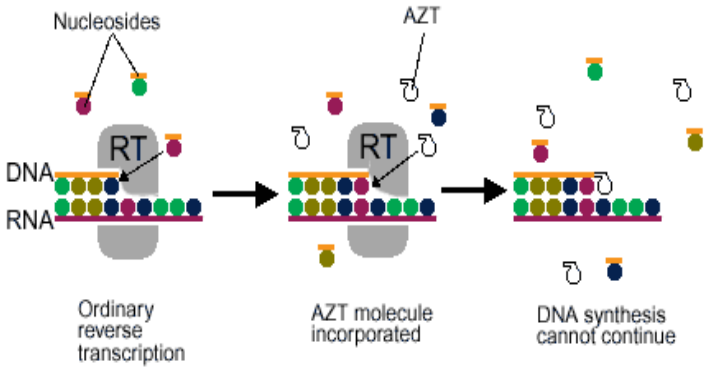
*Triphosphorylated by host cellular enzymes (kinases)

*Incorporated into the growing HIV viral DNA strand by reverse transcriptase.

2- Nucleotide Analog

*Does NOT need to be tri-phosphorylated only di-phosphorylated to active compound.

After incorporation of the NRTI, viral DNA synthesis will be terminated.

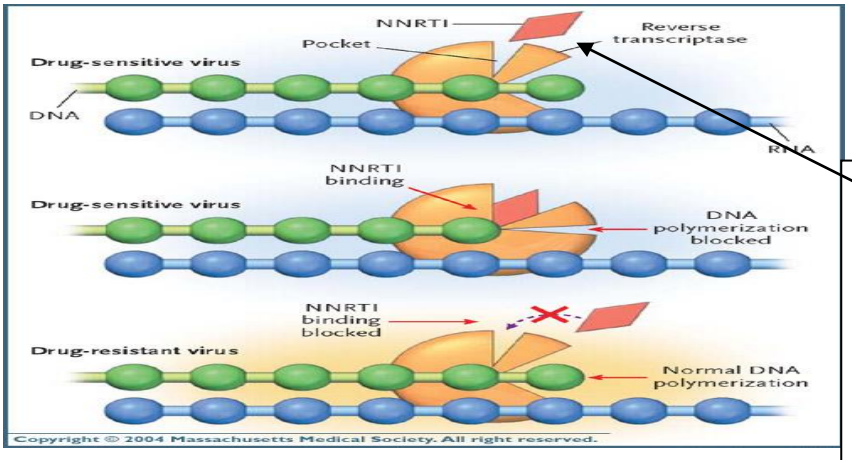


– ***Nucleoside RTIs (NRTIs):*** Azidothymidine (AZT), Didanosine (ddI), Stavudine (D4T), Lamivudine (3TC)

– ***Nonnucleoside RTIs (NNRTIs):*** Nevirapine, delavirdine, efavirenz

– **Nucleotide RTIs (NTRTIs):**Tenofovir, Adefovir.

Here, the affinity of the drugs to virus is more than to our cell and that is why it was approved.



2) NNRTIs: Non-nucleosideRTIs

*These agents directly bind to reverse transcriptase to inhibit transcription.

*NNRTI do not require phosphorylation to be active: "Do not require cellular enzymes to be phosphorylated"

NNRTIs:

• Do not inhibit human **DNA polymerase:"** The **DNA polymerases** are enzymes that create DNA molecules by assembling nucleotides, the building blocks of DNA".

- Know that RTIs inhibit activity of reverse transcriptase, a viral DNA polymerase that is required for replication of HIV and other retroviruses BUT NNRTI:

• Relatively safe: noncytotoxic

• Highly prone to drug resistance.

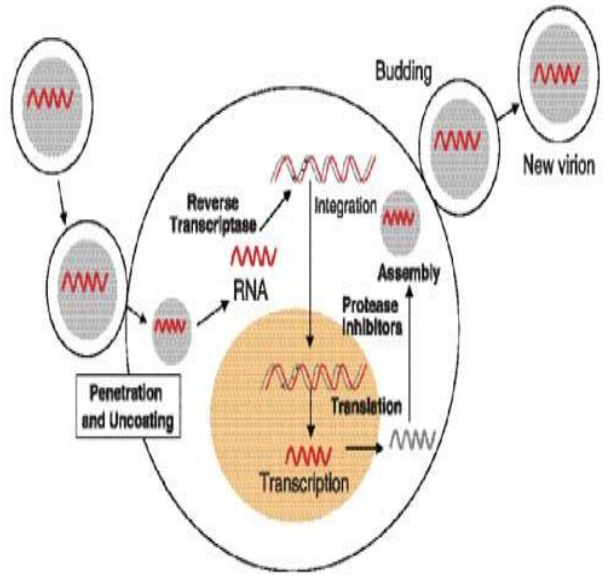
• Used in combination with other drugs active against HIV.

So,it's

4)Protease inhibitors"PIs":

"Never tease a **pro-tease**".
Drugs that end in "**-navir**" are Protease Inhibitors!

-**Protease enzyme** cleaves **HIV precursor proteins** into active proteins that are needed to assemble a new, mature HIV virus.



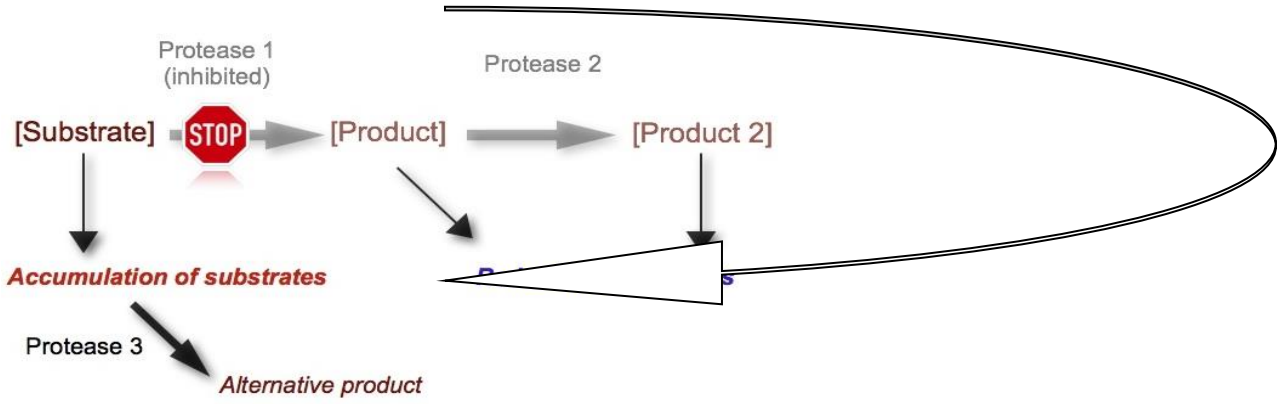
-"PIs" bind to protease preventing the cleavage and inhibiting the assembly of new HIV viruses :

◦ Inhibit the protease retroviral enzyme, preventing viral replication ◦ Inhibition of this enzyme blocks viral assembly and release.

Protease inhibitors end with navir : "Don't memorize them "

◦ Examples: amprenavir (Agenerase) indinavir (Crixivan) nelfinavir (Viracept) ritonavir (Norvir) saquinavir (Invirase)

◦ Hepatotoxic # BUT WHY?DUE TO ACCUMULATION OF SUBSTRATES



◦ Used in combination with other drugs active against HIV.

Note:Most of Retroviral drugs are protease inhibitors and reverse transcriptase inhibitors.

-Now let's focus on the big picture of how to use Anti-retroviral drugs?

• **Combinations** of multiple antiretroviral medications are common:

"3-4 drugs should be used because the data shows these combinations are more effective".

• Due to combination of drugs **adverse effects** vary with each drug and may be severe . "combination of drugs+ target different steps"

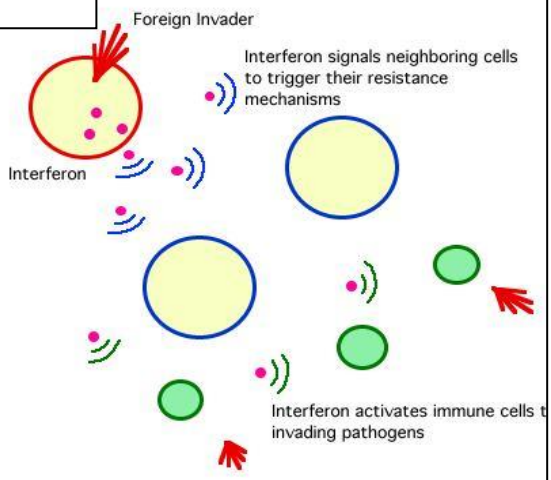
-So,Anti-retrovial medications have a HAART: Highly Active Antiretroviral Therapy.

-monitor for dose-**limiting toxicities** :"The principle behind HAART is the use of several **different agents** "drugs" with **varying mechanisms** of antiviral activity /e.g.(A three drug combination of : two nucleoside reverse transcriptase inhibitors combined with either of protease inhibitor or non-nucleoside analog).

• Monitor for signs of opportunistic diseases:"Antiretroviral drugs should be started for most patients with advanced HIV infections but if the plasma HIV RNA level is very low, treatment can be delayed".

7.4 Interferon drugs : (alpha,beta, gamma)

Interferon



*Natural protein produced by virally infected cells to warn neighboring cells of the presence of virus.

*Presents in each cell and it's being activated upon exposure to the virus.

*Affects the neighboring cells not the cells that secrete it.

• α and β interferons are produced by all the cells in response to viral infections.

• γ interferons are produced only by T lymphocyte and NK(natural killer) cells in response to cytokines – immune regulating effects

Mnemonic for γ interferons:

"**Th1nk BIG Mac Attack**":
Th1 and **NK** cells **B**uild **I**nterferon **G**amma.
Causes **Mac**rophages to have an **Attack** –immune regulating effect.

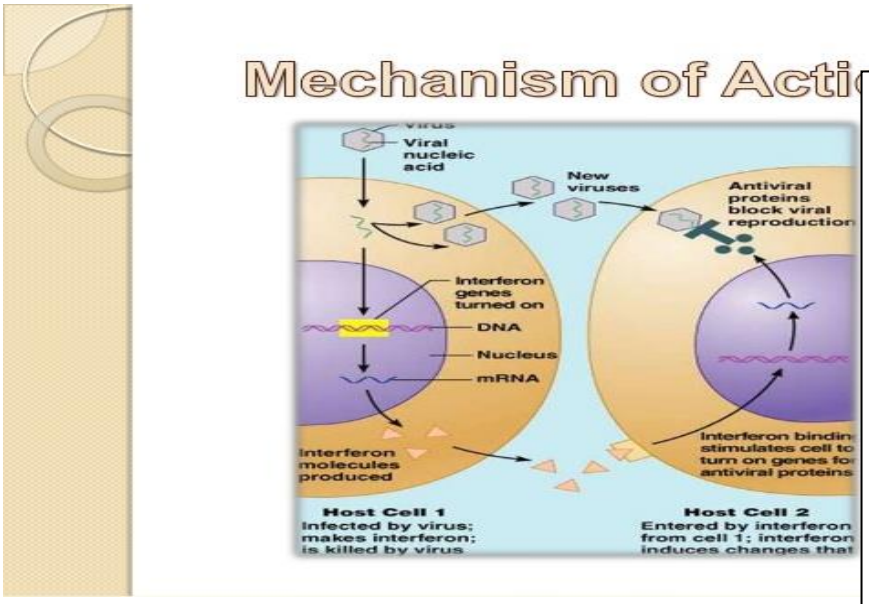
* **note : Th1**(T-lymphocyte Helper cell)

• γ has less anti-viral activity compared to α and β interferons.

Mnemonic for alpha and beta interferon"IFN" producers: (not mentioned by the doctor but they will be benefit to know therapeutic use of interferon):

-IFN-a
αlba (white blood cells)
-IFN-**β**
fibro**β**lasts

Mechanism of action of Interferons :



In general:* Interferons are small proteins released by tissue cells infected with a virus. When a tissue cell is infected by a virus, it releases interferon.

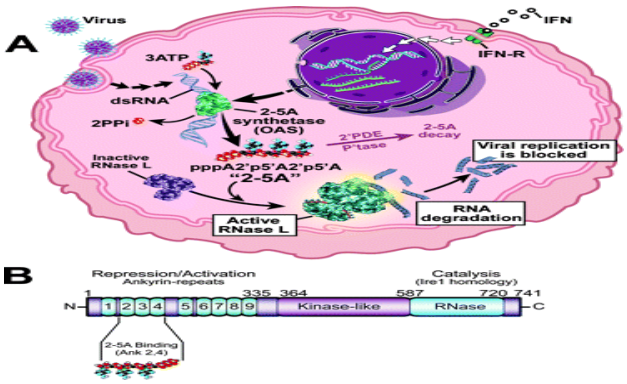
* Interferon will diffuse to the surrounding cells. When it binds to receptors on the surface of those adjacent cells, they begin the production of a protein that prevents the synthesis of viral proteins. This prevents the spread of the virus throughout the body.

Mechanism of action of Interferons :

• **Induction** of the following enzymes:

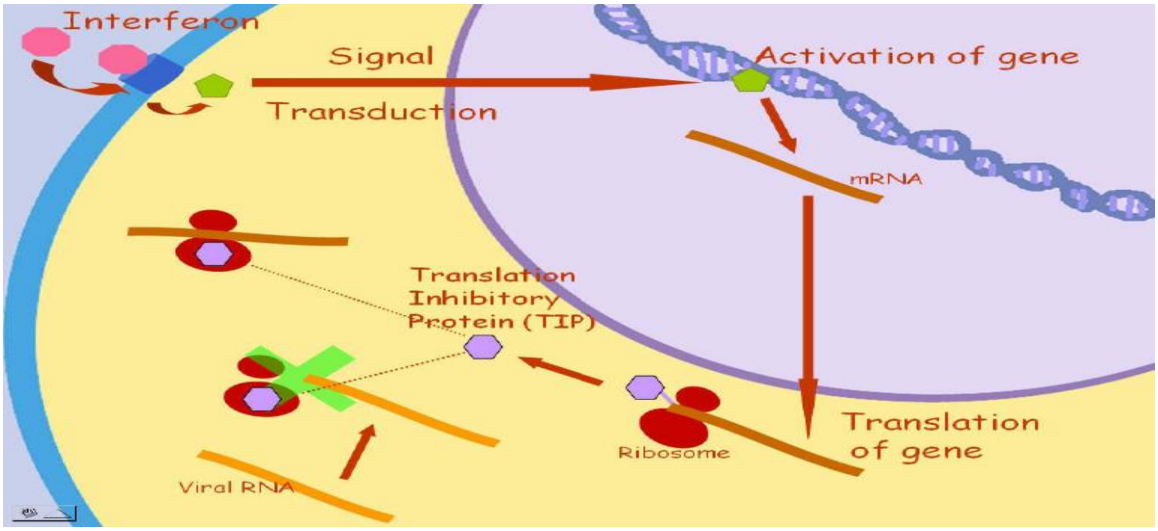
1) induction of ***a protein kinase*** which inhibits protein synthesis .

2) induction of ***an oligo-adenylate synthase (OAS):*** OAS is an antiviral enzyme that counteracts viral attack by degrading viral mRNA.



3) induction of a phosphodiesterase :"**phosphosdiesterase is an enzyme which breaks the phosphodiester backbone of DNA or RNA**" so interferons by this mechanism will ***inhibit t-RNA.***

so The action of all these enzymes leads to an inhibition of translation "protein synthesis".



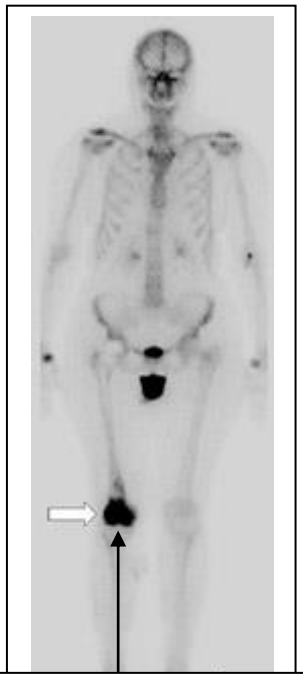
-viral drugs Adverse effects of Interferons:

• Acute flu-like syndrome (fever, headache)

• Cardiotoxicity – arrhythmia

• Neurotoxicity (confusion, seizures)

• Impairment of fertility



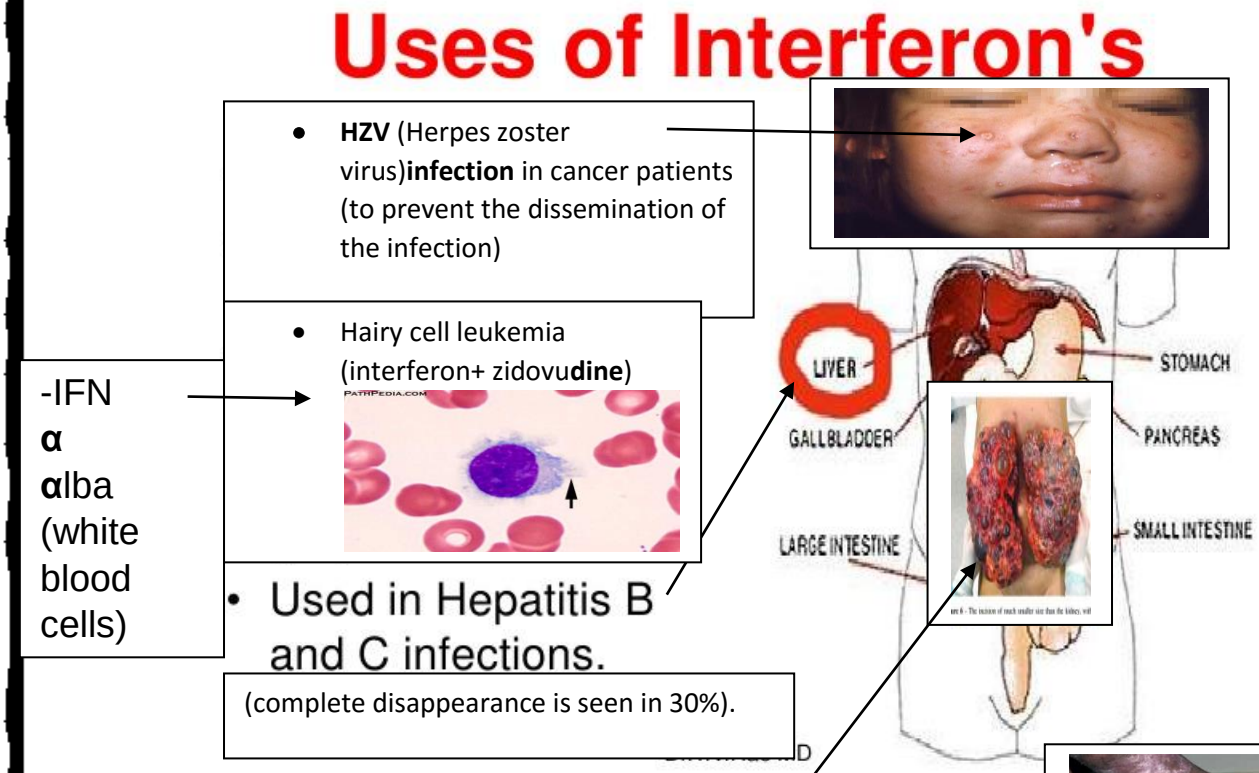
• Bone marrow suppression"BMS"

(granulocytopenia, thrombocytopenia)

*Extra information:

is the decrease in production of cells responsible for providing immunity (leukocytes):granulocytopenia , carrying oxygen (erythrocytes), and/or those responsible for normal blood clotting (thrombocytes: thrombocytopenia.

Anti-viral drugs Therapeutic uses of Interferons :



- **HZV** (Herpes zoster virus)**infection** in cancer patients (to prevent the dissemination of the infection)

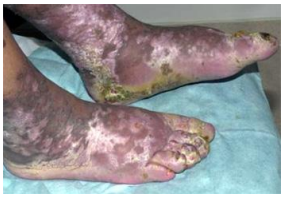
-IFN **α** **α**lba (white blood cells)

- Hairy cell leukemia (interferon+ zidovu**dine**)

- Used in Hepatitis B and C infections.

(complete disappearance is seen in 30%).

- CMV " cytomegalo virus" infections in renal transplant patients.



- **Genital warts** (or **condylomata acuminate**) >>IFN IS given by intralesional injection. Complete clearance is seen ~ 50%.

- In AIDS related **Kaposi's sarcoma:**

***is** a tumor caused by infection with human herpesvirus 8 that can present with cutaneous lesions with or without internal involvement.

* (Extra note)

Antiviral spectrum : Interferon α

• Includes HBV, HCV (Pegylated interferon) and HPV(human papilloma virus)

*Note **pegylated interferon** is a slow release of interferon"

• addition of ***polyethylene glycol*** to the interferon, through a process known as ***pegylation, enhances the half-life of the interferon when compared to its native form***

• Anti-proliferative actions may inhibit the growth of certain cancers - like Kaposi sarcoma and hairy cell leukemia.

Now, I am going to talk about (Defective viruses) which should be in the sheet 5 (viral genetics) but the doctor did not explain this topic in that lecture, so it is found here:

Defective interfering particles (DIP):

Defective viruses: are genetically deficient and incapable of producing infectious progeny virions.

The infecting cells with high multiplicity of infection (the ratio of viruses to the cells (MOI)) leads to drop in the infectious viruses but the question here why??

Because the replication of the viruses is not an efficient process; the result of the replication is 50% is **infectious** and the other 50% is **defective** , so when both of these viruses infect the host cell simultaneously, the infectious virus can supply the genetic deficiency(deficiency in enzyme or protein necessary for the replication) of the defective and make it replicate progeny virions, the defective virus is going to complement itself by infectious virus ***(complementation)*** and that leads to more defective viruses, so as the virus replicates , the complementation increases and more defective viruses are produced. At the beginning, 50% is defective and 50% is infectious , another replication will give 75% which is defective and 25% is infectious and so on.

NOTE: when we are talking about complementation here, this occurs at the functional level (protein or enzyme lost in the defective) NOT the nucleic acid level.

NOTE: the doctor began with the defective interfering particles and did not mention them again during the explanation because when he said defective virus , that means a defective virus which can occupy the cell machinery

necessary for normal virus replication to **prevent virus production** leading to more defective viruses and this is the definition of ***defective interfering particles (DIP).***

Another point discussed during the lecture related to Rota vaccine:

There are two rota viruses : Rota viruses that can infect humans and rota viruses can infect animals which can also infect humans but the infection is asymptomatic illness, so we are going to put the segments of humans (Rota infecting humans) inside the rota infecting animals, and give these viruses as drops in the mouth of children and they are going to replicate in the intestine and the body will be immunized producing antibodies against antigens of human rota viruses.

The end