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اسم المحاضرة الأولى باللغة الإنكليزية : IMMUNOPATHOLOGY

II. Hypersensitivity Reactions

The purpose of the immune response is to protect against invasion by foreign organisms, but they often lead to host tissue damage. An exaggerated immune response that results in tissue injury is broadly referred to as a hypersensitivity reaction.

Classification:

a. According to Gell and Comb's classification, hypersensitivity reactions can be divided into four types (type I, II, III, and IV) depending on the mechanism of immune recognition involved and on the inflammatory mediator system recruited.

b. Types – I II, and III reactions are dependent on the interaction of specific antibodies with the given antigen, whereas, in type IV reactions recognition is achieved by antigen receptors on T-cells.

1) Type I hypersensitivity (anaphylactic or immediate type) reaction

Definition: Type I hypersensitivity reaction may be defined as a rapidly developing Immunologic reaction occurring, within minutes after the combination of an antigen with antibody bound to mast cells or basophilic in individuals previously sensitized o the antigen. The reactions depend on the site of antigen exposure for example in skin – hive, upper respiratory tract – Hay fever, bronchial asthma and systemic reaction – anaphylactic syndrome

Pathogenesis:

* -Presentation of the antigen (allergen) to precursor of TH2cells by antigen presenting dendritic cells on epithelial surfaces

* Newly minted TH2 cells produce clusters of cytokines including IL-3,IL-4,IL-5 and GMCSF

* The IL-4 is essential for activation of B cells to produce IgE and IL-3 and IL-5 are important for the survival of eosinophillic activation

* The IgE antibodies produced has a high affinity to attach to mast cells and basophiles

* A mast cell or basophil armed with cytophilic IgE antibodies is re-exposed to the specific allergen

* In this process multivalent antigens binds to more than one IgE molecules and cause cross-linkage with adjacent IgE antibody.

*This bridging of IgE molecules activates signal transduction pathways from cytoplasmic portion of IgE fc receptors. This signal initiates two parallel but independent processes.

One leading to mast cell degranulation with discharge of preformed (primary) mediators and the other involving denovo synthesis and release of secondary mediators.

(I) Mast cell degranulation discharge preformed granules such as primary mediators including biogenic amines, histamine, adenosine, eosinophlic and neutrophlic chemotactic factors, enzymes including proteases, and several acid hydrolases.

(II) The other involved is de novo synthesis and release of secondary mediators

such as arachidomic metabolites

- Leukotriens C4 & D4 – most potent vasoactive and spasmogenic agents

known by – highly chemotatic for neutrophiles, eosinophiles and monocytes

- Prostaglandin D2 – causes intense bronchospasm & increase mucus

secretion

- Platelet-activating factor release histamine, ↑ed vascular permeability

- Cytokines—activation of inflammatory cells.

Thus, type I reactions have two well-defined phases.

a. Initial phase (response):

- Characterized by vasodilatation, vascular leakage, and depending on the

location, smooth muscle spasm or glandular secretions.

b. Late phase

- As it is manifested for example in allergic rhinitis and bronchial asthma, more intense infiltration of eosinophiles, neutrophiles, basophilic, monocytes and CD4+ T cells are encountered and so does tissue destruction (epithelial mucosal cells).

- Mast cells and basophiles are central to the development of Type I reaction.

Mast cells are bone marrow driven cells widely distributed in tissues around blood vessels, and sub epithelial sites where type I reaction occurs.

Morphology:

+ Histamine and leukotriens are released rapidly from sensitized mast cells and are responsible for intense immediate reaction characterized by edema, mucoussecretions and smooth muscles spasms.

+Others exemplified by leukotriens platelet activating factor (PAF), TNF-α and cytokines are responsible for the late phase response by recruiting additional leukocytes, basophilic neutrophils and eosinophils. These cells secrete other waves of mediators and thus, damage epithelial cells.

+ Eosinophiles are particularly important in the late phase. The armamentarium of eosinophiles is as extensive as the mast cells.

+ Prototype example of Morphologic features in type l reactions is exemplified by bronchial asthma with

-Increased mucous glands with resultant mucous secretion

-Hypertrophy of bronchial smooth muscles with attending brochoconstriction -Edema formations with inflammatory cells infiltrations peribronchially

2) Type II hypersensitivity reaction

Definition: Type II hypersensitivity is mediated by antibodies directed towards antigens present on the surface of exogenous antigens.

Three different antibody-dependent mechanisms are involved in this type of reaction.

(i) Complement-dependent reaction

i. Direct lysis:

a) It is effected by complements activation, formation of membrane attack complex (C5 –9). This membrane attack complex then disrupts cell membrane integrity by drilling a hole. In anucleated cells once and in nucleated cells many attacks of the complex are needed for cell lysis, because the latter ones have abilities to repair cell membrane injuries rapidly.

b) Opsoinization: By C3b, fragment of the complement to the cell surface enhances phagocytosis.

Examples include red blood cells, leukocytes and platelets disorders: Transfusion reaction; haemolytic anemia; Agranuloytosis; Thrombocytopenia; Certain drug reaction

ii. Antibody dependent cell - mediated cytotoxicity /ADCC/

¾ This type of antibody mediated Cell injury does not involve fixation of complements.

The target cells coated with IgG antibodies are killed by a variety of nonsensitized cells that have Fc receptors.

* The non-sensitized cells included in ADCC are monocytes/large granular/ lympholytes/ Natural killer cells, neutrophils and eosinophils.

* The cell lysis proceeds without phagocytosis. Example include graft rejection

iii. Antibody-mediated cellular dysfunction

- In some cases, antibodies directed against cell surface receptors impair or

dysregulated function without causing cell injury or inflammation. For example: In Myasthenia Gravis, antibodies reactive with acetylcholine receptors in the motor end plates of skeletal muscles impair neuromuscular transmission and cause muscle weakness.

- The converse is noted in Graves disease where antibodies against the thyroidstimulating hormone receptor on thyroid epithelial cells stimulate the cells to produce more thyroid hormones.

3) Type III hypersensetivity / immune complex-mediated:

Type III hypersensitivity reaction is induced by antigen-antibody complex that produces tissue damage as a result of their capacity to activate the complement system. The antibodies involved in this reaction are IgG, IgM or IgA.

Sources of antigens include:

a. Exogenous origin Bacteria –streptococcus (infective endocarditis) Viruses –Hepatitis B virus (Polyarteritis nodosa) Fungi – Actinomycetes (farmer's lung) Parasites – plasmodium species (glomerulonephritis) Drugs – quinidin (hemolytic anemia) Foreign serum (serum sickness)

b. Endogeneous origin

Nuclear components (systemic lupus erythematosis) Immunoglobulins (rheumatoid arthritis) Tumour antigen (glomerulonephritis) Therefore, autoimmune diseases are hypersensitivity diseases in which the exaggerated immune response is directed against the self antigens as exemplified by the above three diseases.

The pathogenesis of systemic immune complex diseases has three phases:

a. Formation of Ag-Ab complex

- Introduction of an antigen into the circulation, then Production of specific antibodies by immuno-competent cells and subsequent antigen antibody formation

b. Deposition of immune complexes

- The mere formation of antigen-antibody complex in the circulation does not imply presence of disease.

Immune deposition depends on:

i) Size of immune complexes. Large complexes in great antibody excess are rapidly removed by mononuclear phagocytic system (MPS).Most pathogenic ones are of small or intermediate size / formed in slight Ag excess/

ii) Functional status of MPS: MPS clears circulating immune complexes however, its overload or dysfunction increase the persistence of immune complexes in circulation and resulting in tissue depositions.

Other factors for immune deposition include charge of immune complexes, valence of antigen, avidity of the antibody, affinity of the antigen to various tissue components,

three-dimenstional /lattice/ structure of the complex, hemodynamic factors, etc. Sites of immune complex deposition include:

Renal glomeruli, joints, skin, heart, serosal surfaces, & small blood vessels.

c. Inflammatory reaction

* After immune complexes are deposited in tissues acute inflammatory reactions ensues and the damage is similar despite the nature and location of tissues. Due to this inflammatory phase two mechanisms operate

i) Activation of complement cascades:

- C-3b, the opsonizing, and -C-5 fragments, the chemotaxins are characterized by neutrophlic aggregation, phagocytosis of complexes and release of lysosomal enzymes that result in necrosis.-C3a, C5a – anaphylatoxins contribute to vascular permeability and contraction of smooth muscles that result in vasodilation and edema-C5-9 – membrane attack complexes formation leads to cell lysis (necrosis)

ii) Activation of neutrophiles and macrophages through their Fc receptors.Neutorphiles and macrophages can be activates by immune complexes even in absence of complements. With either scenario, phagocytosis of immune complexes is effected with subsequent release of chemical mediators at site of immune deposition and subsequent tissue necrosis.

Morphology of immune complex-mediated hypersensitivity reaction

- The morphologic consequences are dominated by acute necrotizing vasculitis with intense neutrophilic exudation permiting the entire arterial wall. Affected glomeruli are

hyper cellular with proliferation of endothelial and mesengial cells accompanied by neutrophillic and mononuclear infiltration. Arthritis may also occur.

Classification of immune complex-mediated diseases:

Immune complex-mediated diseases can be categorized into systemic immune complexes diseases (e.g. serum sickness) and localized diseases (e.g.Arthus reaction).

Systemic immune-complex diseases:

Acute forms: If the disease results from a single large exposure of antigen / ex: acute post-streptococal glomerulonephritis and acute serum sickness/ all lesion then tend to resolve owing to catabolism of the immune complexes.

Arthus reaction:

*The Arthur reaction is defined as a localized area of tissue necrosis resulting from an immune complex vasculitis usually elicited in the skin. Arthus reaction occurs at site of inoculation of an antigen and depends on the presence of precipitating antibody in the circulation / with antibody excess/ that resulted in immune complex deposition. Inflammatory reaction develops over 4-8 hours and may progress to tissue necrosis as described above.

* Chronic forms of systemic immune complex diseases result from repeated or prolonged exposure of an antigen. Continuous antigen is necessary for the development of chronic immune complex disease. Excess ones are most likely to be deposited in vascular beds.

4) Type IV hypersensitivity (Cell-mediated) reaction

Definition: The cell-mediated type of hypersensitivity is initiated by specifically sensitized Tlymphocytes. It includes the classic delayed type hypersensitivity reactions initiated by CD4+Tcell and direct cell cytotoxicity mediated by CD8+Tcell. Typical variety of intracellular microbial agents including M. tuberculosis and so many viruses, fungi, as well as contact dermatitis and graft rejection are examples of type IV reactions

The two forms of type IV hypersensitivity are:

1. Delayed type hypersensitivity: this is typically seen in tuberculin reaction, which is produced by the intra-cutaneous injection of tuberculin, a protein lipopolysaccharide component of the tubercle bacilli.

Steps involved in type lV reaction include

a. First the individual is exposed to an antigen for example to the tubercle bacilli where surface monocytes or epidermal dendritic (Langhane's) cells engulf the bacilli and present it to naïve CD4+ T-cells through MHC type ll antigens found on surfaces of antigen presenting cells (APC),

b. The initial macrophage (APC) and lymphocytes interactions result in differentiation of CD4+TH type one cells.

c. Some of these activated cells so formed enter into the circulation and remain in the memory pool of T cells for long period of time.

d. An intracutanous injection of the tuberculin for example to a person previously exposed individual to the tubercle bacilli , the memory TH1 cells interact with the antigen on the surface of APC and are activated with formation of granulomatous reactions.

2. T-cell mediated cytotoxicity

In this variant of type IV reaction, sensitized CD8+T cells kill antigen-bearing cells. Such effector cells are called cytotoxic T lymphocytes (CTLs). CTLs are directed against cell surface of MHC type l antigens and it plays an important role in graft rejection and in resistance to viral infections. It is believed that many tumour-associated antigens are effected by CTLs. Two mechanisms by which CTLs cause T cell damage are:

* Preforin-Granzyme dependant killing where perforin drill a hole into the cell membrane with resultant osmotic lysis and granzyme activates apoptosis of the target cells.

* FAS-FAS ligand dependant killing which induce apoptosis of the target cells.

IV. Autoimmune Diseases:

* **Definition**: Autoimmunity implies that an immune response has been generated against self-antigens /Autoantigens/. Central to the concept of autoimmune diseases is a breakdown of the ability of the immune system to differentiate between self and non-self-antigens. The presence of circulating autoantibodies does not necessarily indicate the presence of autoimmune disease. Thus, pathologic autoimmunity is characterized by

* the autoimmune response is not secondary to tissue injury but it has primary pathologic significance

* Absence of other well-defined cause of disease.

Mechanisms of autoimmune diseases

1. Genetic: Evidences include

-Familial clustering of several diseases such as SLE, autoimmune hemolytic anemia, Hashimoto's thyroditis.

-linkage of several autoimmune diseases such as Hashimotos thyroditis, pernicious anemia, Addion's disease, primary hypothyroidism, etc so-called Schmidt's syndrome.

- Induction of autoimmune diseases with HLA especially class ll antigens exemplified by HLA-B27.

2. Immunologic:

* Failure of peripheral tolerance: Breakdown of T-cell anergy T-cell anergy may be broken if the APC can be induced to express co-stimulatory molecules such as B7-1 and to secrete cytokines such as IL-12 that stimulate the generation of TH 1 cells. This up

regulation of co-stimulator molecule B7-1 has been noted in multiple sclerosis, Rheumatoid arthritis, psoriasis and Insulin dependant diabetes mellitus (IDD).

Failure of activation induced cell death defects in Fas – Fas ligand

*System in generating apoptosis may allow persistence and proliferation of auto reactive T- cells in peripheral tissues. No known disease is incremented but SLE suggested only on experimental basis.

Failure of T-cell – mediated suppression

* Loss of regulatory or suppressor T-cells can limit the function of auto reactive T and B cells and thus, can lead to autoimmunity. There is evidence that patients with SLE have a deficiency of T-suppressor cells activity that would result in hypergamaglobinmea and the production of autoantibodies.

Molecular mimicry (cross – reacting antigens).

* Some infections agents share epitopes with self-antigens. An immune response against such microbes may produce tissue-damaging reactions against the cross reacting self-antigen.

*The classic example is streptococcal pharyngitis, in which antibodies are produced to the streptococcal M – protein and cross-react with M – protein of the sarcolemma of cardiac muscle to produce the acute rheumatic fever. Another example is the immunologic cross-reactivity between the glycoprotein D of the herpes simplex virus and certain bacterial antigens with acetylcholine receptor.

Polyclonal B-lymphocytic activation

* Tolerance in some cases is maintained by clonal anergy. Autoimmunity may occur if such self – reactive but anergic clones are stimulated by antigen-independent mechanisms .Several micro-organisms and their products are capable of polyclonal (i.e antigen nonspecific) activation of B –cells.Examples include Epestein-barr virus (in infections mononucleosis), gram-negative lipopolysaccharides (endotoxins).

*Among the T-cells activated by super-antigens, some may be reactive to self-antigens and thus, autoimmunity may result from arousal of such cells (Certain bacterial products can bind to and activate a large pool of CD4 + T-cells in an antigen independent manner. They do so by binding to class II MHC molecules on APCs and the (beta) B. chains of the T-cell receptor (TCR) outside the antigen – binding groove. Because they stimulate all T-cells they are called super antigens).

3. Microbial agents:

Some bacteria, mycoplasm and viruses are implicated. Viruses and other microbes may share cross-reacting epitopes with self-antigens. Example: Cross-reaction between certain coxsackie viruses and islet cells antigen glutamic acid decarboxylase. Microbial infections with resultant tissue necrosis and inflammation can cause up regulation of co-stimulatory molecules on resting antigen-presenting cells in tissue, thus favouring a breakdown of T-cell anergy. The inflammatory response also facilitates presentation of cryptic antigens, and thus induces epitope spreading.

Classification of autoimmune diseases:

The classification is based on the number of organs involved

* Organ specific autoimmune diseases affect a single organ or tissue including

Hashimoto’s thyroiditis, Graves disease, 1o myxedema, Diabetes, chronic atropic

gastritis, Myasthenia gravis

* Organ nonspecific autoimmune diseases affect many organs and tissues including:

• Systemic lupus erythematosus

• Rheumatoid arthritis

• Systemic sclerosis

• Dermatomyositis

• Polymyositis

• Polyarteritis Nodosa

• Sojourn's syndrome

Here, only SLE (a prototype of autoimmune diseases) is given as an illustration.

V. Immunodeficiency Diseases:

The term immunodeficiency covers a group of disorders of specific immune responses, neutrophil, macrophage and natural killer cells functions, as well as defects in the compliment system that lead to impaired resistance to microbial infections.

Classification – These diseases are crudely classified into primary and secondary types.

1) Primary immunodeficiency diseases (exceedingly rare)

- These disorders usually manifest in early childhood and are almost always genetically determined. Though, some overlap exists primary immunodeficiency diseases are further divided into:

Deficiencies of antibody (B – cells) immunity.

Eg. Infantile X-linked agammaglobinmea

Transient hypogammaglobulinmea of infancy

Deficiencies of cell mediated (T-cell) Immunity

T-cell deficiencies are difficult to trace as T-cells affects B – cell functions

Eg. Di George's syndrome:

Combined T-cell and B-cell deficiencies

Eg Severe combined immunodeficiency disease (SCID).

2) Secondary immunodeficiencies States

These immunodeficiency states may be acquired secondary to various disease processes or drug effects

- Protein deficiency

Lack of protein leads to cell mediated immunity and hypocomplementamia

-Hematologic malignancies

Leukemia and lymphomas where normal functioning cell replaced by neoplastic ones here both humeral and cell mediated immunity are impaired

- Acute viral infection

Especially infectious mononucleosis and misels cause temporary impairment of cellmediated immunity

- Chronic renal failure

Probably due to toxic effects of accumulated metabolites that affects both B and T cell functions.

- Iatrogenic

Steroids etc for organ transplants, cytotoxic drugs or radiotherapy for the treatment of malignancies.

- Splenctomy

After staging operations of lymphomas or traumatic spleen rupture

Splenectomy leads to a characteristic immunodeficiency in which the patient is susceptible to infections by phylogenic bacteria especially pneumococal pneumonia.

-Acquired immunodeficiency syndrome (AIDS):

As a prototype example of secondary immunodeficiency states, AIDS is discussed in some detail below.

Acquired Immunodeficiency Syndrome (AIDS):

* AIDS is a retroviral disease characterized by profound immuno suppression that leads

to opportunistic infections, secondary neoplasms and neurological manifestations.

Overview:

* Prevalence: Currently AIDS affects more than 40 million people all over the world and more than 90 % of the infections prevail in developing countries. Currently, the subSaharan Africa in general and South Africa, Ethiopia and Nigeria in particular shoulder the greatest burden of this pan endemic.

*Age: Mostly affected individuals are those aged between 15 and 49 years of age

however, the epidemiology is quite different in children less than 13 years. Close to 2 % of all AIDS, occur in this age group presently where more than 90 % of this transmission results from transmission of the virus from the mother to the child.

* Sex: Women are more vulnerable than men: Receptive sexual partners-

• Uterine, cervical and vaginal conditions that promote HIV transmission easily include cervical erosion, cervical ectopy, sexually transmitted diseases (STD), and cervical cancer.

• STD often goes unnoticed due to inaccessible anatomic locations.

• Menstruation: May make the transmission of HIV easier just before, during or after menstruation. It results in a large raw exposed area in the inner uterine lining to the virus

• Those with very low socio economic backgrounds are vulnerable to sex trade (HIV is said to be" the holocaust of the poor").

• Age of earlier sexual contact where the very young female genital linings are vulnerable to easy lacerations.

Modes of transmission:

1- Sexual activities 75% of all world-wide transmission is heterosexual transmission

2- Parenteral Transmission In intravenous drug abusers, hemophiliacs who received factor viii concentrates and random recipients of blood transfusion

3- Mother to child transmission: About 25 –30% HIV, positive mother will transmit HIV to their infants. About 60% of this infection is transmitted during child- birth 25% during pregnancy and 15% during breastfeeding.

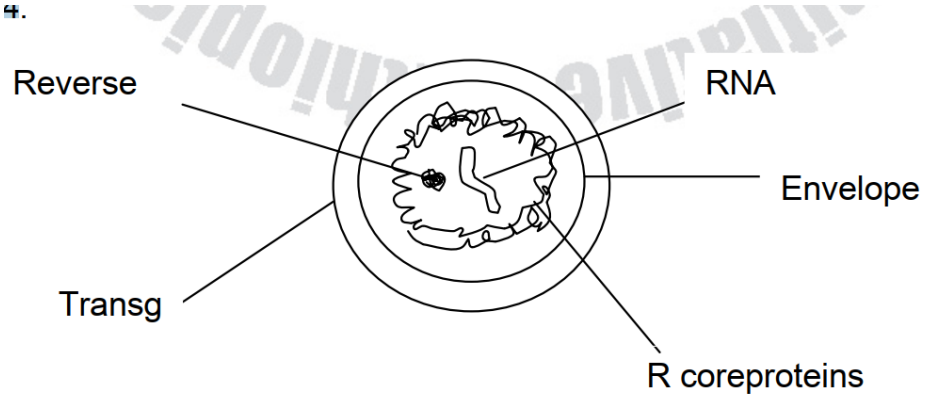
4- Needle Pricking Accidental needle struck injury or exposure to non-intact skin to infected blood in laboratories accounts for about 0.3% risk of stereovision as compared to a 30% risk of accidental exposure to hepatitis B infected blood.

Etiology:

- HIV causes AIDS and HIV is a non-transforming retrovirus belonging to Lentivirus family. The retrovirus undergoes an unusual biologic process in which the genetic material in form of a single stranded RNA, can be converted to double stranded DNA by the effect of reverse transcriptase.

- Two type of HIV viruses: HIV – 1 - USA, EUROPE, East & central Africa HIV - 2 - West Africa

- HIV genome consists of a single stranded RNA enclosed within a core of viral proteins. The core is in-turn enveloped by a phospholipids bilayer deprived from the host cell membrane. The Envelop contains glycoproteins such as gp 120 and GP 41, GP 24.



The viral core consists of two protein shells

* The outer contains the core protein P 18 and the inner core protein P 24. The lipid bilayer consists of the viral glycoprotein gp 41 while gp 120 protrudes into the environment. The RNA genome and the reverse transcriptase are contained within the inner shell.

HIV – 1 proviral genome contains 3 genes -Gag – caspid protein P24, matrix protein P17, nuclocospial protein P7/9

- Pol - revers trancriptase, protease integrase, ribonuclease

- Env – gp120 and gp41

In addition to these standard genes, the HIV contains other genes including

TAT- Potent transactivator of viral transcription

NEF- Essential for viral replication

REV- regulator of structural gene expression

VIF- Requires for maturation of HIV virus and if also promotes infectivity of cell free virus

VEF- essential for efficient viral replication VPU- Required for efficient viron budding

VPR Required for viral replication in non-dividing cells and causing viral replication by causing arrest of cycling cells in G2

*On the basis of genetic analysis HIV- I can be divided into two groups designated as M (major) and 0 (outliers). Group M viruses are the most common viruses worldwide and subdivided into several subtypes or clades designated A -J.

Pathogenesis:

- Targets of HIV infections are: The immune system and Central nervous system

- Target cells are those having CD4 receptors include CD4 + T helper cells Monocytes /macrophages

Tissue cells such as dendritic cells present in genital tracts and anorectal region Certain brain cells (glial cells) Some other cells as well

- CD4 - Receptor molecule is a high affinity receptor for HIV. This explains for the selective tropism of the virus to aforementioned cells.

- Initial binding of gp 120 to CD4 molecule leads to conformational change for the new recognition site on gp120 for the co receptors CCR5 or CXCR4.

- The second conformational change in gp41 results in insertion of a fusion peptide into the cell membrane of the target T-cells or macrophages.

- -After fusion, the viral core containing the HIV genome enters the cytoplasm of the cell (internalization).

The life cycle of HIV virus after internalization, include

* DNA Synthesis- the uncoated viral RNA is copied into double stranded DNA by reverse transcriptase

* Viral integration-the DNA derived from the viruses in integrated into host genome by

the viral integrate enzyme, thereby producing the latest proviral form of HIV-I.

* Viral replication- viral RNA is reproduced by transcriptional activation of the

integrated HIV provirus

* Viral dissemination- to complete the life cycle, nascent viruses assembled in the cytoplasm and disseminate to other target cells after directly lysing the cell (direct cytopathic effect of the virus).

* The HIV virus after internalization assumes two forms of infectivity such as latent

infection and productive infections. In latent infections, the virus may be lacked in cytoplasm (preintegration latency) or after being integrated into host DNA (Post integration latency). Hereafter the highlight of HIV productive infection is surfaced.

- This productive infection is predominantly occurring in lymphoid tissues, within macrophages, dendritic cells and CD4+T CELLS.

- Viremia after 8 weeks of infection supervene

- Viremia is subsequently cleared by the development of an anti viral immune response effected by CD8+cytotoxic T cells

- This results in transient decrease in CD4+T cells and an apparent rise in CD8+T cells.

- As viremia declines, the HIV disseminates into lymphoid tissues and undergoes clinical latency but not viral latency

- Finally the ebbs and flows of the CD4+T cells count with variable time results in AIDS.