Medical Immunology for M.D. Students

IMMUNODEFICIENCY DISORDERS (2)

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Modified by: Hala Zaghloul
what's written in **blue** is the extra info mentioned in the doctor's recording

Secondary Immunodeficiency

- secondary ID disorders are **acquired** and might be treated by the management of the underlying cause. Secondary IDs are far more common than PIDs (primary immune deficiencies).

  → acquired means that they result from different factors that can affect a host with an intrinsically normal immune system including infectious agents, drugs, metabolic diseases, and environmental conditions.

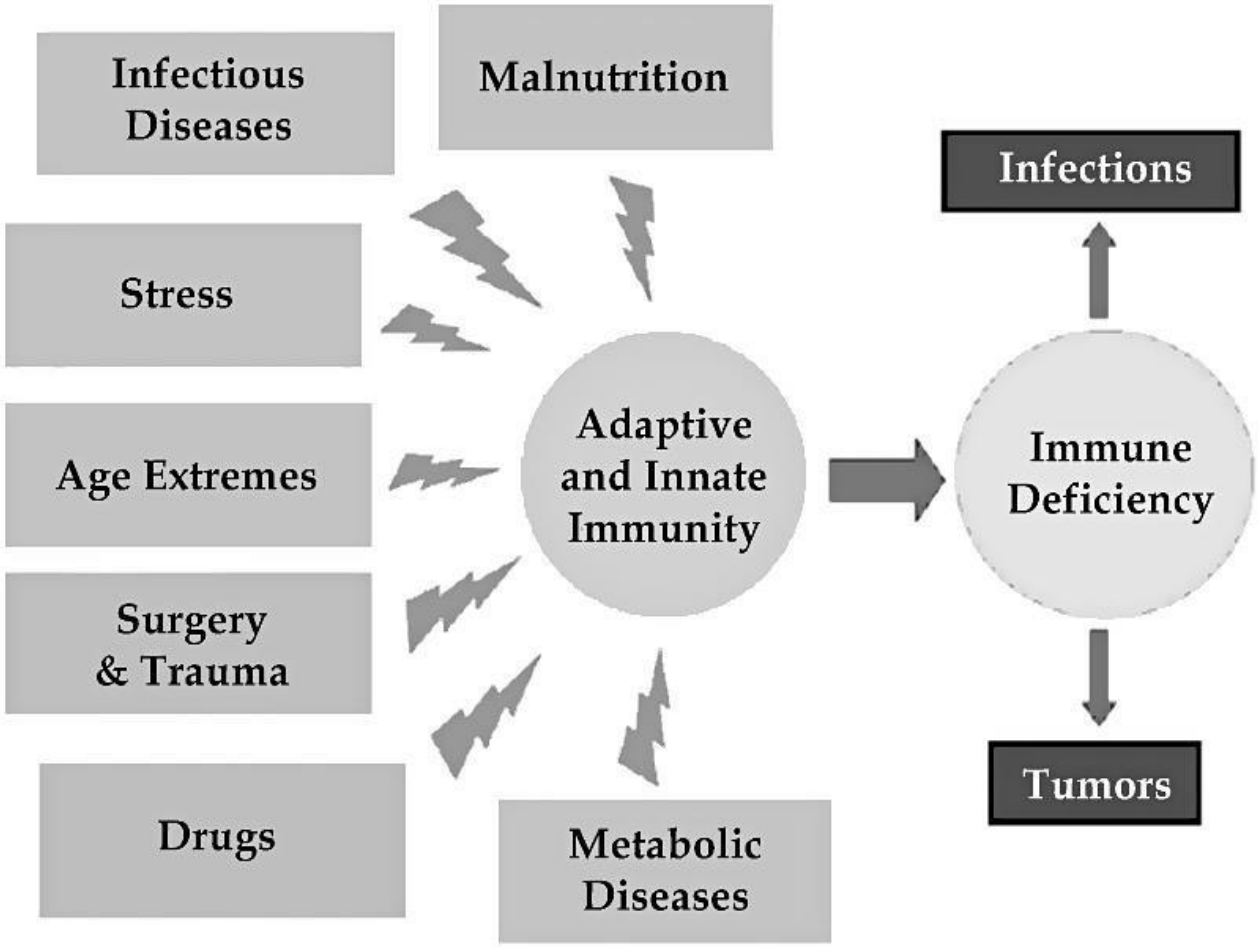
  → they also have a wide spectrum of presentation depending on the magnitude of the offending external condition and on the host susceptibility.

- Healthy individuals are prone to common infections as well, particularly during early life when the immune system has not developed fully.
  The repeated or unusual infections is an important sign of ID. The type of infection can give clues to the cause and degree of ID.

- Examples: Defective antibody production causes increased susceptibility, mostly to bacterial infections (that typically involve the upper and lower respiratory tract (otitis, sinusitis, and pneumonia), whereas Defects of late complement components (C5-C9) are associated with recurrent and invasive neisserial infections.

Secondary Immunodeficiency

these are the different **etiologic factors** of secondary immune deficiency that will be discussed in this lecture.
the **most common** immunodeficiency **globally** results from severe **malnutrition** affecting both innate and adaptive immunity



Secondary ID - Malnutrition

- Protein-calorie malnutrition is the most common cause of ID. Malnutrition can result from limited access to food sources and chronic diseases that induce cachexia, such as neoplastic diseases.
- T-cell production and function decrease in proportion to the severity of hypoproteinemia.

→ **however specific antibody titers and immune responses to vaccines can be detected in the malnourished subject for a relatively prolonged period.**

- The deficiency of micronutrients (e.g., zinc and ascorbic acid) contributes to increased susceptibility to infections through the weakening of barrier mucosa, therefore facilitating a pathogen's invasiveness.
- Vitamin D appears to be necessary in the macrophage activity against intracellular pathogens, remarkably *Mycobacterium tuberculosis*.

→ **Vitamin D is one of the essential molecules have been shown to have specific roles in the immune system**

Secondary ID – Extremes of Age

- Neonates have an increased susceptibility to common andopportunistic infections and sepsis compared with older children.

  →there is an inverse relationship of infection susceptibility and the age of prematurity, and this is related to the following factors:

- In early life there are fewer marginal-zone B cells in lymphoid tissue and a decreased expressionof CD21 on B cells, thus limiting the ability of B cells to develop specific responses.

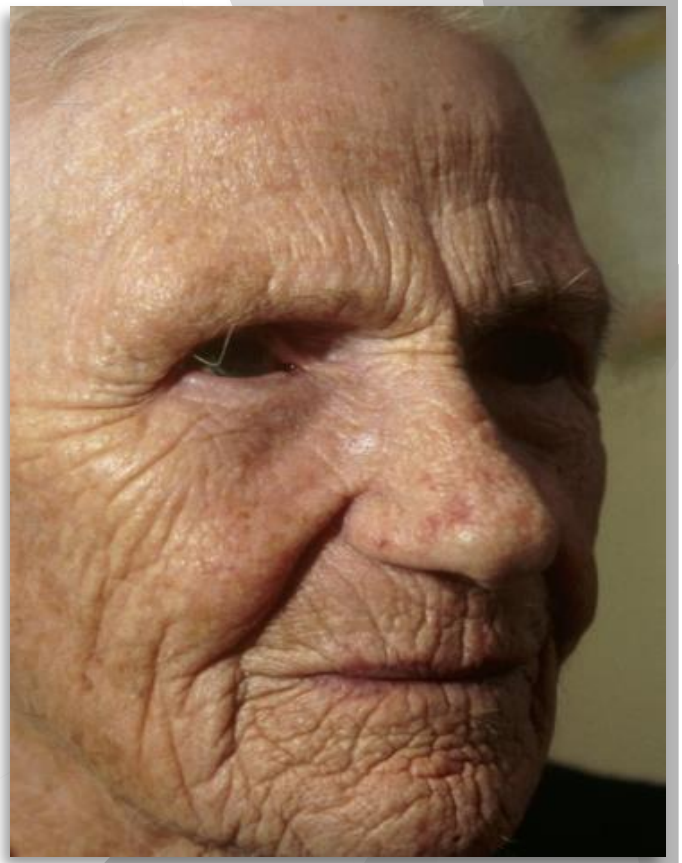
- **Another factor is the relative lack of maturity of secondary lymphoid organs;** Although they can develop humoral responses to some antigens after exposure in utero, impaired immunity innewborns can be attributed to the relative lack of maturity of secondary lymphoid organs, including the lymphoid tissue associated to mucosa in the GI and respiratory tracts.

- **in addition, premature infants are more vulnerable to infections because:**
  1) absence of maternal immunoglobulin G transfer before the 32 weeks of gestational age
  2) other innate factors include decreased neutrophil storage pool, decreased in vitro neutrophil functions like phagocytosis, oxidative burst chemotaxis and adhesion.
  3) decreased natural killer cell activity, decreased toll-like receptor signaling, decreased production of cytokines and reduced complement components.

- This immaturity is related to the absence of memory cell development because of the relative isolation provided by the maternal environment.

Secondary ID – Extremes of Age

- Among the elderly, some subjects experience malignancies and an excessive number of infections caused by viruses and bacteria, reflecting a decrease in the immune defenses, particularly in the cellular compartment. Decreased delayed- type hypersensitivity skin reactions and decreased lymphocyte proliferative responses to mitogens can be demonstrated in this patient population.



- The innate immunity might be compromised in the elderly, with increased breakdown of skin and mucosal barriers and slow healing processes caused by metabolic and endocrinologic changes associated with aging. A diminished production of hematopoietic growth factors has been postulated to occur in the elderly, resulting in decreased ability to upregulate the production and function of macrophages and neutrophils.

Secondary ID – Metabolic Disorders (DM)

- DM and uremia resulting from kidney or liver disease are two common metabolic disorders with known deleterious effectson immunity.
- Optimal control of the metabolic abnormality usually leads to improved immune function.
- The defective immune functions reported in patients with DM include defective phagocytosis and defective macrophage chemotaxis in vitro, T-cell anergy demonstrated by DTH skin tests, and poor lymphoproliferative response to mitogens caused by chronic exposure to hyperglycemia.

***DTH: delayed hypersensitivity skin test.**

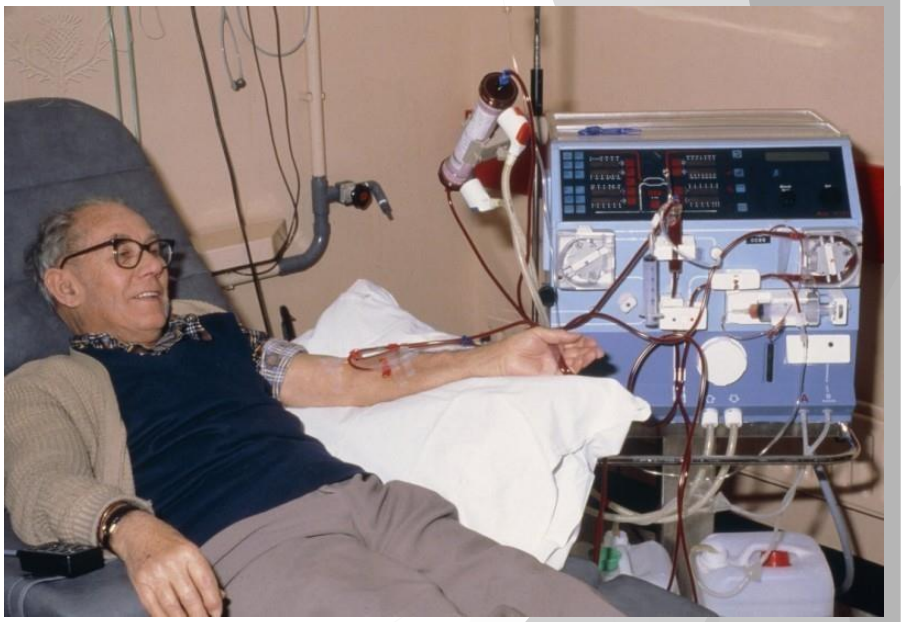
Secondary ID – Metabolic Disorders (Uremia)

- **multiple defects of the innate and adaptive immunity have been described to have a role in the increased frequency of infections in uremia patients.**

- Examples of the immune defects present in uremia patients include:

  1)The diminished capacity to generate memory antibody responses, regardless of repeated vaccination.

  2)defective phagocyte chemotaxis and microbicidalactivity in vitro.



**Extra: Uremia is a buildup of toxins in your blood. It occurs when the kidneys stop filtering toxins out through your urine. Uremia is often a sign of end-stage renal (kidney) disease

Secondary ID – Drugs

- The use of drugs to ameliorate undesirable immune responses is common in clinical practice as a consequence of the increasing prevalence of inflammatory conditions. These diseases include the categories of autoimmune disorders, allergic disorders, transplant rejection, GvHD.
- The overall results **(of pulse therapy with higher doses + receptor saturation):** are decreased cytokine production (IL-1, IL-6, and TNF-α) and impaired leukocyte chemotaxis, cell adhesion, phagocytosis, and lymphocyte anergy.
- Lymphopenia occurs as a result of the proapoptotic activity and inhibition of IL-2–mediated proliferative responses.
- This wide range of immune defects renders the patient susceptible to viral, bacterial, and fungal infections, according to the degree of immunosuppression and the administration route.

  Examples of these are oral candidiasis, a frequent complication of the use of inhaled steroids, and herpes zoster disease, which often presents with chronic use of systemic corticosteroids.

the following slides are exclusively mentioned in the video only.

Secondary ID – Drugs

- the examples include: (more examples mentioned in slides 11+12)
  ① **glucocorticoids** that are well-known for a variety of applications in both general and sub-speciality medicine
  to reduce tissue damage caused by an excessive inflammatory response.

- Mechanism of action: glucocorticoids bind a cytosolic receptor which then translocates to the nucleus to act as a transcription factor affecting the expression of a number of genes resulting in an anti-inflammatory effect, the bound complex glucocorticoid-receptor modulates signal transduction pathways resulting in the activation of the transcription factors, including nuclear factor kappa-B.

→NF-κB the nuclear factor of activated t-cells and activator protein 1

- immune defects associated with the glucocorticoid therapy include oral candidiasis that was discussed in the previous slide.

Secondary ID – Drugs

Second example: **calcineurin inhibitors**

- Mechanism of Action:
  they bind cytoplasmic proteins from the immunophillin family
  and inhibit their interaction with calcineurin which is essential for the
  activation of IL-2 transcription and t-cell function.
- advantage of these drugs over corticosteroids and cytotoxic drugs is
  to spare macrophages and neutrophils functions reducing the spectrum of
  susceptibility to infections
- the first drug in this category was **cyclosporine** which has been extensively used to
  prevent organ transplant rejection, graft vs. host disease and corticosteroid resistant
  autoimmune disorders.
- Third Example: **cytotoxic agents—tacrolimus** that have a similar mechanism
  of action and immune selectivity, for they are used to manage autoimmune and
  inflammatory disorders including graft-versus-host disease and in the prevention
  of graft rejection.

  Examples (drugs names): include cyclophosphamide, and the antimetabolites:
  methotrexate, mycophenolate, azathioprine and six mercaptopurine.

Secondary ID – Drugs

- other drugs other drugs with predominant use in autoimmune disorders are sulfasalazine and hydroxychloroquine.

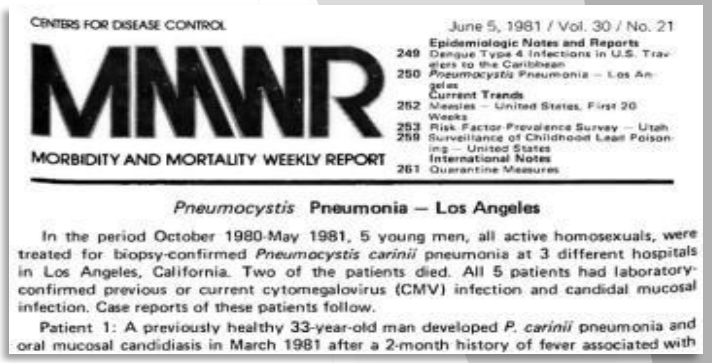
- these compounds interfere with the synthesis of DNA arresting the cell cycle and inducing apoptosis. generally they inhibit both T and B cell proliferation
  therefore any new immune responses, in addition depending on the dose used they inhibit cellular and antibody responses resulting from previous sensitization.

Secondary ID – Infectious Diseases

- Transient periods of immunosuppression have been associated with viral infections.
- Infections with measles virus, CMV, and influenza virus can induce lymphopenia and also T-cell anergy; however, these are transient and usually less severe than the immunodeficiency seen in AIDS.
- Infection of the bone marrow by viral and bacterial organisms producing neutropenia or pancytopenia.
- **the prototypical example is HIV infection or AIDS that will be discussed in the following slides**

Background on HIV/AIDS

- ✓1908 HIV-1 tMRCA
- ✓1930 Group M tMRCA
- ✓1955 Subtype B tMRCA
- ✓1966 Spread to Haiti
- ✓1969 Spread to US
- ✓1981 Reporting of AIDS
- ✓1982 AIDS term coined
- ✓1983 HIV-1 isolated
- ✓1990 AZT approved
- ✓1996 Hit early hit hard



CENTERS FOR DISEASE CONTROL

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MMWR

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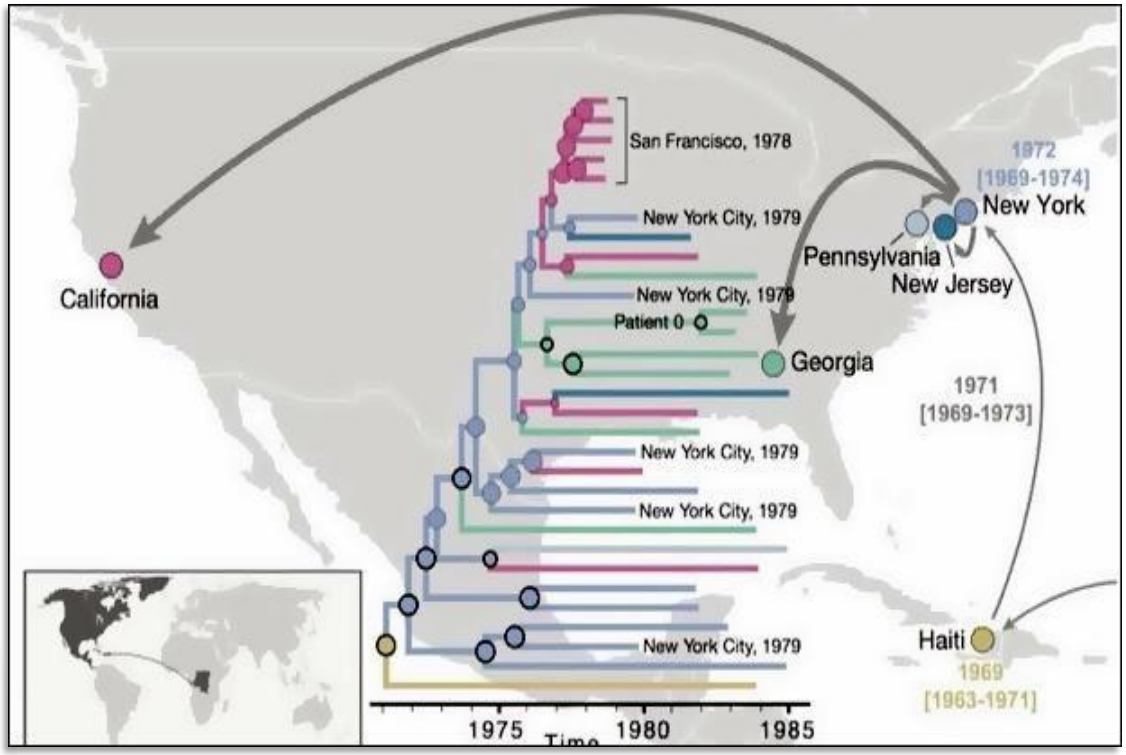
Pneumocystis **Pneumonia — Los Angeles**

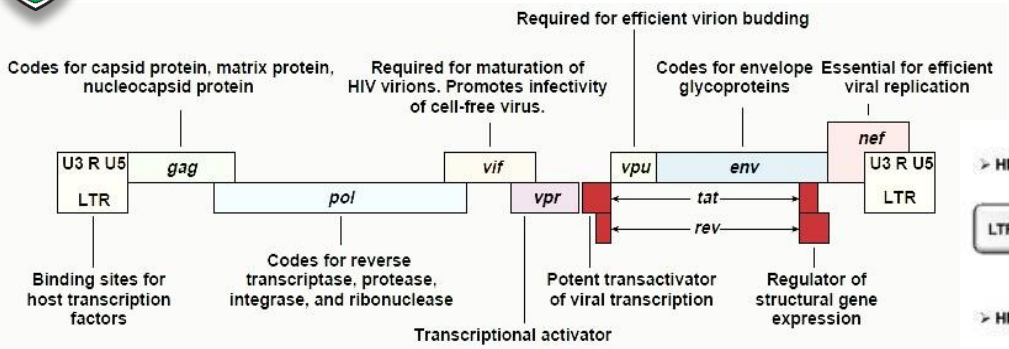
In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

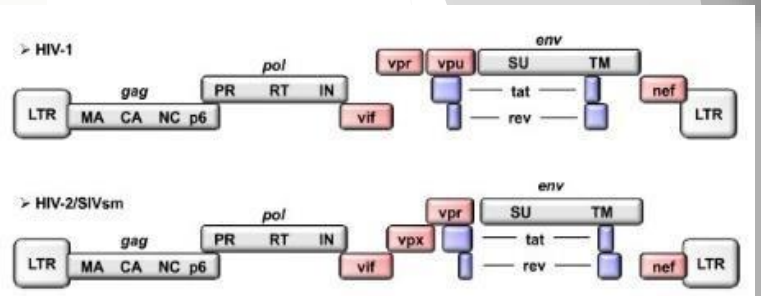
Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with

Background on HIV/AIDS



HIV Genome





- HIV is a double-stranded enveloped RNA retrovirus from the group Lentiviruses.
- the HIV genome contains three structural genes: group antigen, polymerase, and envelope in addition to six regulatory genes.

- the group antigen proteins is spilt by HIV protease into the proteins: capsid B24, matrix nucleocapsid B6MV2 all of each form the viral particle and stabilizes the viral genome.
- the pol proteins is also split to produce 3 enzymes: integrase, reverse transcriptase, and the protease that cleaves the viral proteins.

- after the viral genomic RNA is converted to DNA by reverse transcriptase, the integrase facilitates the integration of the viral DNA into the host genome and uses the host cell 's replication mechanisms to produce more variants.

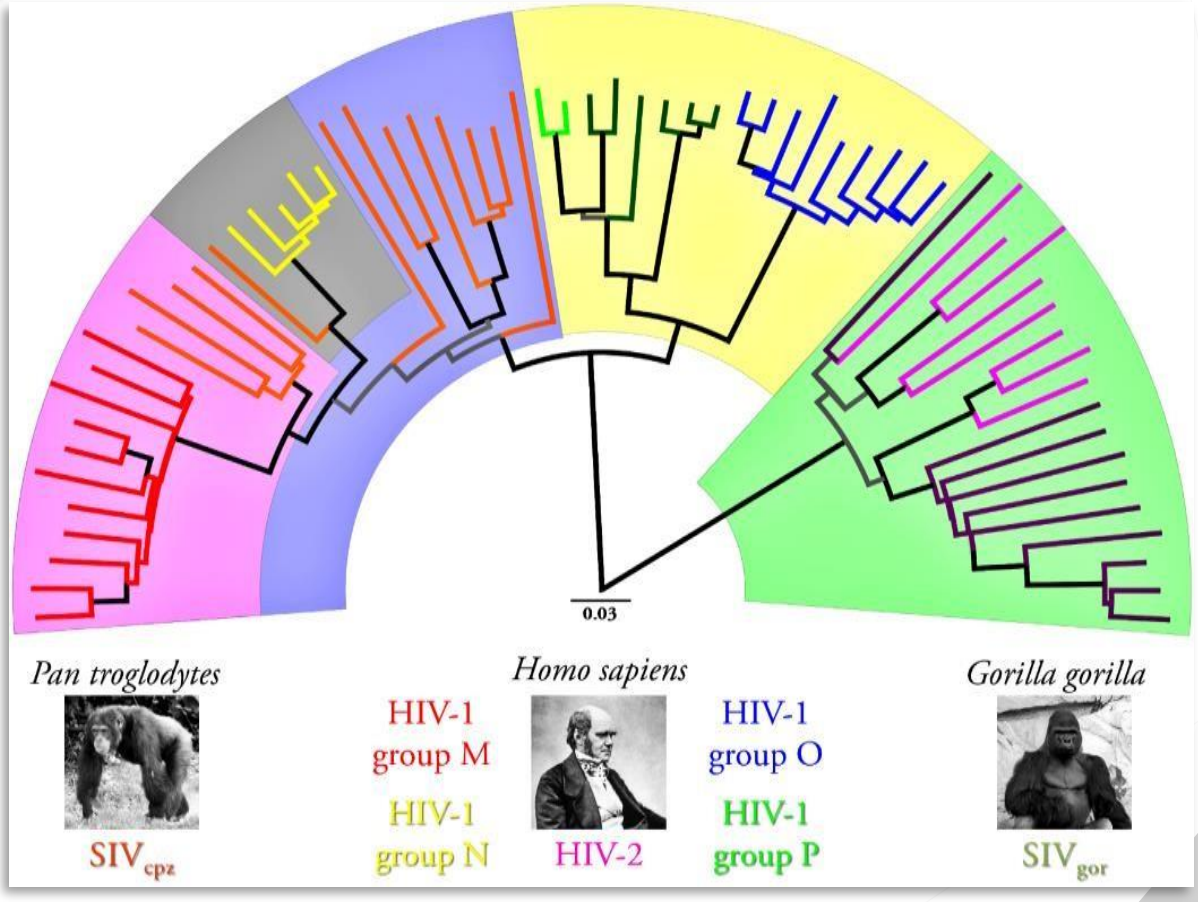
- the envelope protein is also cleaved to produce two envelope proteins: glycoprotein 120 and glycoproteins41 which are involved in the binding to CD4 and the chemokine receptors CXCR4 & CCR5 on the cell surface.

HIV Genome continuation...

- the trans activator protein increases the transcription of HIV genes by 104 whereas the Rev protein allows the expression of the different HIV genes by relating mRNA splicing.
- the roles of other regulatory genes have only been clarified in the last few years, the negativity factor protein downregulates CD4 and MHC class 1 cells expression on the membranes of infected cells, probably facilitating escape from the immune surveillance.
- vif is a protein that induces degradation of the human enzyme—a cytosine deaminase APOBEC C3G (A3G) that causes mutations during viral transcription.
- vpr and vpu proteins seem to facilitate the intracellular transport of viral proteins for viral particle formation.

*zoom in the picture in the previous slide to locate the different proteins and genes mentioned.

HIV Classification

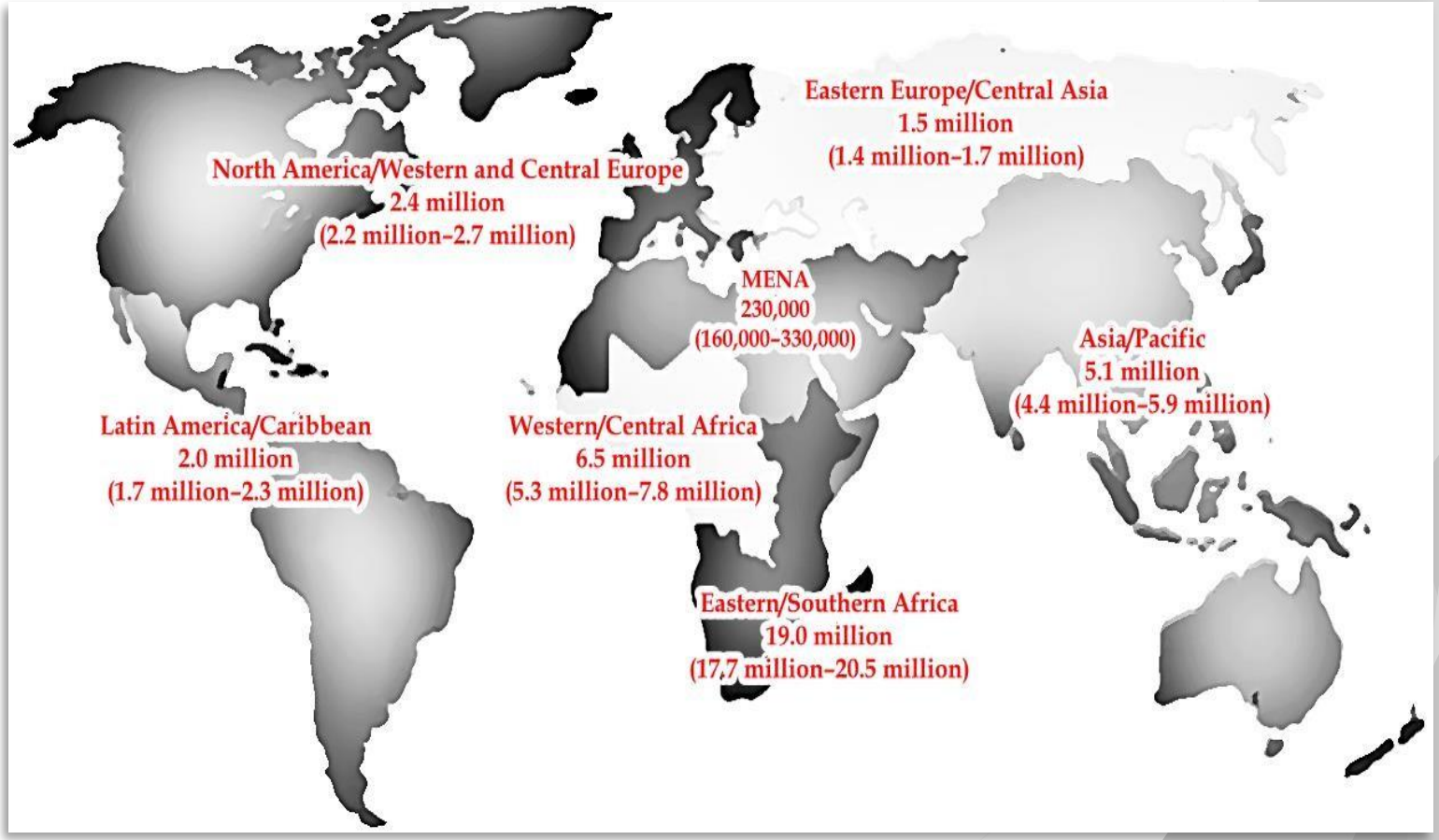


two types of HIV have been identified HIV-1 and HIV-2, both cause human disease.
HIV 2 is more prevalent in West Africa and might take more time from infection to the development of immune deficiency than HIV1.

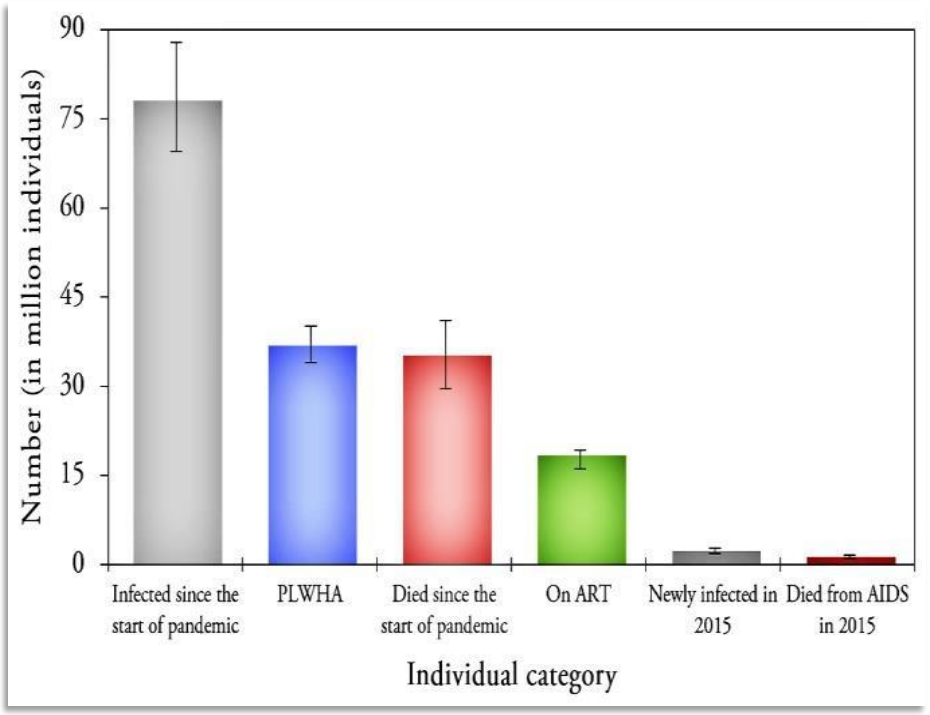
Important Features of HIV

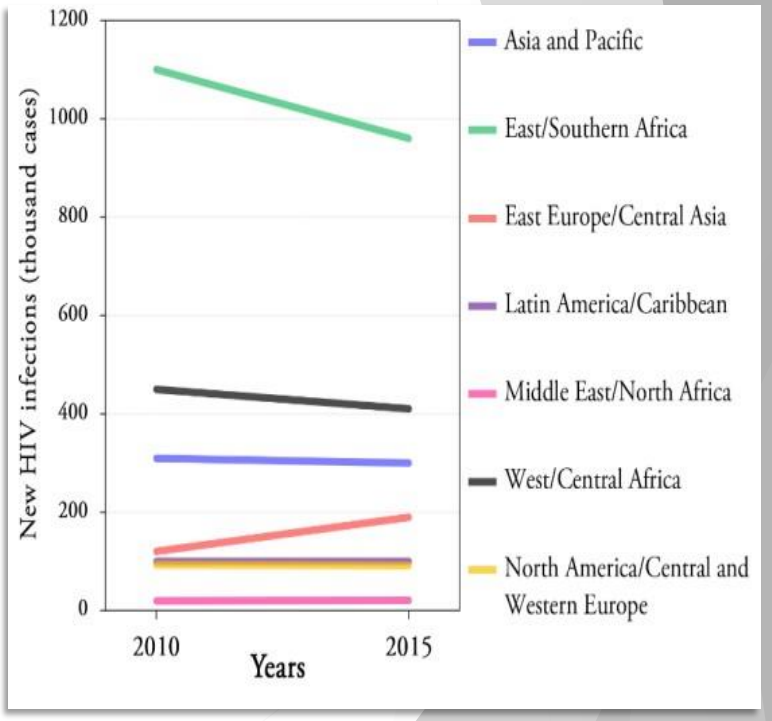
- HIV tropism is for CD4+ T cells, MΦ and DCs. (MΦ: macrophages)
- The cellular receptor is CD4, with either CCR5 or CXCR4 acting as co-receptors.
- HIV-1 has a worldwide distribution, while HIV-2 is endemic in West Africa.
- According to UNAIDS, and by the end of 2015, about 37 million people were living with HIV/AIDS (PLWHA), of which about 2 million individuals acquired the infection in 2015.
- The unequal distribution of HIV/AIDS around the world is notable mostly in Sub-Saharan Africa, with more than two-thirds of PLWHA.

Epidemiologic characteristics of HIV/AIDS



Epidemiologic characteristics of HIV/AIDS

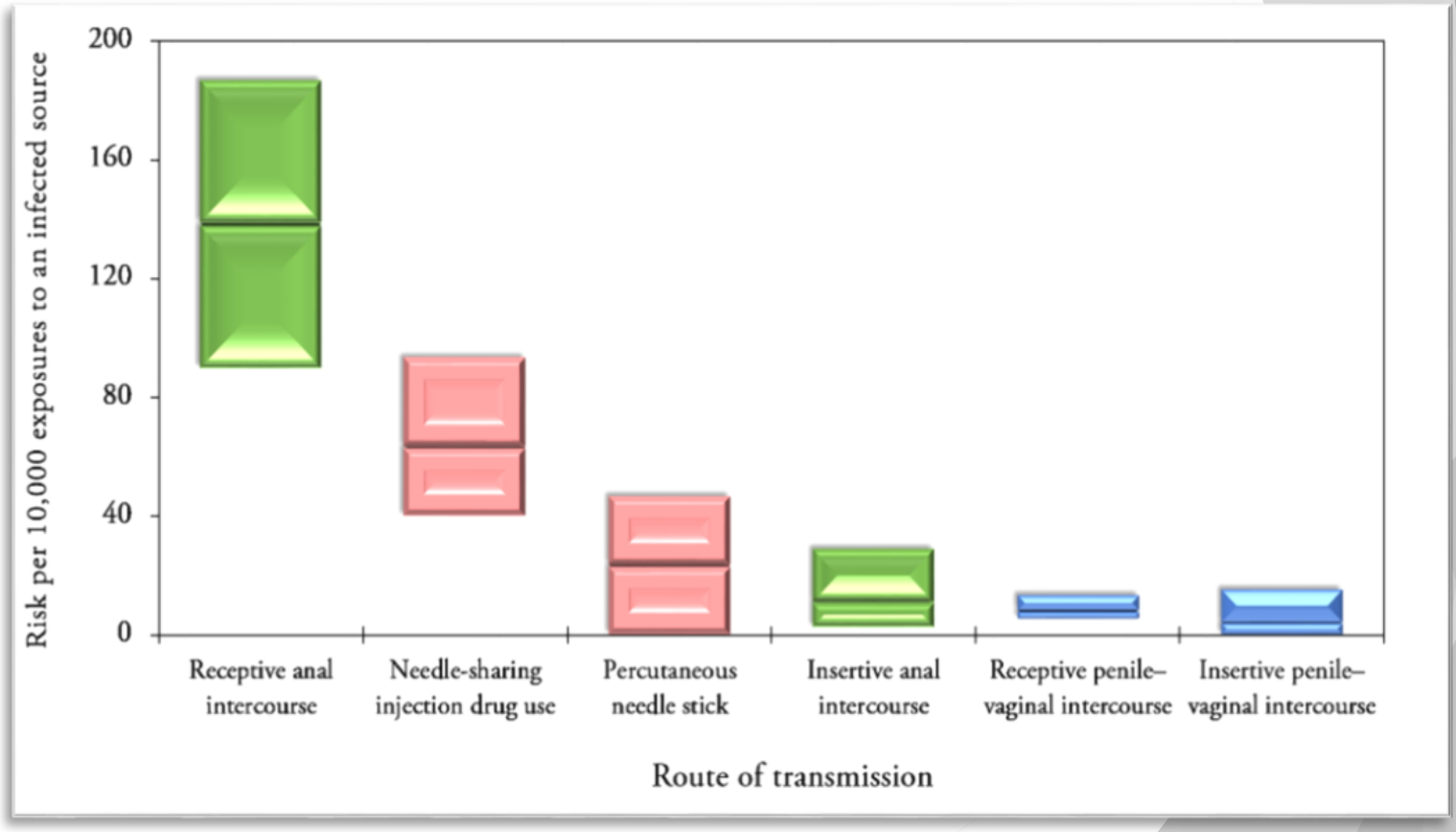




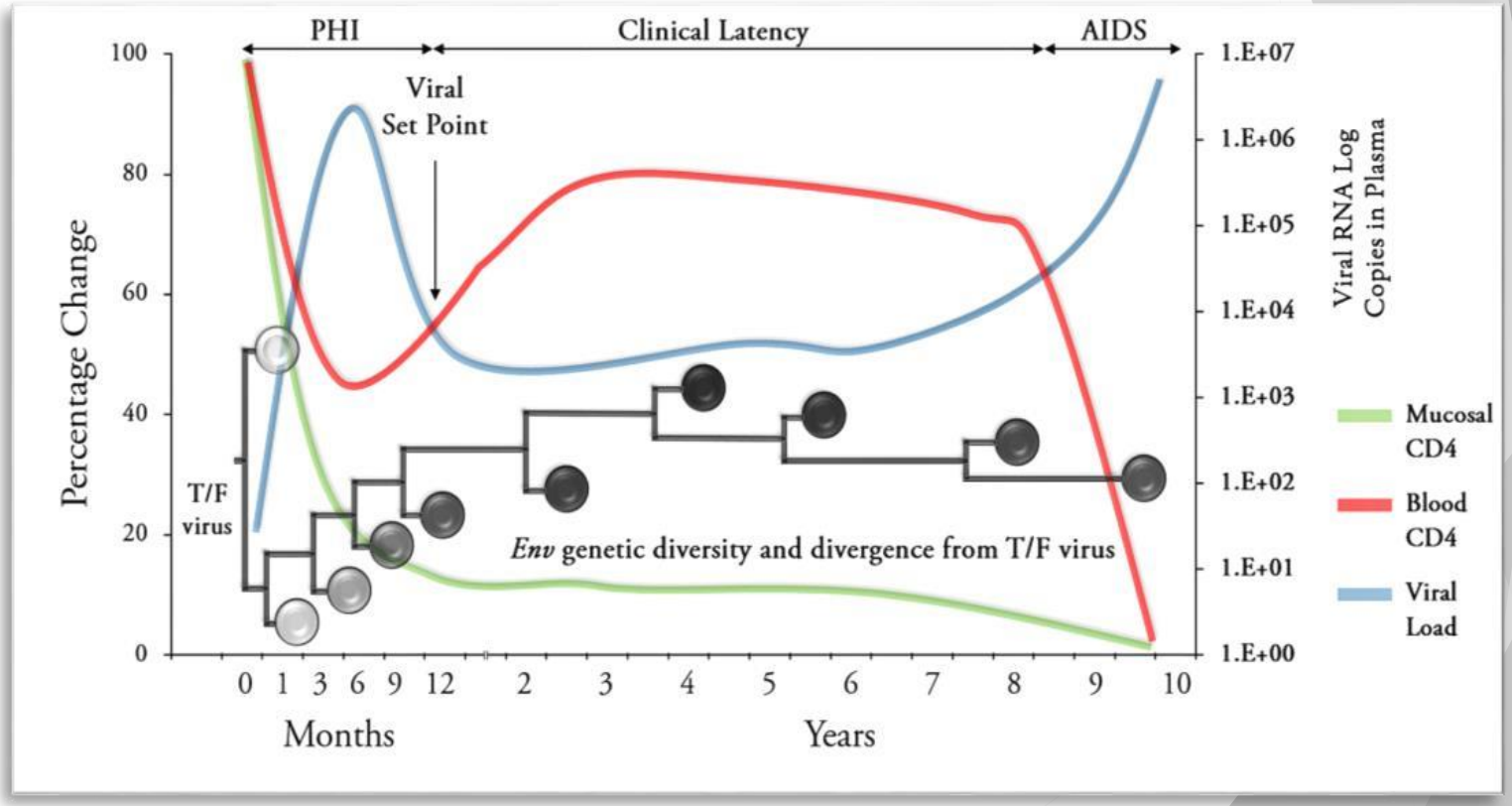
HIV Transmission

- HIV-1 is a blood-borne virus (i.e. it can be transmitted through transfusion, needlestick injury and IDU) and the infection can be considered an STI (occurring through homosexual and heterosexual practices via vaginal, penile and anal mucosa).
- Vertical transmission can occur in utero, perinatally and through breast milk of infected mothers.
- Nowadays, the most common mode of transmission globally is HET contact but different regions differ in the most common route (e.g. MSM in US and Western Europe, IDU in Former Soviet Union countries and HET in sub-Saharan Africa).

HIV Transmission



HIV-1 Pathogenesis



HIV-1 Pathogenesis

- The distinctive feature of HIV-1 infection is the progressive quantitative and qualitative deficiency of CD4+ T cells.
- After HIV-1 inoculation, the virus infects its target cells, mostly macrophages through binding of gp120 (part of ENV) to CD4 andchemokine receptors CCR5 or CXCR4.

- →**i.e., the immunopathogenesis of HIV infection begins with the binding of the HIV gp120 protein to the CD4 molecule and the chemokine receptor CCR5 on target cells.**

  infected cells migrate to the lymph nodes where initial replication and infection of nearby CD4+ T cells occur.

  - →**HIV induces t-cell lymphopenia** (low lymphocyte in the blood) **through several mechanisms like HIV induced apoptosis, viral cytopathic effect, apoptosis caused by nonspecific immune activation and cytotoxicity to HIV infected cells.**

  an additional form of cell death named autophagy in which organelles are sequestered and directed towards lysosomal pathways have been shown to be induced by HIV enveloped protein and uninfected t-cells.

- The virus starts to establish the infection for about 10 days locally before systemic spread

HIV-1 Pathogenesis

- the acute phase of HIV infection occurs one to two to six weeks after infection when nonspecific symptoms such as fever, fatigue, myalgia, and headaches.
- Subsequent virus spread into the lymphoid tissues including the gut-associated lymphoid tissue (GALT), ends-up in the establishment of infection chronically.
- **during acute HIV infection the gut associated lymphoid tissue is severely depleted with predominant loss of memory CD4+ T-cells with viremia and immune activation.**
- Viremia follows, which remains at high levels for about 8–12 weeks, coinciding with mononucleosis-like features in a majority of infected individuals.
- The significant decline of CD4 cells at this phase is related to loss of memory cells in the GALT.
- the period of clinical latency that follows is characterized by virtual absence of signs or symptoms until symptomatic disease occurs and can last as long as 10 years.

the following slides about pathogenesis are exclusively mentioned in the video

HIV-1 Pathogenesis

- The adaptive immune response takes over at this stage to control viral replication manifested in the decline of viral load to a nadir “viral set- point” which fluctuates at low level throughout the clinical latency.
- levels of several cytokines are increased and contribute to determine the degree of control of HIV viremia.
- HIV-1 set-point is considered an important prognostic marker for assessment of disease progression.
- higher viral loads at the initial stage predict shorter clinical latency.
  without the HIV drug treatments CD4+ t-cell counts progressively decrease and the host usually succumbs to infections with opportunistic organisms that take place because of the immunodeficiency.
- investigators have been able to demonstrate the production of specific anti-HIV CD4+ t-cells and CD8+ T cells as well as neutralizing at HIV antibodies.
- however, these immune responses are eventually overcome by viral escape strategies.

HIV-1 Pathogenesis

- at this stage patients present with fever, weight loss, diarrhea, lymphadenopathy, fungal and viral skin infections indicating compromise of the immune system.
- when the peripheral CD4+ T-cell count is less than 200 cells per microliter the patient can present with any of a number of infections that define AIDs such as Pneumocystis jiroveci induced pneumonia, histoplasmosis, toxoplasmosis, and coccidioidomycosis.
- if the patient does not receive antiretroviral treatment repeated infections that are difficult to manage lead to patients' death.
- Small proportion of HIV infected patients remain asymptomatic and do not have AIDS, these patients are called long term non-progresses and have been the focus of multiple studies to understand the basis of their protection those who maintain low levels of HIV without the treatment are called elite controllers.
- this immunity appears to be explained by the front viral and host factors the best-known of these factors is the inherited defect in the gene encoding the CCR5 receptor a t cell surface molecule that is necessary for HIV entry. CCR5 gene mutation have been found with a significant prevalence in persons with northern European ancestry.
- other factors identified in long-term progressors include low number of activated CD8+ T cells, the presence of particular HLA haplotypes and viral mutations that result in low virulence.

Natural History of HIV-1 Infection

- Primary infection (first few months): Nonspecific and resemble those of infectious mononucleosis.
- Clinical latency (3-20 years, average 8-10 years): The majority of HIV-1 infected individuals remain asymptomatic during the clinical latency period, nevertheless, generalized lymphadenopathy might persist from the primary infection period.
- AIDS: The diagnosis of AIDS is made at CD4 T cell count of less than 200/µL or the presence of an AIDS defining condition (MAC, PCP, extrapulmonary TB, PML, KS, toxoplasmosis, cryptococcosis, esophageal candidiasis, lymphomas, etc.).

Diagnosis, Management and Prevention of HIV Infection

- Screening for HIV-1 infection relies on enzyme immune assays with fourth-generation assays combining the detection of Abs (IgM and IgG) to HIV-1 (groups M, O, and N) and HIV-2 together with detection of p24.

- This is followed if positive by a confirmatory test, mostly western blot or detection of HIV-1 RNA.

- The biggest challenge in diagnosis is the presence of an interval between infection and detection (window period) and refinements of different diagnostic tests aimed to shrink this period particularly in testing of blood/blood products.

→diagnosis of HIV infection is made by using sensitive Eliza to detect antibodies against HIV protein B24. positive Eliza result is confirmed by using the more specific Western plot which detects antibodies to several HIV proteins or by the detection of HIV sequences by reverse transcriptase PCR.

Diagnosis, Management and Prevention of HIV Infection

- For management of the HIV-1 infected individuals, CD4 T cell count andplasma viral load measurements are indispensable for evaluation of disease progression and response to ART.
- The cornerstone of HIV-1 management is the so-called HAART.
- Despite the incurable nature of HIV-1 infection so far (with the exceptionof the Berlin patient) the treatment with combinations of antiretroviral drugs aims to suppress viral replication to a degree that permits the recovery of immune system responses in order to prolong the infected-individuals' survival.

- **for treatment in adults specific anti-HIV therapy is recommended when the patient has an AIDs-defining illness or if the HIV viral load is greater than 100,000 copies/mL**
  caution should be exercised in other clinical situations because of the development of viral resistance to anti-retroviral agents with significant drug-induced adverse effects including allergic and metabolic syndromes.

Diagnosis, Management and Prevention of HIV Infection

- The latency of HIV-1 infection is evident upon treatment interruption which will lead to resurgence of viral replication.

- ARV drugs are classified currently based on its mechanism of action into six classes:

NRTI	*NNRTI*	*PI*	*Integrase Inhibitor*	*Fusion Inhibitor*	*CCR5 antagonist*
Zidovudine	Nevirapine	Saquinavir	Raltegravir	Enfuvirtide	Maraviroc
Didanosine	Delavirdine	Ritonavir	Dolutegravir		
Stavudine	Efavirenz	Indinavir	Elvitegravir		
Lamivudine	Etravirine	Nelfinavir			
Abacavir	Rilpivirine	Atazanavir			
Tenofovir		Tipranavir			
Emtricitabine		Darunavir			

- **including the nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors and cell-fusion inhibitors.**
  CCR5 inhibitors and integrase inhibitors have been headed to the arsenal of anti-HIV medications.

- **combinations of three synergistic and HIV drugs from two different classes are known as highly active**
  antiretroviral therapy (HART) with hard protocols shown to be effective in reducing viremia and restoring normal
  t-cell counts with drastic reduction of mortality and number of infections. However, they do not eradicate
  HIV and need to be administered continuously for life.

Diagnosis, Management and Prevention of HIV Infection

continuation...

- as an adjuvant treatment to improve baseline immunity the administration of IL-7 and IL-2 have been independently tested to increase CD4 t-cell counts with promising results.

- the immunologic reactions associated with anti-HIV treatment include the immune reconstitution inflammatory syndrome (IRIS) which is a severe inflammatory response to existing opportunistic infections that can be observed in 15 to 25% of the patients with AIDS 2 to 3 weeks after starting HART treatment.

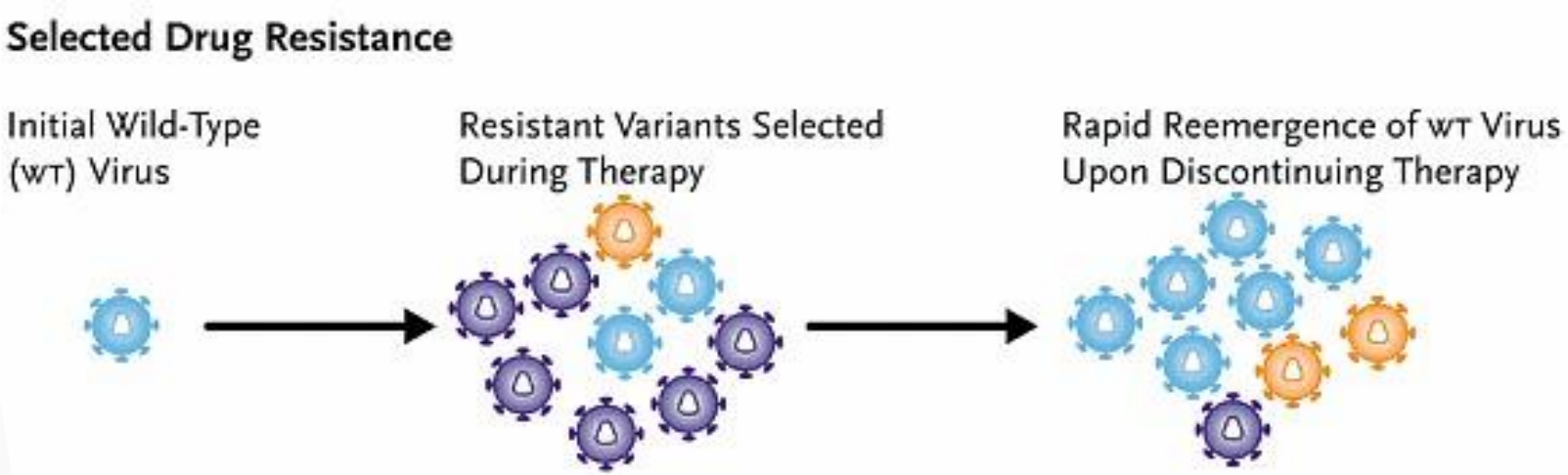
- management of iris consists of corticosteroid therapy and simultaneous treatment of opportunistic infections however iris might not occur if these infections are recognized and treated before starting HART therapy.

- drug allergic reactions have an increased prevalence in this patient population, urticarial rashes, or maculopapular rashes which occasionally present has the stevens-johnson syndrome occurring as many as 60% of patients with HIV. receiving in trimethoprim sulfamethoxazole and 17% of those receiving antiretroviral nevirapine

- abacavir is a nucleoside reverse transcriptase inhibitor that causes a multi-organ hypersensitivity syndrome characterized by fever, rash, diarrhea, myalgia (muscle pain), and arthralgia (joints pain) in as many as 14 percent of patients who take this drug. this has a strong association with the presence of HLA, B5701. this syndrome presents within the first weeks of treatment and can be fatal. However, it usually resolves after 72 hours and discontinuing the drug.

Diagnosis, Management and Prevention of HIV Infection

- Several biologic properties of HIV-1 make the emergence of drug resistance an inevitable outcome in the individuals receiving suboptimal ART (high rate of mutation, possibility of recombination).



Diagnosis, Management and Prevention of HIV Infection

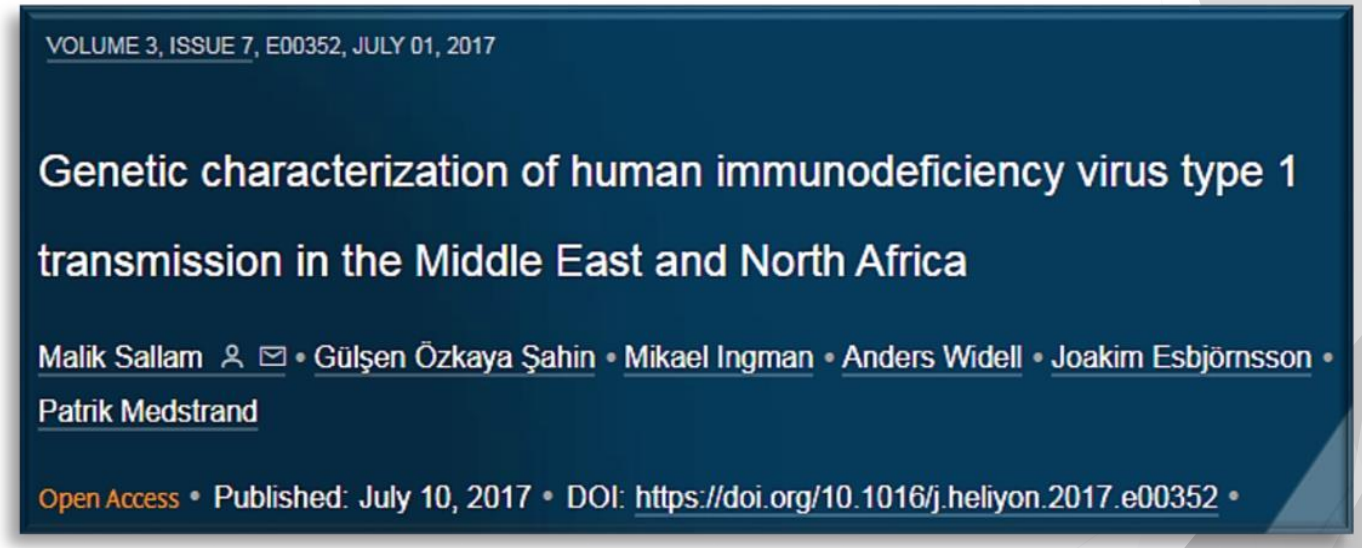
In the absence of an effective vaccine towards HIV-1 infection, the preventive efforts rely on the following measures:

(1) HIV-1 testing particularly among most-at-risk groups.

(2) Consideration of (PrEP) and (PEP) among individuals at risk along with earlyinitiation of ART among HIV-1 infected individuals.

(3) Counselling and education of most-at-risk groups regarding the behavioural practices that are associated with higher probability of transmission (e.g. needle-sharing, unprotected sex, etc.), along with implementing protective measures (needle exchange program [NEP], STI screening and condom use).

Final Note on HIV/AIDS in MENA



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Genetic characterization of human immunodeficiency virus type 1 transmission in the Middle East and North Africa

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THE END