Sheet 20

Immunology

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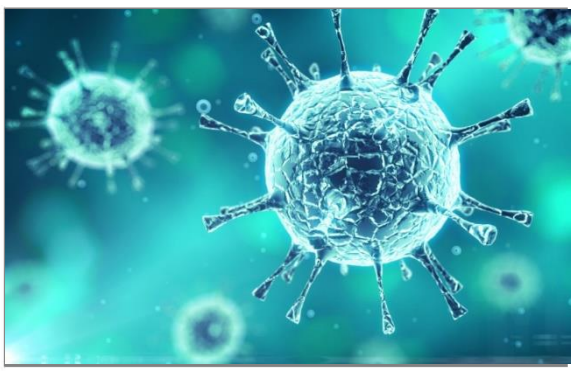
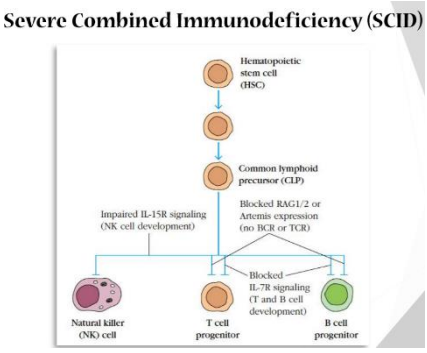
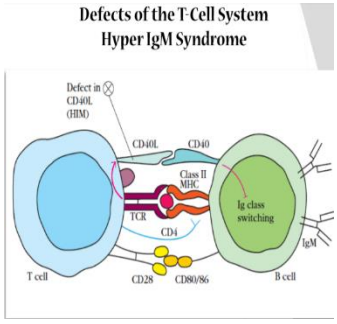


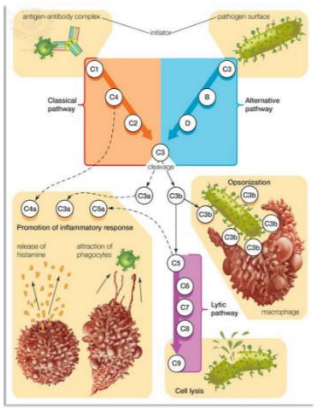
Continuation of ID (1) slide, the primary ID

Severe combined immune deficiency

- The most serious of PIDs is SCID. It is a group of related diseases that all affect T- and B-cell function but with differing causes. X-linked SCID is the most common form of the disease.
- The abnormal gene involved codes for a protein chain called the common gamma chain, which is common to receptors for interleukins- 2, 4, 7, 9, 15, and 21. The gene is referred to as the IL2RG gene and is located on the X chromosome.
- Normal signaling cannot occur in cells with defective receptors, preventing natural maturation. Although this chain was first identified as a part of the IL-2 receptor, impaired IL-7 signaling is likely the source of both T-and B-cell developmental defects, while lack of IL-15 signaling is believed to account for the block to NK cells
- A JAK3 deficiency may be found without the common gamma chain deletion.
- This results in an autosomal recessive form of SCID, affecting both males and females.
- Defects in the pathways involved in the recombination events that produce immunoglobulin and T-cell receptors highlight the importance of early signaling through these receptors for lymphocyte survival.
- Mutations in the recombinase activating genes (RAG1 and RAG2) and genes encoding proteins involved in the DNA excision-repair pathways employed during gene rearrangement (e.g., Artemis) can also lead to SCID.
- Another relatively common defect resulting in SCID is adenosine deaminase (ADA) deficiency.
- Adenosine deaminase catalyzes conversion of adenosine or deoxyadenosine to inosine or deoxyinosine, respectively.
- Its deficiency results in the intracellular accumulation of toxic adenosine metabolites, which interferes with purine metabolism and DNA synthesis.
- This housekeeping enzyme is found in all cells, so these toxic compounds also produce neurologic and metabolic symptoms, including deafness, behavioral problems, and liver damage.







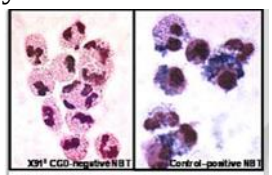
Defects of the t cell system -Hyper IgM syndrome-

- An inherited deficiency in CD40 ligand (CD40L or CD154) leads to impaired communication between T cells and antigen-presenting cells (APCs), highlighting the role of this surface molecule in this co-stimulatory process.

- In this X-linked disorder, TH cells fail to express functional CD40L on their plasma membrane, which typically interacts with the CD40 molecule present on B cells and dendritic cells (DCs).
- The B-cell response to T-independent antigens, however, is unaffected, accounting for the presence of IgM antibodies in these patients, which range from normal to high levels and give the disorder its common name, hyper IgM syndrome.

Defects of neutrophil function -Chronic Granulomatous Disease-

- CGD is caused by an inherited defect in the (NADPH) oxidase enzyme complex present in a variety of cells including phagocytes.
- The NADPH oxidase enzyme complex consists of two membranespanning subunits, gp91phox and p22phox, as well as three cytosolic components p47phox, p67phox, and p40phox.
- Approximately, 66% of all CGD cases result from mutations within the Xlinked gp91phox gene, followed by the autosomal recessive forms of CGD, with defects in the gene coding for p47phox, accounting for 30% of all CGD cases.
- NADPH oxidase is required for the 'respiratory burst' and has a critical role in microbial killing.
- It reduces molecular oxygen to superoxide, which subsequently forms reactive oxygen species (ROS) such as hydrogen peroxide, hypochlorous acid, and hydroxyl radicals.
- Patients are particularly susceptible to fungal infection, typically from Aspergillus species, but also catalase-positive bacteria including Staphylococcus aureus, Serratia marcescens and Burkholderia cepacia.
- Most patients present with infections, typically lymph node abscesses, but also recurrent respiratory infection, deep-seated abscesses and septicaemia.
- Making the diagnosis of CGD is not technically difficult, and historically is based on the use of the "gold standard" nitro-blue tetrazolium assay.
- assay is FCM based on the reduction of dihydrorhodamine (DHR) by stimulated phagocytic cells and is particularly useful as it can demonstrate two populations of cells in carriers.


NBT Reduction Test

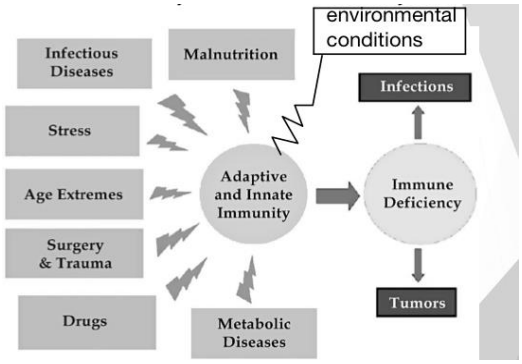
Complement Deficiency

- Deficiencies in the early complement components, C1q, 4, and 2, are usually associated with a lupus-like syndrome.
- C3 deficiency may also have a lupus-like clinical presentation but is more likely to involve recurrent encapsulated organism infection.
- Deficiencies of the later components of complement (C5 through C9) are often associated with recurrent Neisseria infections.
- A deficiency of C1 esterase inhibitor has been found in patients with hereditary angioedema. Most complement deficiencies appear to be inherited in an autosomal recessive manner

Immunodeficiency disorders(2)

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

2ry ID result from different factors that can affect a host with an intrinsically normal immune system including:
infectious diseases, malnutrition, stress, age extremes, surgery and trauma, drugs, metabolic diseases and environmental



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.

For Example, **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.

Different etiologies of secondary ID discussed one by one:

1-Malnutrition

Protein-calorie malnutrition is the most common cause of ID, affecting both innate and adaptive immune systems. 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 a malnourished subject for a relatively long 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.

2A-Extremes of ages-neonates

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

There is an inverse relationship between infection susceptibility and age of prematurity because neonates have:(*premature more susceptible than full term and newborns in general more susceptible than older children than adults, due to impaired immunity)*

1. 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.

2. relative lack of maturity of secondary lymphoid organs, including the lymphoid tissue associated to mucosa in the GI and respiratory tracts. Although they can develop humoral responses to some antigens after exposure in utero.
3. Decreased neutrophil storage pool
4. Decreased in vitro neutrophil function like phagocytosis, oxidative burst ,chemotaxis and adhesion
5. Decreased natural killer cell activity
6. Decreased Tol like receptor signaling
7. Decreased production of cytokines
8. Reduced complement components
9. Premature infants are also more vulnerable to infections because of absence of maternal IgG transfer before 32 weeks of gestation.
10. Absence of memory cell development because of the relative isolation provided by the maternal environment.

2B-Extremes of ages-elderly

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 up regulate the production and function of macrophages and neutrophils

3-Metabolic disorders ,include DM and Uremia

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.

DM: 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.

Uremia:Multiple defects if the innate and adaptive immunity have been described to have a role in frequency of infections in uremia patients ,examples of these immune defects :

1. The diminished capacity to generate memory antibody responses, regardless of repeated vaccination,
2. and defective phagocyte chemotaxis and microbicidal activity in vitro

4-Drugs

Use of the following drugs as a contributing factor for acquired immunodeficiency disease \

1- glucocorticoids

glucocorticoids are known for a variety of applications in both general and sub-speciality medicine to reduce tissue damage caused by an excessive inflammatory response ,glucocorticoids bind a cytosolic receptor which then as the bound complex glucocorticoid receptor translocates to the nucleus to act as a transcription factor affecting the expression of a number of genes resulting in an anti-inflammatory effect, it modulates signal transduction pathways resulting in the activation of the transcription factors 1-NFKB ,2-the nuclear factor of activated t-cells and 2-activator protein 1 (ap1 is also a tf)

Pulse therapy means the administration of large (suprapharmacologic) doses of drugs in an intermittent manner to enhance the therapeutic effect and reduce the side effects e.g. PULSE CORTICOSTEROID THERAPY.

the overall results of pulse therapy with higher doses in relation to receptor saturation are

1. decreased cytokine production including decreased interleukin 1, interleukin 6 and tnf alpha
2. impaired leukocyte chemotaxis and cell adhesion,
3. phagocyte and lymphocyte anergy,
4. lymphopenia occurs as a result of the pro-apoptotic activity and inhibition of interleukin 2 mediated proliferative responses

Immune defects associated with the glucocorticoid therapy include;

oral candidiasis which is a frequent complication of the use of **inhaled steroids** and

herpes zoster disease which often presents with **chronic use of systemic corticosteroids**.

***2*-Calcineurin inhibitors** are medicines which **inhibit** the action of **calcineurin**. **Calcineurin** is an enzyme that activates T-cells of the immune system, calcineurin inhibitors bind cytoplasmic proteins of the immunophilin family and inhibit their interaction with calcineurin which is essential for the activation of interleukin 2 transcription and t-cell function

The advantage of calcineurin drugs over corticosteroids and cytotoxic drugs is that they spare macrophage and neutrophil functions reducing the spectrum of susceptibility to infections.

Cyclosporine, a calcineurin drug, extensively used to prevent **organ transplant rejection, graft versus host disease and corticosteroid resistant autoimmune disorders. Tacrolimus** has same MOA

3-Cytotoxic agents

they are used to manage autoimmune and innate immunity disorders including graft-versus-host disease and also in the prevention of graft rejection e.g. **cyclophosphamide** and the antimetabolites **methotrexate, mycophenolate**, **azathioprine** and **6 mercaptopurine**.

4-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**, they **inhibit** both **T** and **B** cell **proliferation** therefore any new immune responses furthermore depending on the dose used they **inhibit cellular** and **antibody responses** resulting from **previous sensitization.**

5-Infectious diseases (prototypical example is HIV)

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

HIV is a double-stranded enveloped RNA retrovirus from the group Lentiviruses with a tropism for human **cd4+** expressing cells including **T cells** and **macrophages**

- The cellular receptor is CD4, with either CCR5(on macrophages) or CXCR4(on t cells) acting as coreceptors.
- Note that CCR5 and CXCR4 are chemokine receptors utilized as coreceptors in HIV infection
- Two HIV types have been identified hiv-1 and hiv-2 and both cause human disease
- HIV-1 has a worldwide distribution, while HIV-2 is endemic in West Africa.
- HIV 2 takes more time than HIV1 from time of infection to the development of immune deficiency.
- 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.

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 genome

3 structural genes (Gag *(codes for group antigen protien),* **Pol**, and **Env**) and **6 regulatory** genes

1. **Gag** is split by the **HIV protease** into the proteins **capsid p24 matrix nucleocapsid, capsid p6** and **capsid p2** all of which form the viral particle and stabilize the viral genome.
2. **Pol** protein is also split to produce **3 enzymes**, **integrase**, **reverse transcriptase** and a **late phase protease**
   →after entry to the cell, **reverse transcriptase** enzyme converts **viral** RNA to DNA.

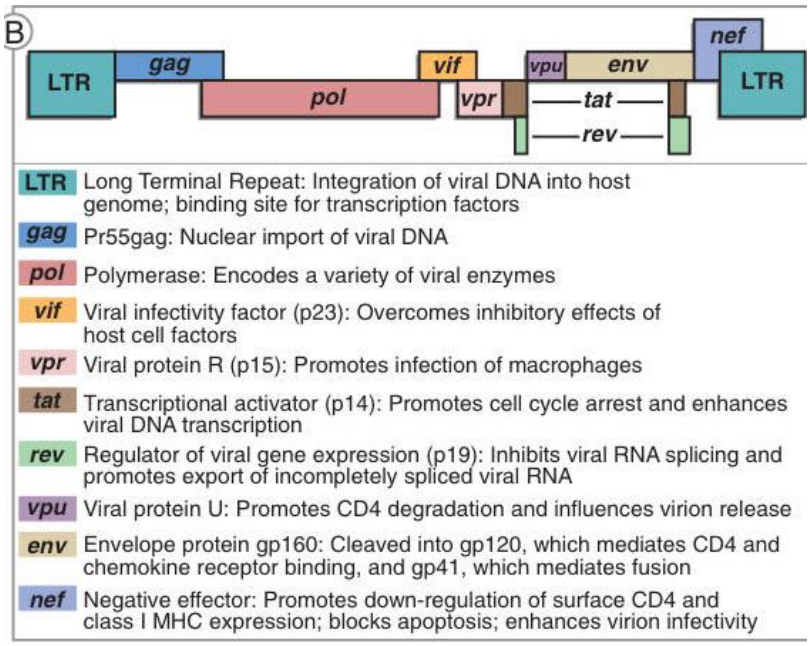
→**Integrase** then facilitates the incorporation of the viral DNA into the host genome which then uses the host cells replication mechanisms to produce more virions.
→ **late phase protease,** the Protein that cleaves the viral proteins in immature virion after it buds from infected cell in order to become mature virion.

3. **Env** protein is also cleaved to produce **two envelope proteins** named **glycoprotein 120** and a glycoprotein **41** which are **involved in the binding to cd4 and the chemokine receptors cxcr4 and ccr5** on target cell.

Regulatory genes:

1. **Transcription activator protein** increases the transcription of HIV genes by 100 fold , **Rev protein allows** the expression of the different HIV genes by regulating mRNA splicing, **negativity factor protein** down regulates cd4 and MHC class 1 cells expression on the membranes of infected cells probably facilitating escape from the immune surveillance. **VIf**, a protein that disrupts antiviral activity of human enzyme APOBEC3G by inducing its degradation (APOBEC3G is a cytosine deaminase that causes mutations during viral transcription, an antiviral protein) ,**Vpr** and **Vbu** seem to facilitate the intracellular transport of viral proteins for viral particle formation .

This pic is extra from the book, remember LTR are areas in our genome used by viruses to insert their genome.



Pathogenesis of HIV infection

1. Starts with the binding of the **HIV gp120 protein(docking protein)** to the **cd4 molecule** and the chemokine receptor **ccr5** on target cells
2. Preferential binding to ccr5(on macrophages)than cxcr4 initially, after replication of virus inside the infected person , mutations take place in viral replication (as reverse transcriptase has low fidelity) leading to change of preferentiality to cxcr4(on t-cells))
3. infected cells migrate to the **lymph nodes** where initial replication and infection of nearby cd4+T cells occurs

The distinctive feature of HIV-1 infection is the progressive quantitative and qualitative deficiency of CD4+ T cells, *HIV infection: primary /acute infection→chronic infection→AIDS*

- **FIRST STAGE: Primary(acute) infection** (first few months): Nonspecific and resemble those of infectious mononucleosis.
- acute phase of HIV infection occurs one to six weeks after infection, with nonspecific symptoms such as fever, fatigue, myalgia and headaches.
- 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.
- The significant decline of CD4 cells at this phase is related to loss of memory cells in the GALT, that is severely depleted.
- Viremia follows, which remains at high levels for about 8 to 12 weeks, coinciding with mononucleosis-like features in a majority of infected individuals
- Immune activation: 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 throughout the clinical latency stage (the next stage of infection aka chronic HIV infection)
- HIV set point level is considered an important prognostic marker for assessment of disease progression.
- HIV induces t-cell lymphopenia through several mechanisms like HIV induced apoptosis, viral cytopathic effect, apoptosis caused by nonspecific immune activation and cytotoxicity in HIV infected cells, autophagy in which organelles are sequestered and directed towards lysosomal pathways have been show n to be induced by HIV envelope protein in uninfected t-cells

NEXT STAGE: 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, absence of signs or symptoms until symptomatic disease occurs which can last as long as 10 years.

- Levels of several cytokines are increased and contribute to determine the degree of control of HIV viremia.
- Higher viral loads at the initial stage predict shorter clinical latency.

Immune system does produce specific anti hiv ab against infected cd4 plus + and cd8 + t as well as neutralizing anti HIV antibodies however these immune responses are eventually overcome by viral escape strategies so without the HIV drug treatment CD 4 + t-cell counts progressively decrease and the host usually succumbs to infections with opportunistic organisms that take place because of the immunodeficiency bringing us to the last stage.

LAST STAGE: 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, Pneumocystis jirovecii induced pneumonia histoplasmosis and coccidioidomycosis if the patient does not receive antiretroviral treatment repeated infections that are difficult to manage lead to patient death.)

→A small proportion of HIV infected patients remain asymptomatic without any antiretroviral therapy and do not have AIDS these patients are called **long term nonprogressors** (aka Elite controllers) and have been the focus of multiple studies to understand the basis of their protection (LTNP's have a detectable viral load)

this immunity appears to be explained by different viral and host factors the best-known of these factors is the inherited defect in the gene encoding the ccr5 receptor that is necessary for HIV entry ,ccr5 gene mutations have been found with a significant prevalence in northern European ancestry, other factors identified in LTNP include low number of activated cd8 + T cells , the presence of particular HLA alleles and lastly viral mutations that result in low virulence.

Diagnosis 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 or by the detection of HIV sequences by reverse transcriptase PCR

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.

Treatment

-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 infectedindiidals survival

-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:

-In adults **specific** ARV (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

-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), thus Caution should be exercised

ARV(anti-retroviral ,anti-HIV) drug classes are classified according to their MOA into 6 classes: nucleoside reverse transcriptase inhibitors ,non-nucleoside reverse transcriptase inhibitors, protease inhibitors ,cell fusion inhibitors ,ccr5 inhibitors and integrase inhibitors.

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			

Combinations of **three synergistic** anti-HIV drugs from **two** different classes is known as highly active antiretroviral therapy (HAART)

HAART protocols shown to be effective in reducing viremia and restoring normal t-cell counts with drastic reduction of a number of infections, however they do not eradicate HIV and need to be administered continuously for life

Adjuvant treatment to improve baseline immunity the administration of IL 7 and IL2 this has been independently tested and found to increase cd4 t-cell counts with promising results.

Significant drug-induced adverse effects including allergic immunologic reactions and metabolic syndromes

-Immune reconstitution inflammatory syndrome (iris)

IRIS 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 HAART

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 HAART therapy

-maculopapular rashes and occasionally **Stevens Johnson syndrome** occurring in as many as 60% of patients with HIV receiving 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 and arthralgia in as many as 14 % of patients who take this drug this has a strong association with the presence of HLA b5701

Multi organ hypersensitivity syndrome presents within the first weeks of treatment and can be fatal however it usually resolves after 72 hours of discontinuing the drug.

Drug allergic reactions have an increased prevalence in patient population in Artic area

FINALLY, 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. needlesharing, unprotected sex, etc.), along with implementing protective measures (needle exchange program [NEP], STI screening and condom use).