CMS 151: GENERAL PATHOLOGY

GENERAL PATHOLOGY II

UNIT 2: IMMUNOPATHOLOGY

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UNIT OBJECTIVES

At the end of the module the learner should be able to: -

1. Describe causes and effects of immune deficiency
2. Describe diseases associated with immune disorders

UNIT OUTLINE

1. Hypersensitivity reactions
2. Allergic and hypersensitivity diseases
3. Autoimmune Diseases
4. Immunodeficiency
5. HIV/AIDS

Lesson 1: Hypersensitivity Reactions

Learning Outcomes

At the end of the lesson the learner should be able to: -

1. Define hypersensivity
2. Classify hypersensitivity reactions
3. Describe the organs and cells are involved in hypersensitivity reactions.
4. Describe the pathogenesis and pathophysiology of hypersensitivity reactions.
5. Outline clinical examples of hypersensitivity reactions
6. Explain the clinical significance of hypersensitivity reactions*?*

1.0. GENERAL INTRODUCTION TO IMMUNE DISORDERS

The specific (adaptive) immune response provides specific protection against infection with bacteria, viruses, parasites and fungi but in the process of these responses there can arise an inappropriate or exaggerated trigger of these immune mechanisms with failure of the body to regulate the reactions leading to unpleasant reactions. The overreaction of the body defence mechanisms may lead to unwanted injury of body's cells, tissues and organs.

Tissue damage results from the effects of pharmacologically active substances liberated from certain cells following antigenic stimulation or antigen-antibody interactions the cell surfaces or cytotoxic action of sensitised cytotoxic T cells.

Immunity was first recognized as a resistant state that followed infection and the system protects the host from infectious agents, foreign material such as tissue grafts, blood products and various chemical substances.

The function of specific immune response is *recognition* and *elimination* of foreign antigens related to infection. Elimination of antigens and the accompanying inflammatory reaction causes damage to tissues as "innocent by-standers". In terms of war think friendly fire or civilian causalities. Hypersensitivity occurs when there is *exaggerated* or *inappropriate* immune response. However, a degree of hypersensitivity is a usual accompaniment to any effective immune reaction. Some immune reactions provide exemption or safety but can provide severe and occasionally fatal results (hypersensitivity reactions) due to excessive or inappropriate response to an antigenic stimuli.

Immunopathology is a disease process with an immunological basis. It can be classified as hypersensitivity reactions, autoimmunity and immunodeficiency.

Immune disorders include: -

1. Hypersensitivity reactions
2. Autoimmune diseases
3. Allergic
4. Immune deficiency syndromes

Hypersensitivity Reactions

1.0. INTRODUCTION

Hypersensitivity (also called **hypersensitivity reaction**) refers to excessive, undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system. Hypersensitivity reactions require a pre-sensitized (immune) state of the host. Hypersensitivity reactions can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved and time taken for the reaction. Frequently, a particular clinical condition (disease) may involve more than one type of reaction. The four-group classification was expounded by P. H. G. Gell and Robin Coombs in 1963.

Hypersensitivity is a situation where there is **excessive** or/and **inappropriate** immune response that leads to **tissue damage** depending on the amount of antigen or the ability of the humoral or cell mediated immunity at high levels. The mechanisms underlying these inappropriate reactions are those normally deployed by the body in combating infection by microbes.Hypersensitivity can result from **foreign antigens**, **autoimmunity**, **passive immunization** (mother-child), **rejection** of tissue grafts and **transplants** and **drugs** and **chemicals**.

The reaction can be **localized** at the site of antigen entry or **generalized**. A localized reaction is inflammatory in nature and causes smooth muscle spasms e.g. in the respiratory system or may be a generalized reactions producing fever, shock, pulmonary disturbances, G.I.T disturbances and circulatory collapse.

2.0. MECHANISMS OF HYPERSENSITIVITY REACTIONS

Human beings live in an environment full of substances capable of producing **immunologic responses**. Contact with antigens induce a **protective response** but can also result in reactions that can be **damaging to the body tissues**. These reactions may originate **exogenous** and **endogenous antigens.** Exogenous antigens occur in *dust, pollen, foods, drugs, microbiologic agents, chemical* and *many blood products used in clinical practice.* The immune responses take a variety of forms ranging from **trivial discomforts** such as **itching of the skin** to **potentially fatal diseases** such as **bronchial asthma**. The various reactions produced are called hypersensitivity reactions and the tissue injury results from **humoral** and **cell-mediated immune mechanisms**.

Injurious immune reactions may be caused by **endogenous tissue antigens**. Some immune reactions are triggered by homologous antigens which differ among individuals such as blood transfusion reactions and graft rejection.

3.0. CLASSIFICATION OF HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions are classified into five classes according to Gell & Coomb's classification on the basis of the immunologic mechanism that mediates the disease. It assists in distinguishing the manner in which the immune reactions cause injury and disease with the accompanying pathologic alterations.

1. Anaphylactic (Atopic/Immediate)Hypersensitivity(Type I Hypersensitivity)
2. Antibody-mediated (Cytotoxic)Hypersensitivity(Type II Hypersensitivity)
3. Immune complex-mediatedHypersensitivity (Type III Hypersensitivity)
4. Cell-mediated (Delayed) Hypersensitivity(Type IVHypersensitivity

5. Stimulatory hypersensitivity(Types V Hypersensitivity)

Table 1.1: Classification of Hypersensivity Reactions

TYPE	DESCRIPTIVE NAME	INITIATION TIME	MECHANISM	MEDIATORS	EXAMPLES
I	IgE-mediated hypersensitivity (Allergy)	2-30 mins	Ag induces cross-linking of IgE bound to mast cells with release of vasoactive mediators	IgE	Systemic anaphylaxis, Local anaphylaxis, Hay fever, Asthma, Eczema
II	Antibody-mediated cytotoxic hypersensitivity	5-8hrs	Ab directed against cell-surface antigens mediates cell destruction via ADCC or complement	IgM or IgG (Complement)	Blood transfusion reactions, Haemolytic disease of the newborn, Autoimmune Haemolytic anaemia
III	Immune-complex mediated hypersensitivity	2-8hrs	Ag-Ab complexes deposited at various sites induces mast cell degranulation via FcgammaRIII, PMN degranulation damages tissue	IgG (Complement)	Arthus reaction (Localised); Systemic reactions disseminated rash, arthritis, glomerulonephritis
IV	Cell-mediated hypersensitivity	24-72hrs	Memory TH1 cells release cytokines that recruit and activate macrophages	T-cells	Contact dermatitis, Tubercular lesions
V					Graves disease Myasthenia gravis

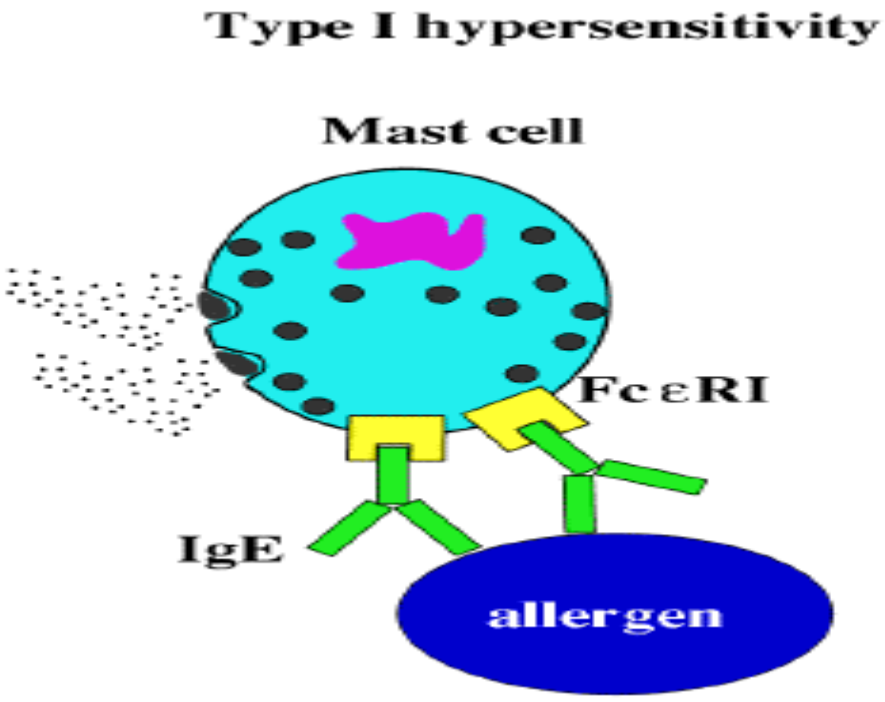
1. IMMEDIATE (TYPE I) HYPERSENSITIVITY

Introduction

*Immediate or type 1 hypersensitivity reactions is a rapidly developing immunologic reaction occurring within minutes after the combination of an antigen and antibody bound to mast cells in individuals previously sensitized.*It is also called **anaphylactic** or **atopic** reactions.

In normal circumstances **IgM initiates** a humoral response and levels of IgE are very minimal but in **atopic** individuals who have a genetic predisposition to allergy usually respond to antigenic stimulation by producing large amounts of IgE.Anaphylactic hypersensitivity is mediated exclusively by immunoglobulin IgE that induces hypersensitivity in conjunction with its effector cells namely the mast cells and basophils.

Diagram 1.1: Type I Hypersensitivity Reaction

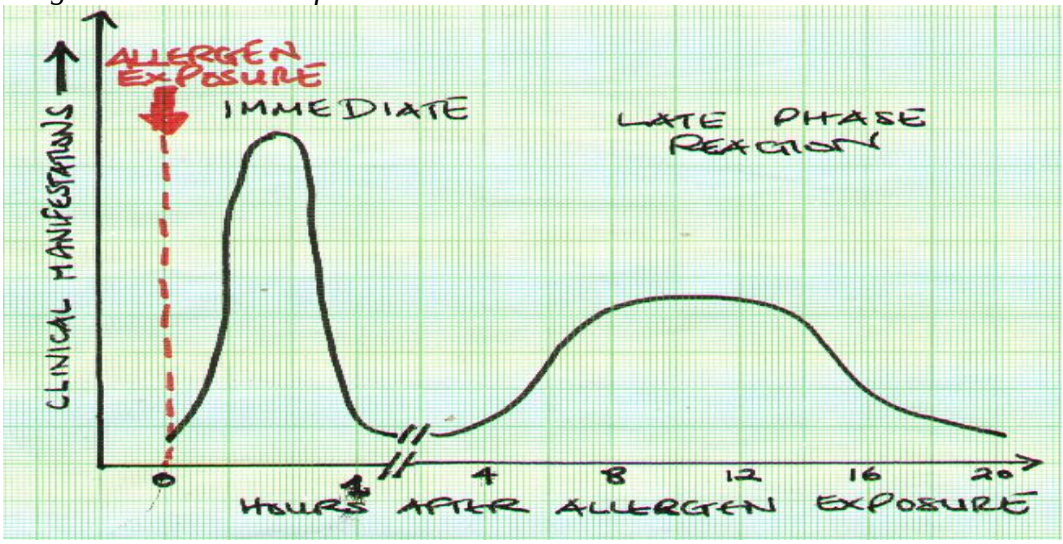


Mast cells and basophils release mediators of inflammation – *histamine*, *heparin* and *tryptase*, which are, preformed mediators already existing in the cells. Mast cells are bone marrow-derived cells that are widely distributed in the tissues. They are predominantly near blood vessels and nerves and in subepithelial sites where local hypersensitivity reactions tend to occur. Histamine release is accompanied by rapid synthesis of arachidonic acid derivatives *leukotrienes*, *prostaglandins* and later platelet activating factors (PAF), which are newly generated factors.The release of preformed and newly formed mediators results in a reaction with a biphasic course comprising of the immediate and late phase.

The immediate response

The immediate response, which is mediated entirely by **histamine** mainly, involves the vascular tissues where it results in dilatation of the blood vessels and contraction of smooth muscles of the bronchi and gut.The skin shows a classical weal and flare reaction, which reaches peak after 15-20 minutes and then, subsides while in the lungs there is intense broncho-constriction.This immediate response is blocked by **antihistamines e.g. chlorphenamine (piriton)** or **mast cell stabilizers e.g. cromoglycate** and steroids do not influence this phase.

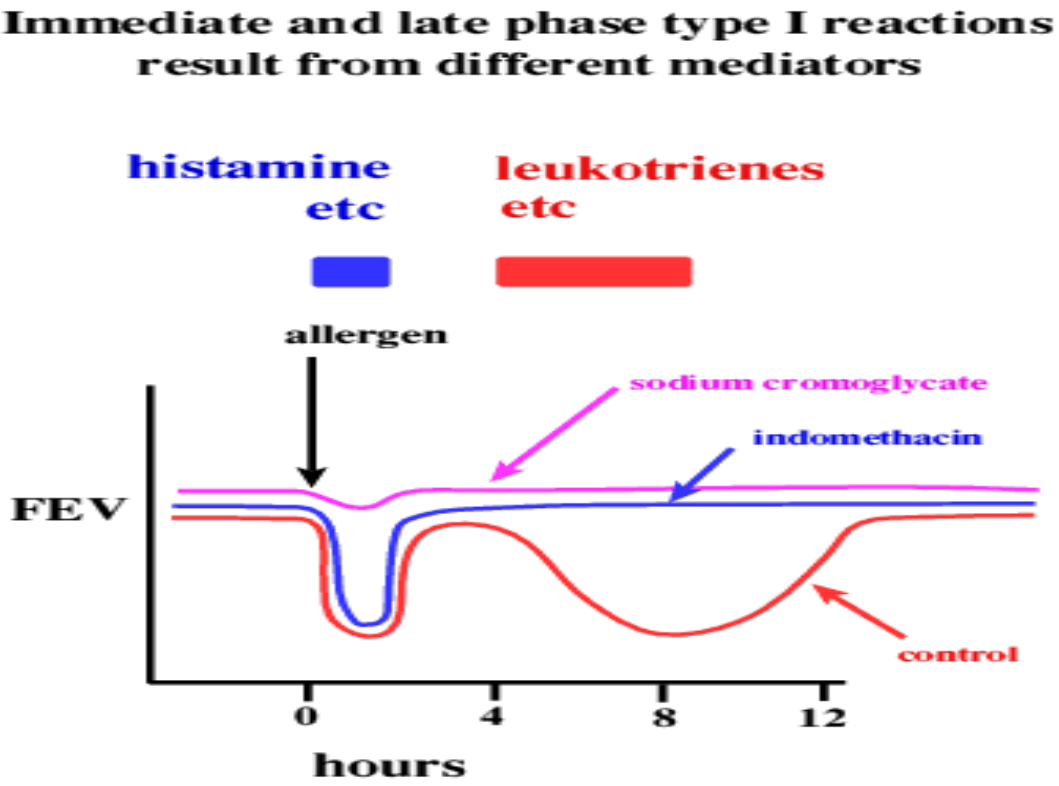
Diagram 1.2: Kinetics of Immediate and Late Phase Reactions



The late phase

The late phase lasts up to 24 hours and is characterized by recruitment of inflammatory cells mainly oesinophils and neutrophils under the influence of the newly synthesized mast cell mediators leukotrienes and PAF. It is abolished by prior treatment with corticosteroids or neutrophils depletion and antihistamines do not affect this phase.

Diagram 1.3: Phases of Type I Reactions



MEDIATORS OF TYPE I REACTIONS

Immediate hypersensitivity reactions are mediated by primary and secondary mediators.

Primary Mediators

Primary mediators contained within mast-cell granules can be divided into three categories namely: -

a) ***Biogenic amines***

This includes **histamine** which is an important vasoactive amine. Histamine causes intense smooth muscle contraction, increased vascular permeability and increased secretion by nasal, bronchial and gastric glands.

b) ***Enzymes***

This includes enzymes such as neutral proteases (*chymase, tryptase*) and several acid hydrolases. The enzymes cause tissue damage and lead to generation of kinins and activated components of complement.

c) ***Proteoglycans***

This includes heparin (an anticoagulant) and chondroitin.

Secondary Mediators

Secondary mediators include **lipid mediators** and **cytokines**. The lipid mediators include *leukotrienes, prostaglandins D_2 and Platelet activating factors (PAF).* The **cytokines** which are produced mainly by mast cells play an important role in the late-phase reaction of immediate hypersensitivity because of their ability to recruit and activate inflammatory cells. The cytokines include TNF, IL-1, IL-3, IL-4, IL-5 and IL-6.

Predisposition

1. Genetic
2. Higher serum levels of IgE
3. Immunodeficiency – reduced IgA
4. Exaggerated reactivity to histamine and other amines

Causes of raised total IgE

1. Allergic
   a. Rhinitis, i.e. inflammation of the mucous membrane of the nose, caused by a viral infection or an allergic reaction.
   b. Asthma (Allergy to environmental allergens)
   c. Dermatitis, i.e. inflammation of the skin as a result of irritation by or allergic reaction to an external agent.

d. Aspergillosis (Allergy following bronchopulmonary exposure), i.e. a condition in which certain fungi infect the lungs or other tissues, especially through inhalation of spores from mouldy hay.

2. Non-allergic
   a. Parasitic infection (protective immunity against parasite)
   b. IgE myeloma (plasma cell neoplasm)

Clinical features

- Skin – urticarial skin rash and intense irritation
- Bronchi – bronchospasms and cough
- Bowel – acute crampling abdominal pain and diarrhoea

ANAPHYLAXIS

If the antigen is introduced systemically e.g. penicillin drugs the reaction results in anaphylaxis. The systemic mediators released cause: -

- Profound and immediate broncho-constriction leading wheezing, Rhonchi and dyspnoea.
- Vasodilatation causes hypotension
- Generalized urticaria
- Convulsions
- Shock

Explain how these features occur?

Pathological changes

- Constriction of small blood vessels with adherence of polymorphs and platelets (leads to leucopoenia and reduced platelets)
- Increased capillary permeability
- Vascular thrombosis and haemorrhage especially in the small intestines
- Later the vessels relax and dilate.
- Less coagulation of blood due to heparin
- Leucopoenia – accumulation of leucocytes in lung capillaries
- Reduced platelets – due to reduced coagubility

Why do these pathological features occur? Explain thepathophysiology

Clinical examples

1. Urticaria
2. Hay fever
3. Asthma
4. Atopic dermatitis
5. Food allergy
6. Penicillin allergy

What complains will patients with such diseases have? Explains how?

ALLERGY AND IDIOSYNCRASY

Allergy occurs when the immediate reaction is mediated by IgE antibodies while when a reaction is mediated by chemicals produced by non-immunologically degranulated mast cells and

basophils leads to a reaction similar to type one reaction is called idiosyncrasy or if systemic it becomes anaphylactoid reaction.

Immediate allergy and Atopy

"Atopy" is a Greek word for out of place. Thirty percent (30%) of the general population produce specific IgE antibodies after natural exposure to environmental allergens.Examples include: -

1) Infantile eczema
2) Atopic dermatitis (adolescents)
3) Bronchial asthma
4) Allergic rhinitis
5) Hay fever
6) Intestinal allergies
7) Angioedema

Diagnosis

1. Accurate history - Describe the reactions and identify the allergens
2. Skin test
3. IgE levels

Table 1:2: Potential Allergens

Group of Allergens	***Examples***
Inhalants	Plant pollens, fungal spores, animal dander, house dust mites, smoke, fumes and gases.
Ingestants	Food (legumes, nuts, nuts, egg albumin, cow's milk, fish, honey), drugs (aspirins, salicylates, penicillin, sulphonamides), vaccines and food addititives.
Injectants	Antibiotics, foreign gamma globulins, vaccines, plant extracts, venoms (stinging bees and wasps)
Contactants	Metals such as cadnium, chromium, silver plated ornaments, rings, cosmetics and soaps

The counter mechanisms for anaphylaxis include: -

a) Identification and elimination of the sensitising antigen
b) Stabilization of mast cells – sodium cromoglycate
c) H_1 receptor blockade – antihistamines
d) Counter inflammatory effects – adrenaline
e) Use of corticosteroids
f) Desensitisation

SYSTEMIC ANAPHYLAXIS

Systemic anaphylaxis is characterized by vascular shock, wide spread oedema and difficulty in breathing. It occurs after administration of foreign proteins, hormones, enzymes, polysaccharides and drugs such as penicillins. The severity of the reaction is determined by the level of sensitization.

Features

- Itching
- Hives
- Skin erythema
- Contraction of respiratory bronchioles and respiratory distress
- Laryngeal oedema – hoarseness of the voice
- Vomiting
- Abdominal cramps
- Diarrhoea
- Laryngeal obstruction

LOCAL IMMEDIATE HYPERSENSITIVITY REACTIONS

Local immediate hypersensitivity or allergic reactions are exemplified by atopic allergy. 10% of the population suffers from allergens involving localized reactions to common environmental allergens such as pollen, animal dander, house dust and foods.

Diseases

- Urticaria
- Angioedema
- Allergic rhinitis (Hay fever)

2. ANTIBODY-MEDIATED (TYPE II) HYPERSENSITIVITY

Introduction

*Type II hypersensitivity reaction is mediated by antibodies directed toward antigens present on cell surfaces or extracellular matrix.*An antigen present on the surface of a cell (**endogenous antigen**) combineswith antibody encouraging the demise of that cell by promoting contact with **phagocytosis** through reduction in ***surface charge***, ***opsonization*** or **complement receptor** uptake after activation of the complement system by the antigen-antibody complexes.

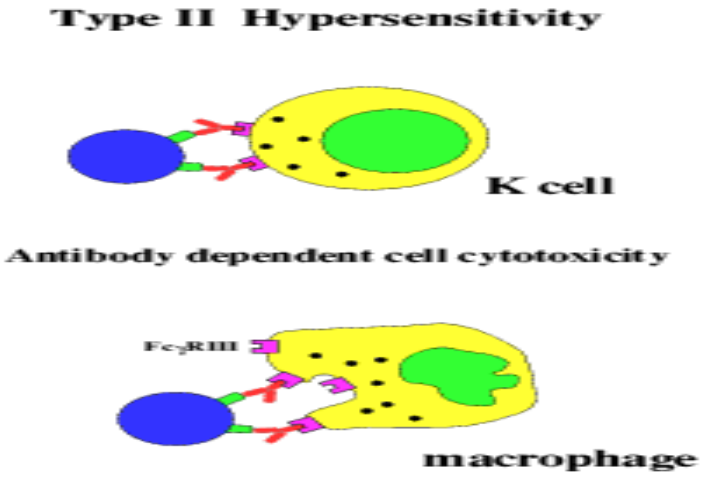
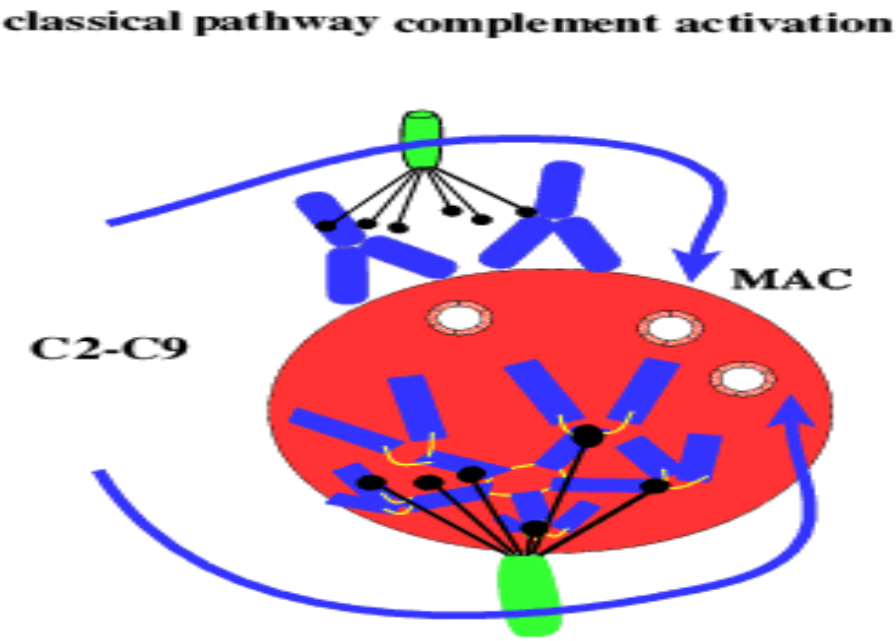


Diagram 1.4: Type II Hypersensitivity Reaction

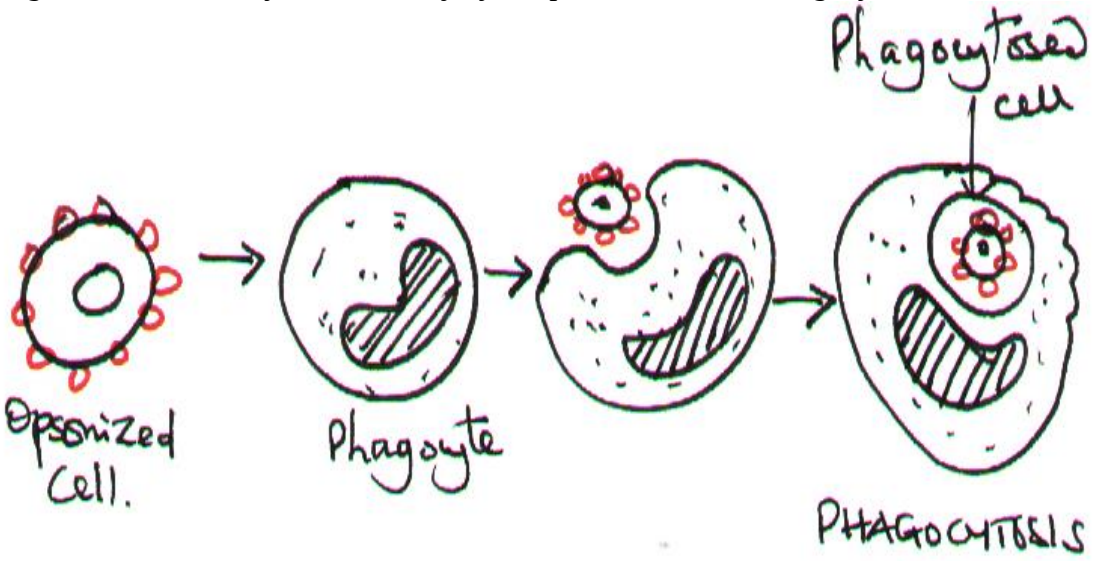


Mechanisms of Reactions

1) **Opsonization and Complement mediated phagocytosis**

The targeted cells are coated (opsonized) with molecules that make them attractive to phagocytes. When antibodies (IgM and IgG) are deposited on the surface of the cells, they activate the complement system generating C3b and C4b by-products. The cells are then recognized by the phagocytes. Cell death is mediated by **activation of the complement** and the action of the **membrane attack complex** (MAC) or by distinct **cytolytic mechanisms** that requires specific target cell-bound antibody. The ADCC is performed by both phagocytic and non-phagocytic myeloid cells (neutrophils, oesinophils and monocytes) and by large granular lymphocytes (killer cells).

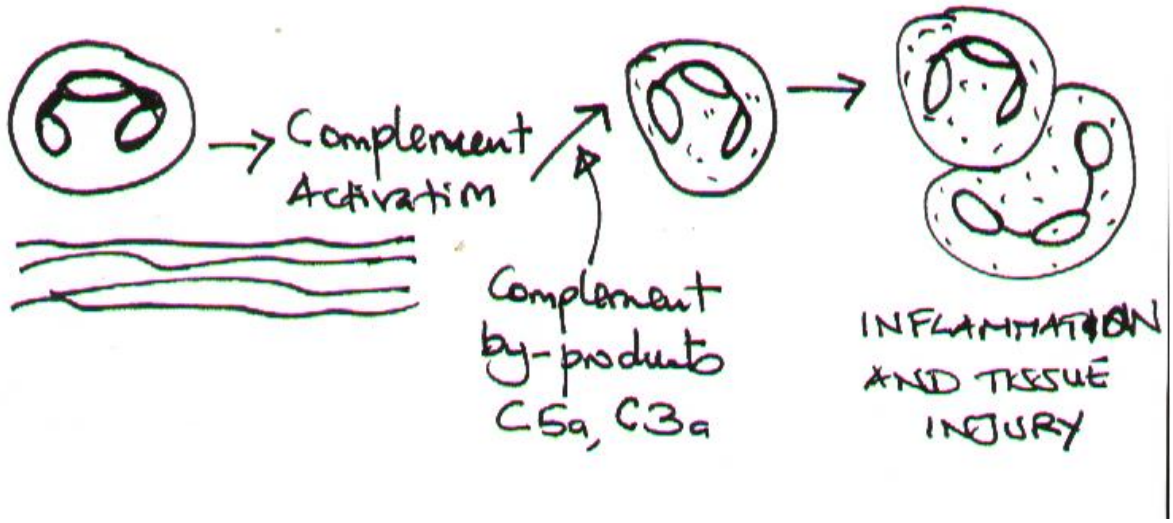
Diagram 1:5: Antibody Mediated Injury – Opsonization and Phagocytosis



2) **Complement mediated inflammation**

When antibodies are deposited in extracellular tissues such as the basement membranes andmatrix, the resultant injury is because of inflammation. The deposited activate the complement generating C5a, C4a and C3a which recruit neutrophils and monocytes. Activated leucocytes release injurious substances such as enzymes and reactive oxygen intermediates which damage the tissues. Examples – glomerulonephritis, vascular rejection of grafts

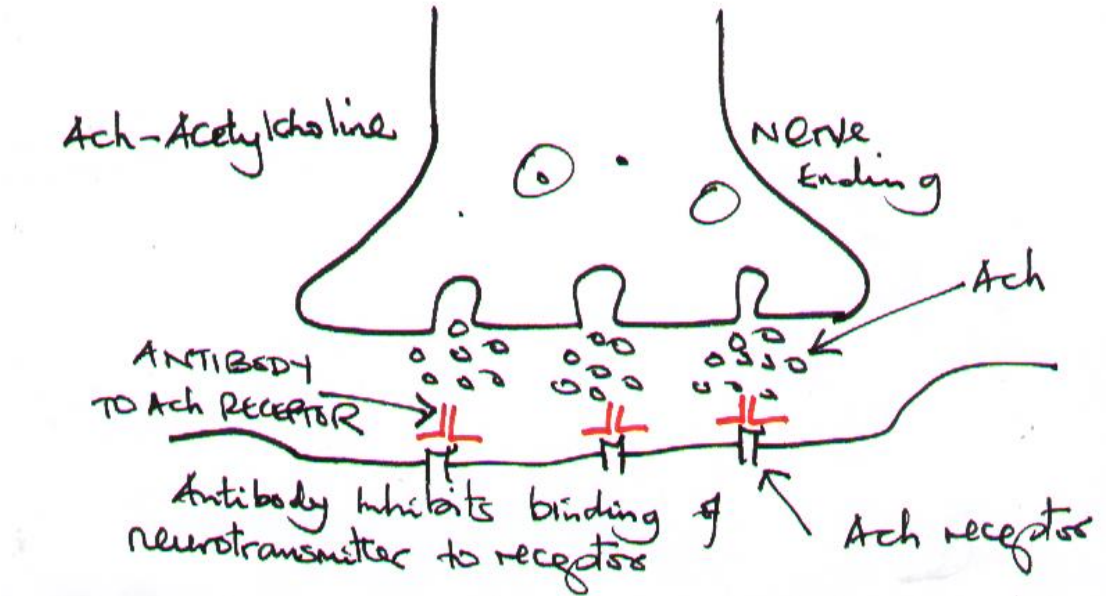
Diagram1:6: Antibody Mediated Injury- Complement Activation



3) **Antibody mediated cellular dysfunction**

The antibodies are directed against cell-surface receptors and impair or dysregulate function without causing cell injury or inflammation. Examples – *myasthenia gravis* and *pemphigus vulgaris* (antibodies against desmosomes disrupt intercellular junctions in epidermis laeding to formation of skin vesicles. Antibody meditated stimulation is seen in *Grave's disease.*

Diagram 1:7: Antibody Mediated Cellular Function



Types

Type II hypersensitivity falls in three main classes: -
a) Iso-immunity (Iso antibodies)
b) Autoimmunity (auto antibodies)
c) Drug-induced cytotoxic antibodies

Cytotoxic Autoantibodies

There is production of antibodies to the patient's own cells with the patient losing self-tolerance it is mediated mainly by IgG and IgM antibodies. IgG antibodies bind to red blood cells to macrophages and activate the complement system encouraging cell lysis while IgM causes lysis via complement activation. This reaction can also be directed against the platelets and other body surfaces or tissues such as the alveolar tissues pancreas, thyroid cells and the glomerular basement membrane or receptor sites.

Clinical examples

1. Systemic Lupus erythromatosus (S.L.E) – generalized autoimmune reaction with effect o may organs such as the heart and lungs
2. Diabetes mellitus Type II – receptor sites for insulin
3. Autoimmune haemolytic anaemia – reduced red cells
4. Leucopenia – reduced number of white blood cells
5. Good Pasture's syndrome – destruction of the alveolar and glomerular basement membrane mediated by IgG
6. Idiopathic thrombocytopenia purpura (I.T.P) – platelets
7. Hashimoto's thyroiditis – thyroid cells
8. Myasthenia gravis – acetylcholine receptor at the end plate of muscles
9. Grave's disease – thyroid-stimulating antibodies leading to autoimmune hyperthyroidism.
10. Bullous pemphigoid – involvement of the skin epidermal basement membrane producing a blistering skin disease

Cytotoxic isoantibodies

Cytotoxic isoantibodies are produced by antigenic stimulation by antigens from the same species.

Clinical examples

1. Blood transfusion reactions
2. Haemolytic disease of the new born (due to Rh incompatibility)
3. ABO/Rhesus incompatibility
4. Autoimmune haemolytic anaemia (warm antibody and cold antibody types, drug induced)
5. Organ transplants rejection

Transfusion reactions

The red cell membrane has antigens that determine eth ABO blood groups implying that the serum contains antibodies. Antibodies in the serum are natural IgM antibodies. Antibodies to A or B occur when the antigen is absent from the red cell surface; thus a person with blood group A will possess anti-B. If an individual is blood group A, he will tolerate antigens closely similar to A and

will only form cross-reacting antibodies capable of agglutinating B red cells. Transfusion of mismatched red cells will be coated by the isohaemagglutins and cause severe reactions and lysis (destruction) of red cells)

Rhesus incompatibility

The rhesus (Rh) blood group has antigen D and the rhesus antibodies are mainly IgG. These IgG antibodies are capable of crossing the placental barrier. An RhD negative mother (dd genotype) can readily be sensitised by reed cells from a baby carrying RhD antigens (DD or Dd genotype). This occurs at birth of the first child when a placental bleed releases a large number of the baby's red cells into the mother's circulation.

Reaction of the D-antigen on foetal red cells with mothers antibodies leads to destruction of red cells leading to haemolytic disease of the new born.

These anti-D antibodies fail to agglutinate RHD+ red cells in vitro (incomplete antibodies) because of low density of antigenic sites restricting formation of antibody bridges between the negatively charged red cells to overcome electrostatic repulsive forces.

If the mother has natural isohaemogglutinins, which can react with any foetal red cells reaching her circulation, sensitisation to D antigens is less likely due to deviation of red cells away from antigen-sensitive cells. For example a group O RH –ve mother with an A Rh +ve baby would destroy ant foetal red cells with her anti-A before destroying the anti-D (reason for prophylaxis for Rh-ve mothers with avid IgG anti-D).

Coomb's test

Erythrocytes coated with anti-D can be made to agglutinate by addition of albumin or an anti-immunoglobin serum (Coomb's reagent).Direst Coomb's test – direct antiglobulin test (DAGT) – tests presence of antibodies bound to red cells in vivo.Indirect Coomb's test - indirect antiglobulin test (IAGT) – tests presence of antibodies in the patient's serum by adding red cells.

Organs transplant

- Kidneys
- Corneal
- Skin grafts

Drug-induced antibodies

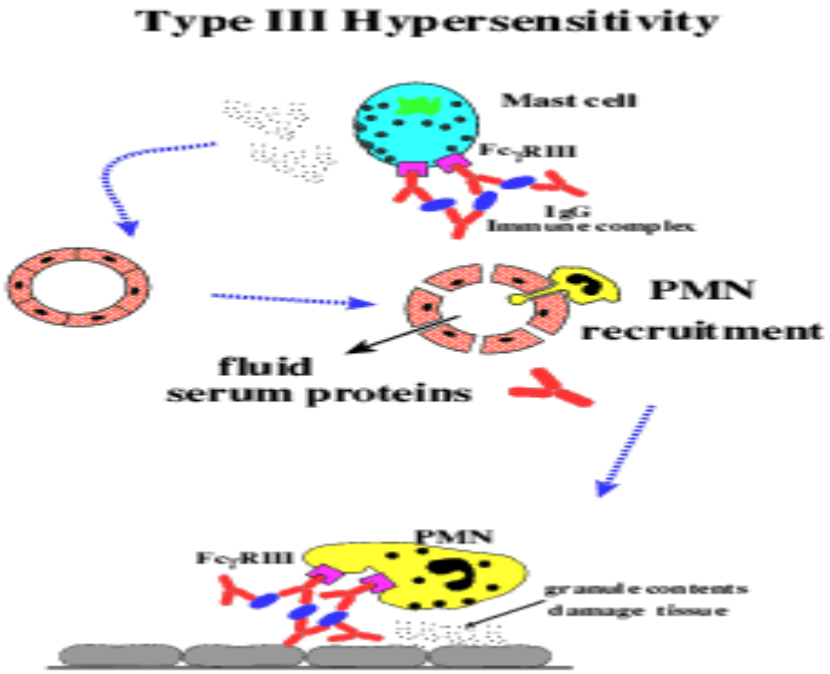
Some drugs and their metabolites bind to the surface of red blood cells, white blood cells and platelets and cat as hapten. This triggers development of antibodies resulting in formation of antigen-antibody complexes with ensuing cell injury and destruction. This can result in production of IgE anaphylactic reactions. Clinical scenarios can be evident in drug induced haemolytic anaemia (chlorpromazine and phacetin), agranulocytosis (quinidine) and thrombocytopenia purpura.

3. IMMUNE-COMPLEX MEDIATED (TYPE) III HYPERSENSITIVITY

*Antigen-antibody complexes produce tissue damage mainly by eliciting inflammation at the sites of deposition.*This type of response results form formation of immune-complexes between

antibodies and **extracellular antigens**. IgM antibodies mediate type III hypersensitivity reaction. The antigen constituents can be derived form microbial products; exogenous inert antigens (inhaled foreign proteins, dust, moulds or autoantibodies against ones intracellular antigens.

Diagram 1.8: Type III Hypersensitivity Reaction



The antigens may be from a localized source e.g. in an organ or tissues as seen in Arthur's reaction where there is local inflammation of the skin after inoculation with protein antigens or may be in circulation resulting in multisystem involvement e.g. serum sickness. Low concentrations of circulating immune complexes are normally encountered in the body during acute viral infection or after a protein meal but these complexes are rapidly inactivated and eliminated before they can localize and deposited on blood vessels to trigger an inflammatory reaction and tissue destruction.

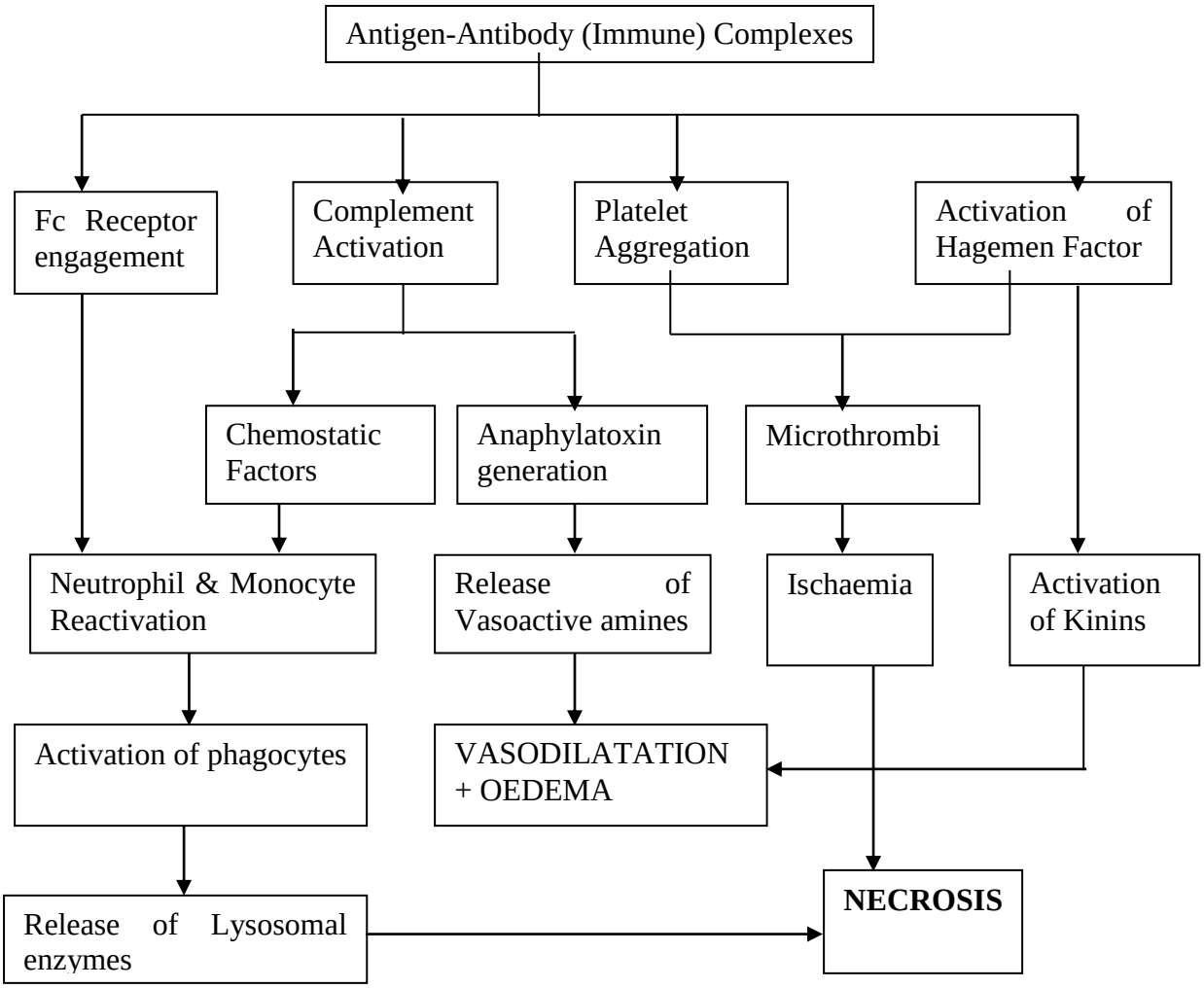
A disease process ensues when the body fails to eliminate the immune complexes or it is overwhelmed by production of immune complexes hence defeating the normal clearance mechanisms of the mononuclear phagocyte system. Local inflammation results form deposition of immune complexes and activation of the complement system resulting in release of mediators of inflammation. Immune complexes may be formed locally at sites distant from the mononuclear phagocyte system resulting in intense immune complex damage e.g. IgG rheumatoid complex in joints of patients with rheumatoid arthritis.

Factors that determine the localization of the immune complexes are persistent availability of the antigen e.g. infection, autoantigen; complement deficiency (the complement system is meant to destroy immune complexes) and tissue binding of immune complex components e.g. streptococcus antigen affinity for the glomerular basement membrane.
Factors that favour removal of immune complexes are: -

- Mononuclear phagocyte clearance of complexes
- Reduction in size and solubility of the complexes by the complement
- Erythrocyte clearance of circulating complexes in the liver and spleen.

The immune complexes show affinity for particular tissues in which they are then deposited. The deposition of the immune complexes is triggered an increase in vascular permeability, high blood pressure and turbulence blood flow while the affinity is directed by antigenic composition in the immune complexes, the charge on the antigens and antibodies, size of the complex and the class of immunoglobulins involved in the reactions.

Diagram 1:9: Illustration of Immune-complex-mediated hypersensitivity



Clinical manifestations

There are three main classical reactions: -

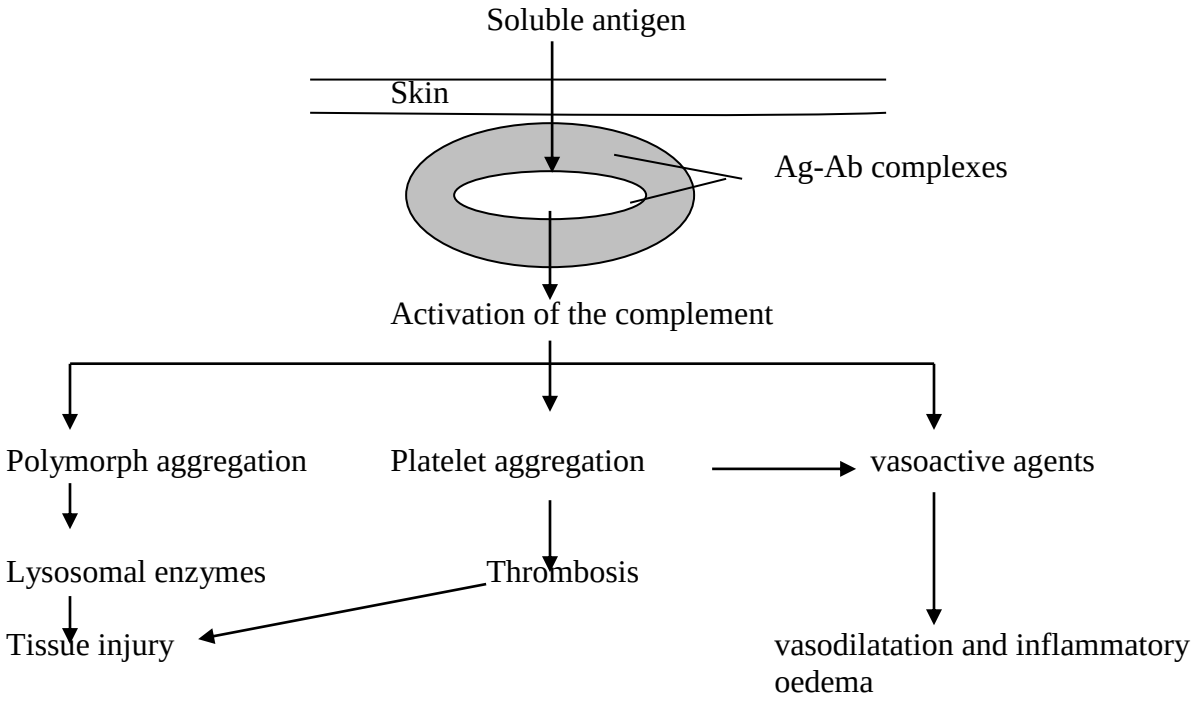
1. Arthur's reaction
2. Serum sickness
3. Autoimmune disorders

Arthur's reaction (Local Immune Complex Hypersensitivity)

Arthur's reaction is a local reaction seen 24 hours after inoculation with antigenic (animal protein) substance into the skin. The complexes are deposited in local blood vessels with subsequent activation of the complement system and inflammation. Polymorphs phagocytose the immune

complexes releasing lysosomal enzymes, which cause further cell damage. A clinical example is the intrapulmonary Arthur's reaction in the Farmer's lung (extrinsic allergic alveolitis).

Diagram1:10: Mechanism of Arthur's reaction



Serum sickness (Systemic Immune Complex Disease)

Introduction

This is a situation arising from the reaction of Ag-Ab in plasma forming immune complexes which in turn activate the complement system and the neutrophils and monocytes in the blood. The immune complexes are deposited on the blood vessels especially the capillaries triggering an acute inflammatory reaction with polymorph infiltration with or without thrombosis and necrosis.

Pathogenesis

This occurs in three phases namely: -

a) Formation of antigen-antibody complexes in the circulation
b) Deposition of immune complexes in various tissues
c) An inflammatory recitation at the sites of immune complex deposition. This is through activation of the complement cascade and activation of neutrophils and macrophages through Fc receptors.

Features

Signs and symptoms of serum sickness commence 8 days after exposure and are characterized by: -

- Fever
- Urticarial skin reactions
- Arthralgia

- Joint swelling
- Lymphadenopathy
- Proteinuria results from underlying immune complexes in the glomerular basement membrane.

Clinical examples include: -

1) S.L.E
2) Post-streptococcal acute glomerulonephritis (AGN)
3) Polyarteritis nodosa (PN)
4) Rheumatoid arthritis
5) Quartan malaria
6) Hepatitis
7) Drug reactions

AUTOIMMUNE DISEASES

There are several diseases that are associated with immune-complex formation in hypersensitivity reactions (some have been explained in the previous texts and will be discussed in the next topics).

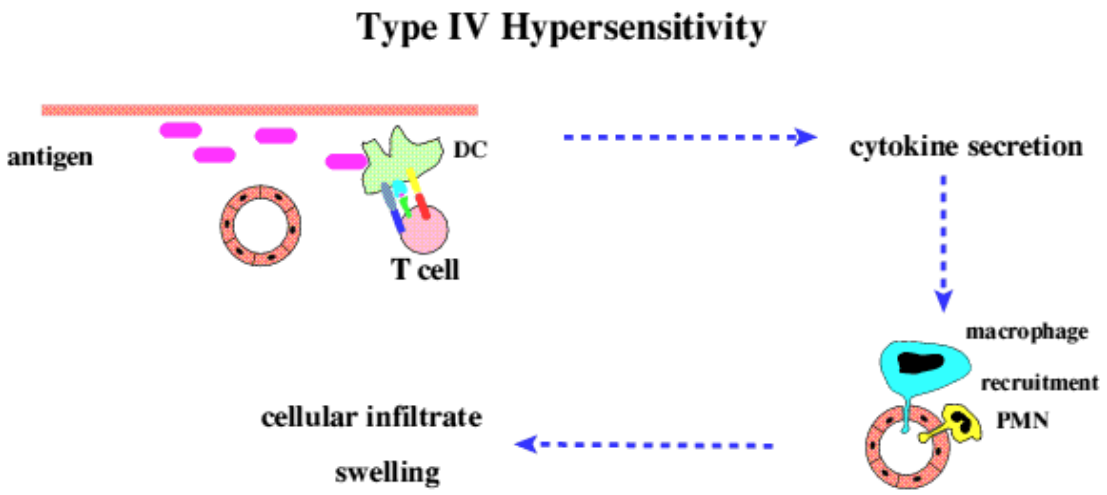
4. CELL-MEDIATED (TYPE IV)/ DELAYED HYPERSENSITIVITY

Delayed hypersensitivity reactions are inflammatory reactions initiated by mononuclear leukocytes. The term delayed is used to differentiate a secondary cellular response, which appears 48-72 hours after antigen exposure, from an immediate hypersensitivity response, which generally appears within 12 minutes of an antigen challenge. These reactions are mediated by T cells and monocytes/macrophages rather than by antibodies. They are also termed type IV hypersensitivity reactions.

Delayed hypersensitivity is a major mechanism of defense against various intracellular pathogens, including mycobacteria, fungi, and certain parasites, and it occurs in transplant rejection and tumor immunity. The central role of $CD4^+$ T cells in delayed hypersensitivity manifests in patients with AIDS. Because of the loss of $CD4^+$ cells, the host response against intracellular pathogens such as *Mycobacterium tuberculosis* is markedly impaired. The bacteria are engulfed by macrophages but are not killed.

If T-cell function is abnormal, the patient presents with opportunistic infections, including infection with mycobacteria, fungi, parasites, and, often, mucocutaneous candidiasis. Undesirable consequences of delayed-type hypersensitivity (DTH) reactions include illness such as contact dermatitis and allograft rejection. Examples of DTH reactions are contact dermatitis (eg, poison ivy rash), tuberculin skin test reactions, granulomatous inflammation (eg, sarcoidosis, Crohn disease), allograft rejection, graft versus host disease, and autoimmune hypersensitivity reactions. Of note, the *Rhus* genus of plants, which includes poison ivy, poison oak, and poison sumac, all cause identical rashes.

Diagram 1.11: Type IV Hypersensitivity



Pathophysiology

The cellular events that result in delayed hypersensitivity reactions primarily involve T cells and macrophages. First, local immune and inflammatory responses at the site of foreign antigen up-regulate endothelial cell adhesion molecule expression, promoting the accumulation of leukocytes at the tissue site. The antigen is engulfed by macrophages and monocytes and is presented to a T cell that has a specific receptor for that antigen. Macrophages secrete interleukin (IL)–1, IL-2, IL-6, and other lymphokines. Cytotoxic T cells can also be activated. The recruited macrophages can form giant cells. The characteristic histologic appearance of the macrophage–T-cell infiltrate is a granuloma. This type of infiltrate in the tissue is called granulomatous inflammation.
Several variants of DTH exist, and their precise pathophysiologic mechanisms are slightly different. For example, in contact hypersensitivity reactions, the epidermis is involved; in pulmonary tuberculosis (TB), lung tissue is involved.

Mechanism of Delayed hypersensitivity reaction

Delayed hypersensitivity reaction cannot be transferred from one individual who is sensitised to another who is not sensitised, as T-cells are the cells powering the reaction. This makes this reaction different form other hypersensitivity reactions that depend on antibodies found in the serum. There is exaggerated interaction between antigens and the normal cell-mediated immune mechanisms.

Mechanism

- Introduction of the antigen
- Processing and presentation of the challenge antigen to the CD4+ cells
- Activation and clonal expansion of specific T-cells and subsequent release of cytokines and tumour necrosis factor (TNF).
- Release of activated monocytes and macrophages
- Tissue damage and granuloma formation.

Primed or memory cells T-cells recognise the antigen and reaction with activated macrophages followed by transformation and proliferation of helper cells (CD4+) which in turn stimulate cytotoxic cells (CD8+) and suppressor T-cells.
The primed cells lead to production of lymphokines, which are responsible for:

- Induction of an acute inflammatory reaction
- Stimulation of mononuclear phagocytic system
  - Chemostatic factors
  - Macrophage migration inhibition factors
  - Macrophage activating factors

- Activation of macrophages results in secretion of enzymes and other factors e.g. interleukin I which are responsible for: -
  - Fever (act on the thermoregulatory centre)
  - Increased production of acute phase proteins
  - Enhancing proliferation of T-cells
  - Promoting differentiation of antigenic stimulated B-cells

Pathophysiology

The cellular events that result in delayed hypersensitivity reactions primarily involve T cells and macrophages. First, local immune and inflammatory responses at the site of foreign antigen up-regulate endothelial cell adhesion molecule expression, promoting the accumulation of leukocytes at the tissue site. The antigen is engulfed by macrophages and monocytes and is presented to a T cell that has a specific receptor for that antigen. Macrophages secrete interleukin (IL)–1, IL-2, IL-6, and other lymphokines. Cytotoxic T cells can also be activated. The recruited macrophages can form giant cells. The characteristic histologic appearance of the macrophage–T-cell infiltrate is a granuloma. This type of infiltrate in the tissue is called granulomatous inflammation.
Several variants of DTH exist, and their precise pathophysiologic mechanisms are slightly different. For example, in contact hypersensitivity reactions, the epidermis is involved; in pulmonary tuberculosis (TB), lung tissue is involved.

Clinical examples

a) Tuberculin test (Mantoux test)
   - Intradermal injection of purified protein derivative (PPD) of tuberculin test in a sensitised individual provokes a formation of a classical weal in 24-72 hours. Sensitisation can be as a result of natural infection or immunization with BCG.

b) Infections
   - Sensitivity to bacterial products resulting in lesions e.g. cavitation, ceasation and general toxaemia in tuberculosis
   - Skin rashes in measles and herpes simplex
   - Dermatomycosis

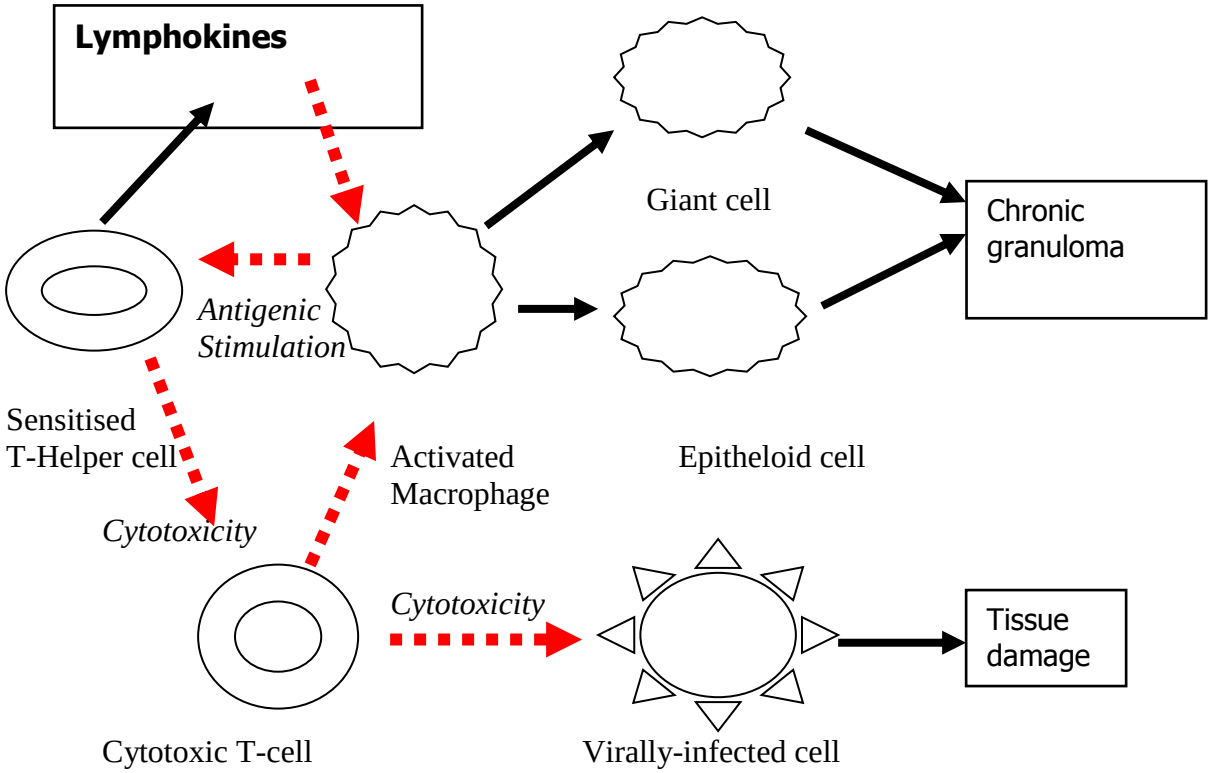
c) Granuloma hypersensitivity
   - Granulomatous skin lesions in leprosy and granulomas in tuberculosis
   - Schistosomiasis

d) Contact hypersensitivity
   - Nickel salts
   - Plant derivatives and poisons

- Environmental chemicals
- Eczematous rash

e) Homograft rejection

Diagram 1:11: Illustration of Cellular basis of type IV hypersensitivity



Pathological Features

- Microvascular congestion
- Lymphocyte accumulation
- Inflammatory oedema
- Cellular infiltration with macrophages and neutrophils

Table 1.2: DHR

Type	**Reaction time**	**Clinical appearance**	**Histology**	**Antigen and site**
Contact	48-72 hr	Eczema	Lymphocytes, followed by macrophages; edema of epidermis	Epidermal(organic chemicals, poison ivy, heavy metals, *etc.*)
Tuberculin	48-72 hr	Local induration	Lymphocytes, monocytes, macrophages	Intradermal (tuberculin, lepromin, *etc.*)
Granuloma	21-28 days	Hardening	Macrophages, epitheloid and giant cells, fibrosis	Persistent antigen or foreign body presence (tuberculosis, leprosy, *etc.*)

5. STIMULATORY (TYPE V) HYPERSENSITIVITY

Type V hypersensitivity reaction occurs where the antibodies react with the key surface component e.g. a hormone receptor "switching on" the cell with resultant hyperactivity of the cell function of the respective cells e.g. excessive production of thyroid hormone in thyrotoxicosis.

"Innate" Hypersensitivity reaction

Results from excessive activation of the alternate complement pathway causing tissue damage e.g. in disseminated intravascular coagubility (D.I.C). The complexes generated cause platelet destruction by active lysis with release of clotting factors.

Table 1.3: Similarities and Differences between Hypersensitivity Reactions

Characteristics	Type-I (anaphylactic)	Type-II (cytotoxic)	Type-III (immune complex)	Type-IV (delayed type)
Antibody	IgE	IgG, IgM	IgG, IgM	None
Antigen	Exogenous	Cell surface	Soluble	Tissues & organs
Response time	15-30 minutes	Minutes-hours	3-8 hours	48-72 hours
Appearance	Weal & flare	Lysis and necrosis	Erythema and edema, necrosis	Erythema and induration
Histology	Basophils and eosinophil	Antibody and complement	Complement and neutrophils	Monocytes and lymphocytes
Transferred with	Antibody	Antibody	Antibody	T-cells
Examples	Allergic asthma, hay fever	Erythroblastosisfetalis, Goodpasture's nephritis	SLE, farmer's lung disease	Tuberculin test, poison ivy, granuloma

Lesson 2: Allergic and Hypersensitivity Diseases

Leaning Outcomes

At the end of the lesson the learner should be able to: -

1. Outline diseases associated with immune disorders
2. Explain the pathogenesis of diseases associated with immune disorders
3. Describe the process of autoregulation
4. Classify autoimmune disorders
5. Describe the factors that play role in pathogenesis of autoimmune diseases
6. Describe the common autoimmune diseases

1.0. INTRODUCTION

Disorders of various tissues and body systems are associated with allergic and hypersensitivity reactions.

Cardiorespiratory system

1. Rheumatic fever
2. Goodpasture's syndrome
3. Allergic asthma
4. Allergic rhinitis
5. Immune complex diseases – lung injury due to deposition of complexes and ensuing chronic inflammation
6. Fibrosing alveolitis
7. Extrinsic allergic alveolitis
8. Sarcoidosis
9. Tuberculosis

Reproductive and Urinary system

1. Haemolytic disease of the new born (HDNW)
   a. ABO incompatibility
   b. Rh incompatibility
2. Male infertility
3. Glomerulonephritis
   a. Post-streptococcal
   b. IgA nephropathy
   c. Malaria nephropathy
   d. Schistosomiasis nephropathy
   e. Mercury nephropathy
4. Granuloma formation

Disorders of Blood

1. Haemolytic anaemia

Disorders of G.I.T

1. Periodontal disease
2. Recurrent oral ulceration
3. Coeliac disease
4. Crohn's disease

Skin

1. Contact dermatitis
2. Atopic dermatitis
3. Bullous impetigo
4. Discoid lupus erythematosus
5. Psoriasis
6. Pemphigus vulgaris

Ocular

1. Allergic conjunctivitis

2.0. DISEASES ASSOCIATED WITH IMMUNITY

CARDIO RESPIRATORY SYSTEM

1. Rheumatic fever
2. Goodpasture's syndrome
3. Allergic asthma
4. Allergic rhinitis
5. Immune complex diseases – lung injury due to deposition of complexes and ensuing chronic inflammation
6. Fibrosing alveolitis
7. Extrinsic allergic alveolitis
8. Sarcoidosis
9. Tuberculosis

Rheumatic Fever

Infection by **group A streptococcal bacteria** results in production of antibodies that lead to formation of Aschoff nodule lesions in the heart muscles. Depositions of the immune complexes cause destruction of heart valves leading to development of rheumatic valvular heart diseases e.g. mitral stenosis and regurgitation and aortic stenosis and regurgitation.

The cytotoxic antibodies that attack Ag-Ab complexes deposited in the tissues usually mediate cardiac tissue damage. Genetic factors and activated cytotoxic T lymphocytes play a significant role.

Goodpasture's syndrome

The body produces autoantibodies against Goodpasture's autoantigens of the alveolar and glomerular basement membrane. This causes progressive glomerulonephritis and pulmonary

haemorrhage. The circulating Ag-Ab complexes are anti-glomerular basement membrane. The destruction of the tissues is carried out by activation of the complement system and antibody dependent cellular mediated cytotoxicity (ADCC) mechanisms resulting in renal glomeruli and pulmonary alveoli damage.

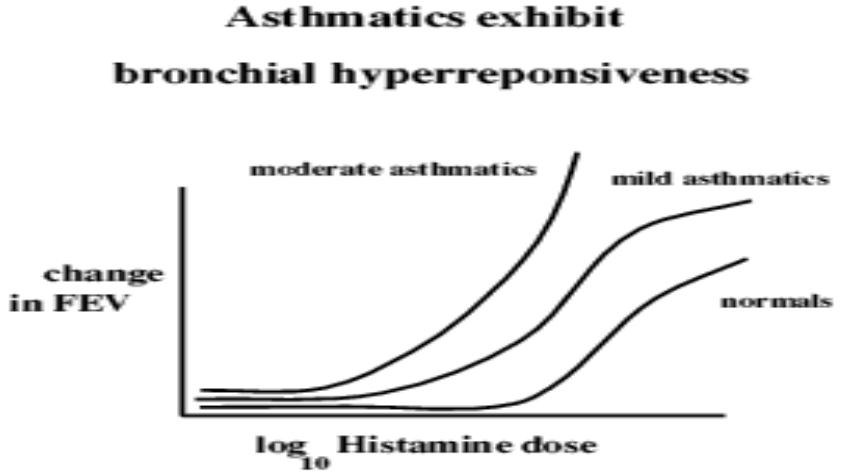
Allergic Asthma

Asthma is essentially a disease in which the primary physiological manifestation is reversible airflow limitation. Although clinical asthma is subdivided into extrinsic (ie where there is a recognised external trigger) and intrinsic (where the trigger is either non-antigenic or not recognised) forms, it is believed that in all cases the initial development of the condition involves type I hypersensitivity to an inhaled antigen. Nevertheless most individuals with such hypersensitivity do not go on to develop the chronic inflammatory condition which we term asthma, whose definition includes long-term changes such as connective tissue deposition and hypertrophy of the bronchial smooth muscles in addition to inflammatory and immunological criteria.

In cases of extrinsic asthma, the patient is believed to be chronically or periodically exposed to the antigenic stimulus at very low level, which may not always trigger an clear response. This exposure leads to a hyperreactivity of the bronchioles to inflammatory mediators. If you measure the reduction in airway function after experimental intrabronchial challenge with an inflammatory mediator (eg histamine), asthmatics show a characteristically high sensitivity which is related to the severity of their disease.

In allergic asthma there is bronchial hyperresponsiveness to various allergens that pass through the bronchial epithelium and are taken up and processed by the APCs before being presented to CD4 T-cells. The T cells induce and regulate synthesis and production of IgE, which sensitise the mast cells. It is a type I hypersensitive reaction where mast cells are activated to release active mediators and cytokines. There is also recruitment of inflammatory cells.

The effects include – shortness of breath, wheezing, tightness of the chest, cough with a tenacious sputum and inflammation of the airway walls and activation of mast cells.



Allergic Rhinitis

This is an atopic hypersensivity disease expressed in the nasal mucosa and conjunctiva where there is profuse watery rhinorrhoea, paroxysmal sneezing, nasal obstruction and itchiness of the nose, eyes and palate.

Fibrosing Alveolitis (FA)

Fibrosing alveolitis is characterised by interstitial fibrosis due to chronic or focal diffuse non-purulent inflammation of the interstitium of the respiratory lung areas. Immune complexes formed in the lungs activate the complement system generating anaphylactic factors accompanied by recruitment and activation of inflammatory cells e.g. alveolar macrophages, T-lymphocytes, fibroblasts and polymorphonuclear leucocytes.

Extrinsic Allergic Alveolitis

Extrinsic allergies due to allergens such as fungi, bacteria, animal protein and chemicals induce damage to the alveoli and interstitial tissues. The immune complexes formed induce and initiate lung injury through inflammatory reactions accompanied with cellular infiltration by neutrophils, macrophages and lymphocytes.

Tuberculosis

In patients infected with *Mycobacterium tuberculosis* there are a range of cell-mediated responses linked to different clinical expressions. Recognition and lysis of bacilli laden cells results in protective immunity initially but later there is marked immunosuppression due to reduced CD4 cells, elevated CD8 suppressor T cells and increased replication of bacilli in macrophages. The Mycobacterium *tuberculosis* produces factors that are toxic to macrophages, which results in necrotic tissue or lesion.

REPRODUCTIVE AND URINARY SYSTEM

1. Haemolytic disease of the new born (HDNW)
   a. ABO incompatibility
   b. Rh incompatibility
2. Male infertility
3. Glomerulonephritis - post-streptococcal, IgA nephropathy, malaria nephropathy, schistosomiasis nephropathy and mercury nephropathy
4. Granuloma formation

Haemolytic Disease of the Newborn

This is due to ABO or Rh incompatibility that results from incompatible blood transfusion, abortions or incomplete pregnancy. ABO incompatibility results from IgM iso-antibodies and Rh due to IgG antibodies.

Male Infertility

Male infertility results from autosomal recessive mutations and immune mediated abnormalities. There are increased levels of circulating anti-sperm antibodies and autoantibodies.

Glomerulonephritis

Glomerulonephritis may result from a wide range of immune complex mediated hypersensitivity reactions causing renal, pulmonary, cardiac and dermatological conditions. Ag-Ab complexes formed stimulate the complement system resulting in non-inflammatory and inflammatory injury to the glomerular basement membrane.

The non-inflammatory injury is via the complement system and liberation of cytokines whereas the inflammatory injury is caused by the circulating inflammatory cells – the neutrophils, macrophages, platelets, lymphocytes and the resident glomerular cells messangial cells).

Granulomas in Schistosomiasis

Granuloma formation in schistosomiasis is as a result of fibrosis initiated by schistosome eggs trapped in portal, intestinal and mucosal tracts due to immunopathological processes. Persistent of the eggs lead to continuous priming of T cells.

DISORDERS OF BLOOD

1. Haemolytic anaemia
2. Pancytopenia

Disorders of blood include anaemia resulting from immune mediated destruction of red cells in haemolytic transfusion reactions and haemolytic anaemia due to incompatible blood groups, allergic reactions, infections (Hepatitis B, non-A, non-B, and C0 and post transfusion hepatitis and HIV infection. The antibodies may be directed to platelets, neutrophils and lymphocytes resulting in pancytopenia.

DISORDERS OF G.I.T

1. Periodontal disease
2. Recurrent oral ulceration
3. Coeliac disease
4. Crohn’s disease

SKIN

1. Contact dermatitis
2. Atopic dermatitis
3. Bullous impetigo
4. Discoid lupus erythematosus
5. Psoriasis

Contact Dermatitis

This is an acute or chronic skin reaction against various allergens characterized by cutaneous erythematic, oedema and scaling resulting from activation T cells by potential T cell allergens such as plant products, drugs (e.g. aspirin, antibiotics) and metals (e.g. nickel, chromium,).

Atopic Dermatitis

Atopic dermatitis is a chronic inflammatory skin disease associated with increased serum IgE levels and presents with intense pruritis and cutaneous reactivity. It is usually associated with allergic rhinitis and bronchial asthma. The allergens which include irritants (wool, soap and disinfectants), aeroallergens (house dust mites and pollen), food (pea nuts, eggs, milk, fish, soya beans and wheat), microbes (*S. aureus*) sex hormones, dermatological factors and stress factors and induce itching, scratching and eczematous lesions

Bullous

Bullous is associated with immune complex destruction of the stratum basement membranes of the horny layer of the skin. Bullous pemphigoid and pemphigus vulgaris (mucosal membranes with blisters) are blistering conditions commonly affecting elderly people. Antibodies generated against intercellular substances of the stratified squamous epithelium.

Discoid Lupus Erythematosus

Discoid Lupus erythematosus manifests as an inflammation of the skin with lesions due to deposition of Igs and complement at the dermal-epithelial junction of the skin.

Psoriasis

Psoriasis is a T-cell mediated disease of the skin triggered by infection with group A haemolytic streptococci. It is a disease of the epidermis characterized by formation of erythematous plagues with heavy white scale of the skin.

OCULAR

Allergic conjunctivitis is a classical types I hypersensivity reaction associated with secondary involvement of inflammatory cells especially oesinophils and local mast cell that may lead to corneal damage.

3.0. TRANSPLANT REJECTION

Transplant rejection involves immunologic reactions whose mechanism depends on recognition of the grated tissues as foreign and involves the HLA. It involves both T cell mediated reactions (**cellular rejection**) and antibody mediated reactions (**humoral rejection**).

Cellular Rejection

This involves two mechanisms namely destruction of graft cells by CD8+ and cytotoxic T lymphocytes (CTLs) and delayed hypersensitivity reactions triggered by activated CD4+ helper cells. The grafts are recognized as foreign via two pathways – **direct and indirect pathways.**

In the direct pathway, T cells recognize allogernic (donor0 MHC molecules at the surface of APCs in the graft whereas in the indirect, receptor T cells recognize antigens of the graft donor after they are presented by the recipients' on APCs.

In antibody mediated reactions antibodies are produced by the host against the graft.

TASK – Complete the table below

System	Disease	Mechanism	Clinical Features

Discuss the task in your clinical groups on 9th April 2010

Lesson 3: Autoimmune Diseases

Learning Outcomes

At the end of the lesson the learner should be able to: -

1. Outline autoimmune diseases
2. Describe the pathogenesis and pathophysiology of autoimmune disease
3. State the clinical features of common autoimmune diseases

1.0. INTRODUCTION

Autoregulation is a normal process in the functioning of the immune system as reflected in the recognition of cell surface MHC (HLA) molecules. **Immunological homeostasis** or **balance** is maintained through several mechanisms. The mechanisms operate in a continuum and include **tolerance induction**, **regulation of T cells** and **cytokine network interaction**. These operations are influenced by signals from the central and endocrine systems forming a complex interaction of the in the **process of immunoregulation**.

Self-tolerance is an antigen specific immunological unresponsiveness induced by previous exposure to a specific antigen. Failure in tolerance or immunoregulation mechanisms leads to disorders of autoimmunity and immunodeficiency

Autoimmunity is a state in which the body's immune system fails to distinguish between "self" and "non-self" due to **failure** or**breakdown of immunological tolerance**. This results in formation of autoantibodies against one's own tissues facilitating self-destruction. In a nutshell, **autoimmunity is the opposite of immune tolerance**.

Autoantibodies are antibodies which react with the individuals' own normal constituents (autoantigens). Immune tolerance is the ability of an individual to recognize self-tissue and antigens. This is a phenomenon that is present since foetal life.

Pathologic autoimmunity exists: -

1. When there is an autoimmune reaction
2. Reaction is of primary pathogenic significance and not secondary to tissue damage
3. When there is absence of well defined cause of disease

2.0. IMMUNOLOGICAL TOLERANCE

Immunologic tolerance is **a state in which the individual is incapable of developing an immune response to a specific antigen.** Self-tolerance is lack of responsiveness to an individual's own antigens. This is an important provision in our ability to live in harmony with our cells and tissues. The mechanisms of development of immune tolerance are ill understood however postulations do exist for example: -

1. Clonal elimination – there is elimination of cells capable of recognizing and responding to self-antigens.

2. Suppressor cells – these are cells that deter antigen responsive cell form proliferating and differentiating.
3. Blocking antigens where the responsive cells are blocked by circulating antibodies or antigen-antibody complexes.

Tolerance state may be achieved via **central** or **peripheral tolerance**. **Central tolerance** occurs due to death (deletion) of self-reactive T and B lymphocytes clones during maturation in the central lymphoid organs (thymus for T cells and bone marrow for B lymphocytes).

Peripheral tolerance is achieved through several mechanisms which silence the auto-reactive T cells in the peripheral tissues. These mechanisms include **anergy** (prolonged or irreversible functional inactivation of lymphocytes induced by encounter with antigens), **suppression by regulatory T cells**, **clonal deletion by activation-induced cell death** ($CD4^+$ T cells that recognise self-antigens may receive signals that promote their death by apoptosis) and **antigen sequestration** (antigens are hidden from the immune system because the tissues in which these antigens are located do not communicate with blood and lymph e.g. testes, eyes and brain)

3.0. PATHOGENESIS OF AUTOIMMUNITY

Development of autoimmunity is related to inheritance of susceptibility genes which influence maintenance of self-tolerance and environmental triggers e.g. infections which promote activation of self-reactive lymphocytes. Mechanisms that cause breakdown of the immune tolerance include **immunological factors**, **genetic factors**, **microbials** and **interaction** of these mechanisms.

Immunological factors

- Results from failure of immunological mechanisms to tolerate due to: -
- Polyclonal activation of B cells with the B cells being directly activated by stimuli such as infections or microorganisms with their products by passing the T cell tolerance.
- Generation of self-reacting B cell clones
- Reduction in T suppressor cells and an increase in T helper cells activity.
- Release of sequestrated antigens from tissues that have been damaged.

Genetic factors

- There is increased familial incidences
- Involves the MHC and HLA genes which influence development of self-tolerance

Microbial Agents (Infections)

- Viruses such as Epstein Barr virus
- Bacteria – Streptococci and Klebsiella
- Mycoplasma

Many autoimmune diseases are associated with infections as are flare-up syndromes precipitated by infections.

Mechanisms

- Infections up-regulate the expression of co-stimulants on the antigen presenting cells (APCs). Infections induce production of cytokines which recruit lymphocytes including potentially self-reactive lymphocytes to sites of self-antigens.
- The microbes – some express antigens that have similar amino acid sequence as self-antigens, induce abnormalities that promote autoimmune reactions and tissue injury that leads to release of cytokines

4.0. INITIATORS OF AUTOIMMUNE DISEASES

Induction of autoimmune diseases involves a number of factors in a genetically predisposed individual under the influence of environmental, immunological and hormonal factors. The critical event in pathogenesis of autoimmune diseases is the breaking of self-tolerance involving activation of self-reactive T-lymphocytes.

The factors playing a significant role in autoimmune diseases include: -

1. Genetic factors
2. Immune defects
3. Hormonal factors
4. Abnormal HLA expression
5. HLA linkage disequilibrium
6. Antigenic mimicry
7. Environmental
8. Polyclonal B cell activation

Genetic Constitution

The genetic composition of an individual determines the genes that encode histocompatibility molecules, immunoglobulins, complement components, protein transporters, T cell receptors, sex hormones, cytokines and metabolic enzymes.

Immune Defects

Immunodeficiency is associated with selective IgA deficiency, complement deficiency, defective immunoregulatory mechanisms, stem cell and thymic defects.

Hormonal factors

Imbalances in hormonal levels e.g. thymic hormones, corticosteroids and oestrogen may induce autoimmune diseases. There is a high incidence of autoantibodies and associated diseases in females during pregnancy, puberty or while on contraceptives and in puerperal periods. Female sex hormones may play a role in the aetiology and course of diseases e.g. rheumatoid arthritis. Pregnancy appears to ameliorate autoimmune disorders due to depressed cellular immunity and the foetal suppression of the maternal immune system via soluble factors alpha-feto protein and foetal suppressor cells in the maternal circulation account for the remissions of autoimmune diseases. . High levels of cortisol and other steroids have an ameliorating effect of autoimmune diseases.

Abnormal HLA Expression

Aberrant or abnormal expression of class II MHC molecules by epithelial and B cell systems results in autoimmune disorders.

Antigenic Mimicry

There is production of antibodies that cross react with the tissues of the body causing extensive injury to the tissues involved e.g. kidney tissue and *E. coli*, brain tissue and *N. meningitides*, the cardiac tissue and streptococcal infection, measles virus and myelin sheath in multiple sclerosis, EBV and synovial membrane in rheumatoid arthritis.

Polyclonal B cell Activation

This forms the central core of the pathogenesis of autoimmune diseases where exogenous and endogenous antigens trigger B cells leading to generation of autoantibodies. Autoreactive lymphocytes are activated by mitogenic factors e.g. polysaccharides, purified protein derivative (PPD) and *staphylococcus aureuas*, cytokines, antibiotics and infectious agents.

Environmental Factors/Chemicals

These factors include UV radiation, infectious agents e.g. retro viruses and chemicals/drugs. These factors alter the autoantigens resulting in formation of autoantibodies forming complexes and largely influencing T cell functions. Autoimmunediseases are broadly classified into two groups: - **organ –specific (localized)** and **non-organ specific (systemic) diseases.**

5.0. ORGAN-SPECIFIC (LOCALIZED) DISEASES

Organ specific (localized) diseases targets specific organs or tissue components causing chronic inflammatory destruction of the tissues such as in the **endocrine glands** (thyroid, pancreatic islets of Langerhans and adrenal cortex), **alimentary tract** and **blood cells**.

Clinical examples

1. Endocrine glands
    a. Hashimoto's (autoimmune) thyroiditis
    b. Grave's disease
    c. Insulin-dependent diabetes mellitus (Type I DM)
    d. Idiopathic Addison's disease
2. Alimentary tract
    a. Autoimmune atrophic gastritis in pernicious anaemia
    b. Ulcerative colitis
    c. Chron's disease
3. Blood cells
    a. Autoimmune haemolytic anaemia
    b. Autoimmune thrombocytopenia
4. Others
    a. Myasthenia gravis
    b. Autoimmune orchitis

c. Good Pastures syndrome (GPS)
d. Primary biliary cirrhosis
e. Chronic active hepatitis
f. Membranous glomerulonephritis
g. Autoimmune skin diseases

Hashimoto's thyroiditis

This is autoimmune thyroiditis that involves all forms of goitrous forms of thyroiditis due to production of anti-thyroglogulin and anti-microsomal antibodies. Destruction occurs due to ADCC and other cellular mechanisms that initiate lymphocytic infiltration and destruction of thyroid cells.

Grave's Disease

Grave's disease (thyrotoxicosis) is characterized by diffuse enlargement of the thyroid gland associated with elevated levels of thyroid hormones (hyperthyroidism) leading to tachycardia, palpitations, anxiety, excessive sweating and acute weight loss. The main problem in Grave's disease is production of antibodies against thyroid stimulating hormone receptor (TSHR), thyroid peroxidase and thyroglobulin. TSHR autoantiobodies are regulated by $CD8^{+}$T cell/$CD4^{+}$T cell ratios and thyroid tissue damage is mediated by activated complement membrane attack.

Type I Diabetes Mellitus

Insulin-dependent diabetes mellitus (IDDM) is a T cell mediated autoimmune disease where the antibodies generated attack the islet cytoplasm (islet cytoplasm antigens) and islet cell surface (islet cell surface antigens), which are components of the insulin secreting β-cells of the islets of the pancreas. The persistent of the antibodies results in development of clinical diabetes mellitus.

The destruction of the β-cells is activation of T cells, abnormal expression of class II MHC products by β-cells and the effects of cytokines and inflammatory cells.

6.0. NON-ORGANS SPECIFIC(SYSTEMIC) DISEASES

A number of autoantibodies are formed targeting many tissues causing systemic lesions for example systemic collagen diseases e.g. *systemiclupuserythromatosus* (S.L.E).

Clinical examples

1. Systemic lupus erythromatosus (S.L.E)
2. Rheumatoid arthritis (RA)
3. Polyarteritis nodosa (PN)
4. Reiter's syndrome

Systemic lupus erythromatosus (S.L.E)

S.L.E is a systemic autoimmune disease affecting multiple organs. The term "*lupus*" is Latin word for wolf as the disease was thought to affect the skin only eating away the skin like the wolf. It can be classified into systemic of disseminated lupus erythromatosus (S.L.E) that is characterized by acute and chronic inflammatory lesions scattered in the body or the discoid form (D.L.E) where

there is chronic and localized skin lesions affecting the nasal bridge and adjacent cheeks with no systemic manifestations.

Aetiology

- The aetiology is unknown
- There is production of autoantibodies against nuclear and cytoplasmic components of the cells (antinuclear antibodies – ANAS).
- This in triggered by immunological and genetic factors, drugs (e.g. penicillamine D), infections (e.g. EBV) and hormones e.g. oestrogen.
- The immune reaction occurs intravascularly.

Pathogenesis

1. Type III hypersensitivity reaction where antigen-antibody complexes are formed in renal glomeruli and walls of small blood vessels.
2. Type II hypersensitivity with formation of autoantibodies against red blood cells, leucocytes and platelets.

Task 1.

1. What are the likely features of S.L.E?
2. Explain how they occur.

Rheumatoid arthritis (RA)

Rheumatoid arthritis is a common and disabling disease of the connective tissues, which is predominantly extravascular. The inflammatory lesions are localized within the synovial lining of affected joints and result in erosion and destruction of the joints. Rheumatoid arthritis is associated with IgA, IgG, IgE and IgM autoantibodies with the IgG being in the joints and the IgM in serum. Type III hypersensitivity reaction is responsible for the joint inflammation in cooperation while cell mediated immune cells (T cells) are blamed for the extravascular complications.

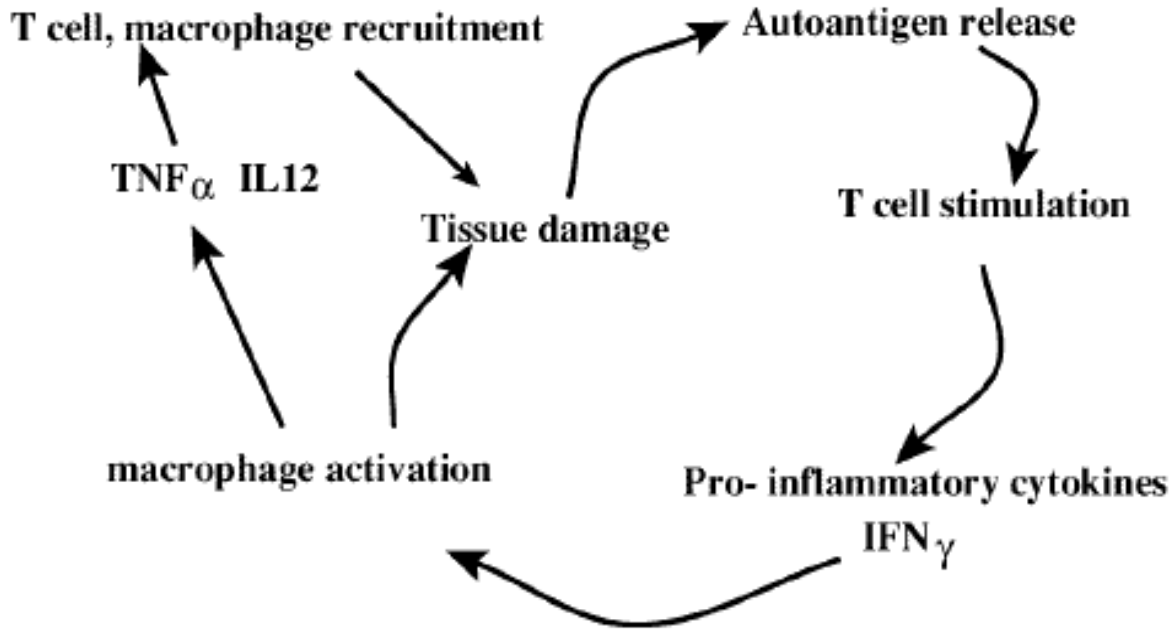
The main factors that contribute to the destruction include: -

- Activation of T cells
- Activation of the complement system
- Generation of the membrane attack complex
- Formation of breakdown chemotactic factors
- Inflammation and recruitment and activation of inflammatory cells

The implications of this are that the continuous stimulation of T cells is required to maintain the inflammatory process and that TNFalpha plays a key role in that process. The currently accepted view is that whatever initiates the disease, once joint damage is established it is a self-perpetuating process in which auto-antigens released as a result of the damage stimulate T cells which recruit and activate macrophages which lead in turn to further damage, the maintenance of inflammation - via vascular endothelial activation - and the perpetuation of the proliferation and cytokine

secretion of local T_H1 cells. Presumptively the key cytokines are TNFalpha and IL-12 released by macrophages and IFNgamma from T cells.

Diagram 3.1: Pathogenesis of Rheumatoid Arthritis



Scleroderma

Scleroderma is a skin disease where the skin is thickened due to oedema and lymphocytic infiltration, which later results in fibrosis with the skin becoming hard and bound to the underlying structures.

Vasculitis

Vasculitis involves destruction of blood vessels due to deposition of immune complexes. It is a cutaneous and systemic disorder associated with inflammation and necrosis of blood vessels. The causes include bacteria, viruses, chemicals, autoimmune disease and malignancy.

Examples:

- Polyarteritis nodosa (affects medium seized vessels)
- Takayasu's disease (affects large vessels)
- Buerger's disease (affects medium and small vessels)

TASK – Complete the table below

System	Disease	Mechanism	Clinical Features

Discuss the task in your clinical groups on 16th April 2010

Lesson 4: Immunodeficiency Syndromes

Learning Outcomes

At the end of the lesson the learner should be able to: -

1. Define immunodeficiency
2. Describe the causes of immunodeficiency
3. Describe the clinical features of immunodeficiency

1.0. INTRODUCTION

The integrity of the immune system depends on the capacity and ability of the innate (natural) and specific immune mechanisms. The functioning of the immune system generally depends largely on the thymus, bone marrow, lymphoid tissues and the normal functioning of the polymorphs, monocytes and the complement system.

Immunodeficiency is the state of impaired normal defence mechanisms against invasion by microorganisms. Immunodeficiency disease results from the absence or failure of normal function of one or more elements of the immune system.

Specific immunodeficiency diseases involve the abnormalities of T or B cells of the adaptive immune system while non-specific immunodeficiency diseases involve abnormalities of the elements of innate immune system e.g. the complement and phagocytes. Primary immunodeficiency diseases are due to intrinsic defects in cells of the immune system and are mostly genetically determined.

2.0. CLASSIFICATION

Classification is based on aetiology

1. Deficiency of non-specific resistance
2. Deficiency in specific immunity
    a) Primary immunodeficiency (mainly genetically determined)
    b) Secondary immunodeficiency
        i. Infections e.g. HIV, Measles,
        ii. Malnutrition
        iii. Ageing
        iv. Irradiation/radiotherapy
        v. Chemotherapy
        vi. Autoimmune diseases
        vii. Tumours

Non-Specific Immunodeficiency

This encompasses the defects in the non-specific immune mechanisms such as: -

a) Breach in mechanical barriers
b) Defective reflexes
c) Impaired secretions
d) Impaired local resistance e.g. obstruction in the urinary tract, air passages and gastrointestinal tract.
e) Defects in phagocytic function
f) Deficiency in leucocytes (agranulocytosis)
g) Deficiency of complement components

Phagocytic function

The defects in phagocytic function can be qualitative or quantitative in nature. Quantitative deficiency includes reduction in blood leucocytes, which can be congenital (e.g. infantile agranulocytosis) or acquired due to bone marrow replacement by tumours or reduced performance as a result of toxic effects of chemicals. The qualitative aspect involves deficiency in function of neutrophils (reduced performance of neutrophils).

Task

1. How do neutrophils function?
2. How does the complement system assist in the defence operations of the body?
3. What is the role of inflammation in innate immune mechanisms?

Specific Immunodeficiency

Deficiency in specific immunity can be **primary** or **secondary**. The deficiency can also be **congenital** or **acquired**.

1.0 PRIMARY IMMUNODEFICIENCY

Primary deficiency occurs rarely with major abnormalities being uncommon, is mainly genetically determined, and manifests often early in life. Complete deficiency of T and B-lymphocytes presents early in life with extreme susceptibility to infections.

Primary immunodeficiency arises from defective antibody responses, defective cell-mediated immunity, hereditary complement component defects or/and deficiencies, defects functions of phagocytes and leucocytes adhesion deficiency.

The primary immunodeficiency diseases can fall in four main groups: -

a) Combined immunodeficiency of T cells, B cells and immunoglobulins
b) T cell defects
c) B cell defects
d) Variable immunodeficiency

1. **Severe combined immunodeficiency (SCID)**

This covers a number of individual syndromes involving faulty lymphocyte development resulting in absence or severe impairment in both antibody mediated and cellular mediated immunity.

Clinical presentation is evident soon after birth resulting in a wide range of infections of great severity. Infants have passive protection from maternal antibodies for about six months hence the first infections seen are usually due to opportunistic agents such as *Candidaalbicans* or *Pneumocysticcarinii* and not acute bacterial infections. However, viral infections are usually fulminant and fatal.

The SCID results from: -

a) Failure to develop primitive marrow reticular cell (reticular dysgenesis)
b) Lack of lymphoid stem cells
c) Cell membrane defects of the haemopoietic stem cells
d) Defective T cell maturation

2. **Selective T cell deficiency/defects**

Is best exemplified by *DiGeorge'ssyndrome,* a rare congenital abnormality comprising of thymic and parathyroid aplasia with abnormalities of cardiac and aortic arch development. There is impaired or absent thymic T cell maturation resulting in deficiency of T cells hence compromising cell mediated immunity.

In severe cases T cell –dependent areas are absent from the spleen and bone marrow. Neonates present with fulminant viral, fungal and pneumonistic infections in the presence of normal immunoglobulins.

There is inadequate function of cell-mediated immunity and the patients are incapable of developing the delayed hypersensitivity reaction (DHR). Immunization with live vaccines is capable of producing generalized infections.

3. **B cell defects**

B cell defects comprise of a number of mechanisms such as: -

a) Defective differentiation of pre B to B cells
b) Defective maturation of IgA synthesizing B cells
c) Defective pre B cell maturation

The main pathology hinges on the failure to produce the three main immunoglobulins – IgM, IgG and IgA grounding the humoral immune mechanisms. It may present as sex linked-X Bruton's agammaglobinaemia where there is complete deficiency of immunoglobulins or autosomal recessive situations.

The outcome of this abnormality is little or not production of antibodies in response to infection or immunization. During the foetal age, the foetus is protected my maternal IgG up to the age of six months. Affected children usually present with severe recurrent bacterial infections (pyogenic, respiratory and pulmonary infections, meningitis and septicaemia), persistent diarrhoea due to

Girdialambia and *Rota*virus and, opportunistic infections – protozoa, pneumocystic carinii. Viral infections are well tolerated except for the echovirus that causes chronic central nervous system infections.

The bone marrow has normal pre B cells, the tonsils and lymph nodes are small and the blood has normal lymphocytes but reduced or absent B-lymphocytes. The thymus is normal however patients suffer prolonged viral, fungal and parasitic infections due to compromised cell mediated immunity following collapse of cell cooperation.

4. **Common Variable immunodeficiency**

This is characterized by decrease in immunoglobulins, serum antibodies and the variable cell mediated immunity. It results from B cell defects due to defective differentiation of pre-B cell to mature B cells, T cell defects with deficiency of T helper cells and presence of activate T cells plus autoimmune antibodies to B and T cells.

2.0 SECONDARY IMMUNODEFICIENCY

Secondary immunodeficiency resulting in impairment of the humoral and cellular immune function is a common feature.The main mechanisms of secondary immunodeficiency include: -

a) Association with lymphoid malignancy suppressing production of B lymphocytes
    i. Non-Hodgkin's lymphoma
    ii. Multiple myeloma (MM)
    iii. Chronic lymphocytic leukaemia (CLL)

b) Loss of immune components – e.g. leakage of individual constituents of the immune system such as loss of IgG in Nephrotic syndrome, CMI components in chronic inflammation of the G.I.T and loss of T cells in Chron's disease and protein losing enteropathy (PLE).

c) Infection induced – a number of infections induce temporary immunodeficiency such as acute reduction in CMI (anergy) in viral infections – HIV, Herpes, CMV, EBV and measles; malaria causes chronic immunodeficiency and is a cofactor in generation of the EBV associated Burkitt's lymphoma.
d) Depression of the immune system
    i. Old age
    ii. Malnutrition
    iii. Diseases
        1. Protozoal – malaria
        2. Viral – HIV, measles, infectious mononucleosis
        3. Storage disorders – sarcoidosis
        4. Bacterial – tuberculosis, leprosy
    iv. Immunosuppressive agents
        1. Radiotherapy
        2. Chemotherapy – drugs e.g. corticosteroids, cytotoxics (cyclophosphamide, methotraxate, cycosporin)
e) Iatrogenic
f) Loss of spleenic function

3.0 NUTRITION AND IMMUNE RESPONSES

Generally nutrient deficiencies are associated with impaired immune responses where the five aspects most consistently affected by malnutrition are cell-mediated immunity, phagocyte function, the complement system, secretion of antibodies and cytokine production.

Malnutrition and infection usually aggravate each other as explained by the impact of pneumonia, diarrhoea, measles and tuberculosis in a malnourished child.

The lymphoid tissues are very vulnerable to the damaging effects of malnutrition where the extent and severity of lymphoid dysfunction arising from nutrient deficiencies depends on factors such as – rate of cell proliferation, amount and rate of protein synthesis and the role of the individual nutrients in critical metabolic pathways. Many enzymes that play significant roles in immune processes require zinc, iron, vitamin B_6 and other micronutrients in order to function.

Moderate/severe malnutrition (protein energy malnutrition) is associated with significant: -

a) Reduction in cell mediated immunity
b) Reduction in $CD4^+$ T helper cells
c) Lower $CD4^{+/}CD8^+$ ratio
d) Decrease in lymphocyte proliferation
e) Immature T cells
f) Reduction in IgA secretion
g) Reduction in thymulin activity
h) Poor phagocytosis and opsonization due to reduced C3 and C5
i) Reduction in production of cytokines e.g. IL-2
j) Reduction in ability of phagocytes to kill intracellular organisms

Discuss the role of nutrition in immune functions and mechanisms of immunodeficiency in nutrition (group work) on 23rd April 2010

Lesson 5: HIV Infection and AIDS

Learning Outcomes

At the end of the lesson the learner should be able to: -

1. Discuss the historical aspects of HIV and AIDS
2. Describe transmission of HIV
3. Discuss the structure of HIV
4. Discuss the life cycle of HIV
5. Describe the pathophysiology HIV/AIDS

1.0 INTRODUCTION AND HISTORICAL BACKGROUND

Acquired immune deficiency syndrome or **acquired immunodeficiency syndrome** (**AIDS**) is a disease of the human immune system caused by the human immunodeficiency virus (HIV).This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and tumors. ***AIDS is a disease caused by the retrovirus human immunodeficiency virus (HIV) and characterized by profound suppression of the immune systems resulting in opportunistic infections, secondary neoplasms and neurologic manifestations.***

AIDS was first reported June 5, 1981, when the U.S. Centers for Disease Control (CDC) recorded a cluster of *Pneumocystis carinii* pneumonia (now still classified as PCP but known to be caused by *Pneumocystis jirovecii*) in five homosexual men in Los Angeles. In the beginning, the CDC did not have an official name for the disease, often referring to it by way of the diseases that were associated with it, for example, lymphadenopathy, the disease after which the discoverers of HIV originally named the virus. They also used *Kaposi's Sarcoma and Opportunistic Infections*, the name by which a task force had been set up in 1981. In the general press, the term *GRID*, which stood for Gay-related immune deficiency, had been coined. The CDC, in search of a name, and looking at the infected communities coined "the 4H disease," as it seemed to single out Haitians, homosexuals, hemophiliacs, and heroin users. However, after determining that AIDS was not isolated to the homosexual community, the term GRID became misleading and *AIDS* was introduced at a meeting in July 1982. By September 1982 the CDC started using the name AIDS, and properly defined the illness.

AIDS is now a pandemic. In 2007, it was estimated that 33.2 million people lived with the disease worldwide, and that AIDS had killed an estimated 2.1 million people, including 330,000 children. Over three-quarters of these deaths occurred in sub-Saharan Africa,retarding economic growth and destroying human capital.

In 1984 the first Kenyan national was diagnosed to have AIDS. He was a married man with children who had no history of travel abroad and involvement in homosexual activities. In 1984, a study under the auspices of WHO[1] Centre for STD (sexually transmitted disease) Resource and Training at the University of Nairobi and KERI[2] conducted a study that revealed a high level of seropositivity among prostitutes based in sections of Nairobi. In 1985 nine cases of AIDS were

[1] World Health Organization
[2] Kenya Medical Research Institute

confirmed by both ELISA and Western Blot tests, which were then reported to the Ministry of Health.

2.0 HIV/AIDS IN KENYA

AIDS became a notifiable disease in Kenya vide a Kenya gazette notice of 31st July 1987. Nineteen years down the lane, 2.2 million Kenyans are infected with HIV making HIV become world's most serious Public Health problem. HIV/AIDS claims the lives of 700 Kenyans daily. In Kenya it has been declared a national disaster. There are concerted efforts towards the goal of HIV/AIDS prevention from a number of UN agencies and bodies such WHO, UNICEF, HABITAT, UNESCO, IMF and World bank just to mention a few.

Global Challenges | Kenya's HIV Prevalence Increases to 7.8% in 2007, Report Finds
[Jul 31, 2008]

HIV prevalence in Kenya increased to 7.8% in 2007; a slight increase from the 6.7% prevalence recorded in 2003, according to a survey released by the government on Tuesday, the *Associated Press* reports. According to the *Associated Press*, the increase in the percentage of the population living with HIV likely is because of wider access to antiretroviral drugs.

The survey, titled "2007 Kenya AIDS Indicator Survey," was conducted by several organizations, including CDC, the World Health Organization and the Kenya Medical and Research Institute (*Associated Press*, 7/29). The survey cost about 400 million Kenyan shillings, or about $6 million, Kenya's *Daily Nation* reports (Gathura/Okwemba, *Daily Nation*, 7/29). The survey is based on tests conducted among 18,000 people between ages 15 and 64 for HIV and other sexually transmitted infections from August 2007 to May 2008 (*Associated Press*, 7/29).

According to the survey, about 1.4 million Kenyan adults are living with HIV/AIDS. In addition, four out of every five HIV-positive Kenyans are unaware of their status, and about two-thirds of the country's 37 million people have never been tested for the virus, the survey found. Fifty-seven percent of HIV-positive people reported that they had never taken an HIV test, and 26% said they were HIV-negative but later tested positive. Ibrahim Mohammed, chief of Kenya's National AIDS and Sexually Transmitted Infection Control Program, said that 16% of those tested did not want to know their status, 14% were unaware of the HIV test or where to receive one and 5% indicated that distance to testing clinics was a "major barrier" (AFP/Google.com, 7/29). Mohammed added that three out of five HIV-positive people are women and that uncircumcised men are three to five times more likely to contract the virus, compared with circumcised men.

Prime Minister Raila Odinga said the survey's finding that 50% of Kenyans used condoms and only 20% used a condom during their last sexual encounter is "alarming," the *Associated Press* reports. "There are now nearly 1.5 million Kenyans living with [the virus]. ... This is nothing less than a national crisis," Odinga said. He added, "The only way to reverse this epidemic is through prevention" (*Associated Press*, 7/29). Kenya's Health Minister Beth Mugo said, "We have made notable progress; however, HIV/AIDS rates among our families and communities remains unacceptably high and the impact severe" (AFP/Google.com, 7/29).

Kenya: Shocking Rise in HIV Prevalence

Arthur Okwemba (Daily Nation)
29 July 2008

Kenya's HIV and Aids prevalence rate has increased to nearly eight per cent, according to a new study to be released Tuesday. Just when Kenyans were beginning to celebrate last year's announcement that the prevalence rate had dropped to 5.1 per cent, the Government is expected to announce that the rate is actually higher.

Based on a new study conducted last year, the findings show HIV prevalence to be higher than last year's 5.1 per cent and the 6.7 per cent captured by a 2003 Kenya Demographic and Health Survey.The study, 2007 Kenya Aids Indicator Survey (KAIS), shows HIV prevalence among pregnant women to be on the rise, returning a figure higher than the 7.3 per cent recorded in the 2003 Kenya Demographic and Health Survey (KDHS).

Last year an upbeat Government announced a decline based on statistics from antenatal clinics: "Kenya is one of three African nations that recently has made significant progress in HIV/Aids prevention and treatment programmes."

But these new findings from a study said to have cost about Sh400 million (US$6 million), have shocked the Government, with officials said to be sharply divided on whether to release the figures.

Several meetings, including a Cabinet discussion, seem to have finally decided to release the statistics after agreement on what to tell the public about the discrepancy in the HIV prevalence trend.

Similar studies in Uganda and Tanzania have not been released several months after they were completed.

It is understood these studies, which are using higher populations in their samples than even the respected Demographic Health Surveys, consistently show higher HIV prevalence rates.According to the 2007 KAIS, Nyanza Province led in infections, followed by Nairobi, Coast, Rift Valley, Western, Eastern, Central and North Eastern

HIV/AIDS in Kenya

36,913,721: population of Kenya (2007 est.)

1,400,000 - 1,800,000: Estimated number of people living with HIV/AIDS by the end of 2007

7.1% - 8.5%: Estimated percentage of adults (ages 15-49) living with HIV/AIDS by the end of 2007

130,000 - 180,000: Estimated number of children (ages 0-15) living with HIV/AIDS by the end of 2007

85,000 - 130,000: Estimated number of deaths due to AIDS during 2007

*Source(*UNAIDS 2008 Report on the Global AIDS Epidemic. July 2008)

3.0 EPIDEMIOLOGY

14,000 new infections occurred *each day, o*f these new infections 6,000 each day were among persons 15 to 24 years old. 2,000 each day were in children younger than 15 years old. Most of the infections in children younger than 15 years old occurred through mother-to-child transmission (MTCT) of HIV.

The AIDS pandemic can also be seen as several epidemics of separate subtypes; the major factors in its spread are sexual transmission and vertical transmission from mother to child at birth and through breast milk. Despite recent, improved access to antiretroviral treatment and care in many regions of the world, the AIDS pandemic claimed an estimated 2.1 million (range 1.9–2.4 million) lives in 2007 of which an estimated 330,000 were children under 15 years. Globally, an estimated 33.2 million people lived with HIV in 2007, including 2.5 million children. An estimated 2.5 million (range 1.8–4.1 million) people were newly infected in 2007, including 420,000 children.

Sub-Saharan Africa remains by far the worst affected region. In 2007 it contained an estimated 68% of all people living with AIDS and 76% of all AIDS deaths, with 1.7 million new infections bringing the number of people living with HIV to 22.5 million, and with 11.4 million AIDS orphans living in the region. Unlike other regions, most people living with HIV in sub-Saharan Africa in 2007 (61%) were women. Adult prevalence in 2007 was an estimated 5.0%, and AIDS continued to be the single largest cause of mortality in this region. South Africa has the largest population of HIV patients in the world, followed by Nigeria and India. South & South East Asia are second worst affected; in 2007 this region contained an estimated 18% of all people living with AIDS, and an estimated 300,000 deaths from AIDS. India has an estimated 2.5 million infections and an estimated adult prevalence of 0.36%. Life expectancy has fallen dramatically in the worst-affected countries; for example, in 2006 it was estimated that it had dropped from 65 to 35 years in Botswana.

4.0 PREVALENCE

See the power point slides attached

5.0 AETIOLOGY

AIDS is caused by a human T cell leukaemia-lymphoma virus (HLTV), **the human immunodeficiency virus (HIV),** a retrovirus of the **lentivirus family**that affects the human T cells. The HIV resembles other HTLVs in shape and size and both target CD4 molecules on T cells. HIV is a member of the slow virus group of retroviruses whose common features are **persistence**, **variation** and **evasion of the defence mechanisms**.HIV is cytolytic for T cells causing immunodeficiency (a cytopathic virus) while other HTLVs transform target cells into T cell leukaemia (transforming) viruses.

The human immunodeficiency virus (HIV exists in 2 forms namely HIV–1 and HIV–2. HIV–1 (HIV type 1) is the commonest cause of infectious and is responsible for the global pandemic. HIV–2 (HIV type 2) is less pathogenic than HIV-1 and is largely confined to certain parts of West – Africa.

HIV–1 is a highly virus and is further classified into three major groups namely **group M** (major viruses), **group O** (outliner virus) and **group N** (non-M and non-O). Group M viruses are further

subdivided into subtypes (clades) A – J which are evenly distributed around the world. Types A, C and D are the most common in Africa where C accounts for 90% of infections in southern Africa. Type B is common in Europe and America. Group O viruses are largely restricted to the central African region while group N viruses are rare only been identified in a few individuals in Cameron.

HIV-1 is a rapidly evolving virus due to the error-prone nature of reverse transcriptase and high viral turnover. The ability of the virus to adapt rapidly and to diversify has serious implications because it: -

a) Enables rapid development of drug resistance
b) Enables the virus to escape detection by the immune system
c) May affect vaccine efficiency
d) May affect accurate diagnosis

Infection with HIV-1 results in progressive destruction of CD4 lymphocytes and the rate of CD T cells declines. This determines the rate of immunodeficiency and subsequent development of HIV related opportunistic infections. The destruction of T cells is mainly due to active viral replication.

Comparison of HIV species

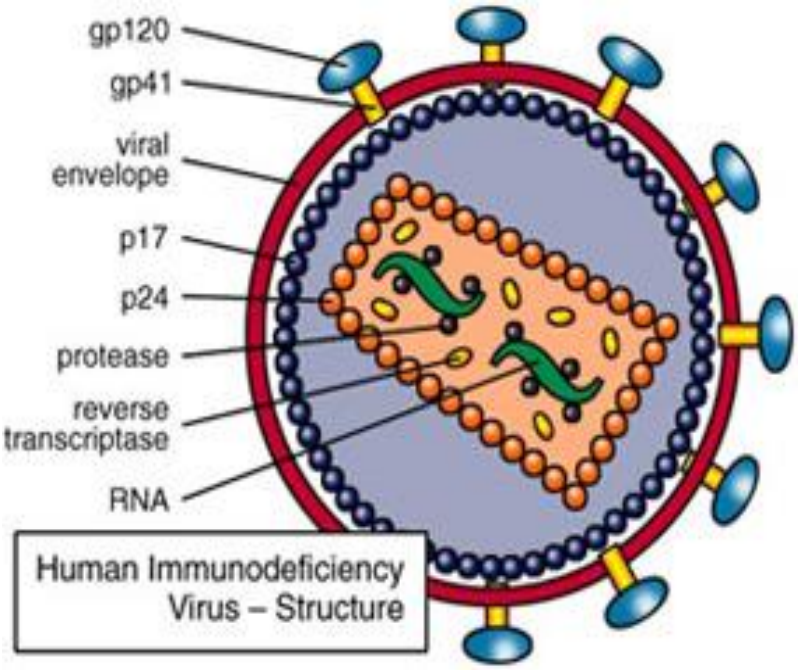
Species	Virulence	Transmittability	Prevalence	Purported origin
HIV-1	High	High	Global	Common Chimpanzee
HIV-2	Lower	Low	West Africa	Sooty Mangabey

6.0 VITAL STRUCTURE AND FUNCTION

General Morphology

The mature retrovirus particles are spherical with a diameter of 80 – 100 nm. The particles have an **outer lipid bilayer** that is host in origin. It has the **surface glycoprotein (gp 120)** and a **transmembrane protein (gp 41**). The viral core is conical in shape and made of **p24 capsid proteins**. The viral particle (**virions**) contains two identical pieces of **viral RNA**. Viral enzymes located within the virions include **reverse transcriptase**, **protease** and **integrase**. The **matrix protein (p17)** is located between the core and the outer lipid layer.

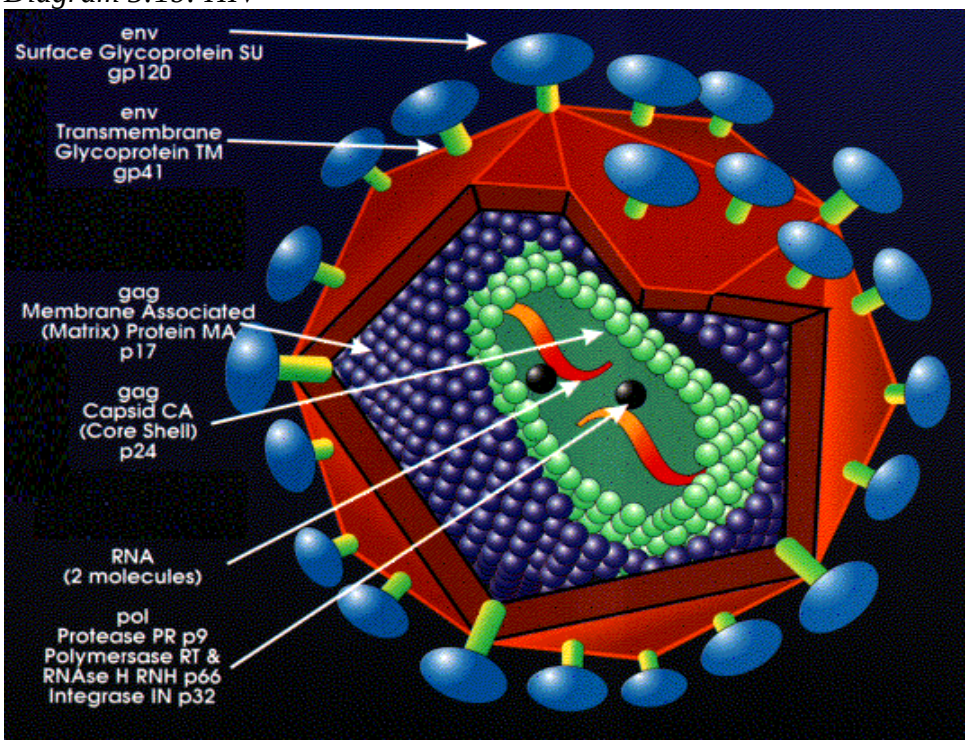
Diagram 5:1a: HIV



Main Parts

1) Envelop antigens - spike antigen gp 120 and transmembrane pedicle protein gp 41
2) Shell antigen - nucleocapsid protein P17/18
3) Core antigens - principal core antigen P24, other core antigens P15, P55
4) D. Polymerase antigens P31, P51, P66

Diagram 5:1b: HIV



HIV Genes and Proteins

The HIV genes encode proteins some of which are polyprotein precursors that become functional proteins.

Cellular Receptors and Viral Tropism

HIV enters the cells through interaction between HIV envelope glycoproteins and cellular receptors and co-receptors. The receptors direct which cells HIV will infect. HIV-1 requires two receptors to enter cells including CD4 and a second co-receptor (chemokine). These receptors are expressed on the surface of a subset of T lymphocytes (CD4), monocytes, dendritic cells and mciroglial cells in the brain.

7.0 TRANSMISSION

HIV is found in body fluids such as: - ***semen, vaginal secretions, cervical erosions, breast milk, CSF, synovial, peritoneal, pericardial and amniotic fluid.*** Sexual intercourse (anal, vaginal and oral) with an infected person accounts for over 80% of infections (70% vaginal and 10% anal). The WHO estimates that approximately 2.5% of all HIV infections in sub-Saharan Africa are transmitted through unsafe healthcare injections.[54] Because of this, the United Nations General Assembly has urged the nations of the world to implement precautions to prevent HIV transmission by health workers.[55]

The risk of transmitting HIV to blood transfusion recipients is extremely low in developed countries where improved donor selection and HIV screening is performed. However, according to the WHO, the overwhelming majority of the world's population does not have access to safe blood and between 5% and 10% of the world's HIV infections come from transfusion of infected blood and blood products.

1. Sexual Transmission

This is a predominant mode of infection (70 – 80%). Heterosexual is a major cause of HIV transmission with homosexuality being a recognized concern in the western world. This can occur in homosexuals and bisexuals. The virus is carried in the body fluids (semen, vaginal secretions and fluids, cervical cells), within lymphocytes and in free cell state and it enters the receptors body through abrasions in the vaginal, glans, rectal and oral mucosa or by direct contact with mucosal lining cells. Viral transmission occurs in 2 ways – **direct inoculation** into the blood vessels breeched by trauma and **into the dentritic cells of $CD4^+$ cells** within the mucosa.

All forms of sexual transmission are enhanced by co-existing sexually transmitted diseases (STDs) especially those associated with genital ulcers such as ***syphilis***, ***chancroid*** and ***herpes***. ***Gonorrhoea*** and ***Chlamydia*** are co-factors in HIV transmission because in these genital inflammatory states there is greater concentration of the virus and virus containing cells in the genital fluids.

2. Parenteral Transmission

This occurs in three main groups such as IV drug abusers, Haemophiliacs (receive factor VIII concentrates) and random recipients of blood and blood products

- Contaminated blood, blood products and organ donations – Haemophiliacs and recipients of blood and blood products
- Instruments contaminated with blood or body fluids from a known HIV infected persons e.g. needles, syringes, razor blades, tattooing instruments and circumcision and drug pushers

3. Mother-to-Child Transmission

Mother-to-child transmission is the major cause of paediatrics AIDS. Infected mothers can transmit the infection to their offspring by three routes ***in utero by placental spread***, during childbirth/delivery through an infected birth canal and after birth by breastfeeding. 40% of children born of HIV mothers in Africa have HIV and this account for 80-90% of all HIV infections in children.

4. Organ and Tissue Donation

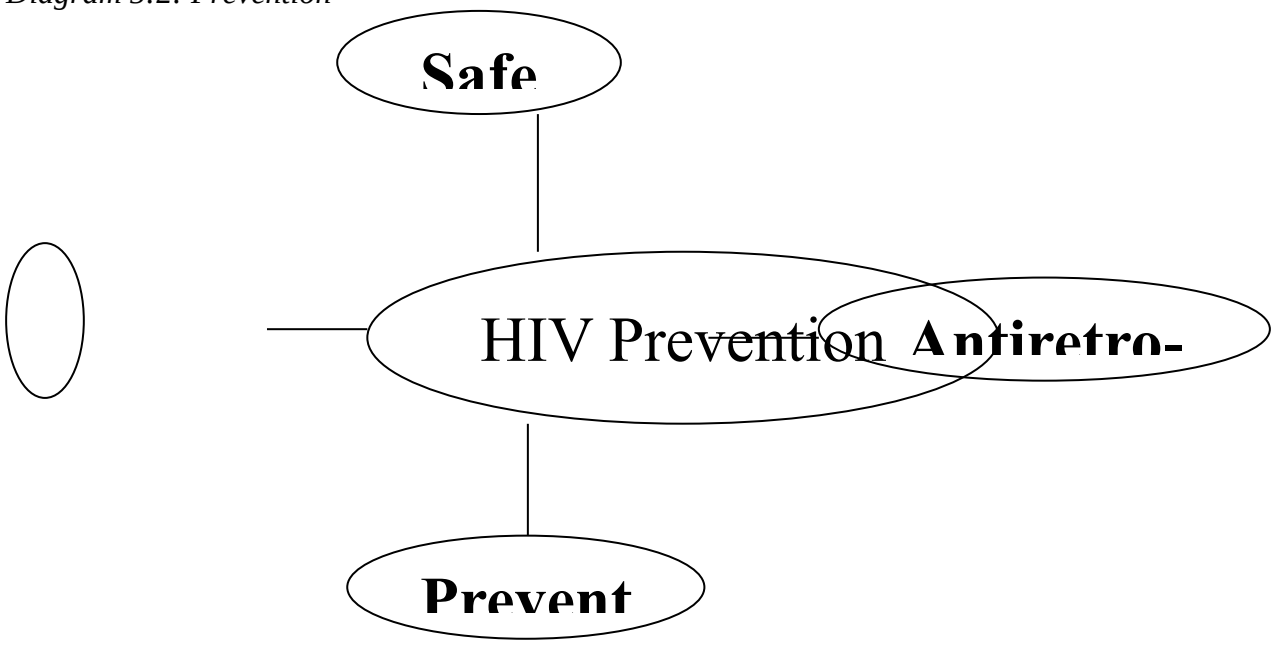
- Bone marrow
- Kidneys

8.0 FACTORS INFLUENCING TRANSMISSION

Factors Increasing HIV Transmission

1. High Viral load in the infecting person
2. Lowered Immune status of the recipient
3. Presence of genital ulcers, abrasions
4. Lack of circumcision (male)
5. Multiple sexual partners
6. Specific sexual practice – anal sex
7. Age of the recipient – very young and very old
8. Type of the HIV strain infecting recipient

Diagram 5:2: Prevention



Factors decreasing HIV Transmission

1) Avoiding exposure (abstinence)
2) Use of condoms during all sexual encounters
3) Treatment of concurrent sexually Transmitted Infections (STIs)
4) Post-exposure prophylaxis
5) Antiretroviral therapy to prevent mother to child transmission

Sexual behavior

- Abstain from or delay start of intercourse
- Decrease number of sexual partners
- Practice monogamy
- Practice non-penetrative sex
- Avoid: - Anal sex, Douching, Dry sex, Sex during menses, Sex while using alcohol/drugs
- Use condoms with every sexual act
- Prevent, identify, and provide early treatment for sexually transmitted infections (STIs).
- Provide access to HIV testing and counselling.

9.0 RISK BEHAVIOUR

These are the types of behaviours that would put one at risk of contacting HIV/aids. The biggest risk is **having unprotected sex**! Therefore **avoid any** risk behaviour in order **not to become infected with HIV** or in order **not to transmit HIV** to someone else. **WHAT IS RISK BEHAVIOUR?**

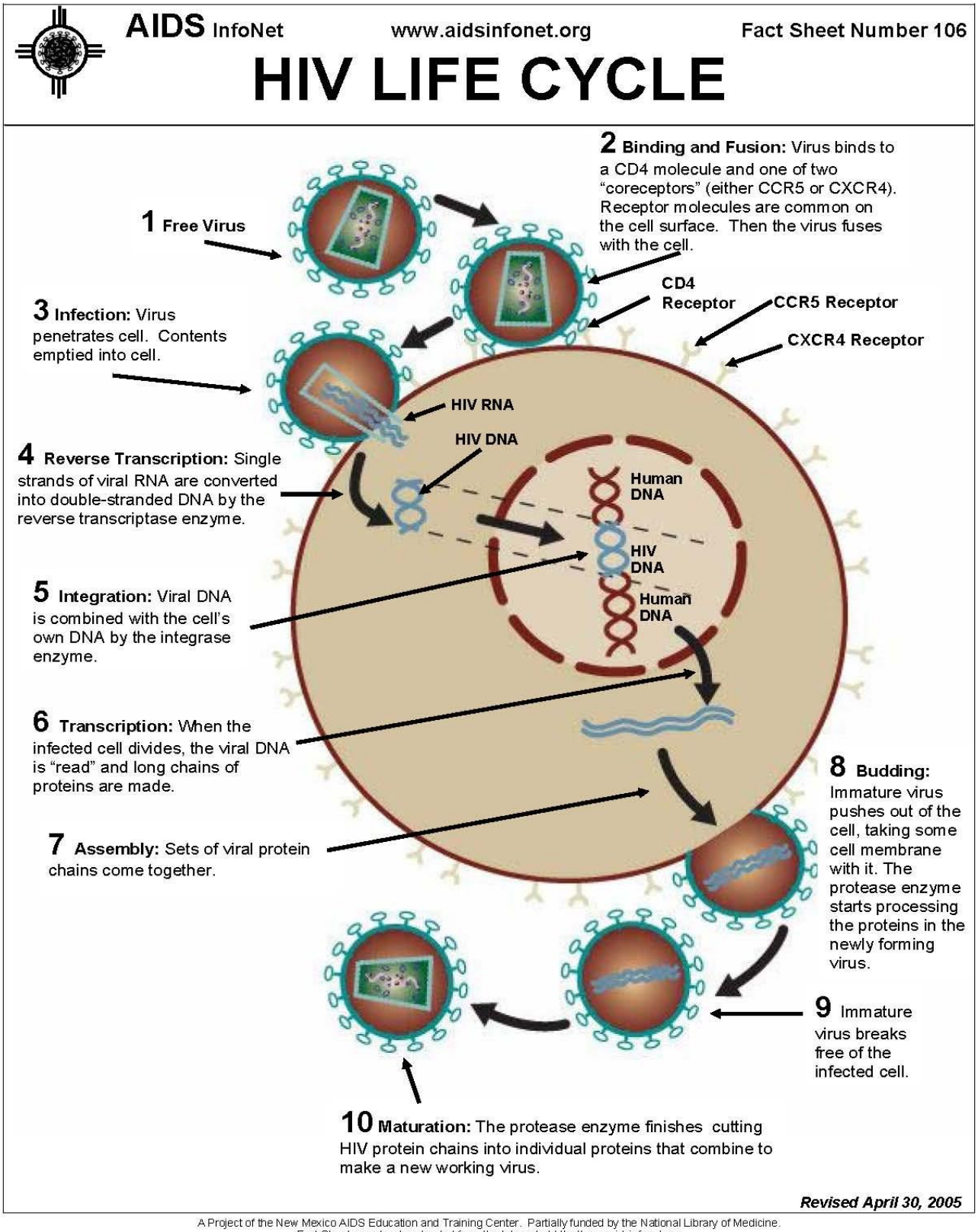
10.0 THE HIV LIFE CYCLE

HIV enters the cells through interaction between HIV envelope glycoproteins and **cellular receptors** and **co-receptors** expressed on the surface of a subset of T lymphocytes (CD4), monocytes, dendritic cells and microglial cells in the brain. . The receptors direct which cells the HIV will infect. HIV-1 requires **2 receptors** to enter the cell that is the **CD4 receptor** and **a second co-receptor (chemokine – CCR5 and CXCR 4**). The CD4 molecule has a high-affinity receptor for HIV; this explains the selective tropism of the virus for CD4+ T cells, monocytes/macrophages and dendritic cells.

Stages/steps of the Life cycle

1. Binding (attachment)
2. Fusion and Viral entry (uncoating)
3. Reverse transcription
4. Integration
5. Proviral transcription
6. Translation
7. Cleavage and Budding
8. Assemble, maturation and release

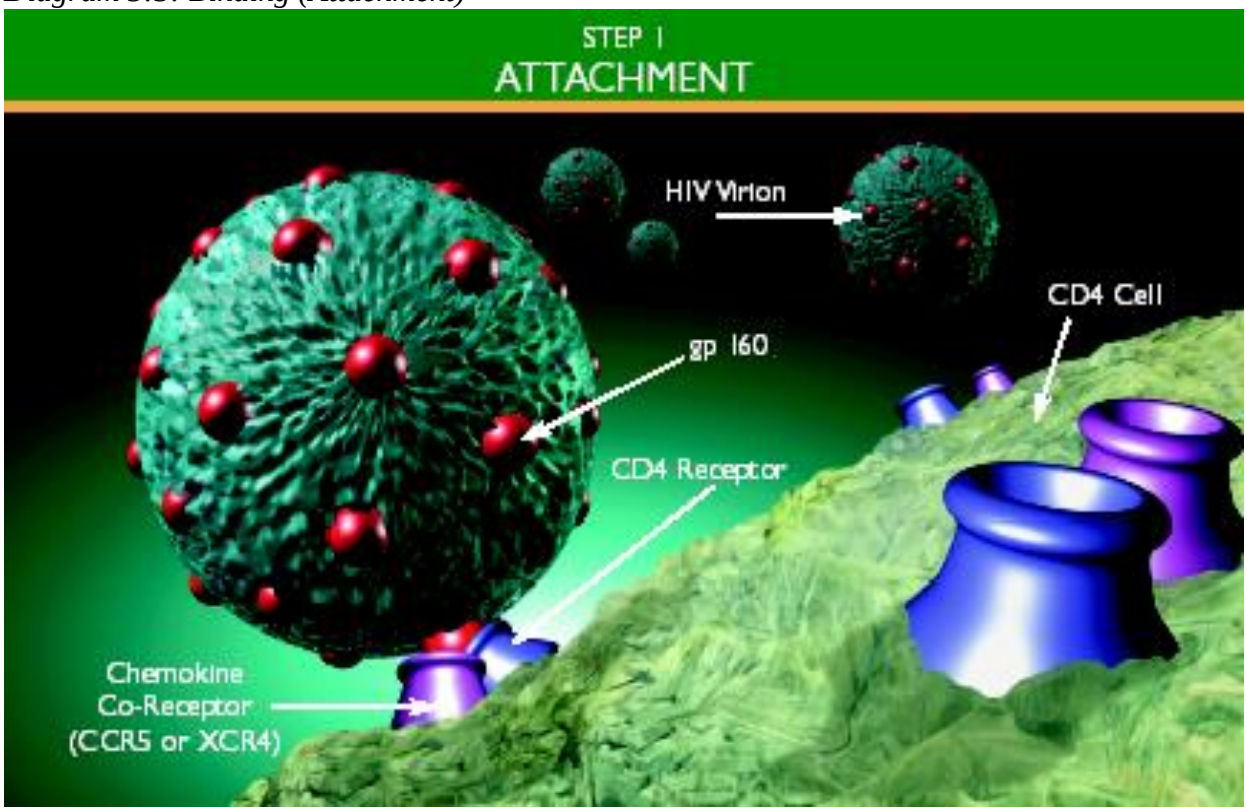
Diagram 5:2a: HIV Life Cycle



1. BINDING (ATTACHMENT)

HIV attaches to the surface of target cells CD4 at specific sites - CD4 receptor and chemokine co-receptor. The virus must attach successfully to both sites in order to fuse with CD 4 cellular membranes. This process can be compared to a key (gp 120) opening a pair of locks. The gp 120 undergoes conformational changes enabling interaction between gp 120 and co-receptors, the chemokines (CCR5 and CXCR4) so as to facilitate entry of the virus. R5 HIV strains use CCR5 whereas X4 HIV strains use CXCR4 and some strains use both (that they are dual-tropic). Conformational changes expose a new recognition site on the gp 120 for the receptors CCR5 and CXCR4.

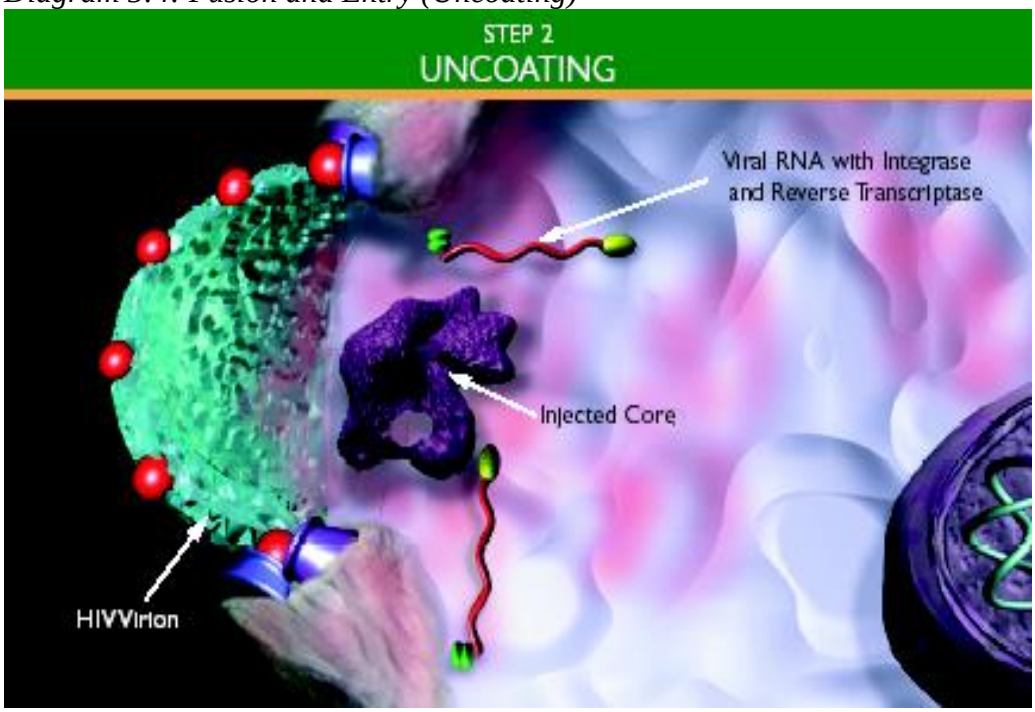
Diagram 5:3: Binding (Attachment)



2. FUSION, VIRAL ENTRY AND UNCOATING

The interaction between the virus and its receptors triggers conformational changes in gp 41 resulting in insertion of a fusion peptide at the tip of the gp 41 into the membrane of the target cell. After fusion the virus core containing the HIV genome enters cytoplasm of the cell. Once inside the virus uncoats and injects its protein coat/core into the cell as well as its two single strands of viral RNA. The viral RNA carries instructions for producing more viruses.

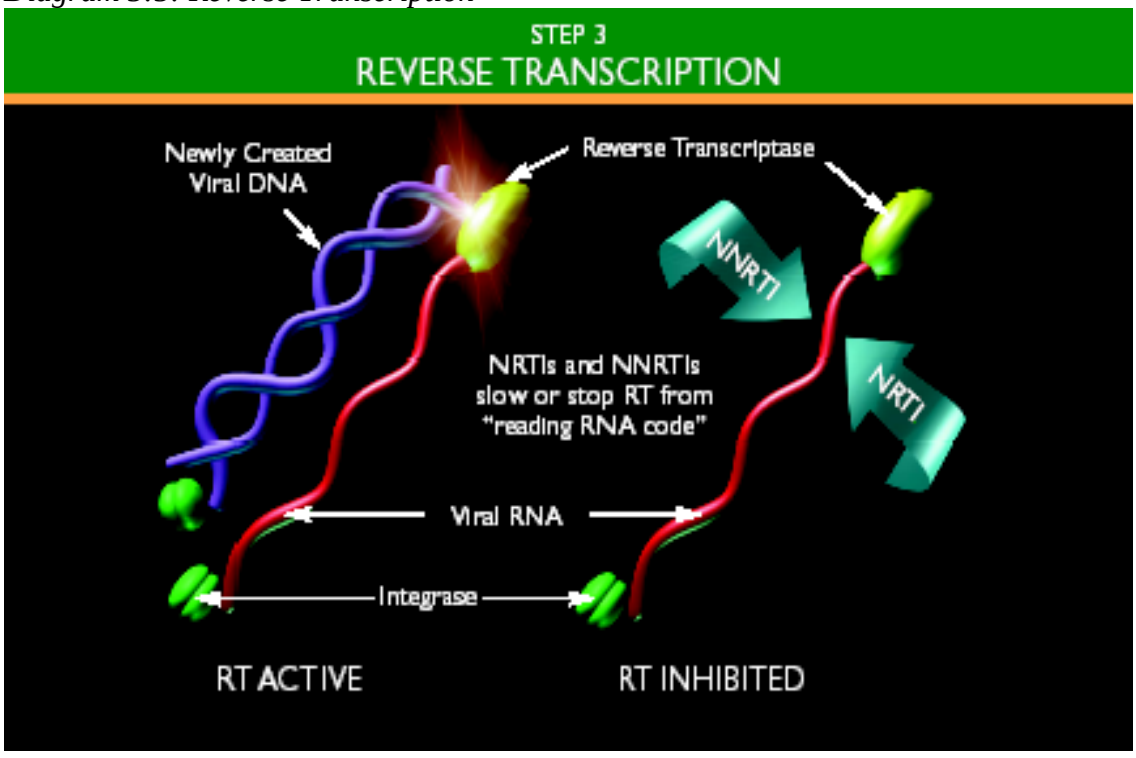
Diagram 5:4: Fusion and Entry (Uncoating)



3. REVERSE TRANSCRIPTION

Once the HIV genome is internalized, the viral single strand RNA converts to double stranded viral DNA. HIV uses an enzyme called ***reverse-transcriptase***. The enzyme travels along the viral RNA strand and makes a copy. The new strand is then copied again but in reverse (in a mirror like image). The result of this process is double – stranded viral DNA

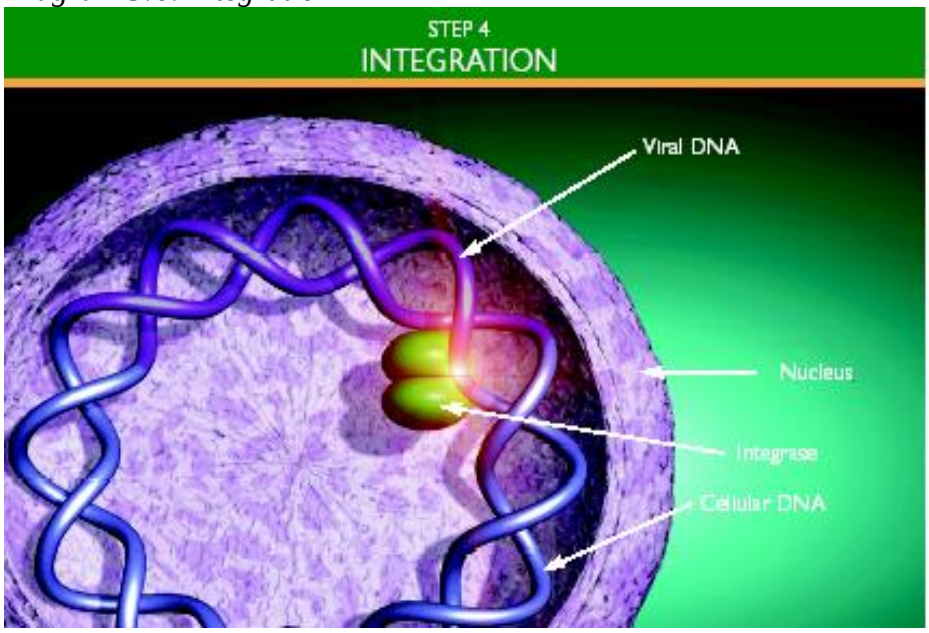
Diagram 5:5: Reverse Transcription



4. INTEGRATION

The new viral DNA (cDNA) enters the nucleus of the CD4 cell. Through the action of enzyme *integrase* the cell is able to fuse with the nucleus. Integrase then inserts the viral DNA into the cellular DNA to form a provirus. In quiescent T cells HIV cDNA remains in the cytoplasm but in dividing cells the cDNA circulates enters the nucleus. After integration the provirus may remain locked into the chromosome for months or years (latent infection).

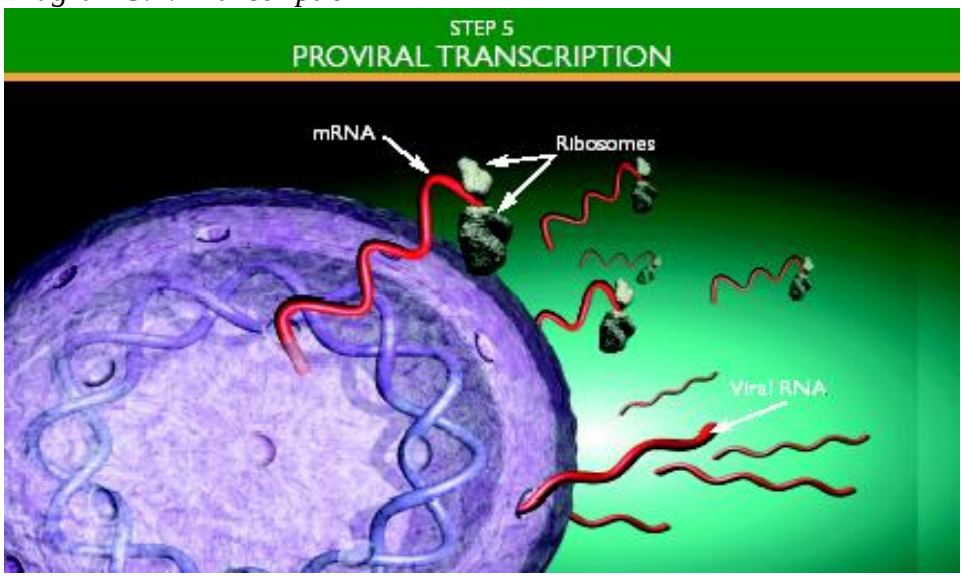
Diagram 5:6: Integration



5. PROVIRAL TRANSCRIPTION

During this stage the viral DNA programs the CD4 cellular machinery to produce components necessary for the formation of new viruses. Viral RNA which will serve as the genetic material for newly produced viral messenger RNA (mRNA) which will produce a chain of proteins also called Poly-proteins.

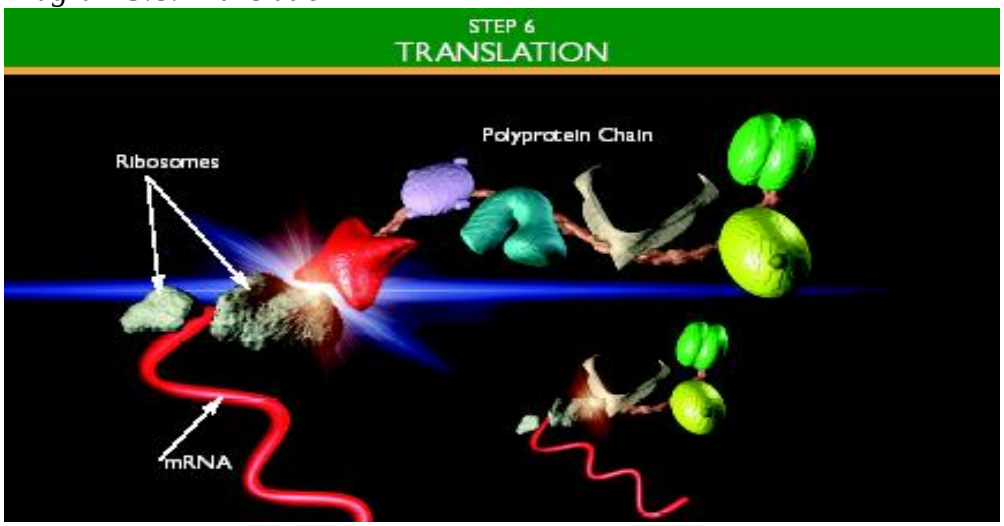
Diagram 5.7: Transcription



6. TRANSLATION

A chain of polyproteins is created using instructions encoded by mRNA. These proteins are essential for the construction of new viruses. The new viruses that are formed are used in the next stages

Diagram 5:8: Translation

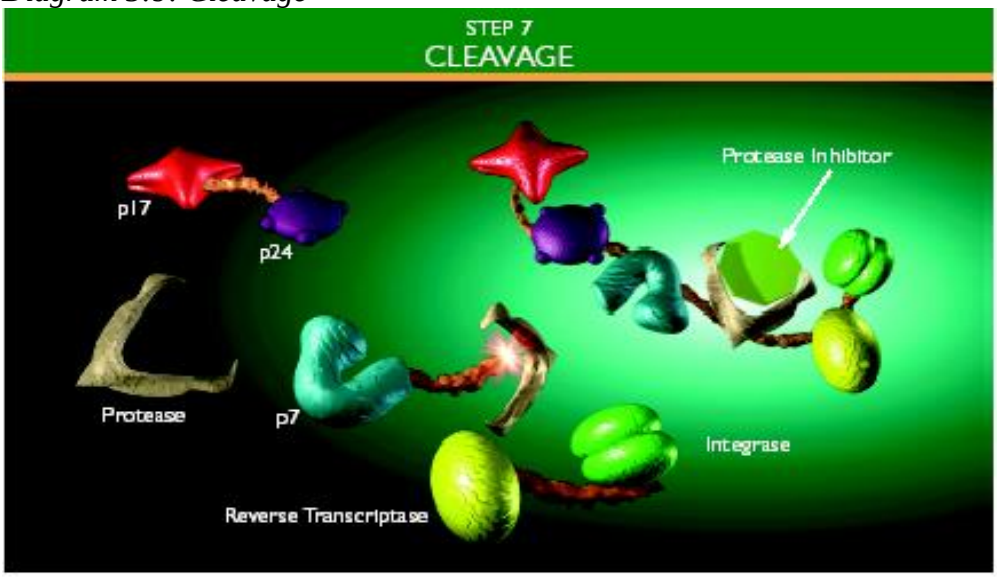


7. CLEAVAGE AND BUDDING

Protease enzyme is one of the proteins formed in the polyprotein chain and acts like a pair of scissors. It cuts or cleaves the polyprotein chain into individual proteins e.g. p17, P24 and p7. These proteins are necessary to complete the assembly of new infectious HIV. Although the stage at which cleavage occurs is unclear this process is known to occur late in the viral cycle. It may occur concurrently with the viral release

The newly formed viral particle buds off from the cell membrane of the infected cells taking with it the cellular bilipid layer. Extensive viral budding causes cell death (target cell) and formation numerous new viruses.

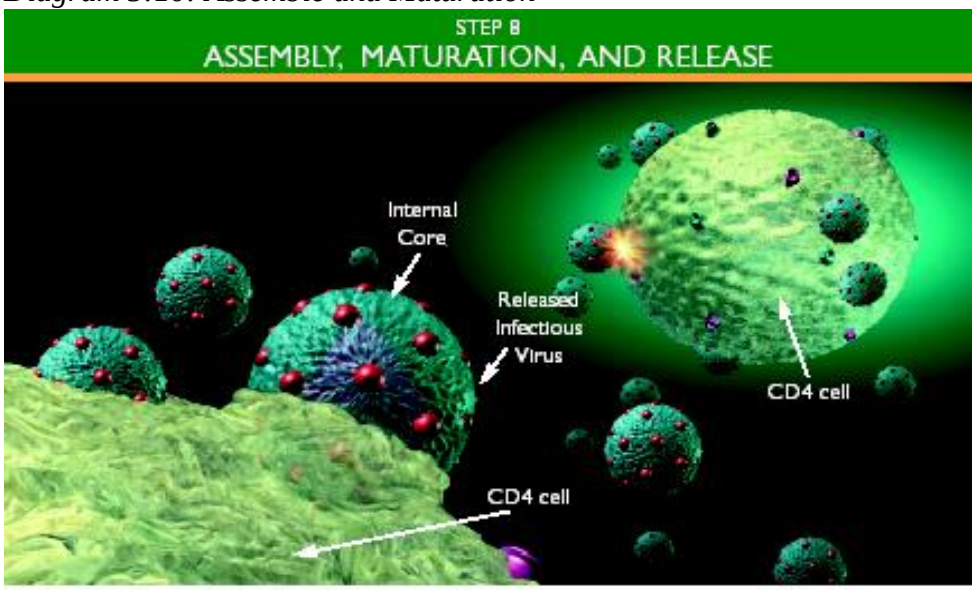
Diagram 5:9: Cleavage



8. ASSEMBLE, MATURATION AND RELEASE

New viral proteins and new viral RNA are gathered together at cell membrane and assembled into new viruses. Once they complete maturation process and become fully functional and infectious viruses they are released to infect new CD4 cells.

Diagram 5:10: Assemble and Maturation



11.0 PATHOPHYSIOLOGY

HIV may infect any cell bearing CD4 antigen receptor. Such cells are mainly the helper inducer subsets of T lymphocytes referred to as T4 lymphocytes. CD4 antigen is also found on 5-10% of B-lymphocytes, 10-20% of tissue lymphocytes and up to 40% of the circulating monocytes. This may explain why macrophages and monocytes are thought to be important reservoirs of HIV. Monocytes are able to carry the virus to various organs in the body such as the lungs and brain.

1. Infection of the Host Cell

When attaching to a T4 lymphocyte or other host cells, the glycoprotein gp 120 on the surface of the virus interacts and binds to the CD4 antigen on the host cell. Only the core of the virus containing the RNA, core proteins and enzymes enters the host cell. The reverse transcriptase catalyses a process that produces a single strand DNA copy of the viral RNA, which is then copied to produce a double, strand DNA. This viral DNA genome is called a **provirus**. The provirus migrates to the nucleus of the host cell and becomes integrated into the cell's DNA. This ensures permanent infection of the cells with the provirus being duplicated together with the host cells own genes every time the host cell is activated and divides.

2. Production of New Virus Particles

Production of new virus particles takes place sporadically and only is some infected cells. The provirus may also remain latent for long periods. Once activated, the DNA produces copies of viral RNA and viral proteins. The new virus particles are assembled at the membrane of the host cell. The mature particles leave the cell by the process of budding. The active process of budding

causes rupture and death of T4 lymphocytes. In the macrophages and monocytes viral duplication can occur without causing cell death. Reduction in the number of T4 lymphocytes in caused by budding, fusion of infected and non-infected T4 lymphocytes caused by the high level of gp 120 on the surface of infected T4 lymphocytes and due to antigens form the virus e.g. P24 and gp 120 becoming attached to infected T-lymphocytes which are then destroyed by the individual's cell mediated immunity.

Summary

1. Cellular receptor for HIV is CD4 molecule which defines the cells that are susceptible that is the CD4 T-lymphocytes, monocytes and macrophages (and other antigen presenting cells e.g. dendritic cells in blood, Langerhan's cells of the skin and follicular dendritic cells of the lymph nodes where much of the early infection and replication of HIV takes place).

2. Infection with HIV-1 results in a progressive destruction of the CD4 lymphocytes with the rate of decline of CD4 T-cells determining the rate of immunodeficiency and subsequent development of HIV related opportunistic infections. The destruction T-cells is mainly due to active viral replication that occurs in three categories.
   a) Rapid developer (approximately 20% of all cases) develops AIDS within 5 years
   b) Average developer – develops AIDS within 10 years
   c) Slow developers (approximately 5% of all cases) who remain asymptomatic for over 10 years without significant decline in CD4 T-cells.

12.0 NATURAL HISTORY OF HIV/AIDS INFECTION AND DISEASE

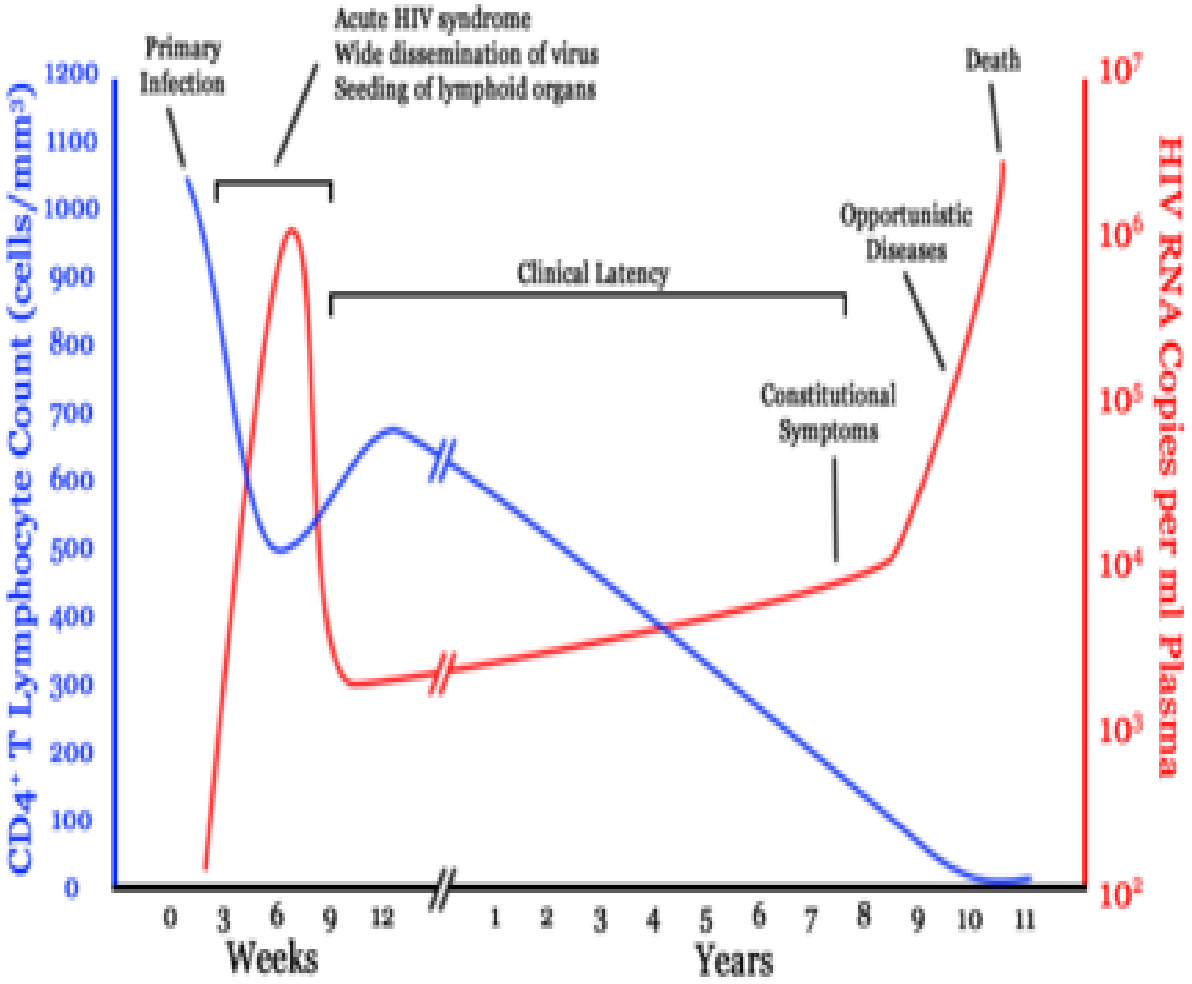
When a person is infected with HIV initially he/she feels well because there are usually no complains/symptoms and features/signs because the HIV infection has not yet destroyed the body immune system resulting in subsequent recurrent debilitating diseases and infections. It is usually during this stage that the disease is transmitted without the persons realizing. It suffices to remember that persons can remain in this state for **over 10 years**.

Based on the time taken for development of AIDS following HIV infection, people can be broadly categorized as: -

(a) "Average developer" – develop AIDS within approximately 10 years.
(b) "Rapid developer" – develop AIDS within 5 years (20%)
(c) "Slow developers" – remain a symptomatic for over 10 years without a significant decline in CD4 T cell count.

HIV primarily infects and destroys cells in the immune system particularly CD4 (helper) T lymphocytes causing profound immune suppression that gradually develops over a period of years and ultimately renders the patient vulnerable to opportunistic infections and malignancy. HIV also infects nerve, renal and bone marrow cells resulting in important clinical consequences.

Diagram 5:11: Natural History of HIV



A generalized graph of the relationship between HIV copies (viral load) and CD4 counts over the average course of untreated HIV infection; any particular individual's disease course may vary considerably. CD4$^+$ T Lymphocyte count (cells/mm^3) HIV RNA copies per mL of plasma

Lesson 6: Pathology and of Clinical Features of HIV/AIDS

Learning Outcomes

At the end of the end of the lesson the leaner should be able to: -

1. Describe the pathogenesis of HIV/AIDS
2. Describe the pathology of HIV/AIDS
3. Describethe clinical features of HIV/AIDS
4. Discuss the process of making a diagnosis of HIV/AIDS
5. Describe the complications of HIV/AIDS

1.0 PATHOGENESIS

The virus enters cells with CD4 + receptors but requires participation of other co-receptor molecules, CXCR4 for T cell tropic HIV strains and CCR5 for macrophage tropic strains.Primary pathogenesis is due to the damage to the CD4+ lymphocytes whose functions become depressed without damage to cells, cells may get damaged or cells die with depletion of total numbers

1. Production of interleukin 2, interferron gamma and other cytokines are disturbed causing marked depression of CMI.
2. Humoral mechanisms also affected since CD4 T cells control B cell functions especially response to Thymus dependent antigens.
3. HIV infection triggers polyclonal activation of B lymphocytes (super antigen) leading to hyper gamma globulinemia. Useless immunoglobulins against irrelevant antigens and autoantibodies. May lead to hypersensitivity reactions and immune complex allergies.
4. Lack of secretion of activating factors leads to depression of monocyte – macrophage functions.Chemotaxis and intracellular killing are depressed due to this.

90% of clinical manifestations of HIV infection are not primarily due to viral cytopathic effect but secondary to immune failure with exceptions being, dementia, other degenerative, neurological lesions, HIV Hepatitis, HIV gastro enteritis etc and HIV interstitial pneumonitis

2.0 PATHOPHYSIOLOGY

HIV causes AIDS by depleting $CD4^+$ T helper lymphocytes weakening the immune system and allows opportunistic infections. T lymphocytes are essential to the immune response and without them, the body cannot fight infections or kill cancerous cells. The mechanism of $CD4^+$ T cell depletion differs in the acute and chronic phases.

During the acute phase, HIV-induced cell lysis and killing of infected cells by cytotoxic T cells accounts for $CD4^+$ T cell depletion, although apoptosis may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in $CD4^+$ T cell numbers.

HIV seeks out and destroys CCR5 expressing $CD4^+$ cells during acute infection. A vigorous immune response eventually controls the infection and initiates the clinically latent phase.

However, $CD4^+$ T cells in mucosal tissues remain depleted throughout the infection, although enough remain to initially ward off life-threatening infections.

Continuous HIV replication results in a state of generalized immune activation persisting throughout the chronic phase. Immune activation, which is reflected by the increased activation state of immune cells and release of proinflammatory cytokines, results from the activity of several HIV gene products and the immune response to ongoing HIV replication. Another cause is the breakdown of the immune surveillance system of the mucosal barrier caused by the depletion of mucosal $CD4^+$ T cells during the acute phase of disease.

This results in the systemic exposure of the immune system to microbial components of the gut's normal flora, which in a healthy person is kept in check by the mucosal immune system. The activation and proliferation of T cells that results from immune activation provides fresh targets for HIV infection. However, direct killing by HIV alone cannot account for the observed depletion of $CD4^+$ T cells since only 0.01-0.10% of $CD4^+$ T cells in the blood are infected.

A major cause of $CD4^+$ T cell loss appears to result from their heightened susceptibility to apoptosis when the immune system remains activated. Although new T cells are continuously produced by the thymus to replace the ones lost, the regenerative capacity of the thymus is slowly destroyed by direct infection of its thymocytes by HIV. Eventually, the minimal number of $CD4^+$ T cells necessary to maintain a sufficient immune response is lost, leading to AIDS

Cells affected

The virus, entering through which ever route, acts primarily on the following cells - Lymphoreticular system(CD_4+ T-Helper cells , Macrophages, Monocytes, B-lymphocytes), Certain endothelial cells, Central nervous system (microglia of the nervous system, astrocytes , oligodendrocytes and neurones - indirectly by the action of cytokines and the gp-120

The effect

The virus has cytopathic effects but how it does it is still not quite clear. It can remain inactive in these cells for long periods, though. This effect is hypothesized to be due to the CD_4-gp120 interaction

1. The most prominent effect of the HIV virus is its T-helper cell suppression and lysis. The cell is simply killed off or deranged to the point of being function-less (they do not respond to foreign antigens). The infected B-cells can not produce enough antibodies either. Thus the immune system collapses leading to the familiar AIDS complications, like infections and neoplasms (vide supra).
2. Infection of the cells of the CNS cause acute aseptic meningitis, subacute encephalitis, vacuolar myelopathy and peripheral neuropathy. Later it leads to even AIDS dementia complex.
3. The CD_4-gp120 interaction (see above) is also permissive to other viruses like Cytomegalovirus, Hepatitis virus, Herpes simplex virus, etc. These viruses lead to further cell damage i.e. cytopathy.

3.0 PATHOLOGY OF HIV/AIDS

The pathogenesis of HIV/AIDS is due to depletion of $CD4^+$ T cells (Helper T cells) resulting in profound immunosuppression. The effect on the CD4 cells is both qualitative and quantitative.

This occurs via the following steps: -

1. Selective tropism and internalisation
   - ➲ HIV on entering the body has a selective tropism for CD4+ cells, monocytes and macrophages
   - ➲ The envelop glycoprotein gp 120 of the virion binds to CD molecule and the virus is internalised into CD4+ cells

2. Uncoating and proviral DNA integration
   - ➲ The virus is uncoated
   - ➲ Its genomic RNA is transcribed to proviral DNA by enzyme transcriptase
   - ➲ Proviral DNA remains unitegrated in the affected cells but is later integrated in the cells

3. Budding and syncytia formation
   - ➲ Infected CD4 cells bear budding viral particles by multiplication further attracting more CD4 cells forming syncytia.

4. Cytopathic effects
   - ➲ Infection may remain in the latent phase for a long period of time (long incubation period)
   - ➲ Antigenic activation of the infected T cells results in cytopathic phase with cytopathic effects.
   - ➲ The cytopathic effects are quantitative depletion of CD4+ T cells due to direct cytolysis and qualitative as a result of inability of T cells to respond to antigens.

5. Effects on monocytes and macrophages
   - ➲ CD4 molecule-bearing subpopulations of monocytes and macrophages e.g. dendritic cells; microglial cells are attacked by HIV.

6. HIV infection of the nervous system- this occurs through: -
   - ➲ Infection carried to the nervous system by HIV infected CD4+ T-cells, monocytes and macrophages
   - ➲ Direct infection of neuronal tissue or endothelial cells
   - ➲ The neurological manifestations include: -Acute aseptic meningitis, Subacute encephalitis, Vacuolar myelopathy, Peripheral neuropathy

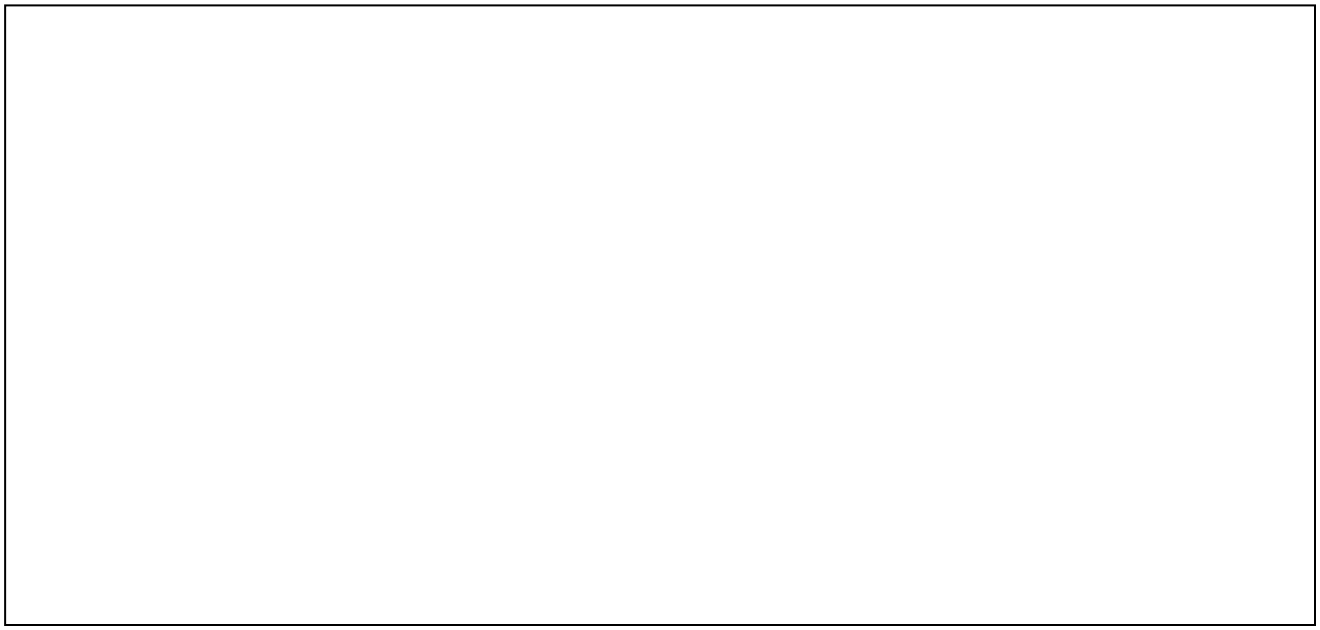
7. B cell dysfunctions
   - ➲ gp 120 of HIV envelop produces derangements of B cell functions resulting in decreased immunoglobulin production, activation and circulating antibodies

4.0 ABNORMALITIES OF IMMUNE FUNCTION IN AIDS

1. T cell abnormalities (cell mediated immunity)
   a. Lymphopenia with depletion of CD4+, reversal of CD4 to CD8 ratio
   b. Susceptibility to opportunistic infections
   c. Susceptibility to neoplasms

   d. Decreased delayed type hypersensivity (type IV reaction)
   e. Decreased specific cytotoxicty
   f. Decreased production of interleukin 2

2. B cell abnormalities (Humoral immunity)
   a. Decreased Ig production
   b. Circulating immune complexes
3. Monocyte-macrophage axis - Decreased chemotaxis and decreased cytotoxicity
4. NK cell abnormalities - Decreased cytotoxicity



5.0 HOW HIV INFECTION DESTROYS THE IMMUNE SYSTEM

The HIV is an RNA virus with the basic gene structure that has gag (core protein), pol (polymersae/reverse transcriptase) and envelope (envelop protein) genes. It also has genes that regulate protein of proteins that make up the virus.

The HIV enters the body and is attracted to body defence cells - white blood cells called CD4 T-lymphocytes infecting them. This is because these cells have a surface that the virus can attach to (an antigen receptor for the virus). The virus also invades other white blood cells for example monocytes, which can now carry the virus to various organs of the body, e.g. the lymph nodes, lungs and brain.

The HIV attaches to lymphocyte and other host cells and the contents of the virus (core proteins and an enzyme called - reverse transcriptase) become incorporated into the lymphocyte and host cells. The enzyme directs formation of a single DNA strand of the RNA virus and then the DNA strand is duplicated to produce an abnormal cell called **provirus** that has genetic characteristics of the HIV. This becomes part of the defence cells and ensues that there is permanent infection of the body cells.

As the cells grow, mature particles leave the infected cell resulting in rupture and death of the defence cells with eventual reduction in the number of defence cells (lymphocytes). The body itself destroys some of the altered cells.

The cells destroyed by HIV are important because they assist the body directly or indirectly protect itself from invasion by bacteria, viruses, fungi and parasites, clear away a number of cancer cells, and produce chemicals for body defence and influence development and function of the body scavenger cells in the immune system.

So what is the problem in HIV infections? – The Overall problem is a WEAK defence system. How?

a) The defence cells are reduced in number
b) The defence cells are abnormal in genetic structure because of the incorporated viral genes.
c) New cells that are dividing produce abnormal cells as directed by the virus
d) The **provirus cells** remain in the **body permanently**
e) The body loses the ability for self-regulation meaning it is capable of destroying its own body cells that are not supposed to be destroyed.

6.0 NATURAL HISTORY OF HIV

Based on the time taken for development of AIDS following HIV infection, people can be broadly categorized as: - **Rapid developer"** – develop AIDS within 5 years (20%)-"**Average developer"** – develop AIDS within approximately 10 years, " and **"Slow developers"** – remain a symptomatic for over 10 years without a significant decline in CD4 T cell count.

HIV primarily infects and destroys cells in the immune system particularly CD4 (helper) T lymphocytes causing profound immune suppression that gradually develops over a period of years and ultimately renders the patient vulnerable to opportunistic infections and malignancy. HIV also infects nerve, renal and bone marrow cells resulting in important clinical consequences.

Diagram 6:1: Natural History of Untreated HIV-1 Infection

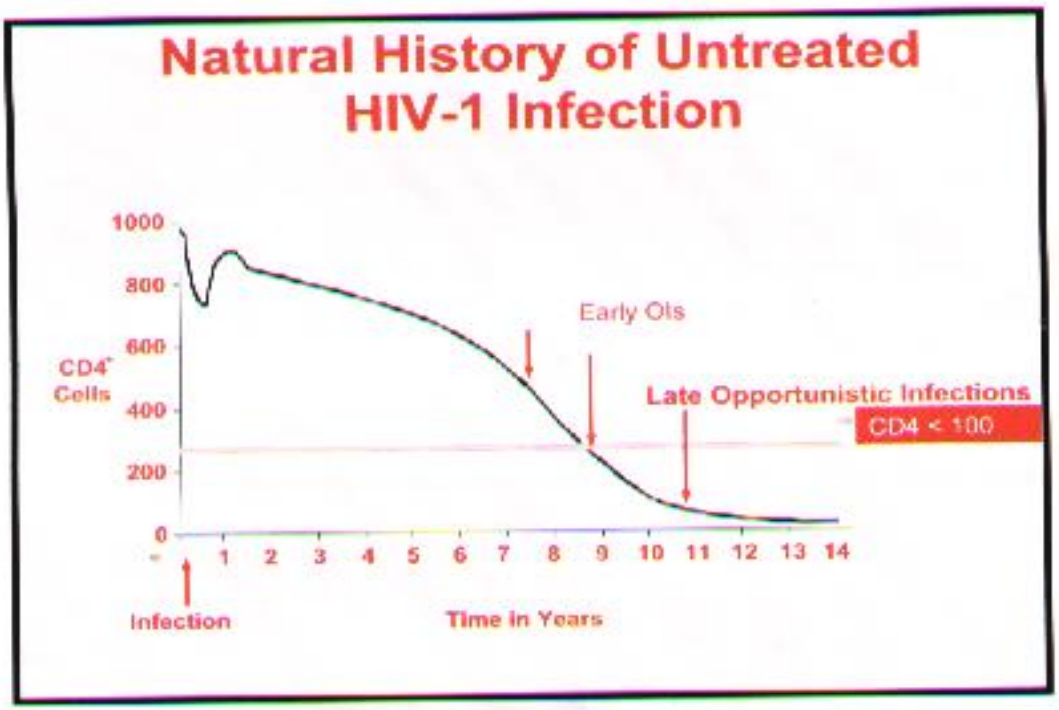
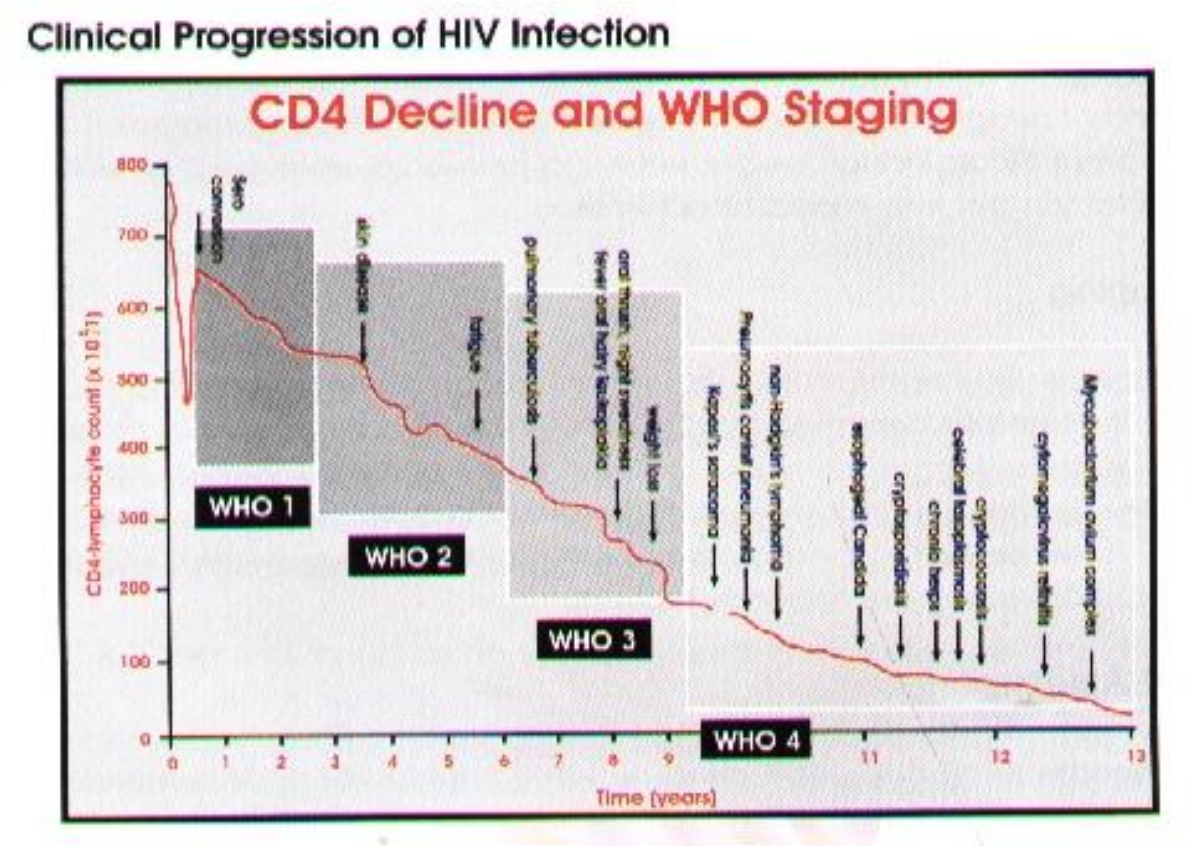


Diagram 6:2: Clinical Progression of HIV Infection



7.0 DIAGNOSIS OF HIV

1. History and Physical examination
2. Clinical staging (WHO) - Acute seroconversion syndrome, Asymptomatic HIV infection and symptomatic HIV disease
3. Laboratory diagnosis
    1. Basic Tests (baseline that should be performed whenever possible)
    a) Antibody detection (ELISA (2 tests – screening and confirmation; Western blot assays)
    b) Antigen detection (PCR, P24)
    c) Testing for viral nucleic acid (RNA or PRO DNA)
    d) Culturing for the virus
    e) Full blood count
    f) LFTs (ALT/SGPT)
    g) Urea and electrolytes
    h) Random blood sugar (serum glucose)
    i) CD4 cell count – a specific type of white blood cell whose normal count in a healthy adult is between 600 and 1200 cells/mm3. When below 200 risk of opportunistic and serious infection is high
    j) Sputum for AAFB where a sample is available
4. Desirable tests – parameters which may be affected by ARVs such as Bilirubin, Amylase, Serum lipids, Screening for cervical cancer , HBV and HCV, VDRL
5. Optional – viral load

Viral load is the amount of HIV virus in the blood. It is measured by the HIV ribonucleic acid polymerase chain reaction blood test (HIV-RNA PCR). It is very high shortly after primary HIV infection, falls steeply when the body develops antibodies and rises again after a number of years as the CD4 count drops.

STAGING OF HIV/AIDS

WHO disease staging system

WHO Disease Staging System for HIV Infection and Disease

In 1990, the World Health Organization (WHO) grouped these infections and conditions together by introducing a staging system for patients infected with HIV-1.]An update took place in September 2005. Most of these conditions are opportunistic infections that are easily treatable in healthy people.

- Stage I: HIV infection is asymptomatic and not categorized as AIDS
- Stage II: includes minor mucocutaneous manifestations and recurrent upper respiratory tract infections
- Stage III: includes unexplained chronicdiarrhoea for longer than a month, severe bacterial infections and pulmonary tuberculosis
- Stage IV: includes toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi or lungs and Kaposi's sarcoma; these diseases are indicators of AIDS.

CDC classification system

CDC Classification System for HIV Infection

There are two main definitions for AIDS, both produced by the Centers for Disease Control and Prevention (CDC). The older definition is to referring to AIDS using the diseases that were associated with it, for example, lymphadenopathy, the disease after which the discoverers of HIV originally named the virus. In 1993, the CDC expanded their definition of AIDS to include all HIV positive people with a $CD4^+$ T cell count below 200 per µL of blood or 14% of all lymphocytes. The majority of new AIDS cases in developed countries use either this definition or the pre-1993 CDC definition. The AIDS diagnosis still stands even if, after treatment, the $CD4^+$ T cell count rises to above 200 per µL of blood or other AIDS-defining illnesses are cured.

CDC CLASSIFICATION OF HIV INFECTION

CDC 1	(stage 1)	Acute seroconversion
CDC 2	(stage 2)	Asymptomatic infection
CDC 3	(stage 3)	Persistent generalized lymphadenopathy (PGL)
CDC 4	(stage 4)	OTHER DISEASES

Stage 4a	Constitutional disease (fever, weight loss and diarrhoea)
Stage 4b	Neurological (e.g. AIDS-related dementia)
Stage 4c	Secondary infection
Stage 4c1	Opportunistic infections diagnostic of AIDS (e.g. *Pneumocystic carinii pneumonia* (PCP), cytomegalo virus (CMV) retinitis or toxoplasma)
Stage 4c2	Other secondary infections not diagnostic of AIDS (e.g. oral candidiasis)
Stage 4d	Secondary neoplasia (e.g. Kaposis sarcoma or lymphoma)
Stage 4e	Other conditions possibly associated with HIV infection (e.g. seborrhoic dermatitis or herpes zoster)

CDC Group I – Acute seroconversion[3] syndrome

This is the stage when the virus is multiplying in the body and development of antibodies against the HIV infection. This occurs 4-8 weeks after exposure to the infection (after the window period – the time period from day of infection to development of features/complains which is approximately up to 3 months). The antibodies produced are not capable of destroying the virus because of its unique structure. It is a self-limiting non-specific illness associated with unexplained fever. Some of the complain this healthy looking individuals have include – fever, rigors, arthralgia, myalgia, malaise, lethargy, anorexia, nausea, diarrhoea, enlargement of lymph nodes, sore throat, headache, photophobia (fear of light), faint pink skin rashes, stiff neck, retro-orbital pain, neuritis, myelopathy, irritability, depression or frank encephalopthy and rarely brain function disturbances. Individuals in the window period and seroconversion phase individuals are **HIGHLY INFECTIOUS** because they are **HEALTHY** with a **HIGH VIRAL LOAD**.

Laboratory

- Lymphopenia
- Thrombocytopenia
- Increased liver transaminases
- Reduced CD4 T-lymphocytes
- CD4:CD8 ratio is reversed
- Antibodies to HIV may be absent but viral core protein P_{24} antigen may be present

CDC Group II – Asymptomatic Infection

The individual has no complains but the virus continues to multiply and the person remains infectious for a **mean duration of 10 years**. This is only diagnosed by routine HIV antibody testing and surprising absence of any signs and symptoms.

Laboratory

- Depletion of CD4 lymphocytes count and percentages
- Raised CD8 lymphocyte counts and percentages

[3] Conversion from HIV negative status to HIV positive status

- Reversed CD4:CD8 ratios
- Increased serum B_2-microglobulin
- Increased serum and urinary neopterim
- Increased P_{24} antigen titre
- Reduced P_{24} antibody titre

CDC Group III – Persistent Generalized Lymphadenopathy

The patients have enlargement of lymph nodes in more than two sites excluding swelling of the nodes in the groin region of which no other cause is found. The nodes that swell include those in the neck region (posterior and anterior cervical), below the tongue and mandible and axillary (arm pit region). The less commonly affected sites are the post auricular, epitrochlear and retroperitoneal.

A subgroup of patients with asymptomatic HIV infection have PGL defined as lymphadenopathy of > 1 cm at two or more extra-inguinal sites for more than 3 months in the absence of causes other than HIV infection. The nodes are symmetrical, firm, mobile and non-tender and there may or may not be associated spleenomegally. On microscopy the nodes show hyperplasia of follicles and proliferation of the capillary endothelium.

CDC Group IV – Symptomatic HIV infection (AIDS)

After a variable period of asymptomatic HIV infection a variety of signs and symptoms herald clinical deterioration of HIV disease due to marked reduction in the capacity and ability of body immune defence mechanisms. There is increased susceptibility to opportunistic infections, cancers and recurrent severe multiple infections. The term AIDS related complex (ARC) is a term that is used to characterize the presence of two or more symptoms and two or more laboratory findings indicative of immune dysfunction. AIDS represents the most advanced state of HIV disease that is characterized by a number of signs and symptoms. This can be placed in a number of sub groups as outlined below: -

Clinical progression of the disease leads to profound immunosuppression, which results in (1) increased susceptibility to opportunistic infections and tumours, (2) presence of multiple infections at one time and (3) lack of typical signs and symptoms due to failure of the inflammatory response e.g. cryptococcal meningitis presents without signs of meningismus and without polymorphonuclear leucocytes in cerebrospinal fluid (CSF).

General features (CDC IVa)

- General weakness
- Weight loss
- Night sweats often soaking the beddings
- Diarrhoea

Skin and mucous membranes

- Itchy skin eruptions (dry flaky skin)
- Weeping/wet skin eruptions
- Recurrent small painful ulcers in the mouth and gums
- Oral thrush (white patches in the mouth)

- Recurrent whitish vaginal discharge
- Small pimple-like eruptions on the lips and genitals
- Herpes zooster
- Recurrent boils

Neurological Disease (CDC Group IVb)

Direct infection of glial cells and or the effects of viral products on the neurons cause neurological disease.

Features

- Sensory polyneuropathy
- Myelopathy – motor signs and sphincter disturbance
- Autonomic neuropathy
- Cognitive impairment e.g. decrease in memory, poor concentration and personality change
- Loss of sensation
- Loss of power in some body muscles
- Impaired memory
- Poor concentration
- Personality change
- Dementia

Respiratory system

- Tuberculosis
- Pneumonia

Gastro-intestinal Manifestations

- Mouth/Oesophagus
  - Dysphagia – candidiasis
  - Retrosternal discomfort – HSV
  - Oral ulceration – CMV

- Small bowel/colon
  - Chronic diarrhoea – parasites
  - Steatorrhoea – Cryptosporidium parvum
  - Weight loss– Isospora beldi, microsporidia, viruses (CMV, HSV, adenovirus), bacteria (salmonella, compylobacter, myocobacterium avium intracellulare, non-infective enetropathy of unknown cause).

- Rectum/colon
  - Bloody diarrhoea – bacterial e.g. shigella

- Weight loss and diarrhoea – neoplasia (Kaposis sarcoma, lymphoma, squamous cell carcinoma) and infection (disseminated e.g., disseminated mycobacterium avium intracellulare

Haematological Complications

- Anaemia – usually mild normocytic normochromic
- Neutropenia usually mild
- Thrombocytopenia (10 –20 X 10^9/L)

Opportunistic Disease in HIV Infection

Protozoa

- Pneumocystic carinii – treatment - cotrimoxazole + IV pentamidine for 21 days
- Toxoplasma gondii – causes encephalitis and cerebral abscesses leading to convulsions and headache – treatment - pyrimethamine/sulphanamide(SP) and clindamycin and pyrimethamine

Cryptosporidium parvum

An acute self-limiting diarrhoea – stool watery, nausea, vomiting and anorexia. Stain stool – Kinyou acid fast stain
Treatment – supportive, try non-absorbable aminoglycosides – paromycin

Micrisporidiosis

- Causes diarrhoea
- Treatment – albendazole

Fungal

Cryptococcus

- Indian ink stain
- Fluconazole or amphotericin B

Candidasis

- Treatment – fluconazole or ketaconazole

Viruses

- Cytomegalo virus
- Herpes virus types 1 and 2 – acyclovir 200 mg 4 hourly, in resistant cases foscarnet
- Papova virus – causes progressive multifocal lymphadenopathy (PML) and has no specifc treatment

Bacterial

- S. pneumoniae , H. influenzae and Moraxella catarrhalis – cause pneumonia
- Non-typhoid salmonella spp. Are frequent pathogens
- Mycobacterium infections – mycobacterium avium intracellulare (MAI) treated with rifabatin with clarithomycin and clofazinine

Tumours

- Kaposis sarcoma (KS) – radiotherapy and drugs
- Lymphoma (Non-Hodgkin’s)

CLINICAL STAGING – WHO

Table 1: Revised WHO Staging of HIV/AIDS for Adults and Adolescents

Primary HIV infection

1. Unrecognized
2. Acute retroviral syndrome

WHO Stage 1

1. Asymptomatic HIV infection
2. Persistent Generalized Lymphadenopathy(PGL)

WHO Stage 2

1. Moderate weight loss ≤ 10% body weight (presumed or measured body weight)
2. Herpes Zoster (past or recurrent within last 2 years)
3. Minor mucocutaneous manifestations(seborrhoeic dermatitis, fungal infection, recurrent oral ulcerations, angular cheilosis, prurigo)
4. Recurrent upper respiratory tract infections (bacterial sinusitis, bronchitis, otitis media and pharyngitis)
5.

WHO Sage 3

1. Severe weight loss > 10% of body weight (presumed or measured body weight)
2. Unexplained chronic diarrhoea (> 1 month)
3. Unexplained prolonged fever (intermittent or constant > 1 month)
4. Oral candidiasis (thrush)
5. Oral hairy leukoplakia
6. Tuberculosis, pulmonary (within previous one year)
7. Severe bacterial infections (peumonia, pyomyositis, empyema, bone and joint infection)

WHO Stage 4

A: Conditions where a presumptive diagnosis can be made using clinical signs and simple investigations

1. HIV wasting syndrome
2. Pneumocystsis carinni Pneumonia (PCP) & Pneumocystsis jivoveci Pneumonia (PJP)
3. Recurrent severe bacterial pneumonia >= 2 episodes within 1 year
4. Cryptococcal meningitis
5. Toxoplasmosis of the brain
6. Chronic orolabial, genital or anorectal Herpes simplex for > 1 month
7. Kaposis sarcoma (KS)
8. HIV encephalopathy
9. Extrapulmonary tuberculosis(EPTB)

B: Conditions where confirmatory diagnostic testing is necessary

Cryptosporidiosis with diarrhoea (> 1 month duration), Isosporiasis, Cryptococcosis, extrapulmonary Disseminated non-tuberculous mycobacterial infection, Cytomegalovirus (CMV) restricted on diseases of organs (other than liver, spleen, lymph nodes), Progressive Multifocal Leukoencephaloptay (PML), Any disseminated endemic (mycosis) - Hisptoplasmosis, Coccidiomycosis, Candidiasis (oesophageal, bronchi, trachea or lungs), Non-typhoid Salmonella (NTS) Septicaemia, Lymphoma cerebral or B cells NHL, Invasive cervical cancer and Visceral leishmaniasis

Table 2: Revised WHO Staging of Paediatric HIV/AIDS

WHO Stage 1
1. Asymptomatic HIV infection 2. Persistent Generalized Lymphadenopathy(PGL) 3. Hepato-spleenomegally
WHO Stage 2
1. Papular pruritic eruptions (PPE) 2. Sebborhoeic dermatitis 3. Fungal nail infection 4. Angular cheilosis 5. Limar gingival erythema 6. Extensive HPV or molluscam infection (> 5% of body area or face) 7. Recurrent ulceration (> 2 episodes /6 months) 8. Parotid enlargement 9. Herpes zoster > 1 episode in 1 month 10. Recurrent or chronic URTI, otitis media, otorrhoea and sinnisitis (> 2 episodes /6 months)
WHO Stage 3
1. Unexplained moderate malnutrition (-2 SD or Z score), not repsondingto standard therapy 2. Unexplained persistent diarrhoea (> 14 days) 3. Unexplained prolonged fever (intermittent or constant > 1 month) 4. Oral candidiasis (thrush) outside neonatal period 5. Oral hairy leukoplakia 6. Tuberculosis, pulmonary 7. Severe recurrent presumed bacterial pneumonia (> 2 episodes in 12 months) 8. Acute necrotizing ulcerative gingivitis /periodontitis 9. Lymphoid interstitial pneumonia (LIP) 10. Unexplained anaemia (< 8 gm/dl), neutropenia, (< 1000/mm^3) or thrombocytopenia (< 30000/mm^3) for 1 month 11. HIV related cardiomyopathy and nephropathy
WHO Stage 4
• Unexplained severe wasting or severe mal nutrition (- 3SD or Z score) not responding to standard therapy , Pneumocystitis pneumonia (PJP, PCP) • Recurrent severe bacterial infections (> 2 episodes/12 months, excluding pneumonia) • Chronic orolabial or cutaneous HSV (lasting > 1/12 months) • Extrapulmonary TB and Kaposis sarcoma (KS), Oesophageal conditions , CNS toxoplasmosis and Cryptococcal meningitis, Any disseminated endemic myocosis • Cryptococcosis, extrapulmonary, Cryptosporidiosis or Isosporiasis (with diarrhoea > 1 month) • CMV infection or organ other than the liver, spleen and lymph nodes (and onset ago > 1 month) • Disseminated mycobacterial other than TB, Candida of the trachea, bronchi and lungs • Acquired recto-vesicular fistula, Cerebral or B cell NHL, Progression multifocal leucoencephalopathy (PML), HIV encephalopathy

CLINICAL FEATURES OF HIV/AIDS

HIV/AIDS presents in a number of ways or with a number of diseases best grouped in four main groups, which have done by the Centre for Disease Control (CDC) or WHO

DIAGNOSIS

Bangui Criteria – weight loss, diarrhoea and fever

1. Antibody detection - IgG antibody to envelop components (gp 120 and its subunits)- this is the most commonly used marker of infection with HIV – ELISA. The widow period of approximately 3 months. Have no protective function. 3rd generation ELISA's are highly sensitive. Should do two ELISA tests for antibody to diagnose HIV. Viral nucleic acid (PCR) should be done.
2. Antigen detection - Viral P24 antigen (P24 Ag) is detected shortly after infection but disappears by 8-10 weeks after exposure.
3. Viral nucleic acid (RNA or ProDNA) - Polymerase chain reaction (PCR) can be used for confirmation of sero status or Western Blot assays
4. CD4 count (normal 500-800 cells/mm^3)
5. Isolation of the virus
6. Full blood count and ESR
7. Liver function tests (LFTs)
8. Urea and electrolytes (U/E)
9. Chest X-ray
10. Cervical cytology
11. VDRL, toxoplasmosis serology, crtptococcal antigen.

HIV test

Many people are unaware that they are infected with HIV. Less than 1% of the sexually active urban population in Africa has been tested, and this proportion is even lower in rural populations. Furthermore, only 0.5% of pregnant women attending urban health facilities are counselled, tested or receive their test results. Again, this proportion is even lower in rural health facilities. Therefore, donor blood and blood products used in medicine and medical research are screened for HIV.

HIV tests are usually performed on venous blood. Many laboratories use ***fourth generation*** screening tests which detect anti-HIV antibody (IgG and IgM) and the HIV p24 antigen. The detection of HIV antibody or antigen in a patient previously known to be negative is evidence of HIV infection. Individuals whose first specimen indicates evidence of HIV infection will have a repeat test on a second blood sample to confirm the results.

The window period (the time between initial infection and the development of detectable antibodies against the infection) can vary since it can take 3–6 months to seroconvert and to test positive. Detection of the virus using polymerase chain reaction (PCR) during the window period is possible, and evidence suggests that an infection may often be detected earlier than when using a **fourth generation EIA screening test.**

Positive results obtained by PCR are confirmed by antibody tests. Routinely used HIV tests for infection in neonates, born to HIV-positive mothers, have no value because of the presence of maternal antibody to HIV in the child's blood. HIV infection can only be diagnosed by PCR, testing for HIV pro-viral DNA in the children's lymphocytes.

IS THERE TREATMENT FOR HIV/AIDS?

There is **NO CURE** for HIV infection and AIDS disease. Therefore it is very important for one to **PROTECT HIMSELF/HERSELF** from contracting HIV/AIDS. Currently there are antiviral drugs that are used to reduce the viral load in the body so as to give the body a chance to enhance the number of defence cells to boost the immunity. These drugs are also being given to HIV positive pregnant mothers to reduce transmission to the unborn baby. The drugs are very expensive and have to be administered throughout the infection. Studies on underway to try and develop a vaccine against HIV infections.

PREVENTION

The main stay in protection of oneself from contracting HIV infection it is paramount that ALL the youths change their ATTITUDES towards their sexual life styles. Attitude can define as a "mental set" held by an individual that affects the ways that a person responds to other people, objects, events, occasions or ideas.

1. **Abstinence**
2. Being faithful to one partner
3. Condoms
4. Other measures
    a. Proper sterilization of items containing fresh blood and body fluids from HIV infected persons
    b. Use of protective gear when handling blood and body fluids of HIV infected persons
    c. In case of accidental contact there is prophylactic treatment that must be given **WITHIN 24 HOURS** of contact