# PHARMACOLOGY

◉ Sheets ○ Slides

**Number:** 22

**Done by:** Dana Alkhulaifat

**Corrected by:** Noor Isbeih

**Subject:** Anti-Viral Drugs 2

**Doctor:** Dr. Malik

00/00/0000

.....

# Anti-Viral Drugs

## HIV Life Cycle

→ It is similar to most RNA virus life cycles, but the difference is in integration.

We usually start with fusion. There are receptors that are going to accept the virus and will fuse with the cell, and which in turn will release RT (reverse transcriptase).

RT is going to change RNA to DNA. And an enzyme called integrase is going to integrate the viral DNA into the chromosomal DNA, and then it's going to stay there in the body of the patient for a long time.

Then, this DNA is going to produce proteins through transcription. These proteins usually come in single polypeptide chains, which we will cut through with an enzyme called protease. After that, it will be packaged and released.

In order to treat HIV, we're going to use harsh treatment by using different kinds of mechanisms and drugs in order to fight HIV infection.

### *What kind of therapy do we use?*

→ Combination therapy.

This is the first viral infection that we are going to treat with combination therapy (similar to pseudomonas). We are going to combine drugs together. The more difficult the virus is, the more combinations you'd want to use. ***HIV is the most difficult virus to treat and therefore requires a lot of combinations.***

The first option is to give a drug called **azidothymidine (AZT)**, which is also called **Zidovudine**. This drug is an anti-metabolite, and will inhibit RT (reverse transcriptase). However, this drug is ***non-selective***; it will inhibit transcriptase and will even inhibit DNA polymerase within normal human cells.

This implies that AZT is going to induce bone marrow suppression, so it is toxic to the bone marrow. For example, it causes severe **anemia** (reduction of synthesis of red blood cells), **leucopenia** (reduction of synthesis of white blood cells) (the immunity of this patient will be affected), and **thrombocytopenia** (bleeding easily due to reduction of platelets) in patients receiving high doses. Headache is also a common side effect of the drug.

## Vertical Transmission

It is the transmission of the virus from the mother to the baby during pregnancy or childbirth.

### *How can we reduce vertical transmission?*

→ During pregnancy: administration of **oral** zidovudine beginning between 14 and 34 weeks of gestation.
→ During labor: **intravenous** zidovudine.
→ Neonate from birth through 6 weeks of age: Zidovudine **syrup.**

This method has been shown to reduce the rate of vertical (mother-to-newborn) transmission of HIV by up to 23%.

---

The better alternative is a drug called **Nevirapine**.

Here, we're going to give 1 anti-metabolite drug and another drug from **Non-nucleoside Non-competitive RT Inhibitors (NNRTI)** which are **direct**, non-competitive inhibitors for RT.

*So, this drug binds to viral RT, inducing conformational changes that result in enzyme inhibition.*

Use of this drug: **combination therapy with AZT** (resistant mutants rapidly emerge, so ***we shouldn't use it for monotherapy***).

**General notes:**

- This drug is approved for AIDS patients, and it is a good blocker of mother to child transmission (perinatal - breast feeding)

- Single dose at delivery reduced HIV transmission by 50%. However, resistance towards this drug developed because we used it alone between 2008 and 2009, which made us eventually get back to AZT.

- This drug is linked to rash. Rash is a signs of allergic reactions. Some NNRTI side effects include effects in the CNS, like sedation, insomnia, vivid dreams, dizziness, confusion, and feeling of "disengagement" (which are not very common).

### *How does it cause rash?*

This drug is administered orally, not through injection. **Women** appear to have an increased incidence of rash (this is an example of gender-related side effect).

### *How can we avoid this side effect?*

When initiating therapy, gradual dose escalation over 14 days is recommended to decrease the incidence of rash (an example of escalation therapy), which is the opposite of tapering (reduction of dose over a period of time).

---

The third strategy that we can use is **protease inhibition**, through HIV protease inhibitors. These inhibitors have significantly altered the course of the HIV disease.

### *Why?*

Because this strategy was new. In 1996, all the focus was on inhibiting RT, so we either used nucleotide based inhibitors (direct inhibitors), or non-nucleotide based inhibitors. After getting to know the molecular mechanism of HIV, we were able to produce great drugs called protease inhibitors.

All of them are reversible inhibitors of HIV protease, which is the viral enzyme responsible for cleavage of viral polyprotein into number of essential enzymes (reverse transcription, polymerase).

Examples of those drugs: **Saquinavir**, and **Ritonavir**.

Side Effects:

- These are examples of drugs that ***inhibit cytochrome P450***. They are orally active, and the bad news is that protease has similarities with cytochrome P450, so these drugs cause a side effect called '**Buffalo Hump**', and **fat redistribution** in their bodies (like accumulation of fat in the abdominal area).

*To cut it short, this is what you need to know about the drug:*

1. They are great drugs against HIV.
2. They revolutionized treatment by using a different strategy rather than targeting RT.
3. They have many side effects, the most important is 'buffalo hump' (redistribution of lipids).
4. They inhibit the activity of cytochrome P450, because there's a homology between protease in HIV and cytochrome P50.

---

Note:

**Raltegravir** is an integrase inhibitor and targets integrase (an HIV enzyme that integrates the viral genetic material into human chromosomes, which is a critical step in the pathogenesis of HIV). It's becoming an important component of **Highly Active Anti-Retroviral Therapies (HAART).**

## *In conclusion, the drugs we use to treat HIV virus are:*

1) Azidothymidine (Zidovudine)
2) Nevirapine
3) Saquinavir (protease inhibitor)
4) Raltegravir (integrase inhibitor)

We combine them all together to form **HAART [Highly Active Anti-Retroviral Therapy]**. They are very effective and can reduce viral load in the patient below detectable levels, which implies that HIV replication has ceased.

| Examples: (not for memorization) |
| --- |
| (1) NNRTI–Based Regimens (1-NNRTI + 2NRTIs) + |
| (2) PI-Based Regimens (1 or 2 PIs + 2 NRTIs) + Integrase inhibitors |

→ The trouble with all of these complicated drug regimens is compliance. The components of HAART must be taken at different times. Non-compliance with protease inhibitor therapy is of serious concern **as the new virus that emerges is resistant to the inhibitor being taken and also resistant to other protease inhibitors**.

→ So, if the patient misses 2 or 3 doses of Protease Inhibitors, they will develop resistance towards Protease Inhibitors. It's all about keeping the drug in the therapeutic level.

---

## Hepatitis B and Hepatitis C

### *How common is Hepatitis C in Jordan?*

Not common but it is present. However, it's very common in other countries like Egypt.

### *How do we treat Hepatitis C?*

It's a 6-month treatment, using the following drugs:

1) Interferon Alfa (pegylated) [**24 injections**]
2) Ribavirin [**on daily basis**]

### *Now, what does the word 'pegylated' mean?*

- → It means that we added to the interferon a polyethylene glycol [PEG]
- → Interferon should be taken daily or every other day, but if it's pegylated then it should be taken one a week, which adds more relief to the patient. Basically, pegylated interferon has a longer half-life than non-pegylated interferon.
- → If interferon is not pegylated, then the patient requires 72 injections.

We may also use protease inhibitors and polymerase inhibitors but those are not important now.

**Ribavirin** is a nucleotide based anti-viral polymerase. It's used for Hepatitis C and is an anti-viral and anti-metabolite.

**Interferon alfa** is an endogenous anti-viral substance present in our body, and we need to activate it by giving **interferons**.

### The mechanism of action of interferons:

Interferon enters the body, which induces signal transduction. Then, it activates certain genes which are translated into **TIP [Translation Inhibitory Protein]**. TIP then binds to ribosome, and inhibits host expression of viral proteins.

**Side effects** are very common: flu-like symptoms: increased body temperature, feeling ill, fatigue, headache, muscle pain.

### *How do we treat Hepatitis B?*

Hepatitis B is asymptomatic. You may only find symptoms in 5% of Hepatitis B patients. We treat it with either **pegylated interferon alfa-2b** or any other anti-metabolite nucleotide-based inhibitors.

---

# Anti-Cancer Drugs

**General notes:**

- The most drugs being approved in the world are anti-cancer drugs, and cancer is the one of the most common causes of death in the world, along with cardiovascular diseases.
- Quitting cigarette smoking would lower cancer mortality by about 40% in America and Europe. In the 19th century, lung cancer was virtually unknown. It was the American cigarette invented in the late 1800s and World War I that transformed the western world's cancer patterns. There is currently a smoking epidemic, and lung cancer is sure to follow. **Smoking is also one of the main causes of cardiovascular diseases, mainly strokes**.

## *What is cancer?*

Cancer is not one disease, but 200 diseases. Every disease has its own characteristics.

During this course, we're going to discuss 3 types of cancers:

1) Breast cancer [the most common cancer between women in Jordan]
2) Colon cancer [the most common cancer between men in Jordan]
3) Acute lymphocytic leukemia [the most common cancer in children in Jordan]

→ Cancer is of **monoclonal origin**, and results in a **heterogeneous lump**.

→ Initiation begins with **a mutation in oncogenes or in tumor suppression genes**, which will result in an **uncontrolled proliferation**.

The problem is that the rate of mutation is uncontrolled. Normally, when our cells divide, we have a rate of mutation which is 3 nucleotides for every replication. So, out of 3 billion nucleotides, 3 nucleotides are going to be changed from the mother cell to the daughter cells.

This is called single nucleotide polymorphism, or spontaneous mutation. In cancer, you lose those checkpoints (**tumor suppression genes**, which are responsible for arresting the cell until the mutation problem is repaired) and that will result in too many mutations.

So, when replication happens, the new cells that emerge are different from the original cells, and the cells that result from replication after that also end up being more different than the original cells.

→ All of these result in something called **Heterogeneity of Cancer**.

---

Every patient has a different mutation. There are common mutations, but the driver mutation is not always the same in each patient. Breast cancer alone can result from 4000 different gene mutations… all of this with the exception of **CML (Chronic Myelogenous Leukemia)**, whose only driver chromosome is **Philadelphia chromosome [BCR-ABL]**.

The only thing we can do is to kill every single cancerous or mutated cell in the body, by using chemotherapy.

In 2011, the next generation of Hallmarks of Cancer was written. In order for a tumor to become malignant, more than one thing needs to happen such as *evading of apoptosis, sustained angiogenesis, and self-sufficiency in growth signaling, limitless replicative potential*…

### *How does malignancy actually develop?*

It's really simple: we **promote oncogenes**, we **inhibit tumor suppression genes**, plus **angiogenesis**.

### *How do we treat it?*

→ We either have an option of **surgery** (removing the cancer) which is the only way of curing cancer
→ After that we perform **radiotherapy** or **chemotherapy** (or all together).

And then there's an exception called **Target Therapy** for cases like CML.

In surgery, we remove the primary tumor. However, we have to be aware that the cancer may have metastasized somewhere else.

### *How do we make sure the cancer doesn't reoccur?*

Chemotherapy must be administrated to make sure that the patient doesn't redevelop the cancer. This is called **adjuvant therapy**.

❖ Sometimes the lump is too big to be removed surgically, with unclear edges. In that case, we use **neoadjuvant therapy**. That means that we use chemotherapy to decrease the size of the tumor, to make it easier for the tumor to be removed through surgery.

- ❖ If the cancer has metastasized to different areas of the body, we use something called **palliative therapy** (to make the patient's life 'easier' and more tolerable in cases of deadly cancer such as Non-Small Cell Lung Cancer).

### *In conclusion there are 3 ways to use chemotherapy:*

1) Adjuvant therapy [**after surgery**]
2) Neoadjuvant therapy [**before surgery**]
3) Palliative therapy **(علاج تلطيفي)**

## Side Effects:

The side effects are common between all 3 of them. Most anti-cancer drugs are unselective, so they're going to kill all dividing cells (ones that replicate often such as hair follicles, lining of GI tract, lymph nodes, bone marrow, germ cells). The unaffected cells are the cells that aren't replicating in the body, or have a long replication time (healthy tissues with no mitotic activity) such as liver, kidney, heart… etc.

### *Side effects of all anti-cancer drugs include:*

→ Damage to hair follicles [**alopecia**]
→ Frequent nausea and diarrhea [because those drugs are toxic to the GI tract]
→ Reduction of spermatogenesis
→ Bone marrow suppression [reduction of RBC, WBC, platelets...] which leads to **leucopenia**, **thrombocytopenia**, **anemia**, and **general immune suppression**.
→ Lymph nodes suppression, therefore lymphocytes are affected.

This sheet is over

اهداء خاص الى ريم الموسى