Medical Immunology for M.D. Students

IMMUNODEFICIENCY DISORDERS (2)

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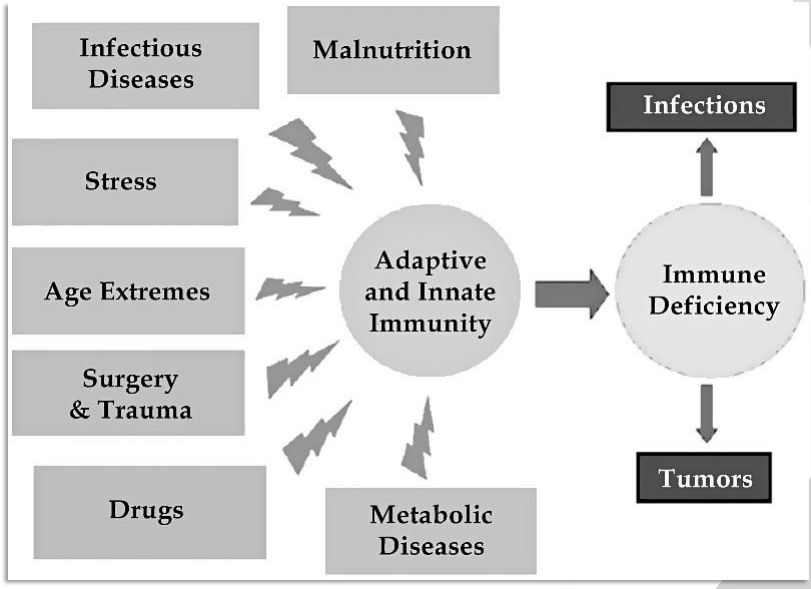
Secondary Immunodeficiency

- Secondary ID disorders are acquired and might be treated by the management of the underlying cause. Secondary IDs are far more common than PIDs.
- 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



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.
- 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*.

Secondary ID – Extremes of Age

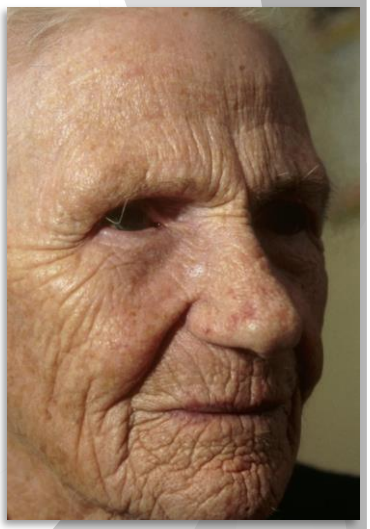
- Neonates have an increased susceptibility to common and opportunistic infections and sepsis compared with older children.
- In early life there are fewer marginal-zone B cells in lymphoid tissue and a decreased expression of CD21 on B cells, thus limiting the ability of B cells to develop specific responses.

Secondary ID – Extremes of Age

- Although they can develop humoral responses to some antigens after exposure in utero, impaired immunity in newborns 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.
- 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

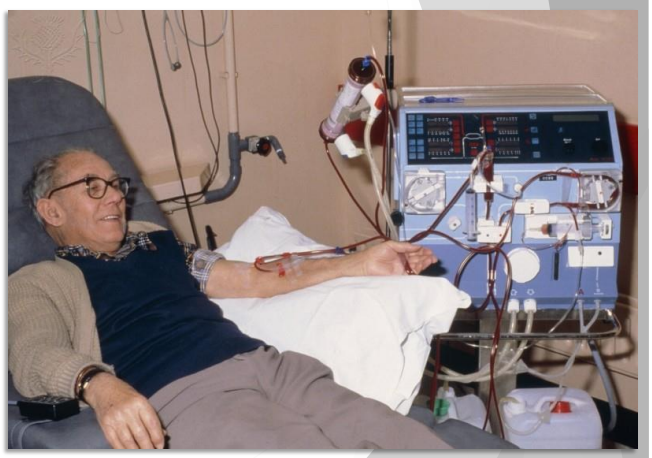


Secondary ID – Metabolic Disorders (DM)

- DM and uremia resulting from kidney or liver disease are two common metabolic disorders with known deleterious effects on 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 MΦ chemotaxis in vitro, T-cell anergy demonstrated by DTH skin tests, and poor lymphoproliferative response to mitogens caused by chronic exposure to hyperglycemia.

Secondary ID – Metabolic Disorders (Uremia)

- The diminished capacity to generate memory antibody responses, regardless of repeated vaccination, and defective phagocyte chemotaxis and microbicidal activity in vitro are examples of the immune defects present in uremic patients



Secondary ID – Drugs

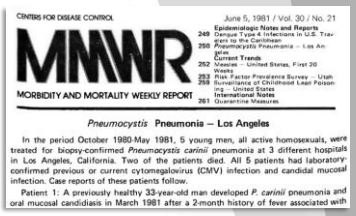
- The use of drugs to ameliorate undesirable immune responses is common in clinical practice as a consequence of the increasing prevalence of inflammatory conditions. These diseases include the categories of autoimmune disorders, allergic disorders, transplant rejection, GvHD.
- The overall results are 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.

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.

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 June 5, 1981 / Vol. 30 / No. 21

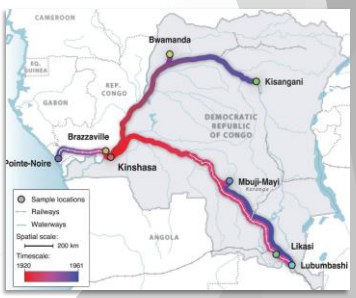
MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

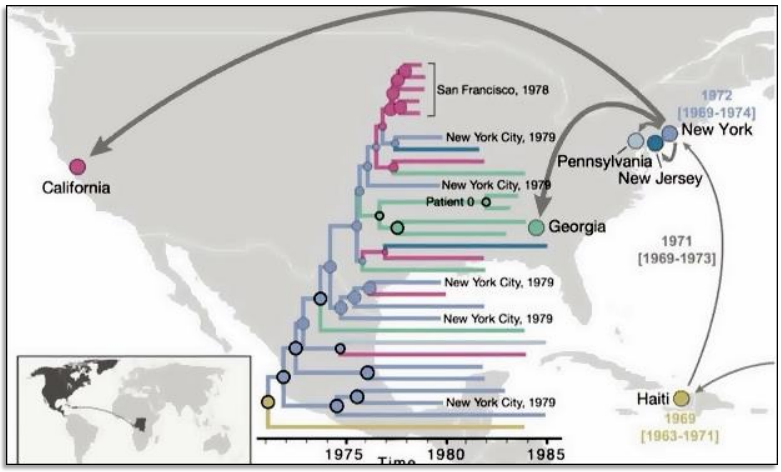
Pneumocystis Pneumonia — Los Angeles

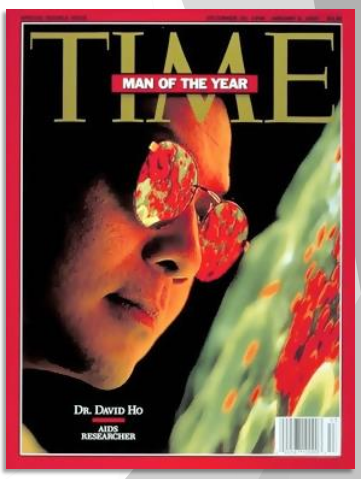
In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV)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

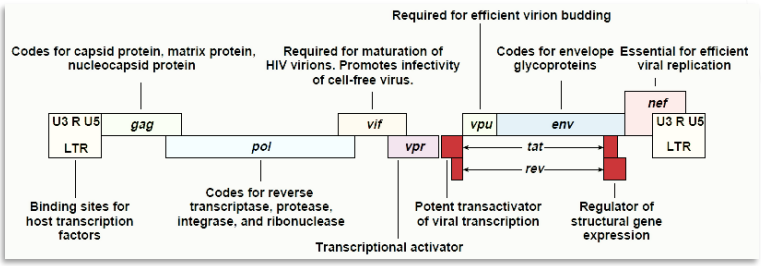


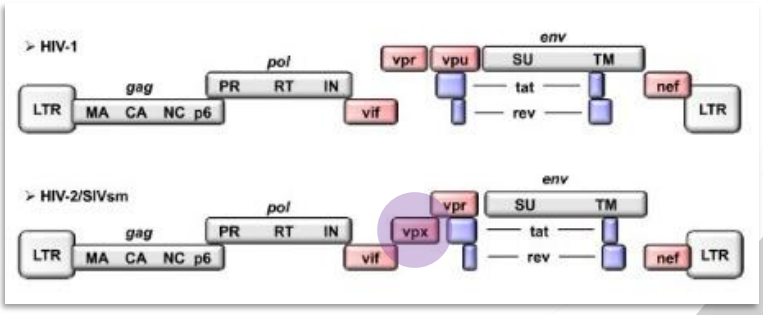
Background on HIV/AIDS



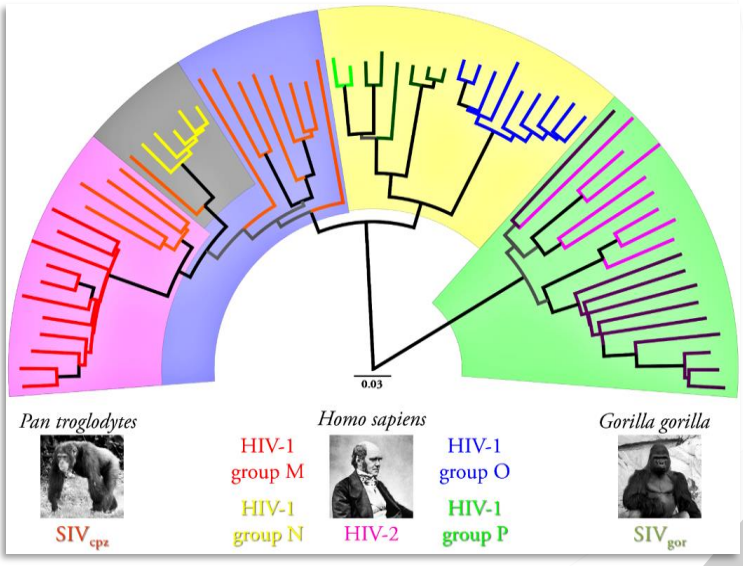


HIV Genome


Required for efficient virion budding
Codes for capsid protein, matrix protein, nucleocapsid protein
Required for maturation of HIV virions. Promotes infectivity of cell-free virus.
Codes for envelope glycoproteins
Essential for efficient viral replication
U3 R U5
LTR
gag
pol
vif
vpr
vpu
env
tat
rev
nef
U3 R U5
LTR
Binding sites for host transcription factors
Codes for reverse transcriptase, protease, integrase, and ribonuclease
Potent transactivator of viral transcription
Regulator of structural gene expression
Transcriptional activator


HIV-1
LTR
gag
MA CA NC p6
pol
PR RT IN
vif
vpr
vpu
env
SU TM
tat
rev
nef
LTR
HIV-2/SIVsm
LTR
gag
MA CA NC p6
pol
PR RT IN
vif
vpr
vpx
env
SU TM
tat
rev
nef
LTR

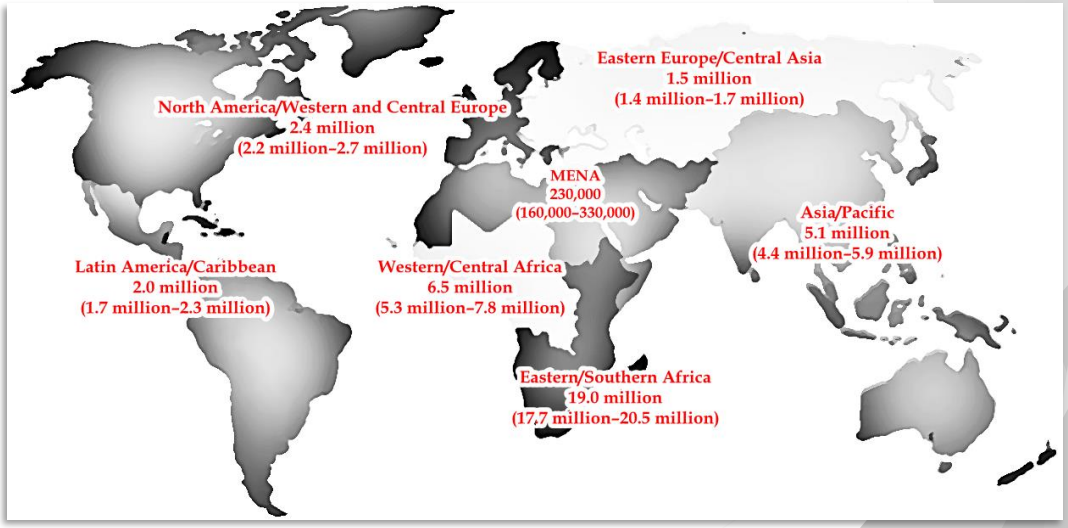
HIV Classification



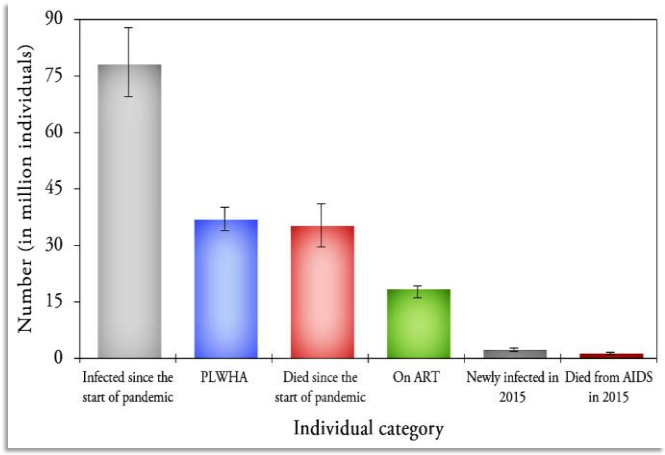
Important Features of HIV

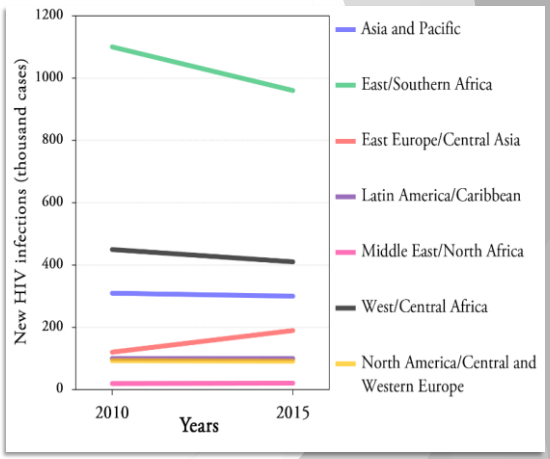
- HIV tropism is for CD4+ T cells, MΦ and DCs.
- The cellular receptor is CD4, with either CCR5 or CXCR4 acting as co-receptors.
- HIV-1 has a worldwide distribution, while HIV-2 is endemic in West Africa.
- According to UNAIDS, and by the end of 2015, about 37 million people were living with HIV/AIDS (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

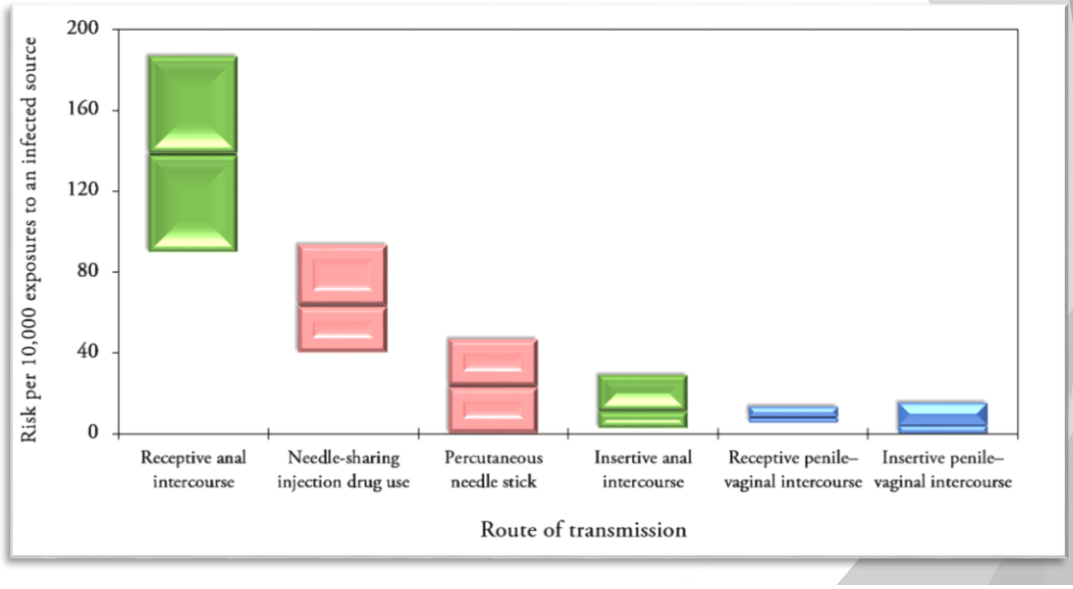




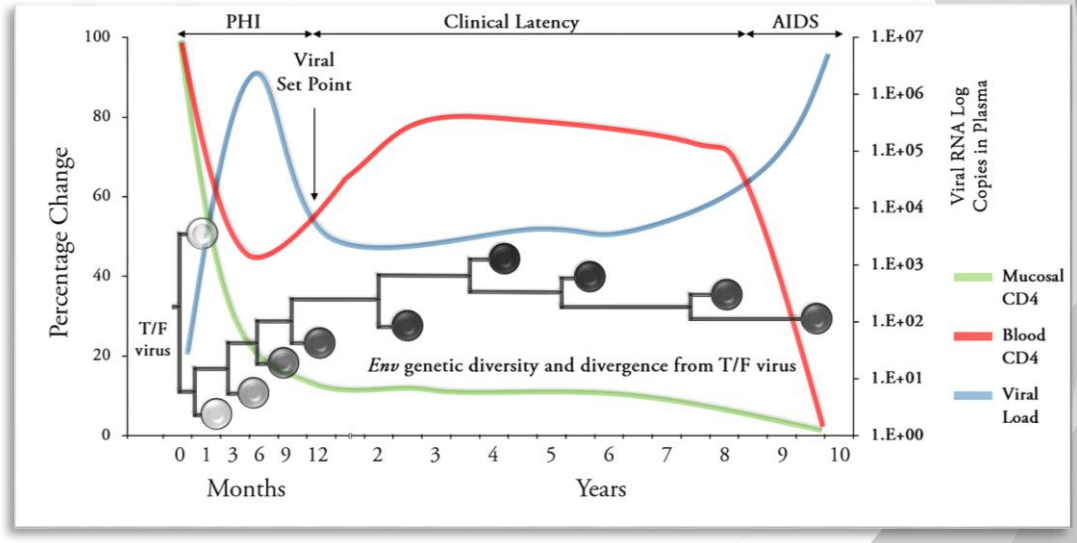
HIV Transmission

- 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 and chemokine receptors CCR5 or CXCR4.
- The virus starts to establish the infection for about 10 days locally before systemic spread.
- Subsequent virus spread into the lymphoid tissues including the gut-associated lymphoid tissue (GALT), ends-up in the establishment of infection chronically.

HIV-1 Pathogenesis

- 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 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.
- HIV-1 set-point is considered an important prognostic marker for assessment of disease progression.

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, Management and Prevention of HIV Infection

- For management of the HIV-1 infected individuals, CD4 T cell count and plasma 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 exception of 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.

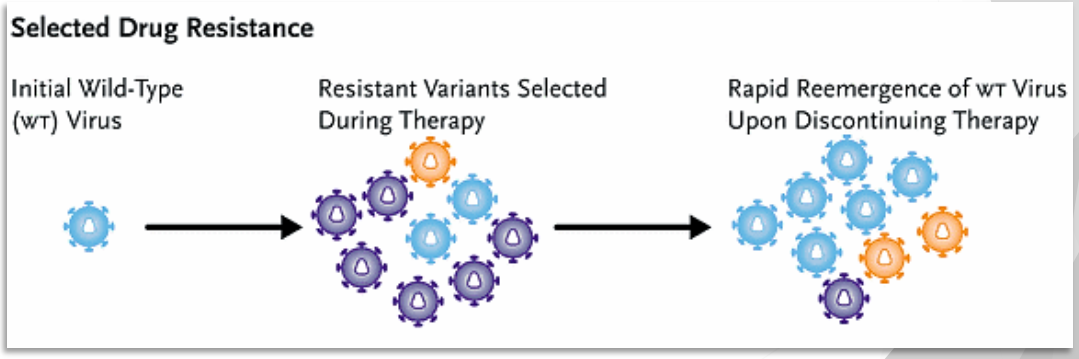
Diagnosis, Management and Prevention of HIV Infection

- 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			

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 early initiation 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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Any Questions?

Thanks for Listening