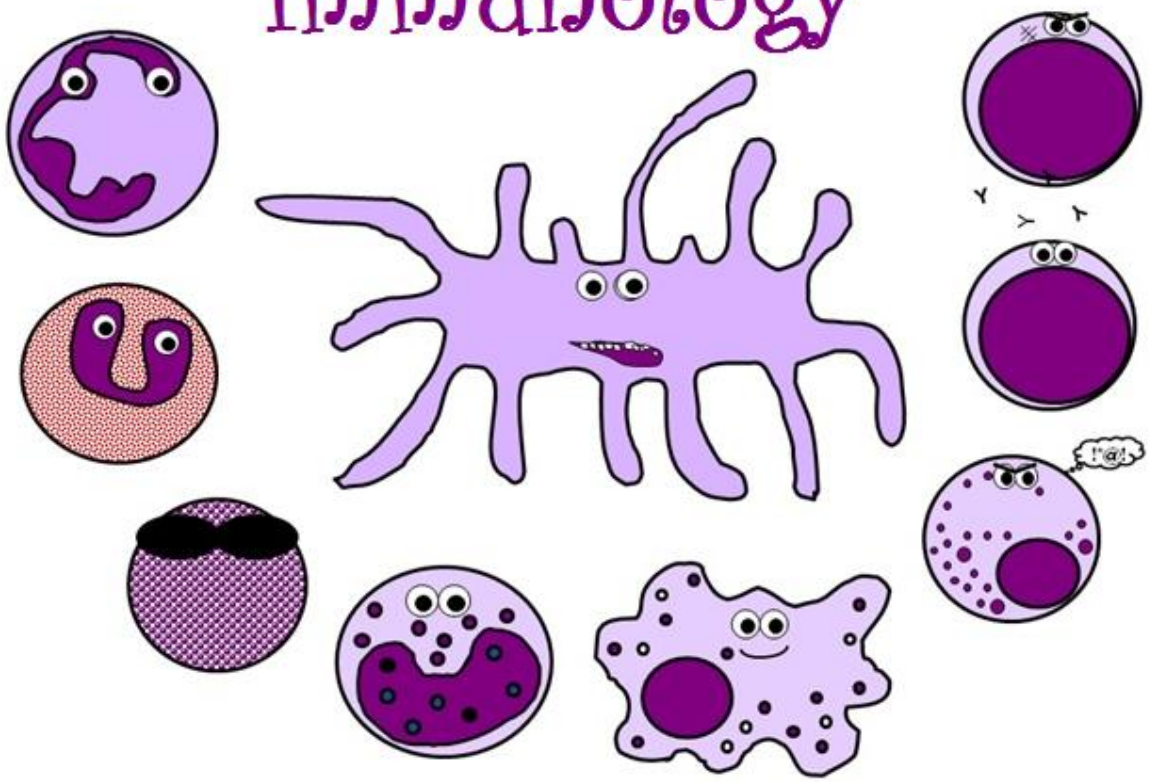
Immunology



Sheet Slides

Number: 22

Subject: ImmunoDeficiency

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بسم الله الرحمن الرحيم

This sheet was written according to the recording of section 2

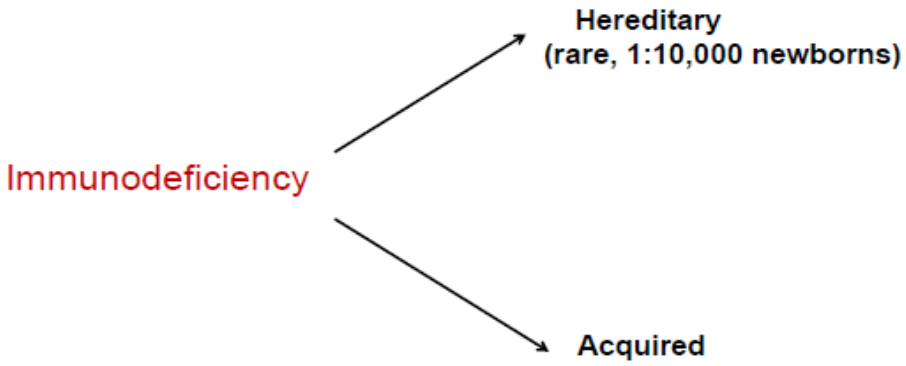
Introduction

- We talked previously about the innate and the adaptive immune systems, the components of each one of them, and how they work together, and that the adaptive immune system would be blind without the directing of the innate immune system.

- Then we talked about the immune system going wrong, one of the examples was the exaggerated response of the immune system like sepsis, which initiates in the first place to get rid of the bacterial infection.
- We also talked about misguided immune response, like asthma, allergies, and anaphylactic shock and how they're initiated by TH2 mediated IgE production.
- We also talked about , exaggerated immune response towards auto antigens , that results from breaking one of tolerance mechanism steps producing auto immune diseases . Like myasthenia gravis and multiple sclerosis.
- Those were all examples of exaggerated immune responses, but today we'll talk about the opposite case, when the immune response has less reaction than it's supposed to have, which is immunodeficiency.

Immunodeficiency

We have two main types:



1) **Hereditary:** when a baby is born with weak or compromised immune system, it includes any cases, the baby might not have B cells or hypo-functional B cells, or he has no T cells or hypo-functional T cells, in other cases he might not have both types of cells. And some other cases the immunodeficiency could be in macrophages or in neutrophils.

- In general, **any defect in the immune system at birth is considered hereditary immunodeficiency!.**
  - for example: omenn syndrome , and how **RAG1** and **RAG2** that are involved in VDJ recombination are deficient , and they are unable to produce healthy T and B cells , that's why it's one of SCID forms (severe combined immunodeficiency).

It's very rare, only 1:10,000 newborns, although we have many pathways to cause immunodeficiency it's still rare in newborns, why**?**

- Because in immune system we always have redundant (alternative) pathways, which means we have pathways that compensate the absence of other pathways, so we don't reach the stage of having **ID**.

2) **Acquired**: the cases where individuals are born with normal immune system but for some reasons later in their life their immune system gets compromised, and they get immunodeficiency.

- **What's the most common cause of acquired immunodeficiency? malnutrition**

First: Hereditary immunodeficiency

Examples:

1. **Hyper IgM syndrome (case study)**: Those patients have CD40L deficiency, which is important in class switch, co-stimulation and somatic hyper-mutation.

   Absence of CD40L makes B cells unable to do class switch from IgM to other isotypes, which causes accumulation of IgM, it also causes deficient T cell mediated immune response, so we have highly deficient B cells and also deficient T cells, which results in immunodeficiency.
2. **CD40 deficiency**: causes a phenotype that's similar to hyper IgM syndrome.
3. **DiGeorge Syndrome** : in these cases patients are born with deletion in chr 22q 11.2 (22 : #of chr / q : short arm / 11 : area on the short arm) this deletion causes these patients to be born without thymic tissue so they don't have functional T cells , and that causes them to be immune compromised or deficient .
4. **Severe combined immunodeficiency (SCID)**; we took a lot of cases that are considered SCID, like omen syndrome.

   SCID is a generic word, describes any problem that causes deficiency in more than one part of the immune system.

   There're a lot of problems that can cause SCID, like X-Linked SCID, those patients have deletion in their X chromosome, and that deletion caused problems in T or B cells function,

   another example in nucleoside deaminases deficiency, basically what they do is they process and deaminate nucleosides that makes the DNA, and in case they are absent that causes toxicity in B cells and T cells which would also cause SCID. This is an autosomal case.
5. **C3 deficiency (very rare)**: this is an example of a deficiency in the innate immune system.

   Patients are born with inability to build C3; there are other similar deficiencies like C2 and C4.

   Patients with C3 deficiency have abnormal lymph node structure, because complement components are a very important function to go to the lymph nodes and activate B cells, so the absence of these complement components causes lymph nodes with no germinal centers and the B cells in these lymph nodes are abnormal in function.

Second: Acquired Immunodeficiency

Main causes:

1) **Malnutrition:** (most important cause) and it's the highest cause of immunodeficiency worldwide. It includes lack of nutrient availability which is important in building our body cells including immune cells. Also lack of vitamins and antioxidants, which their absence cause cellular damage and damage to the immune system. (discussed more later)

2) **Medications / treatment** :

- in some cases we want suppress the immune system or causing a deficiency in the immune system on purpose , like in renal transplants , we give the patient **cyclosporine** , and those cyclosporine are intended to lower the immune response in the patient to avoid rejection .
- In other cases, like cancer patients, we give them **chemotherapeutic agents** to affect the BM or destroy certain tumor. These agents affect the BM and also mature immune cells.
- Also, we have **ionizing radiation** which is given to cancer patients and it has a detrimental effect on the immune system.
- That's why cancer patients who are treated with chemotherapeutic agents or ionizing radiation are always immune compromised, and should be isolated from others so they won't catch any infections.

3) **Infections** : examples , HIV (most popular cause) and measles,

So you should know that not only HIV virus can cause ID, although it's special for targeting CD4 cells, but many other organisms can Cause ID including measles.

In TB patients that get infected my measles , even after a while they get cured from measles , they would stay negative to DPT test , because their immune system is compromised and they can't even induce a late hypersensitivity response , and they would be more projected to infections .

Let's talk more about nutrition

Nutrition and infection

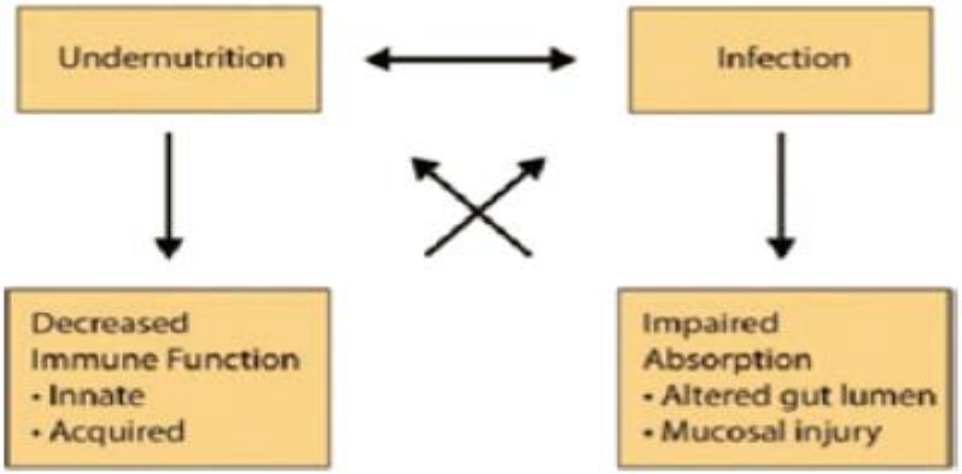
Under-nutrition is underestimated for not being the most common cause of a lot of diseases including being immune compromised.

*Under nutrition is connected directly with infections.

Malnutrition doesn't always mean that the person is poor or there is no source of food, it could be caused by a problem in absorption (**impaired absorption**), a person who can't utilize the nutrients very well will suffer malnutrition, or it could be due to infections, specially parasitic infections in the third world countries, it affects the ability to absorb nutrients and it affects the integrity of the GI tract and make them less able to utilize the nutrients.

- **That's why we're saying that there's a direct relation between infections and under nutrition, under nutrition makes you more exposed to infections, and infections make you more exposed to being under nutrition. (Vicious cycle) it's a bidirectional relationship.**

- infections → more projected to alteration in GI lumen or mucosal injury → this causes impaired absorption → under nutrition
- under-nutrition→this causes a decrease in the immune function (innate/acquired) → more likely to get infections



Human Immunodeficiency Virus (HIV)

Today, there are 37 million people that are infected worldwide. Actually from the point of discovering HIV till now 70 million people were infected but almost half of them died and today we have 37 million left.
In 2015, 1.1 million died of HIV. (High number)

HIV wasn't understood until 1981, when physicians could differentiate HIV from other pathogens. As HIV patients had cases of pneumocystis carinii pneumonia, and rare cancers such as Kaposi sarcoma (most type of cancer found in HIV patients), this sarcoma is caused by human herpes virus 8 (HHV 8) and manifests in the skin but especially in the epithelium lining blood vessels and lymphatics"*it's not a skin cancer!, only manifests on it"*.

- We have two strains of HIV, HIV-1 and HIV-2!

HIV-1 was discovered in 1981 and over a billion dollars is spent every year to research it.

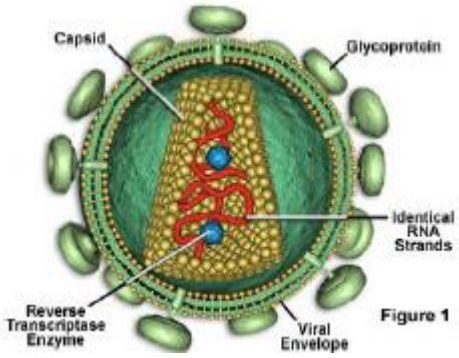


Figure 1

- HIV is an RNA virus, the RNA is surrounded by a capsid and a viral envelope, and we have a group of proteins present on the surface of the virus.

- Also we have a set of enzymes for replication, most important one is **RT enzyme** (reverse transcriptase enzyme) which transforms the RNA into DNA when it enters human cells, and then the DNA form incorporates itself with the human DNA via an Enzyme called **Integrase** which helps to cut and paste the DNA of the virus into the Human DNA to replicate.

- It has glycoproteins on its surface which bind to host cells, most important one is protein 120 **(GP 120).**

❖ We're going to talk just briefly on **HIV-2**, it's usually ignored or not very focused on in researches because it's mostly restricted to west Africa and few other countries that deals with west Africa (France , Portugal), and it's less aggressive than HIV-1 , it has a longer asymptomatic stage (in HIV-1 it could be 5 years in HIV-2 it could be 15 years), it has lower plasma RNA levels, and it has lower mortality rate, but despite all this it will eventually develop AIDS .

These patients require modified treatment plans, when patients are diagnosed with HIV, we do further tests to know if it's HIV-1 or HIV-2, because treatment for HIV-2 is slightly different.

But because it's ignored in researches the optimal strategy for treatment are not well defined yet.

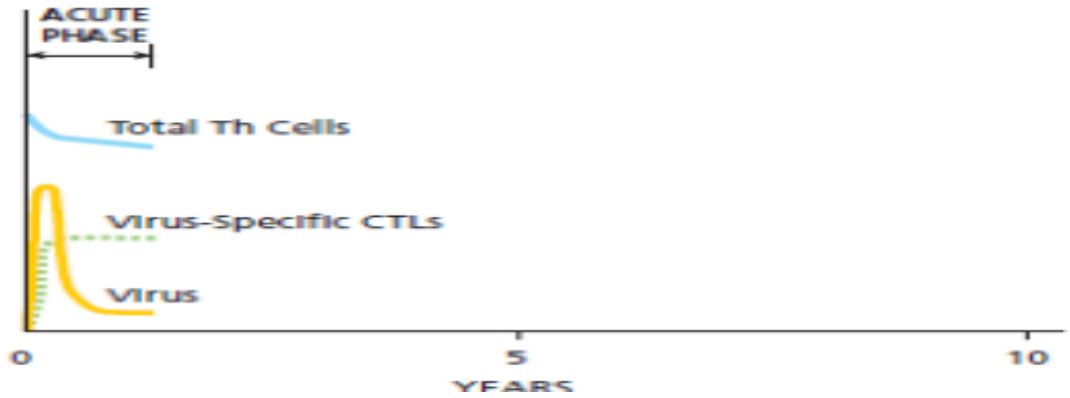
The rest of the lecture will be on **HIV-1…**

☆ *HIV infection*

- It starts when the virus penetrates rectal or vaginal mucosa; other means of entry is blood “IV”, so sexual intercourse is one of the main causes of HIV today.

- Rectal path is a more dangerous mean of infection because it's more complicated, that's why at the beginnings of HIV, homosexuals was the main group that was infected with HIV, but today things are different, we're not only talking about homosexuals anymore, vaginal mucosa is rich source of the virus, and with the increased promiscuous sexual relations or the indigenous heterosexual sexual relations that's happening, the relationship between the male and female became equally important in transmitting the virus.
- Transmitting the virus via blood transfusions is another source of the virus, but that's before there was blood screening against HIV and other viruses. But nowadays, unsterilized syringes that are used by drug abusers are still one of the means of HIV infections.

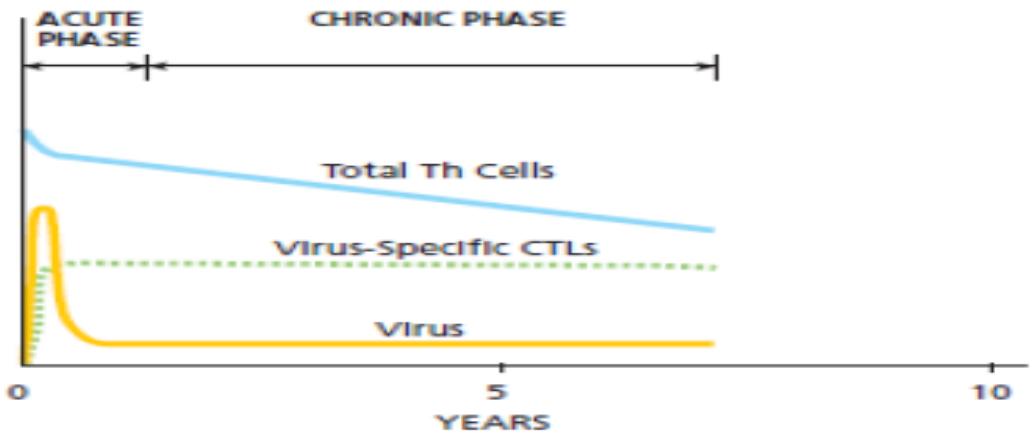
- When the virus enters the body, its target is Th cells, and it uses the cell machinery to produce more of the virus which goes on to infect other cells.



When the virus enters the body, we get first into the **acute phase**, in this phase:

1. The innate immune system detects the virus and it's trying very hard to fight it
2. The virus is trying to increase its load.

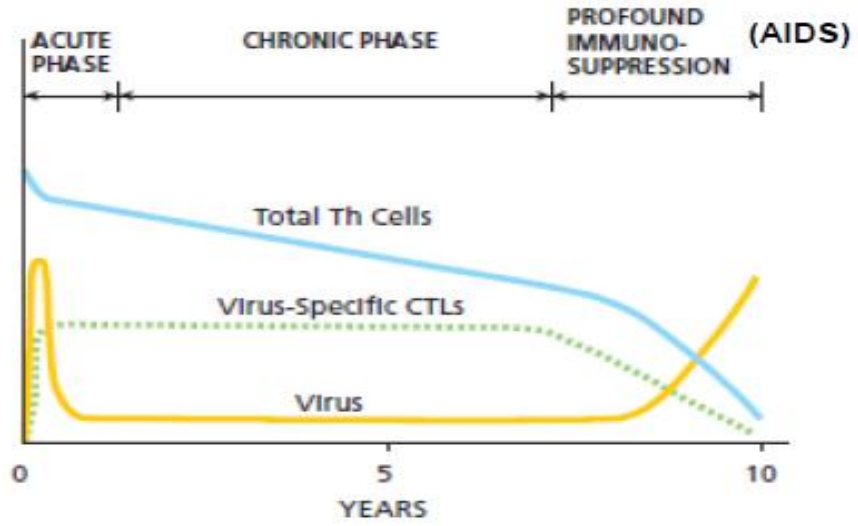
- At the beginning of this phase, we can find the virus in big numbers because it hasn't been suppressed by the adaptive immune system.
- After 48-72 hours after entry (acute phase = 2-6 week) , the adaptive immune system will start working, Th cells will recognize the virus , B cells will recognize the virus , and the virus' specific CT cell will fight the virus , in this Part of the phase , the CT cells are high because they are activated to kill the virus , and the Th cells are activated to give the signal to the CT cells to kill the virus , and B cells will start producing ABs against the virus , so the immune system is working very hard to kill the virus and it actually succeeds and the viral load drops .
- When the viral load drops, then we enter **the chronic phase**.
- In the acute phase, 80% of the patients would only have flu like symptoms.
- The chronic phase in asymptomatic and can go on for more than 10 years.



- In the chronic phase, a continuous war in going on between the virus and the immune system, in this phase the virus is using his RT enzyme to transform itself to DNA, and through its integrase enzyme it's hiding its DNA within the human genome of the Th cells that were infected, so it’s hiding away from the immune system inside Th cells.
- at a certain point (unknown why) , these integrated cells are being activated upon activation of some cellular components , and these cells start to build viral components that makes the virus , so we start assembling these proteins for the virus , this makes more viruses , then they go out to infect other Th cells , and at this phase , symptomatic response will appear (symptomatic phase) .

- In the chronic phase we find that CT cells were able to control the virus load and maintain the chronic phase, but after the activation of the cells to build new viruses, we would see a gradual decline in the number of Th cells (CD4 cells).

- We don't feel this gradual decline in Th cells, because we have a certain **threshold** of Th cells that is enough to activate CT cells to keep the virus under control, until we reach appoint where Th cells are not enough to activate CT cells, and here will reach a phase called (AIDS).



  - You should now differentiate between HIV and AIDS!

- **HIV** is the virus; any person who has the virus is HIV patient.
- **AIDS** is a phase of HIV infection when the patient arrives to a phase of immunodeficiency that makes him more prone to opportunistic pathogens.

In AIDS phase, there is a decline in the number of virus- specific CT cells, because they are not getting activation from Th cells, and increase in the viral load that was previously suppressed by CT cells, and this profile of immune suppression is called AIDS, and usually we wait for the patient to reach the AIDS phase then we will start his treatment. :/ *"it's a contradiction but that's what the doctor said"*

☆ *HIV vs. the Immune System*

- Why does the immune system eventually fail to kill the virus?

1. **Nature of the virus**: RT converts RNA to DNA, which is then inserted into our DNA using a viral enzyme within 5-10 days, and then the virus goes into a latent state that goes undetected by CT cells.

   So the virus being in a latent state allows it to escape the immune system and to stay in our bodies for many years causing damage without being detected.

2. **RT is error-prone**: this enzyme tends to make a lot of mistakes, so when it's replicating the virus RNA into DNA it causes a lot of mistakes, but these mistakes are to the advantage of the virus, because when our immune system recognizes the virus RNA, it produces specific CT cells and specific ABs to kill it, but this virus is always changing, the structure is changing so it's escaping our immune system. The virus is always one step ahead of CT cells and ABs generated against it.

3. **Virus mainly targets CD4+ Th cells** : the virus targets the immune system in the center , many other organism that targets the immune system affect it in other aspects but this pathogen chooses Th cells which are key cells in the co-stimulation and activation of almost all immune cells. So when this virus destroys these Th cells and cause them to decline in number, the activation of the innate immune system and CT cells is highly affected.

4. **Virus uses normal trafficking of the immune system**: when the virus enters the body, it will actually use the lymphatics to spread by attaching itself to the surface of dendritic cells. HIV is like Trojan horse (حصان طروادة); it can attach itself to dendritic cells and to macrophages and use them to spread.

so it reaches the lymph nodes in 2 ways , it attaches itself to the dendritic cells that take them to lymph nodes , or it gets opsonized by complement components or Igs , and those opsonized HIV viruses now will find their way to the lymphatics, Once it gets into the lymphatics, it reached exactly the place it wanted to be, as lymph nodes have a lot of Th cells and it's the ideal place for the virus to spread eventually to the blood stream.

☆ *Living with AIDS*

If untreated, then it's fatal and death occurs within 10 years (HIV-1).

These cases of untreated AIDS existed long ago and not anymore, because with long researches about HIV treatment, it introduced what is called **HAART** "Highly Active Anti- Retroviral Therapy". With better understanding of the virus, drug combination is being made.

- **HAART** contains nucleoside reverse transcriptase inhibitors, integrase inhibitors, non-nucleoside reverse transcriptase inhibitors and others.
- So we have this combination of 4-5 drugs, and each one of these drugs targets certain part of the viral component, and they found that it's very efficient in lowering viral loads to almost zero. But the moment you stop therapy the viral load will come back, it doesn't remove the virus but it blocks it from replicating and increase in number.
- This therapy was able to extend life for HIV patients by many years.

Side effects of the therapy:

1. Cognitive disorders
2. Increase risk of cancers
3. Kidney , liver , bone , and heart diseases

We have a certain group of people called **Elite controllers**, those are <1% of HIV patients, and they remain asymptomatic for a very long time.

HOW?

1. They found that in these people , the immune system is firing up more strongly upon infections , and that they can produce higher amounts of Type 1 interferon (alpha and beta) than others .
   The production of high amounts of type 1 interferon in the first stages of the infections means they're better at killing and controlling the virus, so they're better controllers.
2. MHC molecules are very efficient at presenting the viral peptide of HIV in this group of people, and that helps in controlling the infection very early.
3. CTLs in elite controllers are more aggressive than normal patients, and that also helps to control the infection very early.
   (These CTLs can mobilize granzyme B very well and deliver it into target cells more efficiently.

But we also have to know that these patients “Elite controllers” also get infected, they are not like superman, and they will eventually develop AIDS if they remained without medication for a long time!.

Note:

Th cells are high CD4+ expression cells, but we also have cells that are low CD4+ expression which are macrophages and dentritic cells.

That's why we have HIV that are called macrophage tropic or DC tropic , because dentritic cells and macrophages can be infected with HIV virus , but to a lower rates , because their expression of CD4 is much less than Th cells .

☆ *AIDS in mother and child (case study)*

<u>HIV can pass from mother to child during:</u>

1. **Pregnancy** : HIV can cross the placenta (like IgG)
2. **Childbirth**: by cervical secretions or blood.
   when we find out the mother (HIV patient) is pregnant, it's a key to control HIV, she should get treatment and her viral load should always be low during pregnancy and she should have a C-section rather than normal birth.
3. **Breastfeeding:** HIV virus is also found in mother's milk, that's why HIV positive moms should not breastfeed.

Untreated mothers have a 25% chance of transmitting the virus to the baby وحدة (من كل 4 حالات).

Babies born to HIV positive moms usually receive HIV medications for 4-6 weeks after birth to reduce risk of infection. This showed a promising potential to decrease chances of HIV infection.

☆ *Lab testing for HIV*

HIV-1 &2 Antibody test : was used in the past but now it's less used , because it's diagnostic window is very high , the patient is required to seroconvert for a whole 3 months for the test to be able to diagnose him .

HIV-1&2 Antigen Antibody combo test: used nowadays, most relevant, used in Jordan.

- It tests for HIV-1 and for HIV-2 and at the same time it tests for a certain antigen that is found on the virus and the antibody that our body is producing against that antigen.
- It looks for one of them or both (HIV / Antigen antibody).
- Its diagnostic widow is much lower, within 1 month we're able to diagnose the patient (95%) but other patients still need 3 months to be diagnosed (5%).

HIV-1&2 by PCR: most accurate test, to looks for the RNA of the virus, and it has a short diagnostic window; in 10-14 days we're able to see the virus up to 3 weeks. Not very popular because it's expensive.

- For established cases : (follow up tests)

Flow cytometry and PCR

- In flow cytometry : we look for CD4+ cells (Th cells) and CD8+ cells (CT cells) and we calculate the CD4:CD8 ratio (usually 2:1 = 2) , in HIV patients the ratio will keep decreasing reaching less than 1 (meaning that CT cells are now more than Th cells) , when they reach less than 1 , then they are now in AIDS phase and they should start treatment

- PCR: gives the viral load (unit RNA copies / ml), this test shows us how the viral load is responding to the treatment.

☆ ***HIV Hotline***

HIV hotline number: 06/5697933

They answer any questions about HIV

Advice and counseling

Reporting cases

Free treatment for HIV patients in Jordan

Le Fin.

"We must accept finite disappointment, but we must never lose infinite hope." - Martin Luther King

Sorry for any mistakes

Done by Aseel Hababeh (مع شدّة)

Revised by: ***Omar Saffar***