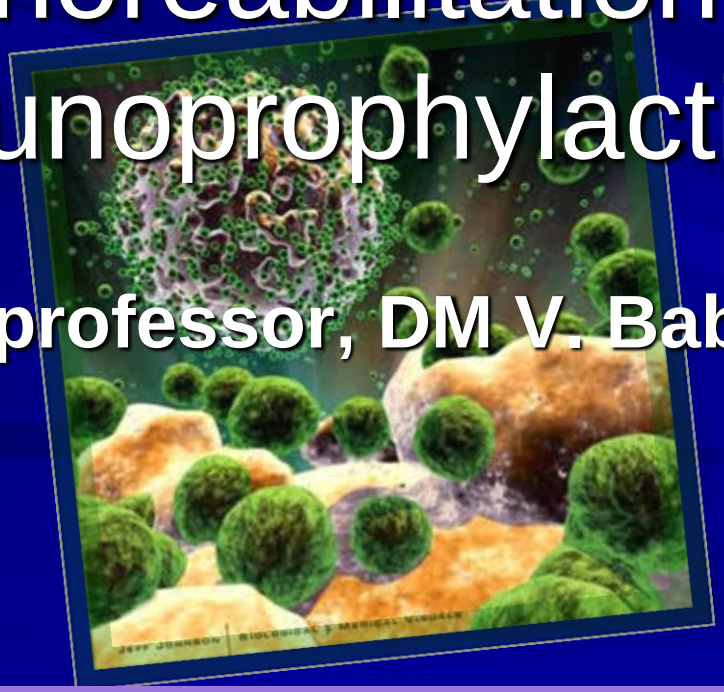
LECTURE 2

Diseases of the immune system. Principles of immunodiagnosis, immunotherapy, immunoreabilitation and immunoprophylactics.



Lecturer: professor, DM V. Babadzhan.

Immunodeficiency Disorders

- Immunodeficiency disorders associated with:
  - Defect or impairment in immune function.

OR

  - Induced through infections and various environmental factors.

Immunodeficiency Diseases

Primary: **Usually congenital, resulting from genetic defects in some components of the immune system.**

Secondary: (Acquired): **as a result of other diseases or conditions such as:**

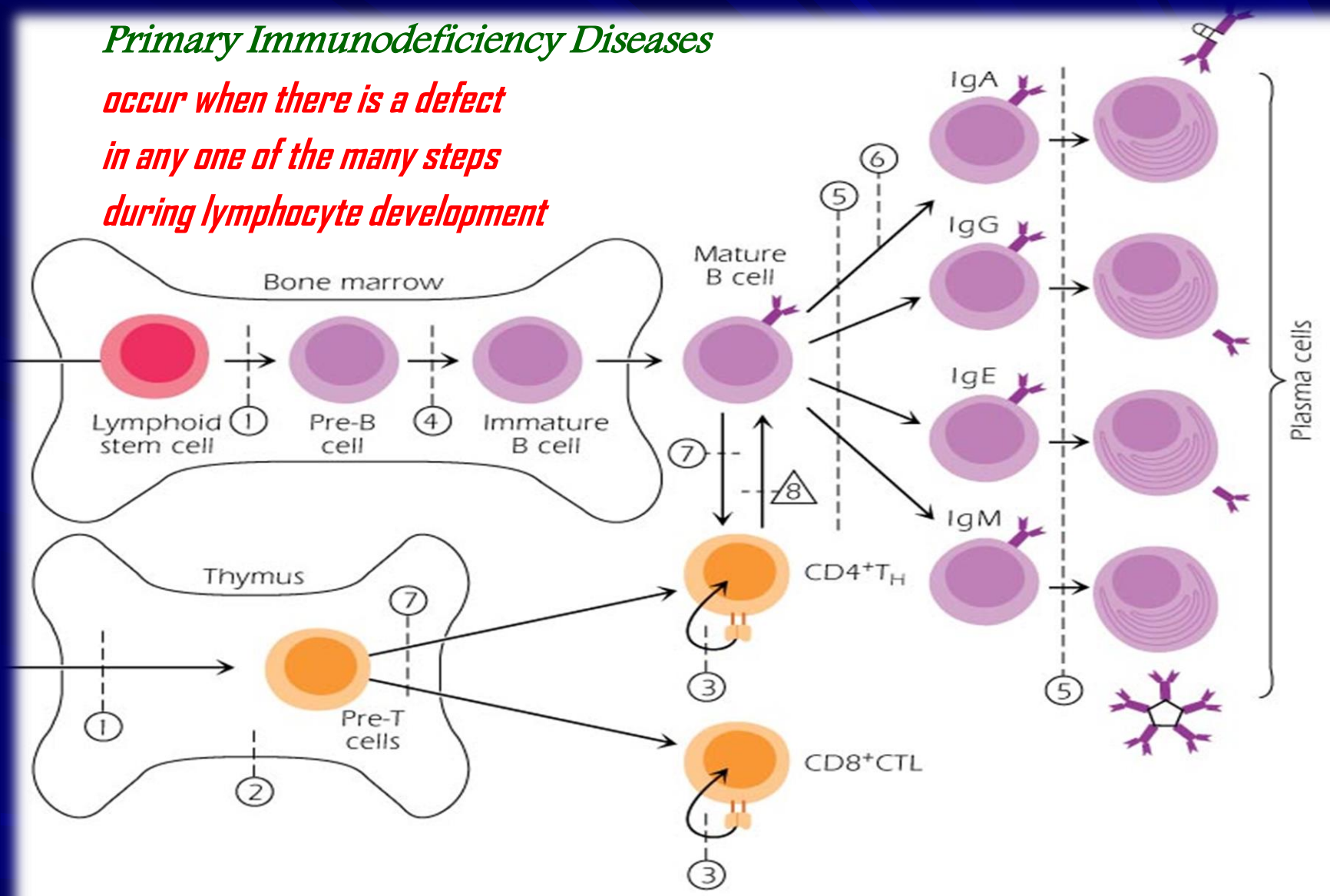
- **»HIV infection**
- **»malnutrition**
- **»immunosuppression**

Primary Immunodeficiency Diseases

occur when there is a defect

in any one of the many steps

during lymphocyte development



Key:

1. Severe combined immunodeficiency syndrome
2. Congenital thymic aplasia (DiGeorge Syndrome)
3. T cell signaling deficiency
4. X-linked agammaglobulinemia (Bruton's)
5. Common variable immunodeficiency disease (various forms)
6. Selective IgA deficiency
7. Bare lymphocyte syndrome
8. Hyper IgM syndrome

Manifestations:

- Recidivic bacterial-viral infections which are characterized:
- a) chronic curse;
- b) incomplete reconvalescence;
- c) unsteady remissions;
- d) unusual microflora (opportunistic infection, with multiresistence stability to the antibiotics).
- Unusual reactions on vaccines.
- Information of physical investigation:
- delay of development; decline of body mass; subfebril tempereture; increase, excalation or complete absence of lymphatic knots, amygdales, thymus; dermatitises, skin abscesses; candidosis of mucous membrane of mouth cavity.
- Haematological changes: leukocitopenia, thrombocitopenia, anaemia.
- Paratherapeutic interferences:
- chemotherapy; splenectomy; irradiation.
- Protracted stress.
- Autoimmune diseases.
- Tumour.

Symptoms:

- Recurrent respiratory infections.
- Persistent bacterial infections →sinusitis, otitis and bronchitis.
- Increased susceptibility to opportunistic infections (OIs) and recurrent fungal yeast infections.
- Skin and mucous membrane infections.
- Resistant thrush, oral ulcers and conjunctivitis.
- Diarrhoea and malabsorption.
- Failure to thrive and delayed or incomplete recovery from illness.

Classification of Primary IDDs

- **Primary B cell immunodeficiency:**
  - X-linked Agammaglobulinaemia (Bruton,s disease)
  - Selective IgA deficiency
- **Primary T cell immunodeficiency:**
  - Di George syndrome
  - Ataxia – telangiectasia
  - Wiskott – Aldrich syndrome
  - Acquired immunodeficiency
  - Chemotaxis deficiency
  - Chronic granulomatous disease
  - Chediak – Higashi syndrome
  - Leukocyte adhesion deficiency
- **Complement system deficiency**

Etiology

- Etiology associated with
  - Genetic defects of missing enzymes.
  - Specific development impairment (pre-B-cell failure).
  - Infections, malnutrition and drugs

Primary B Cell Immunodeficiency

- **Common variable immunodeficiency associated with**
  - **Mature B cells failure to differentiation into mature plasma secreting cells (antibody forming cells).**

X-linked Agammaglobulinaemia (XLA)/Bruton's Disease:

- Deficiency of B cell tyrosine kinase causing failure in the development of pre-B cell maturation to B cells.

- Majority of XLA patients show:
  - Profound hypogammaglobulinaemia involving all immunoglobulin classes with <1% B cells in normal peripheral blood.

X-linked Agammaglobulinaemia (XLA)/Bruton's Disease

inherited recession, meets for boys and to show up on 1 of life as recidivic bronchitis, pneumonias, otitides, sinuitiss, enterokolity, conjunctivitises, pyodermas, limfadenity.

Diagnostics: a double decline of concentration of immunoglobulines is in blood (IGG - less than 2 g/l, on 1 - less than 1 g/l, IGA and IGM for the children of school age less than 0,2 g/l), low amount of B-lymphocyts (< 5/1000 limfocitov).

Treatment: intravenous immunoglobulines (IVIG) enter in day's dose 400 mgs/kg of iv tiny for 1 ml/kg/h prematurely born and 4-5 ml/kg/h to the worn children. With mass of <1500 g and IGG of <3 g/l of IVIG it is entered prematurely born children for the prophylaxis of infections. IVIG enter to achievement of concentration IGG in blood not below than 4-6 g/l daily or in a day 3-5 injections to 1-2,5 g/kg, after - 1 time per 7 days or 1 time per a month.

X-linked Agammaglobulinaemia (XLA)/Bruton's Disease

Leucocytes		11,3		Norma 4 – 9 x 10^9/л				
Neutrophilles 43 – 71 % 2000-6500	st\n 1 – 4 % 80-400	segm\nuc	Eos. 0,5 – 5% 80-370	Bas. 0 – 1% 20-80	Mon. 3 – 9% 90-720	Lymph. 25 – 37% 1600-3000	B. lymph. 1-5% 80-500	Plasm. 0 – 1% 20-80
58	5	53	4	1	8	29	0	
5800	490	5310	410	20	700	2900	0	

Index		Result	Norma (Un)	Index		Result	Norma (Un)
T- lymph	%	76	50 – 80	Ig G		15	8,0-18,0 g\l
CD-3	Abs. ind.	2110	1000-2200				
T- helpers	%	30	33-46	Ig M		3,3	0,2-2,0 g\лл
CD-4	Abs. ind.	302	309-1571				
T- cytotoxic	%	30	17-30	Ig A		0,1	0,3-3,0 g\лл
CD-8	Abs. ind.	870	282-999				
IRI	CD4 /CD8	1,01	1,4-2,0	CIC		45	30 – 50 Un opt. density
NK-cells	%	25	12 – 23	Absorbing activity	Ph. Ind.	83	60 – 80%
CD-16	Abs. ind.	247	72-543		Ph. number	3,9	1,5 – 3,5
B-lymph	%	29	17-31	NBT-test	Spontaneous	13	≤ 10%
CD-22	Abs. ind.	496	109-532		Inductive	31	-
RBTL	Spontaneous	9	До 10%		Result	18	≥16%
	Inductive	60	50-70%	Complement	CH-50	45	30 – 60 hem. Un/ml

Selective IgA deficiency (IgA D)

- Patients with IgA deficiency have:
  - IgA levels < 5mg/dL with normal levels of other Igs and
  - 50% have chronic otitis, sinusitis or pneumonia.

- IgA committed B lymphocytes:
  - Fail to mature into IgA-secreting plasma cells caused by intrinsic B cell defect.

- **Patients of IgA deficiency are susceptible to:**
  - **Allergic conjunctivitis, urticaria and asthma.**
  - **Autoimmune and neurological disorders.**
  - **Various gastrointestinal diseases (food allergy).**
  - **recurrent sinopulmonary infections.**

Severe Combined Immunodeficiency Disease (SCID)

Disorder characterized by:

- **Deficiency in both B and T lymphocyte functions with markedly low IgG, IgA and IgE levels.**

- **SCID associated with:**
  - **Children failure to thrive.**
  - **chronic respiratory infections.**
  - **Gastrointestinal and/or cutaneous infections particularly recurrent viral, bacterial, fungal and protozoan infections in 6 months' infants.**

- SCID manifests early with:
  - Persistent and recurrent diarrhoea, otitis, thrush and respiratory infections in the first few months of life.
- T cell defects associated with:
  - Candidiasis, CMV infection, measles and varicella leading to life threatening pneumonia, meningitis and sepsis.
- SCID managed through Ig infusion, stem cell transplantation and gene replacement.

T Cell Immunodeficiency Diseases

- **T cell congenital disorders display:**
  - **Little or no cell mediated immunity and may involve B cell deficiencies.**

- **Patients particularly susceptible to:**
  - **Repeated fungal (*Candida*) infection.**
  - **Protozoan and viral infections.**

Primary T cell immunodefiency includes:

- Di-George syndrome
- Wiskott-Aldrich syndrome
- Cartilage hair hypoplasi,
- Ataxia - telangiectasia
- Defective expression of class II MHC molecules
- Defective expression of CD3-T cell receptor (TCR) complex

Di George Syndrome (Thymic Aplasia)

Congenital disorder characterized by:

- **Lack of embryonic development or underdevelopment of the 3rd and 4th pharyngeal pouches.**
- **Thymic hypoplasia, hypothyroidism and congenital heart disease.**
- **Patients susceptible to uncontrolled opportunistic infections.**
  - **Impaired in cellular mechanisms.**
  - **Profound lymphopenia (T cell <1200μL).**
- **Treatment: transplantation of thymus; prescription of thymalin 1 ml of im 1-2 times per a week. If a patient experiences 6-monthly age, there is gradual spontaneous renewal of T-cell immunity.**

Di Gorgi syndrome - isolated T-cells immunodeficit

Leucocytes		10,5		Norma 4 – 9 x 10^9/л				
Neutrophilles 43 – 71 % 2000-6500	st\n 1 – 4 % 80-400	segm\nuc	Eos. 0,5 – 5% 80-370	Bas. 0 – 1% 20-80	Mon. 3 – 9% 90-720	Lymph. 25 – 37% 1600-3000	B. Lymph. 1-5% 80-500	Plasm. 0 – 1% 20-80
74	5	80	9	1	5	10	1	
7390	590	6210	560	25	505	995	98	

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	Abs. ind.	198	309-1571				
T- cytotoxic CD-8	%	10	17-30	Ig A		3,9	0,3-3,0 g\l
	Abs. ind.	102	282-999				
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Ataxia Telangiectasia (AT)

Autosomal recessive progressive neurodegenerative childhood disorder associated with:

- **Lack of coordination (cerebella ataxia) and dilation of facial blood vessels (telangiectasis) and slurred speech.**
- **Patients have defective mechanisms of DNA repair and are predisposed to leukaemias and lymphomas.**
- **Extremely sensitive to radiation exposure and susceptible to chronic respiratory infections.**

Wiskott-Aldrich Syndrome (WAS)

An X-linked recessive disorder associated with thyrombocytopenia and eczema.

- Patients have
  - Elevated IgA and IgE
  - Low IgM

Variable T cell dysfunctionsT cell dysfunction manifested by:

- Severe herpex virus and *Pneumocystis carinii* infections
- Increased lymphomas and autoimmune diseases.
- Recurrent pyogenic bacterial infections.
- Usually affecting ears, sinuses and lungs.

Hyper-IgE syndrome (Job' syndrome)

- primary ID, which find out the high level of IGE (more than 1000 ME in 1 ml) and presence atopic dermatitis and repeated pneumonias, deep festerings infections with coldstream ("cold" abscesses) in anamnesis, frequent breaks of tubular bones.

Protracted (lifelong) antibiotic treatment is indicated.

Phagocytes defects

Inherited neutropenias, cyclic neutropenia, granulomatosis (violation of killer function of neutrophils and monocyts, forming of infectious granulomes, especially in lymphnods, liver and lungs), deficit glucose-6-phosphatdegydrogenase of neutrophyls, syndrome of «lazy phagocytes».

Defects of complement

The deficit of S1-inhybitor is passed on an autosomas-dominant type and associated with the inherited angioneurotic edema (**Kvinke disease)**.

Secondary immunodeficit state is violation of the immune system, developing in a postneonatal period (in adults) and not subsequent upon genetic defects.

Secondary immunodeficit is dysimmunity, which arise up as a result of somatic and other diseases, and also other factors and have clinical symptoms.

Secondary immunodeficit

a) develops on a background before normally functioning immune system;

b) characterized the proof decline of quantitative and functional indexes of immune status;

c) it is the area of risk development of chronic infectious diseases, autoimmune pathology, allergic diseases and tumor formations.

(Dranik G.N., 2005)

Forms of secondary immunodeficits

The squared **secondary immunodeficit is a syndrome of AIDS, developing as a result of defeat of the immune system the virus of immunodeficit (HIV).**

The **inducting (specified) secondary immunodeficit (ICD-10, code D.84.8) arises up as a result of concrete reasons, causing its appearance: x-ray radiation, cytostatic therapy, application of corticosteroids, traumas and surgical intervention, dysimmunities, developing the secondary in relation to a basic disease (diabetes, disease of liver, kinds, malignant tumors).**

The **spontaneous (unspecified) secondary immunodeficit (ICD-10, code D.84.9) is characterized absence of reason, causing violation of immune reactivity. Clinically shows up as chronic, recidivate infectiously-inflammatory processes of bronchial vehicle, additional bosoms of nose, urogenital and gastroenteric highway, eyes, skin, soft tissues, caused opportunistic microorganisms.**

CLASSIFICATION OF SECONDARY IMMUNODEFICITES

- By the rates of development:
- Acute immunodeficit (conditioned an acute infectious disease, trauma, intoxication and other).
- Chronic immunodeficit (develops on a background of chronic festering-inflammatory diseases, autoimmunity, tumors, persistent viral infection).
- II. By the level of breakage:
- Violation of cellular (T-cells) immunity.
- Violation of humeral (B-cells) immunity.
- Violation of phagocytes.
- Violation of complement system.
- Combined defects.
- III. By prevalence:
- «Local» immunodeficit.
- Systemic immunodeficit.
- IV. By the degree of severity:
- Compensated (miled).
- Subcompensated (moderate).
- Decompensated (severe).

What is HIV/AIDS?

HIV stands for:

Human Immunodeficiency Virus **(HIV)**

AIDS stands for:

Acquired Immune Deficiency Syndrome **(AIDS)**

How does HIV affect the immune system?

- HIV specifically attacks the CD4 cells
- The HIV antibodies produced by the immune system are unable to overcome the infection.
- Over time, HIV progressively weakens the immune system.
- The person becomes “immunodeficient”
- A weak immune system can no longer effectively defend the body.

What is the difference between "having HIV" and "having AIDS" ?

- When the HIV virus enters the body, the person "has HIV".
- HIV is diagnosed by a blood test.

- When the immune system is severely weakened by HIV, resulting in severe opportunistic infections, the person "has AIDS".

- There are specific criteria for diagnosing AIDS.

Acquired Immunodeficiency Syndrome (AIDS)

- HIV-1 predominantly found in East, Central, South Africa and other parts of the world
- HIV-2 reported mainly in W. Africa.

Modes of transmission :

1. Sexual

- The predominant mode

2. Parenteral

•Contaminated needles and syringes

- Contaminated instruments
- Blood and blood product

3. Vertical

Mother to Child Transmission (MTCT)

- Occurs *in utero* during the last few weeks of pregnancy and at child birth.
- MTCT during pregnancy, labour and delivery high.

HIV cannot be transmitted by:

- Casual contact
- Food, air, water
- Vectors-Coughing, sneezing, spitting.
- Shaking hands, touching, dry kissing or hugging.
- Swimming pools, toilets, etc.

Sources of infectious material

All body fluids & tissues are infectious

- The virus has been isolated from various body fluids, particularly blood, CSF, pleural, peritoneal, semen, saliva, breast milk, synovial and vaginal fluids, tear.
- Body organ :spread through transplantation.
- Urine, faeces: rare causes of spread to staff.

HIV Infection/AIDS Staging System

Clinical Stages& Major Clinical Features:

Stage 1: Asymptomatic; persistent generalized lymphodenopathy (PGL) and acute retroviral infection (ARI).

Stage 2: Loss of weight (< 10% of body weight); minor mucocutaneous infections; herpes zoster and recurrent upper respiratory tract infections (URTI).

Stage 3: Loss of weight (>10% of body weight); chronic diarrhoea(> 1 month); prolonged fever; oral candidiasis; oral hairy leukoplakia; pulmonary tuberculosis; severe bacterial infections and vulvovaginal candidiasis.

Stage 4: HIV wasting syndrome; extrapulmonary tuberculosis; Pneumocystis carinii pneumoniae, Candidiasis of the oesophagus, trachea, bronchi or lungs; toxoplasmosis of the brain, cryptosporidiasis with mycobacteriosis; lymphoma; Kaposi's sacoma (KS) and HIV encephalopathy.

Immunopathological Mechanisms of HIV infection

HIV infected patients progress to AIDS disease in three phases:

Early phase: lasts about 2 weeks accompanied by:
Fever, aches and flue-like symptoms with high levels of virus in blood.

Middle phase: lasting months or several years (latent) with:

- Anti-HIV antibodies
- Continuous depletion of CD4 T cells

Late phase (AIDS): characterized by:

- Rapid decline in CD4 T cells,
- Opportunistic infections including viral (herpes simplex, herpes varicella zoster, EBV), bacterial (*M*. t*uberculosis*), fungi (*Candida*-thrush) and protozoan (*Microsporidia*) .
- Cancers (lymphoma; Kaposi's sarcoma).

Pulmonary Infections:

M. Tuberculosis and Pneumocystis pneumonia common when CD4 T cells <200/µl.

- TB in advanced HIV infection often presents atypically with extrapulmonary diseases affecting:
  - Bone marrow, bone,
  - Urinary and gastrointestinal tracts:
  - Liver, regional nodes and the central nervous system.

Gastrointestinal illness:

- Inflammation of the lining of the oesophagus (oesophagitis).
- Fungal (candidiasis) or viral (herpex simplex or cytomegalovirus) infections.
- Chronic diarrhoea also occurs that may be caused by bacteria (*Salmonella, Shigella, Listeria* or *Escherichia coli*).

Major neurological illnesses:

- **Toxoplasma encephalitis of the brain caused by *Toxoplasma gondii*, progressive multifocal leukoencephalopathy (PML), demyelinating disease.**
- **Crytococcal meningitis caused by fungus *Cryptococcus neoformans.***

Malignancies:

AIDS-defining malignancies include:

- **Kaposi's sarcoma presenting as purplish nodules of the skin, mouth, gastrointestinal tract and lungs.**
- **Hodgkin's disease, anal and rectal carcinomas.**
- **High grade B cell lymphomas (Burkitt's lymphoma).**


Thank you