HIV AND AIDS

HISTORY

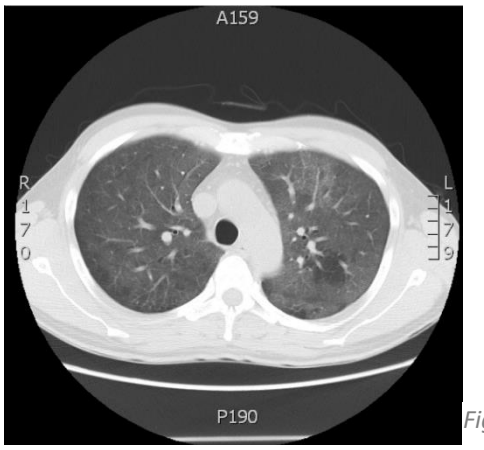


Fig.1

The first cases appeared in **1981** when a few general practitioners from the US reported cases of atypical pneumonia: 5 young men, all active homosexuals, were presenting 2 disorders really uncommon in healthy people: Pneumocystis carinii pneumonia (PCP) and Kaposi's sarcoma. They can be both observed in severely immunocompromised people but not in young healthy males.
This (*Fig. 1*) is the usual presentation of PCP: bilateral infiltrate in the interstitium of the lung with a brown appearance and acute lung injury. There is a progressive dyspnea, which could lead to intubation since lung insufficiency could be deadly.
Kaposi's sarcoma is an angiosarcoma related to the infection by Herpes Virus A. Normally, Kaposi's sarcoma is present in severely immunocompromised individuals affecting the lower limbs. In these cases instead, the lesions are observed everywhere (skin, mucosa, GI tract, and lungs).

Pneumocystis carinii pneumonia was biopsy-confirmed at 3 different hospitals in Los Angeles, California. Los Angeles and San Francisco were the two most relevant cities for the beginning of the epidemic in the US. All 5 patients were also positive for CMV (cytomegalovirus) infection, candida mucosal infection, and Kaposi's sarcoma. The mortality at that time was about 90% because no treatment was available.

In **1983** the disease was named Acquired Immune Deficiency Syndrome (AIDS). The mortality was really high: 90% of people diagnosed with AIDS died in the first 6 months. It was a severe pandemic.
Since **1984** there has been exponential growth of cases without the availability of serological tests, at that time the only diagnosis was a clinical diagnosis with all the pitfalls such a complex clinical picture implies.
In **1985** two different groups, Montagner/Barré-Sinoussi (France), which received the Nobel prize, and Robert Gallo (USA), identified and isolated the virus, obtaining also the first images of the virus.
For a long time, it was not compulsory to notify any case of HIV infection and this increased even more the extent of the diffusion. During the same year, after the isolation of the virus, the first IgG serological test was developed.
The first case in Italy occurred in **1985** in IDUs (injecting drug users) and hemophilic patients.
In the same year, the heterosexual transmission was confirmed.
In **1987** the first drug against HIV was released: **zidovudine** (**AZT**). It has been tested for cancer since it is a thymidine analogue, so it can impact DNA synthesis. Side effects were linked to the onset of anemia, thrombocytopenia, and peripheral neuropathy and for these reasons it was discarded. It was repurposed as an antiretroviral drug since it can selectively inhibit reverse transcriptase, which is one of the key enzymes of HIV replication (the virus uses the enzyme to make a DNA copy of its RNA).
In several African countries, the first test was done in **1995**, so for 10 years the diagnosis of HIV has been clinical-based (weight loss, chronic diarrhea, chronic lymphadenopathy).

Q: What IDU's stand for?
A: Intravenous Drug Users (reference to the slides).

These events have been followed by a **worldwide diffusion** of HIV/AIDS. A huge increase in cases occurred especially in Sub-Saharan Africa (more than 80% of cases) countries, where HIV/AIDS had a tremendous impact in terms of life expectancy and economic burden.

At the beginning of the ‘90s HIV/AIDS was the first cause of death in people aged 25-29 years old.

In those years the disease was considered by the general population only associated with drug abusers and homosexual people and so the real risk of the diffusion was underestimated.
To inform and sensitize people, many commercials were created. The main message of the commercials was “If you know AIDS, you avoid it. If you don’t, you die”. This message was useful but really scary. This contributed to the creation of stigma towards infected people.

Many famous people were infected and died because of HIV, while others decided to talk about it (*Fig. 2*).
Freddie Mercury, Bruce Chatwin, Rudol'f Nureev, Isaac Asimov, Majic Johnson (the first NBA player who openly talked about HIV), and Keith Haring (who died because of HIV).

Fig.2

This picture (*Fig. 3*) is really important: Professor Aiuti from Milan was an immunologist, who here kisses a patient (who is still alive) on the lips. The message is that it is possible to touch, kiss, and live with somebody who has HIV. Because many people were scared even to touch HIV-positive people.
Someone could think that this is something that belongs to the past, but just 8 years ago, in a survey conducted among several countries, it was asked if people would be ok to buy fruits and vegetables from vendors that are HIV-positive; 40% of the surveyed said no. Again, 40% of the survey participants said that children with HIV should stay in separate schools.
You might think that the stigma is not present anymore but actually, it is.

Fig.3

There are 3 movies related to HIV that the Professor suggests to watch:

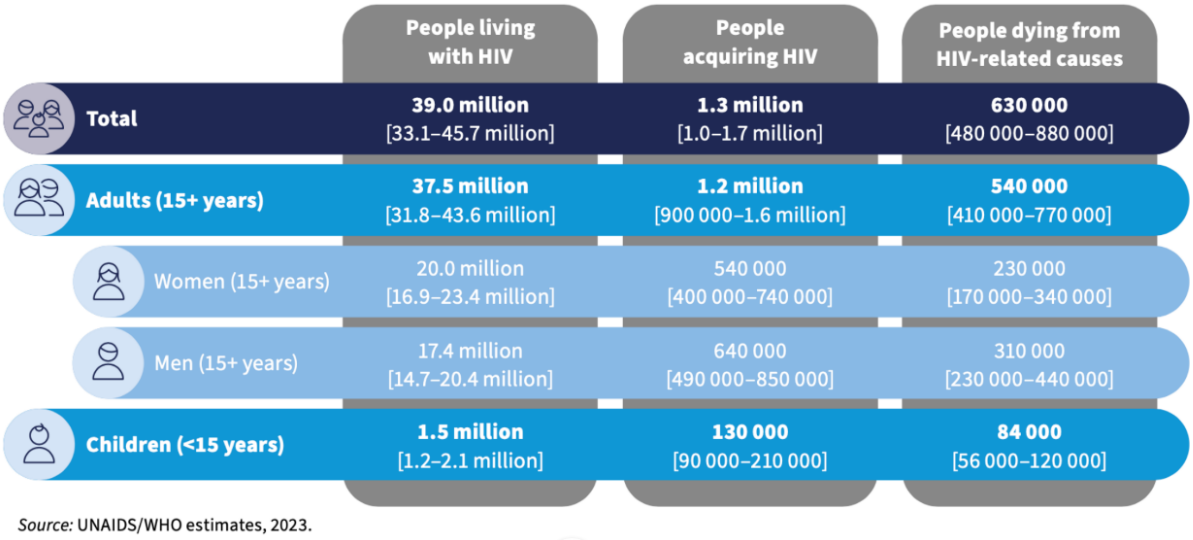
- Philadelphia (1993).
- Dallas Buyers Club (2013).
- The Normal Heart (2014).

EPIDEMIOLOGY

How many people with HIV are living in the world?
Most recent data from the United Nations Program on HIV/AIDS (**UNAISD**), suggest that they are 39 million. Focus also on the confidence interval (*Fig. 4*): 33.1 to 45.7 million, which is huge. This is because notification rates are really poor in many countries. It is more of an estimate: WHO takes notification rates from a few hospitals in each country, and then they model them in the population. There is no real number,

it is an estimation of people that might have HIV based on incidence and prevalence.
There is a significant portion of people who don't know that are HIV positive. Hence the real notifications are much smaller. This again explains the big confidence interval.

Regarding **incidence**, people acquiring HIV are about 1.3 million. It went down, because, in the last 20 years, it was about 2 million.
Regarding **mortality,** 630.000 people die every year. It is 50% lower in respect to early 2000.
Mortality decreased considerably, while incidence did not so much.
There are also 1.5 million **children** living with HIV. If they do not follow an antiviral therapy the onset of AIDS is about 5-10 y.o. dying around 10 y.o.



	People living with HIV	People acquiring HIV	People dying from HIV-related causes
Total	**39.0 million** [33.1–45.7 million]	**1.3 million** [1.0–1.7 million]	**630 000** [480 000–880 000]
Adults (15+ years)	**37.5 million** [31.8–43.6 million]	**1.2 million** [900 000–1.6 million]	**540 000** [410 000–770 000]
Women (15+ years)	20.0 million [16.9–23.4 million]	540 000 [400 000–740 000]	230 000 [170 000–340 000]
Men (15+ years)	17.4 million [14.7–20.4 million]	640 000 [490 000–850 000]	310 000 [230 000–440 000]
Children (<15 years)	**1.5 million** [1.2–2.1 million]	**130 000** [90 000–210 000]	**84 000** [56 000–120 000]

Source: UNAIDS/WHO estimates, 2023.

Fig.4

As for **prevalence**, the countries with the highest values are South Africa, Botswana, Eswatini, Lesotho, and Mozambique.
At the beginning of 2000, some countries had a prevalence of 33%. 1 person out of 3 was HIV-positive, it was really high.
GDP in certain countries went down because of AIDS, and life expectancy dropped by about 10 years.

Incidence is very similar: some countries still have a significant incidence. These countries are in South Africa, South America, and a few in Asia (Myanmar, Papua New Guinea).
In many countries there are no data about incidence. For instance, in Italy we started collecting incidence data in 2005, before it was only recorded data about AIDS.
Looking at the curve (*Fig. 5*) the incidence has incredibly decreased in age groups. Probably just at the age of 50, the incidence is more stable with respect to the others. A reason could be that some people get HIV when they are older or they get it when are younger but are then diagnosed when are old.

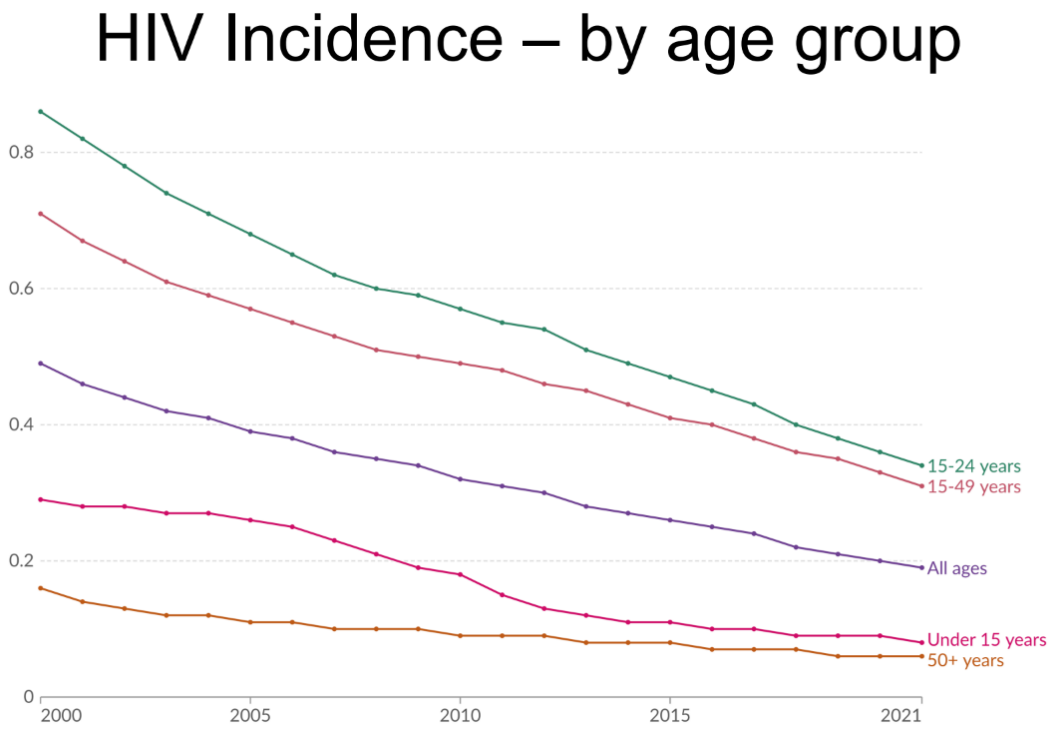


Fig.5

Globally speaking, certain areas are really doing good: in Eastern and Southern Africa new cases are decreasing (minus 57% of incidence), Western and Central Africa too. At the same time, the central part of the world is not doing good: Middle East and North Africa have an increase of 61% of the incidence; Eastern Europe and Central Asia have an increase of 49%. Latin America is quite stable.
This tells something about prevention, pre-exposure prophylaxis, and stigma.

WHO created this idea of "cascade of care", the target for 2020 was 90-90-90: 90% of people with HIV must know their status, 90% of infected people must be in care, 90% of the treated people must have an undetectable viral load = virus is controlled. Today the target is 95-95-95, so super hard to get.

Every one of these boxes (*Fig. 6*), requires different approaches. To increase the number of people who live with HIV that know their status what must be done? Testing. How to increase testing? Campaign of sensitization; the professor doesn't think that making the test mandatory would be an option; make the test free so that people are more prone to do it; expand the places and the time available to do the test.

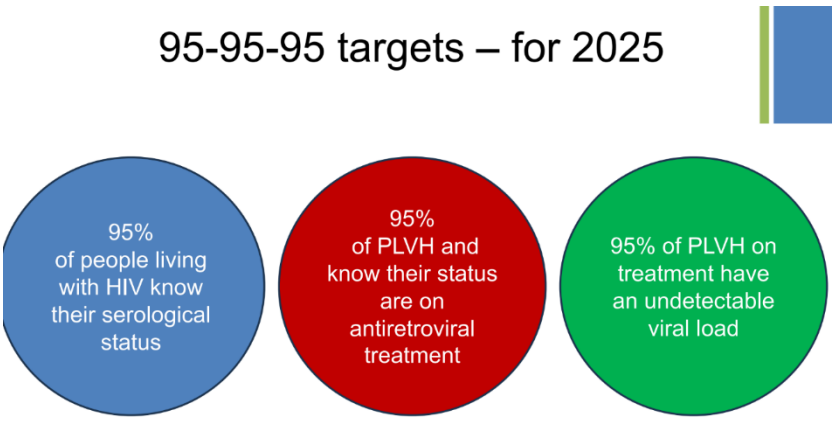


Fig.6

To increase the number of HIV-positive people on treatment is more complex. Sometimes people refuse to have the disease or don't want to go to the hospital. Some patients, since they had symptoms for many years, don't see it necessary to start the treatment.
Keeping infected people strictly adherent to the treatment and so having an undetectable viral load, depends on the drugs that are used. Nowadays is one pill once a day, so not that hard, but they have to take it for their whole life. For this reason, adherence is very low.

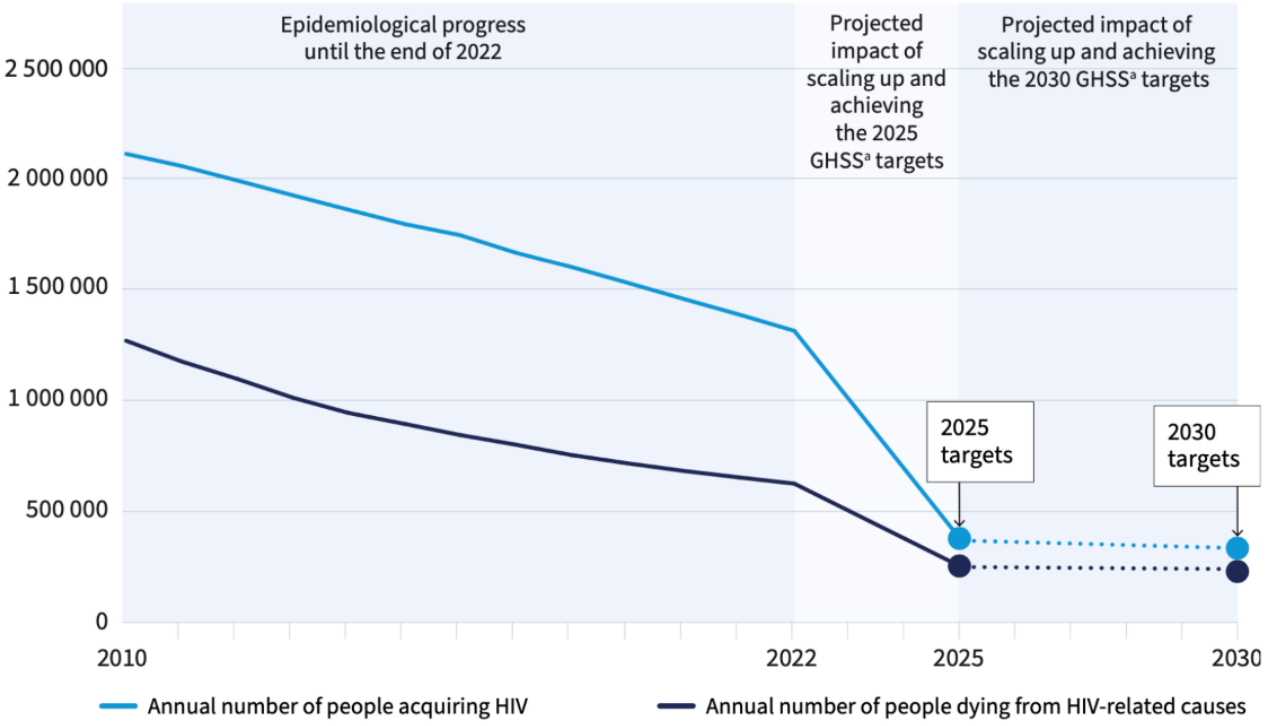


Fig.7

Targets for incidence and mortality are represented in the graph (*Fig. 7*). In one year (2025) we should reach the targets designated. Since in 2022 we were here (*Fig. 7*), we are probably not reaching the target in time.

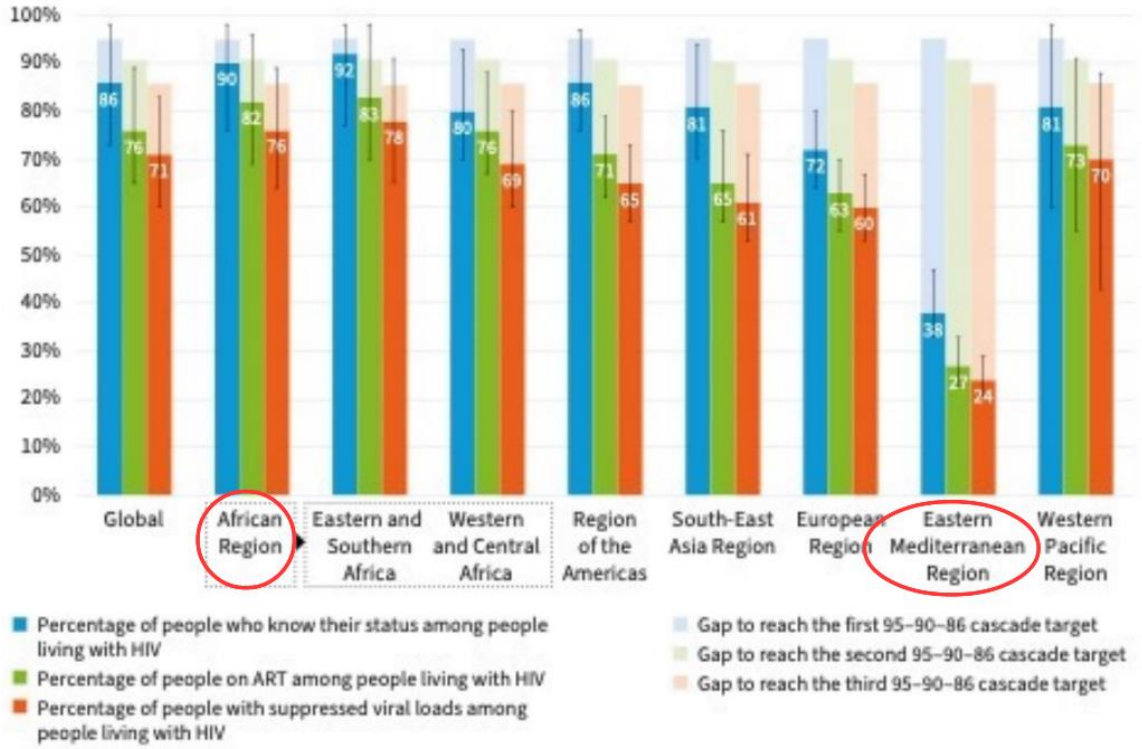


Fig.8

This is how different parts of the world are coping with the 90-90-90 target (*Fig. 8*): Africa is doing well in terms of how many people are getting tested, how many people are on treatment and how many have suppressed viral load. European regions, Eastern Mediterranean region, and South-East Asia are not doing good.

Every country has a different story: in Mongolia, only 15% of people know their HIV status.

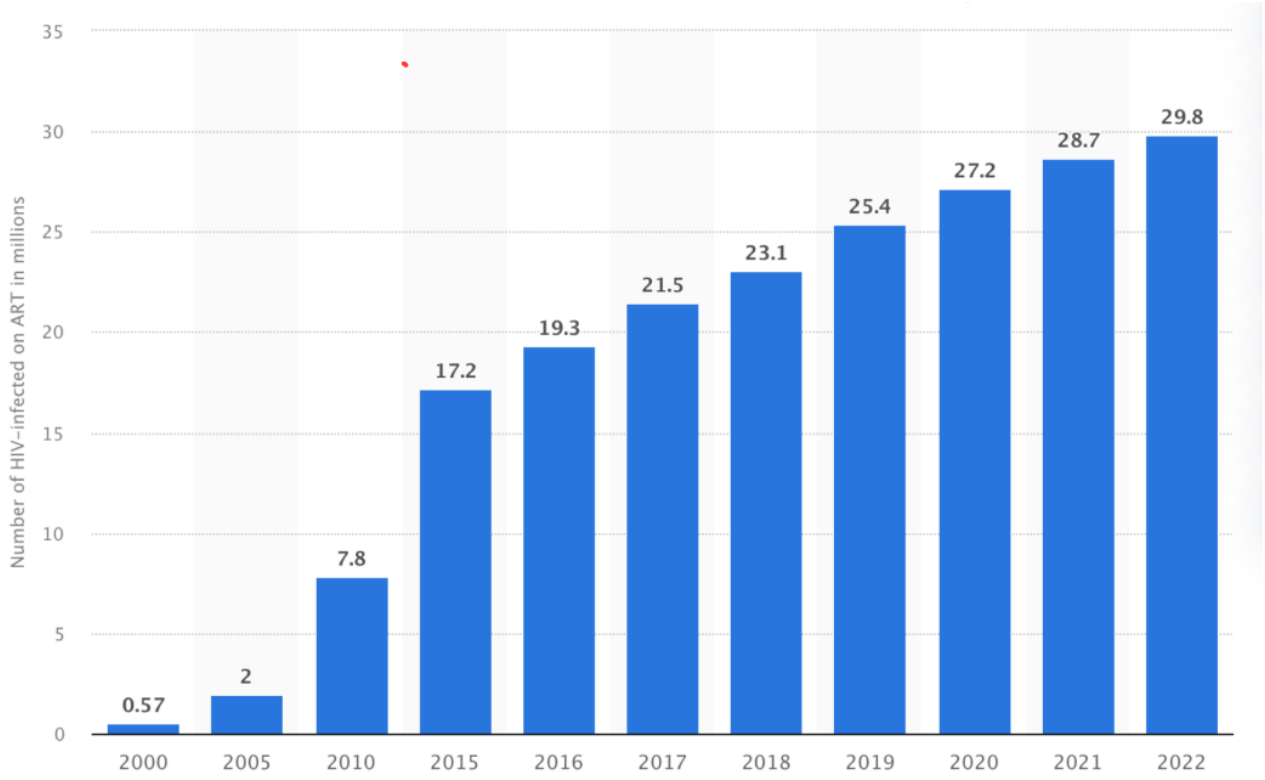


Fig.9

Starting from 20 years ago, now it has reached a value of 30 million people on treatment. How much does it cost 1 month of treatment for a single patient in Italy? 700-1000 euro. So in 1 year it's around 10.000, that multiplied by 40 (years of life expectancy) gives 400.000 for one patient.
This is why in early 2000 only people living in high-resource countries were on treatment.
What happens here (*I think the professor refers to the gap between the 2010s column and the 2015 column in Fig. 9*)? It was politics: From that moment the drug could be produced in India and Uganda decreasing the cost of 1 year of treatment to 15 dollars.
Hence today there is good coverage of 30 million out of 40 million HIV-positive.
The costs are not only related to the drug: also the doctors, the nurses, the health-officers, people bringing drugs to small villages, and HIV tests have a cost. The cost is not covered by the countries but by PEPFAR, WHO, and other organizations.

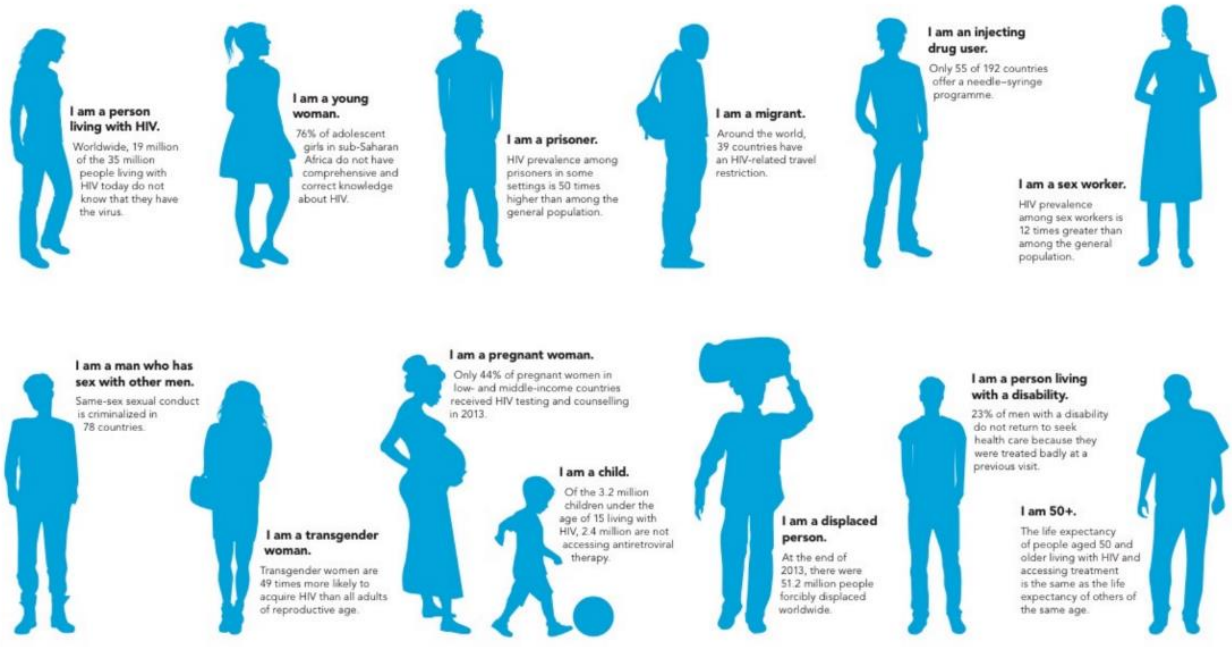


Fig.10

To reduce the incidence of HIV, is necessary to target key populations. WHO identifies 12 key populations (*Fig. 10*) in which there is either a high prevalence of HIV or a low coverage of 90-90-90 target. Some of them are young women in certain scenario, prisoners, migrants, sex workers, injecting-drug users etc.

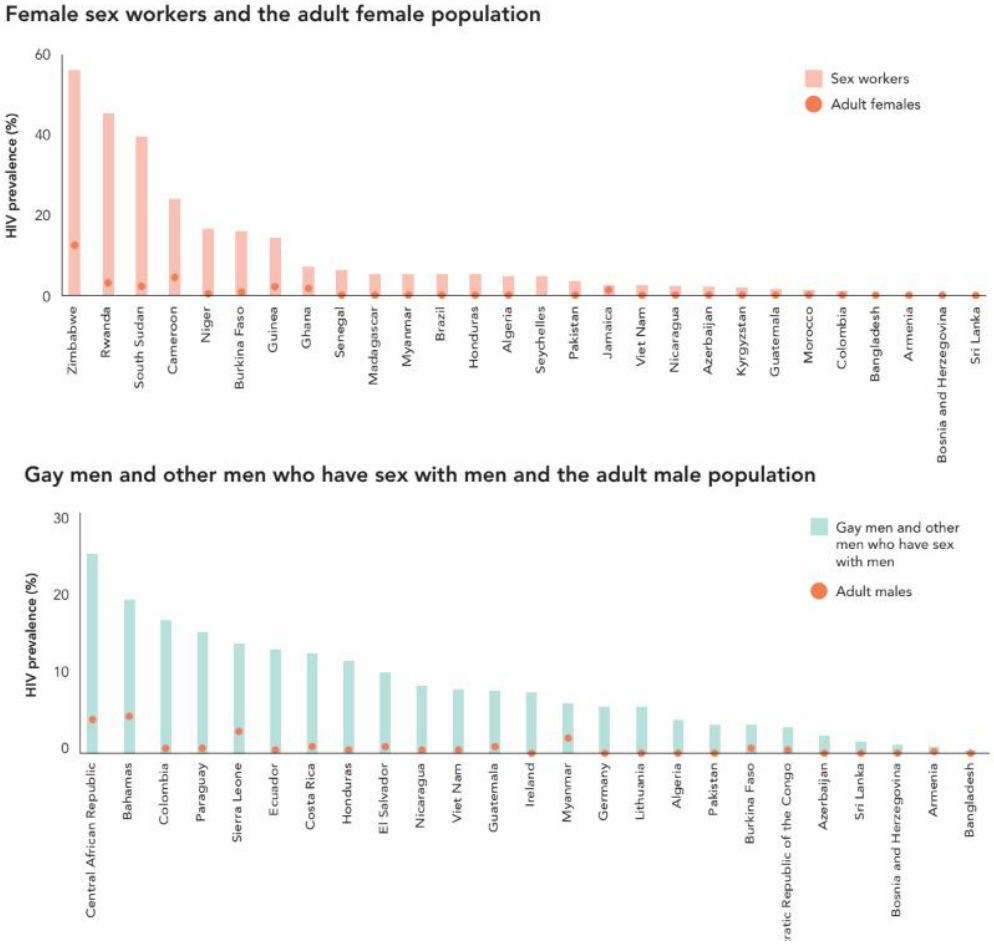


Fig.11

This graph (*Fig. 11*) is from a few years ago, but important: the dots are the prevalence of HIV in the female population (Zimbabwe 12%; Rwanda 5%; South Sudan 2%) while the bars are the prevalence in sex workers.

Sex workers are at high risk for HIV, so testing and treating them reduces the complications for them but also reduces the transmission of HIV because they are not contagious anymore.
Again, in the lower part, the dots are the prevalence in male populations, while the bars are the prevalence in MSM (which is several times higher). It is necessary to work on key populations.

FIGURE 1.3 HIV prevalence among key populations, reporting countries in eastern and southern Africa, 2017–2021

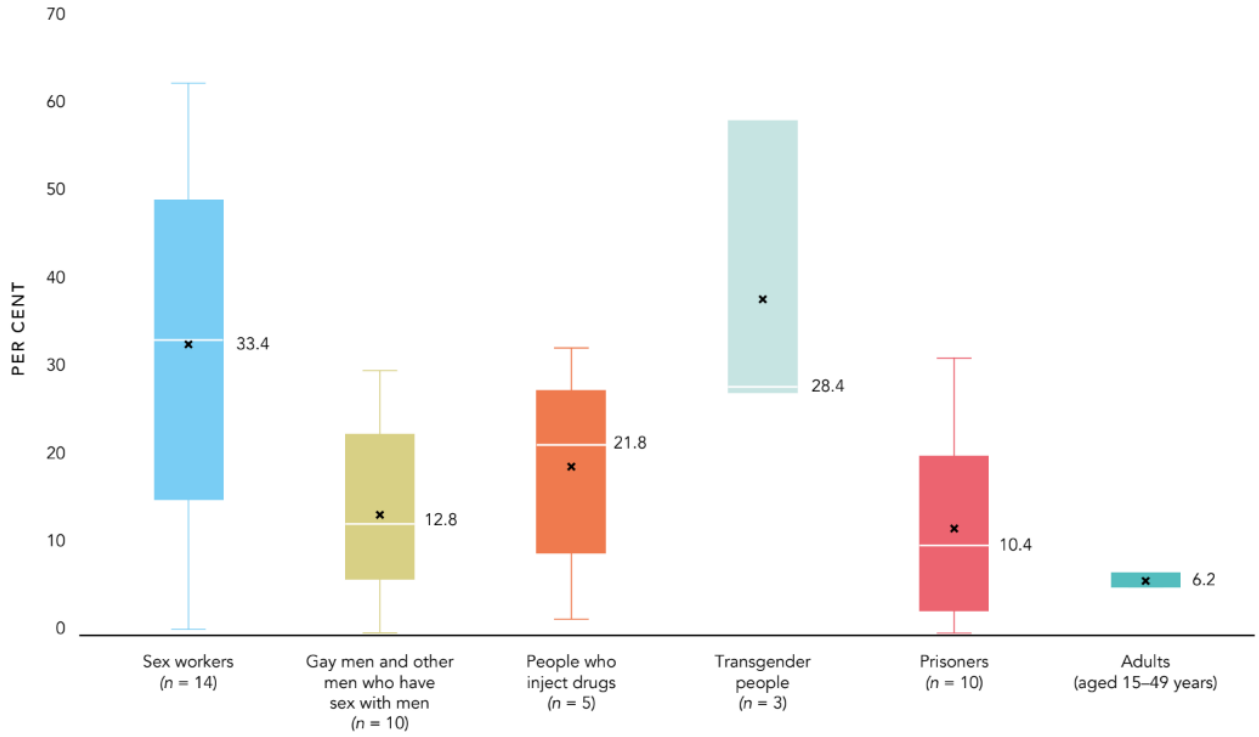


Fig.12

South and East Africa have (*Fig. 12*) a prevalence of 6% in the adult population, while for transgender women it's at 28%; for sex workers at 33%.

One problem is **criminalization**: what does it happen if in a country being gay is actually illegal? Homosexual people cannot declare themselves about it. Also being a transgender woman in some countries is a risk of imprisonment. So in these countries, there are no data about how many people are homosexual or transgender. How can HIV be prevented in these categories at risk if it is not known where, who and how many they are? Criminalization reduces the possibility of focusing on these categories.
Even possessing (not selling) drugs is a risk of imprisonment in some countries. So is not possible to reduce the risk also in this category of people.

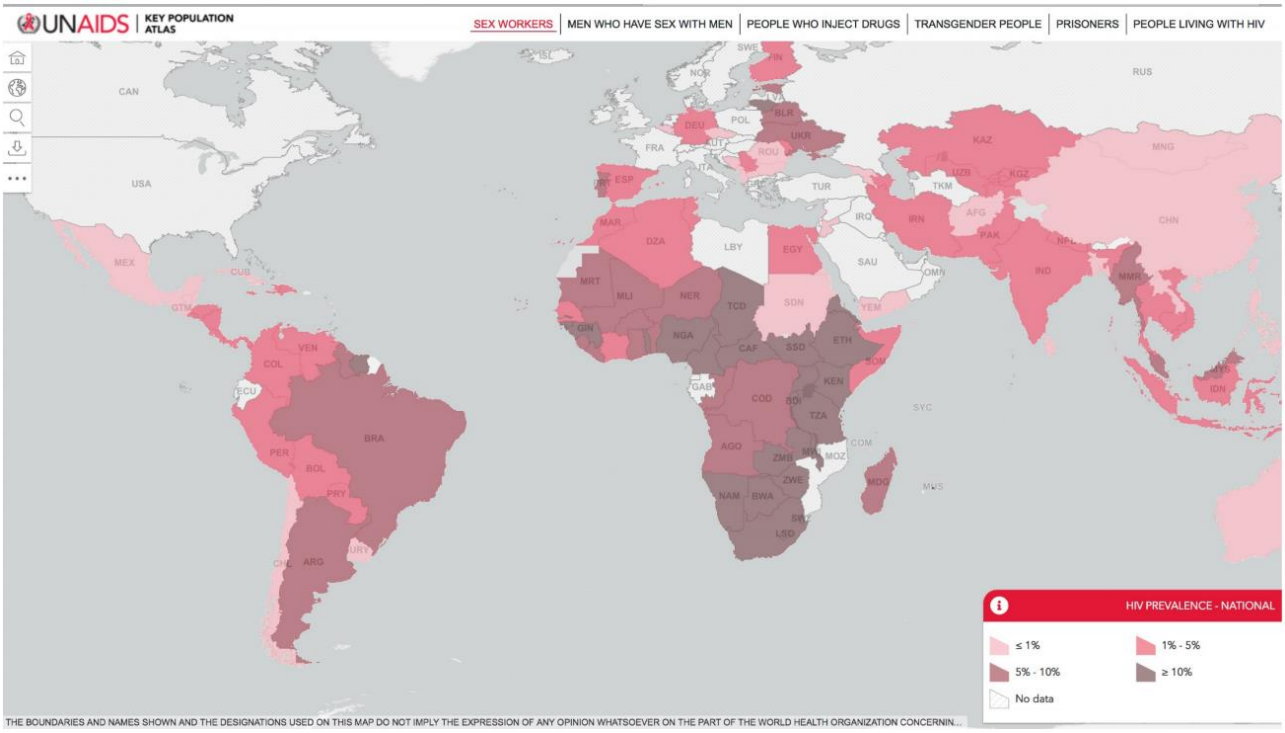


Fig.13

The atlas of the UNAIDS (*Fig. 13*) gives some data about the prevalence in several countries according to sex workers (brown area means a prevalence of more than 10%), MSM, people who inject drugs (prevalence of HIV in Eastern Europe is super high), transgender women (very few data around the world), prisoners (because of IV drug use and sex done among prisoners. Indeed Switzerland decided to screen prisoners giving them also syringes and condoms). *Fig. 13 is the atlas relative to sex workers, the atlas relative to the other mentioned categories are present on the slides.*

PrEP is necessary to cover these risk categories if the goal is to reduce the incidence of HIV. Oral PrEP is less effective in women because it needs to be absorbed and distributed to the genital area, while in males it stays in the GI tract reaching the anus and protecting it during anal sex. This is why women need a higher dosage of oral PrEP or to use a vaginal ring or a vaginal gel.
One treatment being approved in the US and Europe (but not yet present because of the costs) is an injection to do every 2 months called Cabotegravir. It protects nicely, and in women acts even better than in men.

Risk compensation theory: a person has a high risk of HIV infection because they do unprotected sex, but if they do the PrEP they could do even more unprotected sex, increasing the risk of infection of Chlamydia, Syphilis, Gonorrhea etc. Hence, many people were worried that giving PrEP would cause an increase in all the other STDs.
Studies so far suggested that there is a very small increase in the risk of STDs, that however doesn't compensate for the decrease in the risk of HIV.
So if someone argues with you proposing the risk compensation theory, you may reply that studies suggest that the risk is so small that PrEP is still cost-effective.

EUROPEAN PERCENTAGES

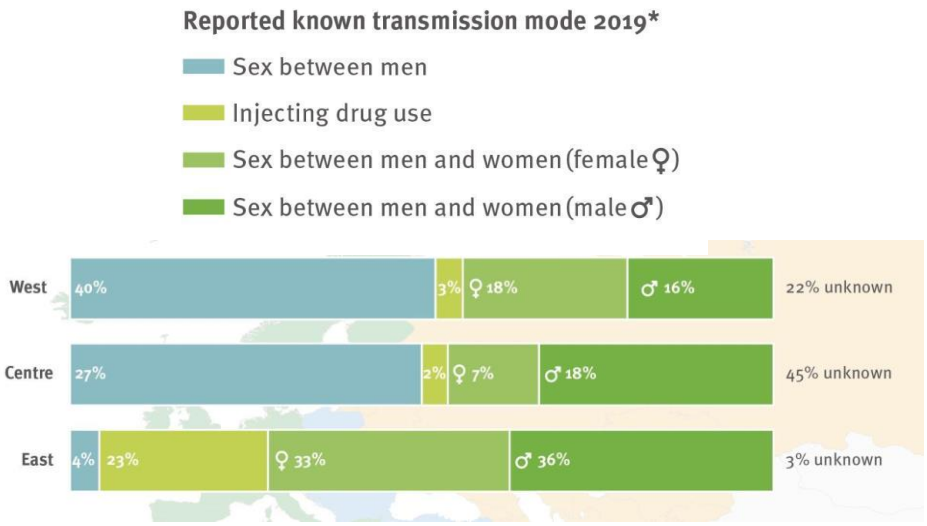


Fig.14

ITALIAN PERCENTAGES

At the moment probably there are around 150 000 people infected with HIV, a very low percentage because it accounts for less than 0.3% of the population and is decreasing over the years. Fig.15 shows data about the incidence and risk factors in Piedmont and it can be noticed that all the risk categories are decreasing except the MSM.

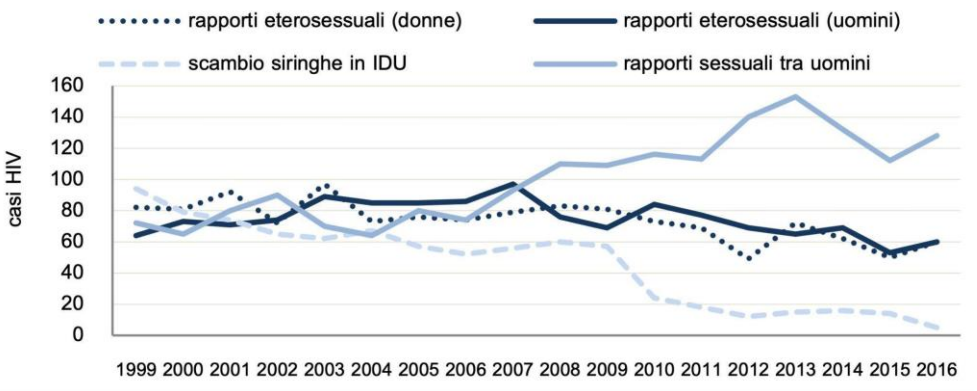


Fig.15

WHEN IS THE HIV TEST PERFORMED?

Only 6% of the risk categories perform the test thanks to the screening campaigns. In fig.16 there are the most common reasons why an HIV test is performed. Unfortunately in Italy the late diagnosis is still prevalent (25-45% of the cases).

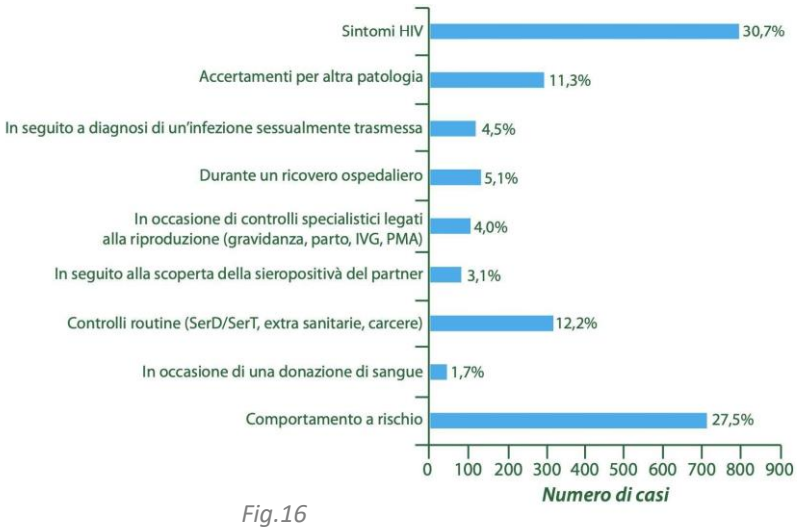


Fig.16

THE AIM OF THE HEALTH SYSTEM WAS THE PROGRESSION FOR THE 2021 TOWARD THE 90-90-90 CONCEPT

- *90% of people living with HIV who are aware of their status*
- *90% of HIV patients on treatment*
- *90% of HIV patients virally suppressed*

In fig.17 the real data of 2022 are shown.

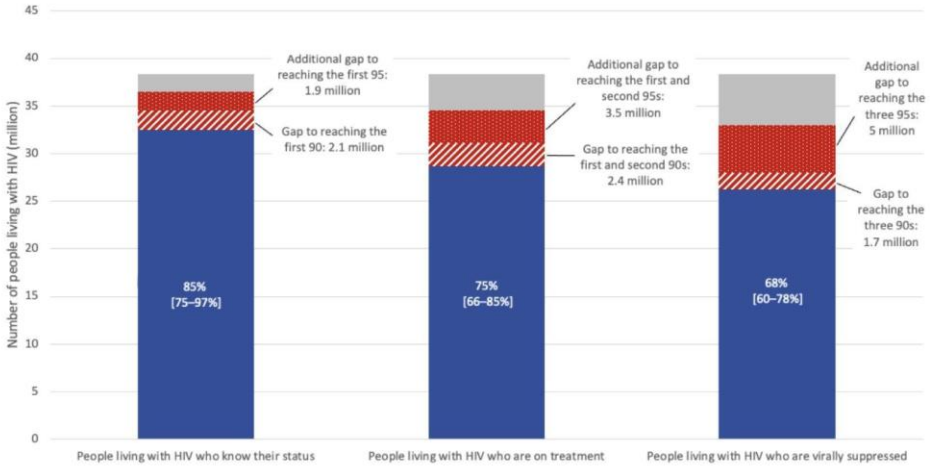


Fig.17

GOAL FOR THE FUTURE

In the graph of fig.18 the annual data about 2 trajectories are shown:
In blue is the number of people newly infected by HIV;
In yellow is the number of people dying from HIV-related causes;
In the right part of the graph are indicated the objective for the 2025 and 2030 (the professor comments that in his opinion it will not be reached).

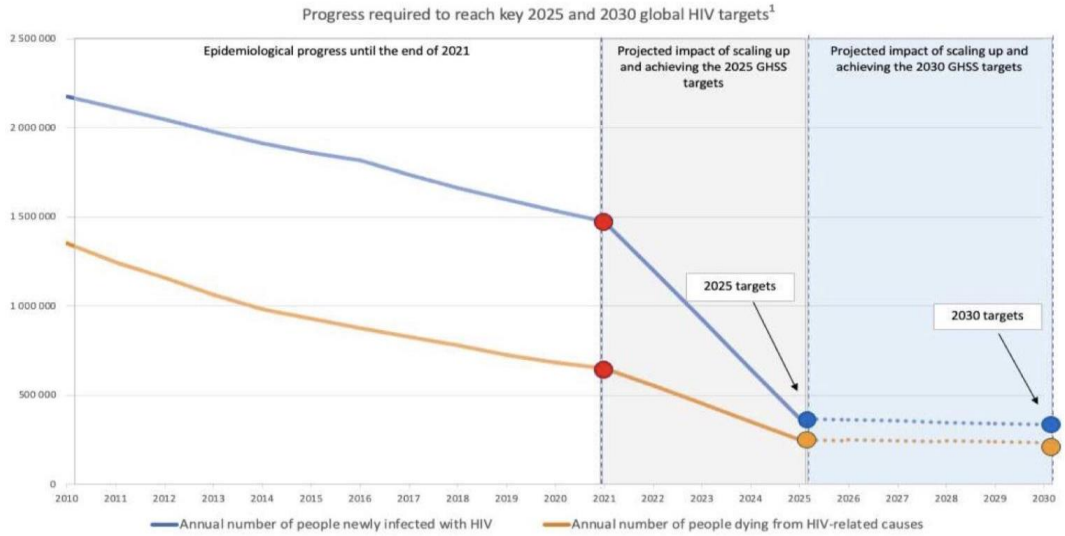


Fig.18

ORIGIN THEORY

HIV is a **retrovirus** and it is part of the **Lentivirus** family. The structure of the virus is very similar to the one of SIV (Simian immunodeficiency virus). The theory is that the first case at the end of the 19th century was a hunter who entered into contact with macaques in Central Africa, and the spillover happened. Hence, probably SIV adapted to humans and started spreading in Central Africa.
There is also an interesting story about King Leopold, who decided to build railways in the current Democratic Republic of Congo for the mines. This was the actual way through which HIV spread through DRC and the adjacent countries and after that all around the world.
The first death, certified by the collection of blood sample, occurred at the end of the 50s in Congo.
There was a paper in Nature suggesting through phylogenetic analyses that the first case was probably in 1931. Hence, why HIV was stable from the '30s to the '80s and then spread so quickly? A possibility could be the treatment for syphilis that has facilitated the spreading. Other possibilities are commercial sex and iatrogenic distribution (in Egypt HSV had a iatrogenic spread through vaccination).
It is interesting to note that in some hosts this virus replicates and produces a disease very similar to the one caused by HIV, in other hosts (e.g. Green African monkey, Sooty, Mangabey) it replicates but it does not produce any damaging effect. Immunologists are still working on these differences to understand the relation of the virus with the host's immune response.

VIROLOGY

HIV is a retrovirus (*Retroviridae-Lentiviridae*), so a virus which needs reverse transcription from RNA to DNA, and then DNA integrates with the one of the host cell for its own replication.
Humans, theoretically, do not have retrotranscriptase, this is why we can block this enzyme with some drugs without side effects.

HIV is very **heterogeneous**: retrotranscriptase is an enzyme that makes a lot of mistakes. So, by retrotranscription, in many copies mutations occur. Hence, some copies of the virus are defective, but some copies acquire mutations that increase the number of variants of HIV in the world. There are many variants of HIV1 characterized by different surface proteins and genome. It is not so important from a replicative POV, but resistance represents a concern: every subtype has a pathway to resist in some way.
*There is a high heterogeneity in viral **quasispecies** due to the fact that many mistakes are made by RT, resulting in the transcription of defective parts with significant differences. 10^9 approximate virions produced every day and 10^5 errors performed by the RT. This means that there is a constant evolution of the virus over time.*
There is also a great global variability in HIV-1, which is divided into three groups:

- ***M** (major)*
  There are several subtypes within the M group: A, B, C, D, E, F, G, H, J, K, recombinant (CRF) and mixed (A_E). The presence of a recombinant and a mixed form suggests a complex evolution of the virus in the human host.
- ***O** (outlayer): located in West-Central Africa and is not usually seen outside of that area.*
- ***N** (non-M, non-O).*

How is it composed?
Outside there is an **envelope**, going more internally there is the **matrix**, the **capsid (core)**, and inside of the latter the **2 RNAs**.
*The **virion** is composed of:*

- *Matrix, internal capsule, and nucleocapsid made of proteins;*

- *Enzymes: **reverse transcriptase** (RT), **integrase** (which allows the virus to integrate its DNA into cellular DNA) and **protease** (the DNA gets translated into large peptide sequences which are into single proteins by viral protease);*
- *Membrane proteins of cellular or viral origin (gp120 and gp41);*
- *Viral **RNA**: 9.7 Kb.*

HIV-2

It is very similar to HIV1 in terms of genome sequences but very different in terms of transmission and progression to AIDS:

- Slower progression of the infection
- Less contagious
- Mostly observed in West Africa and Portugal (because some people that were born in West Africa moved to Portugal).

Usually, tests include both HIV-1 and HIV-2. However, HIV-2 RNA is less standardized, so the monitoring of HIV-2 infection is more complicated but the prevalence is lower.

PATHOGENESIS

Fusion and cell entry:

The first phase of the process is the recognition from HIV of CD4+ T lymphocytes (T-helper) receptors (but this is also present in some other cells) by **gp120**, a viral glycoprotein which binds with CD4. T-helper are very important in the regulation of immune response.

This binding is very unstable and needs to be stabilized by **co-receptors** which are other proteins found in the human cell (host cell). These co-receptors are called **CCR5** (mainly, is more important) or **CXCR4**.

When the binding is stable the virus takes out a fusion protein called **gp41**: a sort of channel forms between the two membranes and so the virus can get into the cytoplasm of the target cell.

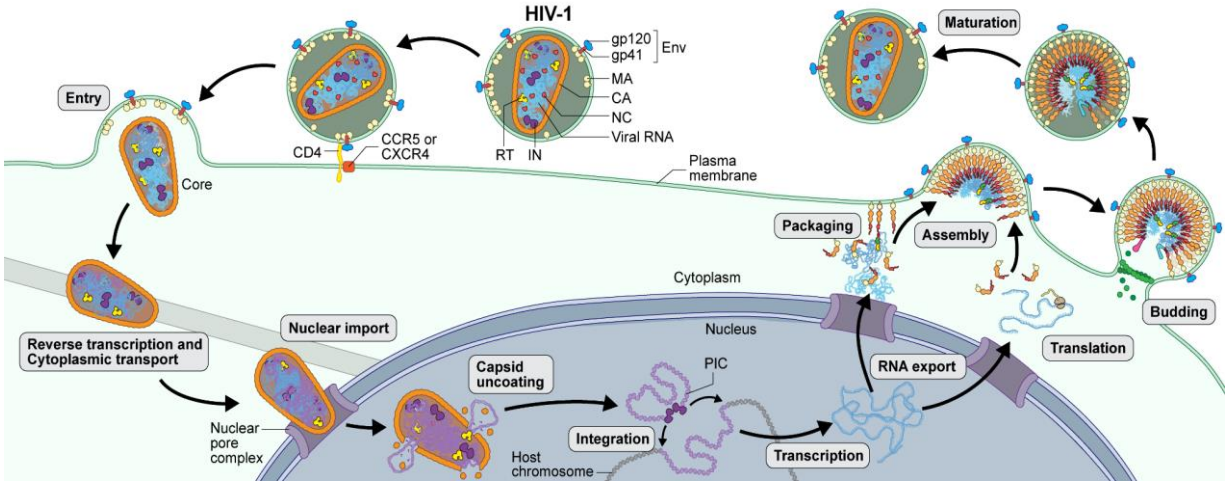


Fig.19

Why CCR5 is important? A study from the '90s showed that many sex workers from Nigeria exposed to HIV didn't get infected because they lacked the gene for CCR5. Hence by not having CCR5 they were resistant to HIV infection. It came out that 1% of the European population is actually resistant to HIV because they do not have CC5R5 on their T-cells. This deletion is called **delta32 mutation** and it causes a lack of the CCR5's external part. The mutation can be present in 2 forms:

- patients having the mutation in one of the two alleles coding for CCR5 usually have a slow progression to AIDS.
- patients having the deletion on both copies of the CCR5 gene are virtually resistant to HIV infection.

Prevalence of Delta32 alleles is concentrated in Northern Europe and in Central-Northern Asia. The deletion seems to be apparently linked to some smallpox epidemics of several centuries ago, during which the lack of CCR5 was a genetic advantage providing better chances of survival.

This finding is at the basis of one of the most important papers on the cure strategies for HIV: the Long-Term Control of HIV by **CCR5 Delta32/Delta32 Stem-Cell Transplantation**.

In 2009 the New England Journal of Medicine reported the case of Timothy Brown, an American HIV+ patient who lived in Germany. He developed acute myeloid leukemia which relapsed after both chemotherapy and radiotherapy, therefore, he underwent an allogeneic stem cell transplantation. The HLA matched donor was homozygous for CCR5/delta32. After 10 years of follow-up, the patient reached 100% chimerism: all his cells derived from the bone marrow of the donor were chimeric and lacking CCR5. He still had the HIV virus (a small amount of HIV RNA was found) but there had been no replication within the new cells. This meant that if the HIV reservoir is very, very low the immune system might be able to control it. This is the first case of a patient who was actually treated for HIV with a **functional cure**.

Of course, it is impossible to perform a bone marrow transplant for 36 million people living with HIV but this is a potential way of controlling the infection: reducing the number of cells which can be infected by the virus. Furthermore, allogeneic stem cell transplantation has a mortality rate of >20%, hence it cannot be performed in all patients. Anyhow, it probably represents a "road" to some kind of strategy for a functional cure for HIV. If we understand how to delete CCR5 through gene therapy, or T cell transfer, people could be cured.

Life cycle:

The life cycle of the virus is composed of many steps which approximately last 8-16 hours and some of them (*the 5 in bold in the list below*) can be targeted by drugs to inhibit HIV replication. Usually, the inhibition of at least two different mechanisms is combined to obtain better results:

1. **Fusion**: inhibition of the interaction between CD4 and gp120.
2. **Reverse transcription:** inhibitors of reverse transcriptase.
3. DNA translocation: DNA gets into the nucleus.
4. **Integration:** most important class of drugs, inhibition of integration of DNAv into human cells' DNA. Because once it gets integrated, it cannot be eradicated.
5. Transcription.
6. **Virion formation:** targets the viral proteases which is an enzyme that humans do not posses.
7. Assemblement
8. **Maturation** and buddying.

Today there are 26 drugs that can be used to deal with the 5 steps mentioned.

TRANSMISSION

Humans are the only reservoir of HIV. Other animals, for instance cats, might have immunodeficiency viruses but they are not transmitted to humans and the same applies to SIV.

HIV+ positive (not under treatment) can pass the infection to HIV- subjects if an adequate amount of virus is transmitted through an adequate route of transmission. HIV can be found in several biological liquids but can only be transmitted by:

- **Blood**
- **Sperm**
- **Breast milk**
- **Cervical secretions**

They are considered epidemiologically responsible for the transmission. This is because of the greater amount

of virus they contain (which is highest in blood and slightly lower in sperm, cervical secretions and milk).
What about saliva? No, because even if the virus is in it, the viral load is very low. This is because it is rich in IgG and lysozymes that do not allow the virus to replicate.
The virus is also in urine, but again is not contagious.

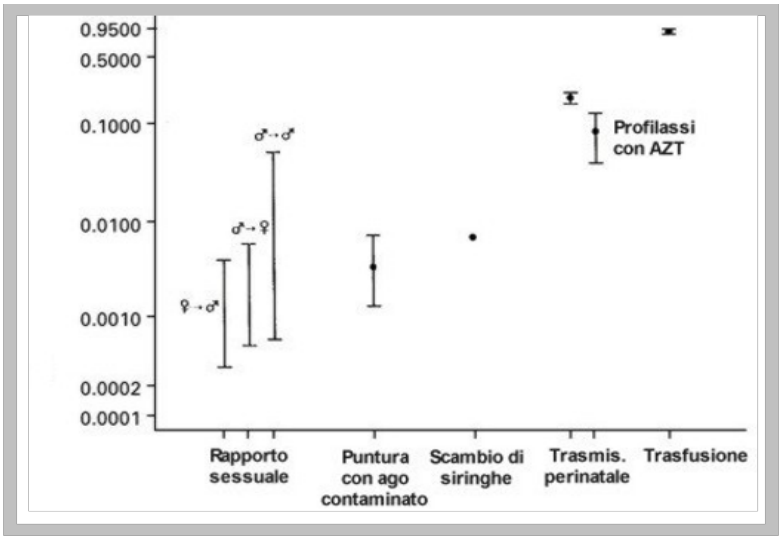


Fig.20

Three transmission routes are identified:

- Sexual:
  The risk of transmission for a single sexual intercourse is very low but the risk increases if it is multiplied by the number of multiple intercourses and by the number of different partners. It can also be noticed that the risk of transmission differs in case of the different infective partner:
  - WSM (vaginal transmission with female HIV+ and male HIV-): around 0.1%. Is not really high. How can it be so that there are 40 million people with HIV? It is basic epidemiology: it must be multiplied by the number of sexual acts, by the number of partners, by the risk percentage. Consider also that this risk is enhanced by STDs (2-6 times higher risk if someone has an STD).
  - MSW (vaginal transmission with male HIV + and female HIV-): around 0.2%, slightly higher than in the case of infected women. This is because semen stays in the vagina and also because in the vaginal wall there could be microlesions that allow entrance of HIV.
  - MSM (anal transmission): around 1%, 10 times higher compared to heterosexual transmission. This is because of the anal sex: anal mucosa is much more fragile and prone to rupture compared to the vaginal one and in blood there is the highest viral load.

  Q: What about anal sex in which the receiving partner is positive and the giving partner is negative?
  A: It seems to be similar, always around 1%, because anal secretion allows blood to get out into the mucosa. Hence the risk for the giving partner is balanced, just as the HIV-positive semen of a giving partner can infect the receiving partner because of the microlesion in the anal canal. However receiving has a slightly higher risk than giving.

- Parenteral:
  - Needle exchange among IDUs: risk around 1%.
  - Blood transfusions and hemoderivatives: risk around 95%.
- Vertical (i.e. from mothers to newborns. 24-40% of risk of transmission):
  - Transplacental (low).
  - During breastfeeding (medium).
  - During delivery (high, 70% of risk).

  Q: I heard that breast could be contagious because by biting it there could be bleeding more than because of breastfeeding. Is it true?
  A: It is wrong, HIV is contained in breastmilk, so breastfeeding is a route of transmission. HIV is contained in high amounts in breastmilk.

What should be done?
We want all women to be tested for HIV and treated before pregnancy. However, in many countries, women are not often screened, and just go to the hospital for delivery. The second measure which can be taken is to do a **Cesarean section** which is faster and cleaner than vaginal delivery but again in many countries there are not enough surgeons. Finally, **prophylaxis** is necessary, together with **artificial breastfeeding**, which however needs clean drinking water which is not accessible in many places in the world.
If prophylaxis (testing and treating pregnant women) is combined with cesarean section and followed by artificial breastfeeding, the risk of transmission can get lower than 1%. This is the strategy that has been adopted by most of the developed Countries.
There are however many problems related to this strategy:

- In certain countries there is a surgeon every 10.000 (*I think he refers to deliveries*), so is impossible to do C-sections in all of them.
- Water is necessary to dilute the powder for artificial breastfeeding. If the water source is not clean, the newborn will die of diarrhea. A study in Botswana in the '90s suggested that more children die because of diarrhea than HIV.
  If a mother is in treatment, breastfeeding is suggested until 6 months of age, then there is the switch to food. However, it is important to not mix breastfeeding and food, because there could be an inflammation of the gut, increasing the risk for HIV.
  In certain countries, women breastfeed until the age of 3, for 2 reasons: absence of food and the fact that breastfeeding stimulates prolactin, which decreases fertility. Hence in some countries it's difficult to convince a woman that she should not breastfeed.
  In certain countries (Nigeria, Angola, Chad, and Ghana) there is still a rate of transmission (through breastfeeding) above 15%. In Angola specifically, many women do not go to the hospital, anti-natal care is basically absent, delivery is done even at home. A possibility could be going to do the tests at home.

PATHOGENESIS

Very few viruses directly attack the immune system (*EBV is one of those, attacking B lymphocytes leading to lymphoma*).
HIV integrates into the cell genome, causing first a chronic infection before becoming deadly, which is a crucial mechanism for the spread of infection. In fact, up to 10 years can pass from the HIV infection to the development of AIDS. During that time, positive patients usually feel pretty well and thus might be unaware of their situation and infect others. This is a favourable factor for the spreading of the virus, different from Ebola which with its high mortality causes epidemics in small villages and cannot diffuse more since everyone dies.
The infection is not only directed to T lymphocytes, because the late-stage pathology can affect any type of cells: macrophages, microglia (leading to problems in the brain), Kupffer cells (in the liver), in the skin, myocardial cells (leading to myocardial infarction), cervix cells (leading to cervical carcinoma), etc… except for neurons, not known why.
It's very important to notice that on one side affected people are subjected to severe immunosuppression, but they also have a Th2 shift which leads to a lot of allergies and immune disorders. This unbalanced response is an attempt by T lymphocytes to attack pathogens.
Hence at the same time, there is immune activation and immune deficiency.
It hanges quite frequently in the host, therefore, it is hard for the immune system to kill it and it is also difficult

to develop a vaccine.
Why is HIV eradication not possible at the moment?
Free virions can survive just a matter of minutes/hours while resting CD4+ with integrated provirus might survive years. They can stay in lymph nodes even for 15-17 years, and when they proliferate, they do so with the HIV DNA starting a new cycle of HIV replication. This, together with the facts that in several organs (including brain, lymph nodes and gut) the antiviral drugs concentration that can be reached through treatment is not enough, is evidence of the fact that HIV cannot be eradicated.

Immunodeficiency: (slide skipped by the professor)
HIV causes a reduction of T lymphocytes, specifically of CD4+ T lymphocytes which are the cells coordinated in response to external pathogens.

- *Direct damage to the cells (cytopathic effect).*
- *Syncytium formation.*
- *Increased susceptibility to apoptosis (infected cells die earlier than other cells).*
- *Phagocytosis-lysis from the immune system (there is an auto-destruction of CD8- NK and a further reduction of CD4+ T cells). Hence, even if the final **deficit is in CD4+ T lymphocytes**, there is an additional reduction of function in several other cells.*
- *Shift to Th2 response, meaning that there is an increased risk of allergies and adverse reaction to drugs.*

NATURAL COURSE

The natural course of HIV consists in (*Fig. 21*):

1. **Primary (acute) infection**: from the exposure it occurs in 1-3 weeks. It can be symptomatic or asymptomatic, but the vast majority are asymptomatic. Hence they are not aware of it
2. **serological conversion:** after 1 month there is the development of antibodies against HIV, which is the phase when HIV tests turn out positive.
3. After seroconversion, the infection runs several years (7-10 years) as asymptomatic (just HIV-test can detect it), *with just some **lymphadenitis**.*
4. In the **pre-symptomatic phase**, the patient develops minor opportunistic infections until the development of major opportunistic infections (**symptomatic phase**) that are diagnostic for AIDS.

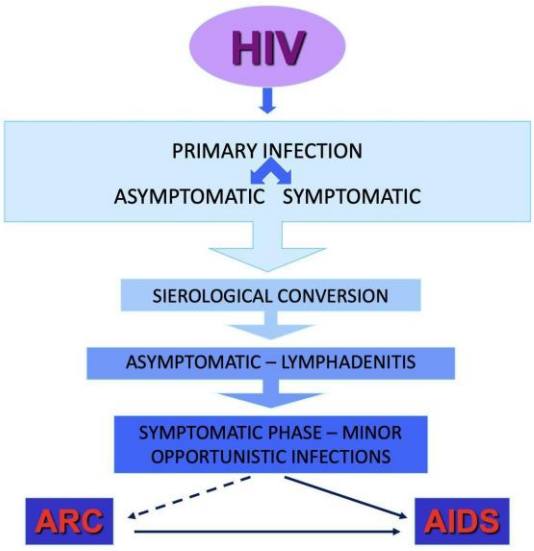


Fig.21

BIOMARKERS

Look at this graph (*Fig. 22*):

- number of **CD4+ T lymphocytes** (in green): usually they are around a 1000
- number of **viral load**, the number of copies of HIV per mL of blood. (in blue)

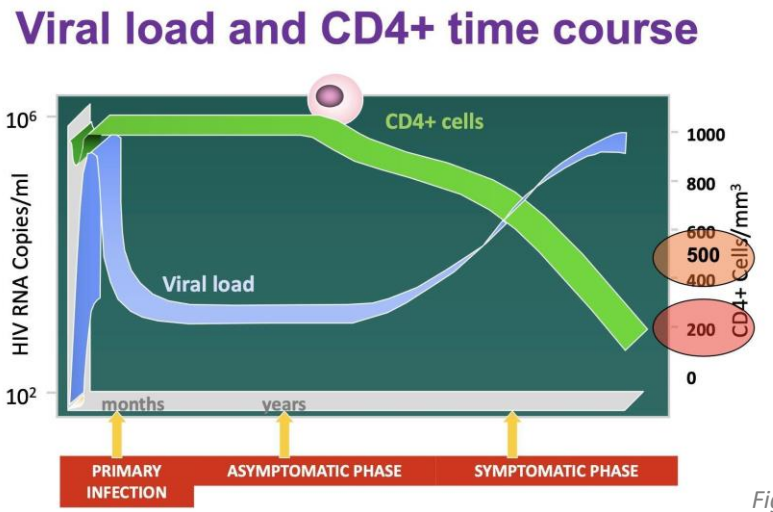


Fig.22

Once the virus enters in contact with the mucosa, it takes 48 hours to enter the circulatory system (blood). This is why to do post-exposure prophylaxis there is a window of 48 (maximum 72 h) hours.
The virus starts to replicate in millions of copies while CD4+ starts decreasing a little bit and then goes back to normality (very first brief slop on the left), this is the **asymptomatic phase**: there is an equilibrium between the immune system and the virus.
When the immune system is not able to renovate all the cells (B cells, T cells, MK cells) HIV starts to replicate again. Hence the number of CD4+ cells decreases and the patient becomes in immunodeficiency status.

2 values that must be remembered are:

- **CD4+ below 500**: clinical manifestations start appearing.
- **CD4+ below 200**: onset of AIDS.

The viral load increases during infection but actually CD8+ cells are able to control the spread of infection for the whole latent phase but once CD4 cells start to decrease, the viral load increases exponentially. Thus, the most infectious people are either those in the acute phase or patients in the late stages.

PRIMARY INFECTION

Why the focus on HIV primary infection?

- Because is necessary to recognize people with HIV primary infection.
- They are really contagious and they do not know to have it, so they have sex. Hence if primary infections are recognized, the HIV transmission is reduced.
- If the patient is treated during acute infection, it's possible to reduce the number of tissue in which HIV could be. HIV gets quickly in blood and then requires a few days to get into brain, lymph nodes, gut, bone marrow etc. By treating patients at this stage, the number of cells infected by HIV is reduced. Hence these people will have a very healthy life expectancy

Most primary infections are asymptomatic, but patients can present with mononucleosis-like symptoms:

- Fever: *Mild to high-grade fever, usually above 100.4°F (38°C).*
- Rush.
- Swollen lymph nodes: *Enlarged and tender lymph nodes, especially in the neck and armpits.*
- Headache: *Mild to severe headaches, often described as a throbbing or pulsating sensation.*

Since they are very specific symptoms, no one would think about HIV. If a sexually active patient presents mononucleosis-like symptoms it should be asked tests for EBV, CMV, toxo, and HIV.

Other symptoms that my present during primary infection not mentioned this year:

- *Loss of appetite: Reduced desire to eat or a decreased interest in food.*

- *Swollen spleen and liver: In some cases, the spleen and liver may become enlarged, leading to upper abdominal pain or tenderness.*
- *Muscle aches and joint pain: Generalized muscle and joint discomfort, which may be more prominent during physical activity.*
- *Sore throat: A severe and painful throat, often accompanied by redness and swelling.*
- *Night sweats: Excessive sweating during sleep, which may disrupt sleep patterns.*
- *Nausea or digestive issues: Mild stomach discomfort, nausea, or changes in bowel habits.*
- *Fatigue: Persistent tiredness or lack of energy that may not improve with rest.*

***Minor disorders**:*
1. Oral Candidiasis (Thrush): A fungal infection characterized by white patches in the mouth and throat.
2. Herpes Simplex Virus (HSV) Infections: Recurrent or severe infections caused by the herpes virus, resulting in oral or genital ulcers.
3. Bacterial Pneumonia: Infections of the lungs caused by bacteria such as Streptococcus pneumoniae.
4. Tuberculosis (TB): An infectious disease caused by the Mycobacterium tuberculosis bacteria that primarily affects the lungs but can also affect other organs.
5. Cytomegalovirus (CMV) Infection: A viral infection that can affect various organs, including the eyes, gastrointestinal tract, and lungs.
6. Mycobacterium avium complex (MAC) Infection: A bacterial infection that can affect multiple organs, particularly the lungs and gastrointestinal tract.
7. Toxoplasmosis: An infection caused by the parasite Toxoplasma gondii, which can affect the brain and other organs.
8. Bacterial Infections: Increased susceptibility to various bacterial infections, such as pneumonia, skin infections, and bloodstream infections.
9. Fungal Infections: Increased risk of opportunistic fungal infections, including Pneumocystis jirovecii pneumonia (PCP) and cryptococcal meningitis.

DIAGNOSIS

PHI is diagnosed using **IV generation serological test** (immune assay); that is because the IV generation also includes a viral antigen (i.e. it does not only detect the production of IgG against HIV but also the presence of p24 antigen). This is of enormous importance with HIV because the test turns out positive even in the first few days after the infection and is therefore useful to catch the infection in the very first phase.

Q: Is this test available everywhere?
A: Yes.

Q: Is there any chance of false positive and false positive?
A: IV generation tests have very high sensitivity and specificity (above 99%). So the probability of having a false positive or false negative is below 0.01%

Diagnosis needs to be **confirmed by HIV RNA** (which is the most rapid marker of HIV infection).
Western blot was used in the past as a confirmatory test, but nowadays it is only useful for staging PHI. There is also an **avidity test,** but it is not really widespread.
In some countries where there is no PCR, they do 3 different tests.

This (*Fig. 23*) was a study done in Thailand and East Africa in collaboration with Yale University and Bangkok.
It was conducted in bars, clubs and nasty places where they enrolled people with an age between 18 and 50 with these features:

- They exchange moneys for sex.
- They had unprotected sex with somebody HIV-positive.
- They did unprotected sex with 3 more partners in the previous months.
- They had an a STD.

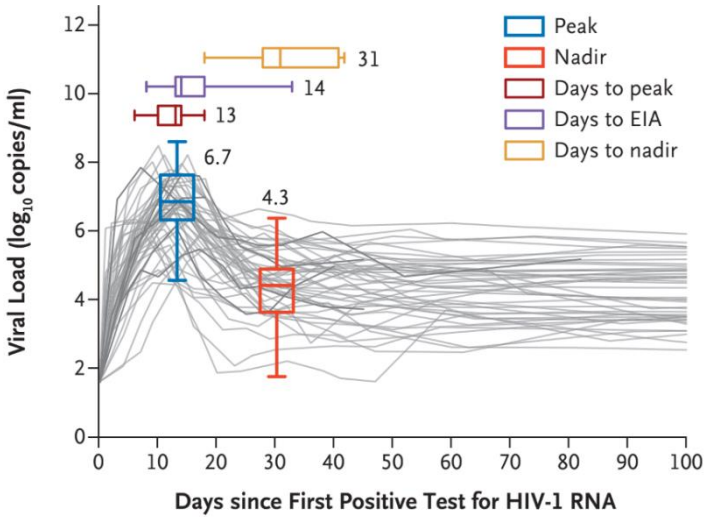


Fig.23

These people came twice a week for a small finger blood collection, just a drop, and they did the HIV RNA test. If one of these drop was positive, they all had to come back to test their peripheral blood. They tested 4000 people and they were able to capture 261 acute infection within a year. They were able to understand that the peak of HIV is around 10 days, so they knew when they got HIV. Also symptoms were around 10 days. The unlucky part is that symptoms are fever, headache, and malaise, so it's really difficult to diagnose acute HIV. However, some of them had other symptoms such as lymphadenitis and encephalitis.

ASYMPTOMATIC PHASE

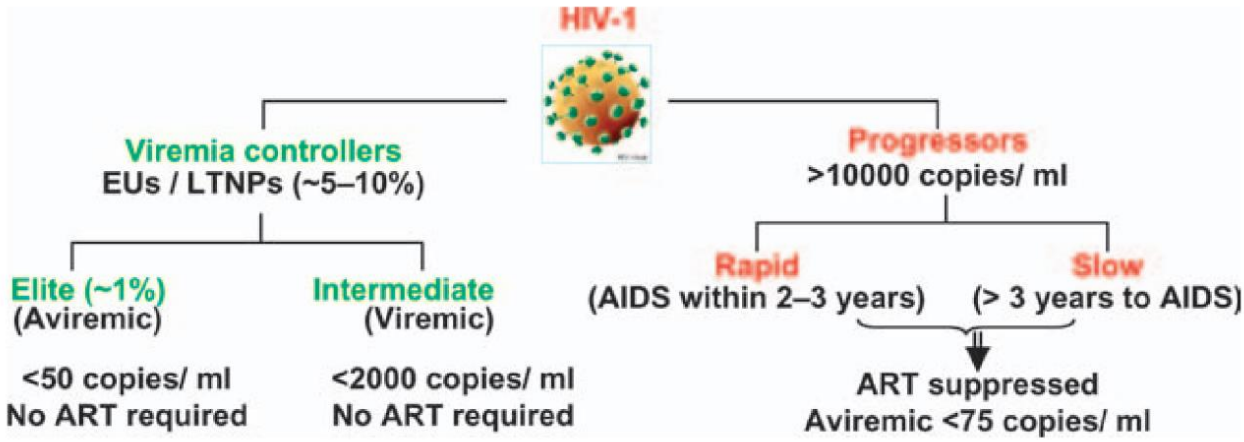


Fig.24

Represents the equilibrium between viral replication and immune system. The **plasma viral load** is correlated with the rapidity of clinical progression (the higher the viral load the quicker the progression). Therefore, in the past, it was common to treat patients in relation to their viral load; nowadays instead, every HIV+ patient undergoes the same treatment and viral load is used only to measure the response to treatment.

As for the progression, it typically takes a few years to get to the AIDS phase. The higher the viral load, the quicker the evolution: people with 1 million HIV copies per mL go much faster to AIDS compared to those with a thousand.

The average progression to AIDS is 7 to 10 years, however, there are some peculiar categories:

- **Rapid progressors,** in which AIDS is observed within 2-3 years;

- **Elite controllers** are patients (approx. 1% of HIV patients) that are able to control HIV without treatment. Why? Is it because of the virus or the immune system? Mostly it's the immune system. There are certain HLA subtypes that are associated with control, which contributes to keep the virus integrated in the genome without having its transcription. The virus is silent.
  These patients could result positive with an HIV test, but negative with PCR. In this case is not a false positive but an elite controller. If Western blot is done, antibodies against several bands of HIV would appear.

AIDS RELATED COMPLEX (ARC)

They can happen in all kinds of immunodepression. They are early signs of immunodepression. Hence if these signs are present even in someone who doesn't have HIV, there could be something wrong with their immune system.

- **Persistent generalized lymphadenitis (PGL)**
- **Fever > 1 month**
- **Chronic diarrhea > 1 month**
- **Weight loss > 10% body weight**
- **Thrombocytopenia:** there are several cases of people followed by hematologists because none linked thrombocytopenia to HIV in the past. They used to look just for antibodies anti-platelets, corticosteroids etc.
- **Minor opportunistic infections:**
  - **Oral candidiasis** (*Fig. 25*): several categories of patients may develop oral candidiasis (they can be young, old, diabetics, under steroid therapy, immunosuppressed). Suspicion of HIV should arise if someone not at risk develops persistent oral candidiasis.
  - **Hairy leukoplakia** (*Fig. 26*)**:** is a manifestation in the tongue commonly related to EBV reactivation, anyhow it provides information about the status of the patient's immune system.
  - **Herpes Zoster** (*Fig. 27*)**:** one of the most important manifestations is multi-metameric or relapsing Herpes Zoster (called Fuoco di Sant'Antonio) because it highlights a deficit in the immune system. When there is an activation of the zoster is dermal: is just a skin part related to one nerve. Herpes Zoster should never cross the median line because dermatomes stop at the median line. Therefore, if a Herpes Zoster affects one part of the body and crosses the median line reaching the other part of the body it is evidence of something affecting the immune system, hence HIV should be suspected. It should be one-sided, so if the lesion is on the right side, it

Fig.25

Fig.26


Fig.27

shouldn't be also on the left. Even if it is on one side but on different dermatomes, there is an immune system problem.
It is characterized by vesicles, pustules, and crusts.

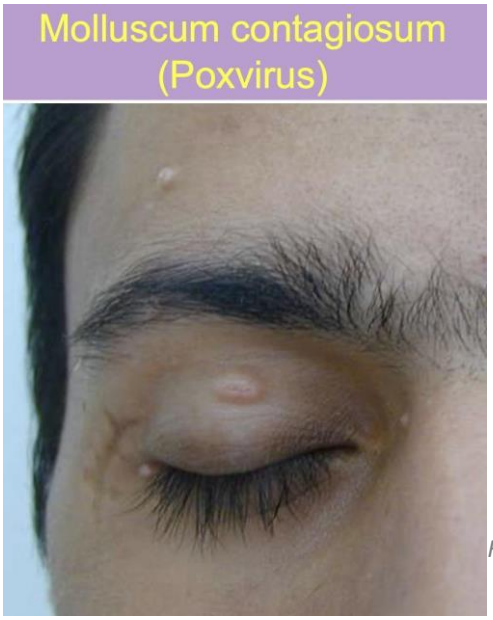


Fig.28

- **Molluscum contagiosum** (*Fig. 28*): is an infection caused by poxvirus usually observed in children (small epidemics in kindergarten or primary school). Soft vesicles are umbilicated in the lid. It could be self-infectious. It can also be seen in HIV positive patients especially on face and arms.
- **Seborrheic dermatitis**: even healthy people have it. It is caused by the overgrowth of a fungus. In people with HIV is more widespread, is recurrent and doesn't respond to treatment. Because the immune control in the skin fungus is zero. There is erythema around the nose and the scalp, and there is a patchy greasy formation over it.
- **Condyloma**: They might be present in the anus being asymptomatic.
- **Tuberculosis**: it is much more common in HIV patients, who also have a high probability of reactivation (almost 100%, and often associated with extrapulmonary expressions of the disease). The problem is that immunosuppressed patients need to have TB eradicated to the last bacteria, as they lack any immune response to remove even the smallest traces of mycobacterium. Moreover, in severe cases of AIDS, granulomas are not formed, leading to complete lung destruction and pleural effusion, but TB is not visible on the X-Ray because of the lack of granulomas.
  The clinical presentation of TB in patients living with HIV (fig.20) is variable and it depends on $CD4^+$ cell count:

Fig.29

  - In **high $CD4^+$** cell count, the clinical presentation is very similar to that of HIV-negative patients (e.g. cavities)
  - In **low $CD4^+$** cell count, there might be only mediastinal lymphadenopathy, pleurisy, effusion or even a normal chest X-ray. Because the granuloma is not formed, and this is because the immune system is not working. *Fig. 29* represent a normal CT scan of the lungs of a patient with HIV.
- ***Eosinophilic dermatitis.***
- **Multiple warts.**

If there is something relapsing, uncommon, and recurrent, think about HIV.