

Immunodeficiency

Imunodeficiency states

- Primary
 - Caused by defined genetic defect
 - Usually rare, but severe (exception: IgA deficiency)
- Secondary
 - Consequence of some other disease, treatment, environmental factors...
 - Usually frequent, but usually clinically mild (exceptions: HIV disease, secondary aganulocytosis).

Immunodeficiency – Clinical manifestation

- Susceptibility to severe and complicated infections.
- Infections may be caused by atypical pathogens.
- Increased frequency of ordinary infections is a less significant sign.
- Insufficient response to antibiotic treatment.
- Increased frequency of tumors, mainly of the lymphatic system.
- Increased frequency of autoimmune and allergic diseases.

Severe combined immunodeficiency (SCID)

- Early clinical manifestation (weeks-months)
- Severe and complicated infections affecting respiratory and gastrointestinal tract and the skin
- Failure to thrive
- Frequent diarrhea
- Usually lymphocytopenia
- T-cell deficiency, B cell present in some patients
- Decreased immunoglobulin levels

SCID, t-GVHR, generalised BCG-itis



SCID

infections caused by atypical pathogens

- Pneumocystis pneumonia
- Cytomegalovirus pneumonitis
- Disseminated BCG-itis
- Infections caused by atypical mycobacteria
- Candidiasis of oropharynx, skin

Patient with SCID



Immunoglobulin Deficiencies

Clinical manifestations begins at 6-12 months (or later), after disappearance of maternal antibodies.

Susceptibility to infection by encapsulated bacteria (Pneumococcus, Haemophilus).

Respiratory tract predominantly affected; patients suffer from recurrent otitis media, bronchitis, sinusitis, pneumonia.

Some patients also suffer from meningitis or chronic diarrhea.

X-linked agammaglobulinemia

- Only boys affected
- Caused by mutation of Bruton's tyrosine kinase.
- Defect in B-cells development - B-cells are not present in blood.
- Clinical manifestation usually begins at 6-12 months
- Severe and complicated respiratory tract infections.
- Very low levels of all immunoglobulin isotypes.

Common variable immunodeficiency (CVID)

- The most frequent (approx 1:10,000) symptomatic primary immunodeficiency.
- Both sexes affected.
- Clinical manifestation begins at any age.
- Frequent and severe respiratory tract infections.
- Proneness to autoimmune diseases.
- Variable decrease of immunoglobulin isotypes, usually markedly decreased IgA and IgG levels.
- B-lymphocytes usually present.

Selective IgA deficiency

- Frequency: 1:400
- Usually only mild manifestation
- Predominantly respiratory tract infections
- Patients are prone to autoimmune diseases
- Beware of anti-IgA antibodies that can cause a severe anaphylactic reaction after artificial IgA administration (by blood, immunoglobulin derivatives)!

T-cell Deficiencies

- Early onset of clinical manifestation.
- Increased susceptibility to viral, fungal, mycobacterial, and protozoal infections.
- Respiratory system most frequently affected, but also other systems can be involved.

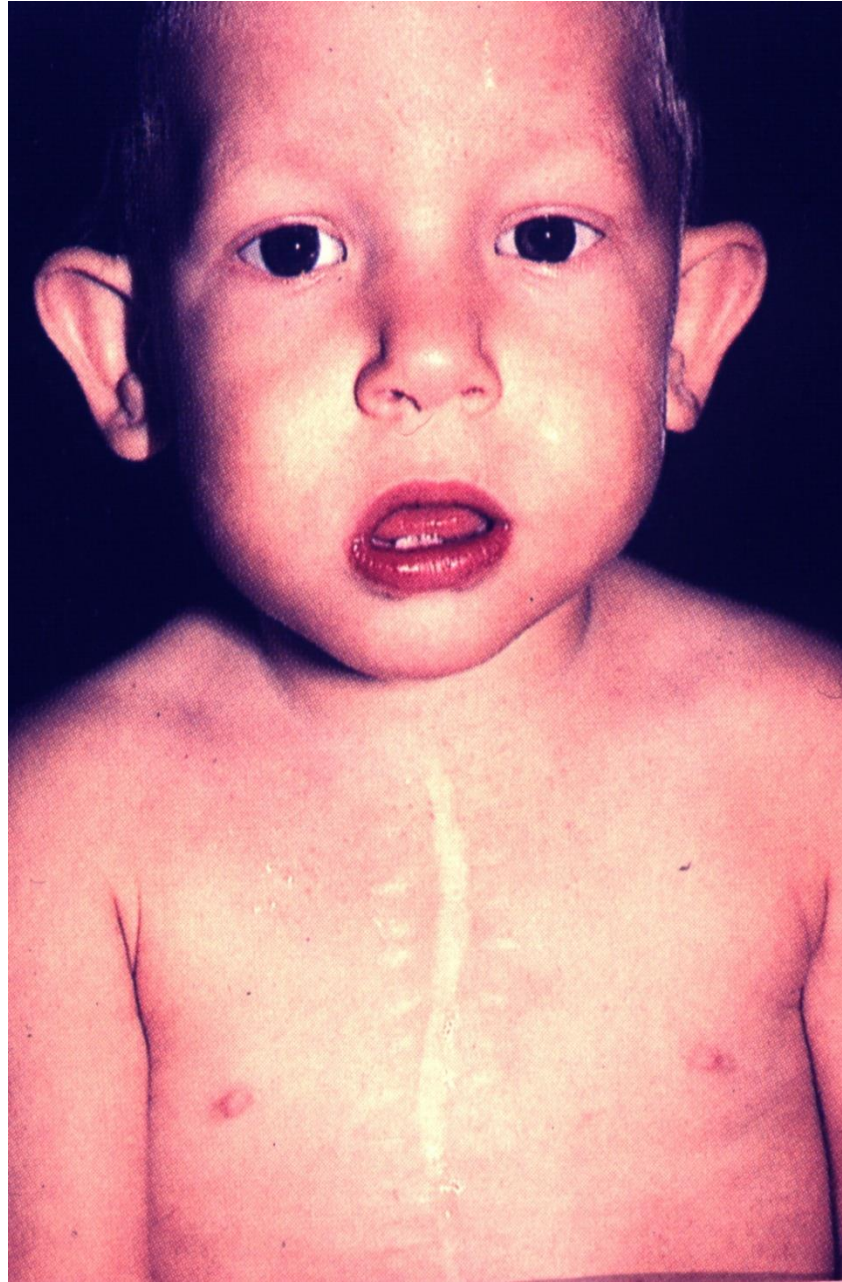
DiGeorge syndrome

- Defect in embryonic development of the 3rd and 4th pharyngeal pouches.
- Cardiovascular defects (e.g Fallot's tetralogy, interrupted aortic arch..)
- Hypoparathyroidism → hypocalcemia → seizures
- Thymic hypoplasia → T cell deficiency
- Typical facies: hypertelorism, micrognathia, low-set, posterior rotated ears.

DiGeorge syndrome



DiGeorge syndrome



Complement deficiencies

- Deficiency of C1-C4: autoimmune systemic disorders, susceptibility to bacterial infections
- Deficiency C5-C9: susceptibility to bacterial infections, mainly to meningococcal meningitis
- Deficiency of C1 INH: hereditary angioedema

Hereditary angioedema

- Deficiency of C1 inhibitor (C1 INH)
- Uncontrolled activation of the complement system after trauma, infection, surgical operation....
- Vasoactive peptides (bradykinin, C3a, C5a) cause increased vascular permeability
- Oedema of the skin, respiratory tract (dyspnoe), gastrointestinal tract (cramps, vomiting)



HEREDITARY ANGIOEDEMA (HAE)

Phagocytic dysfunction

- Early onset of clinical manifestation.
- Susceptibility to bacterial and fungal infections.
- Abscess formation, mainly of the skin, periproctal area, liver, but any area may be affected.

Chronic granulomatous disease

- Recurrent abscesses mainly of the liver, lungs, periproctal area, suppurative lymphadenitis, osteomyelitis.
- Infections are caused mainly by catalase-positive organisms: *St. aureus*, *Candida sp.*, *Serratia marcescens* .
- Usually early onset of symptoms.
- Production of reactive metabolites of oxygen is disturbed (defect of NADPH oxidase).
- Diagnostic tests are based on oxidative-reduction capacity of granulocytes – tetrarrhodamide reduction (“burst test“), NBT (nitro blue tetrazolim) reduction.

Wiskott-Aldrich syndrome

- X-linked disease
- Thrombocytopenia → bleeding tendency
- Severe eczema
- Immunodeficiency
- Severe allergic and autoimmune manifestations
- B-cell lymphomas

Wiskott-Aldrich syndrome



Chromosomal instability disorders

- Recessive inheritance.
- Lead to by disturbed chromosomal breaks repair.
- Patients are markedly prone to malignancies, mainly lymphoid malignancies.
- Accompanied by various other symptoms.
- As regards accompanied immunodeficiency the most typical are: ataxia telangiectasia, Nijmegen breakage syndrome, Bloom's syndrome ..

Ataxia telangiectasia

- Autosomal recessive
- Progressive cerebellar ataxia
- Telangiectasis especially on ear lobes and conjunctival sclera
- Immunodeficiency
- Frequent tumors
- Cause: mutation in ATM gene

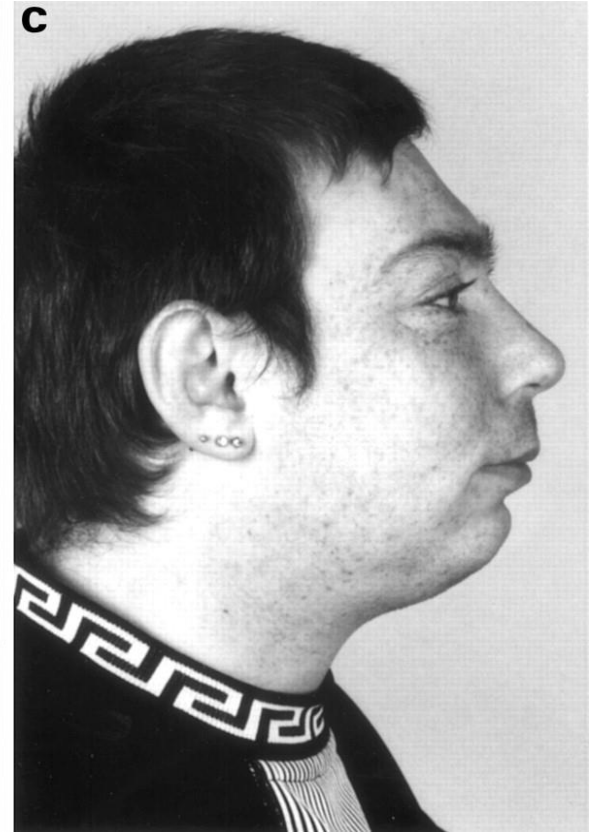
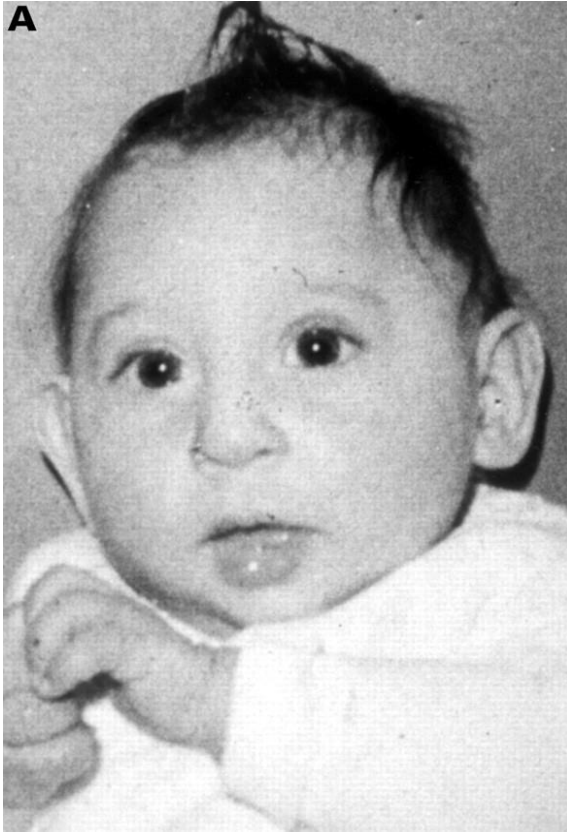
Ataxia telangiectasia



Nijmegen breakage syndrome

- Autosomal recessive disease of chromosomal instability
- Clinically characterized by microcephaly, a distinct facial appearance (bird-like face), short stature, immunodeficiency, radiation sensitivity, and a strong predisposition to lymphoid malignancy.

Nijmegen breakage syndrome



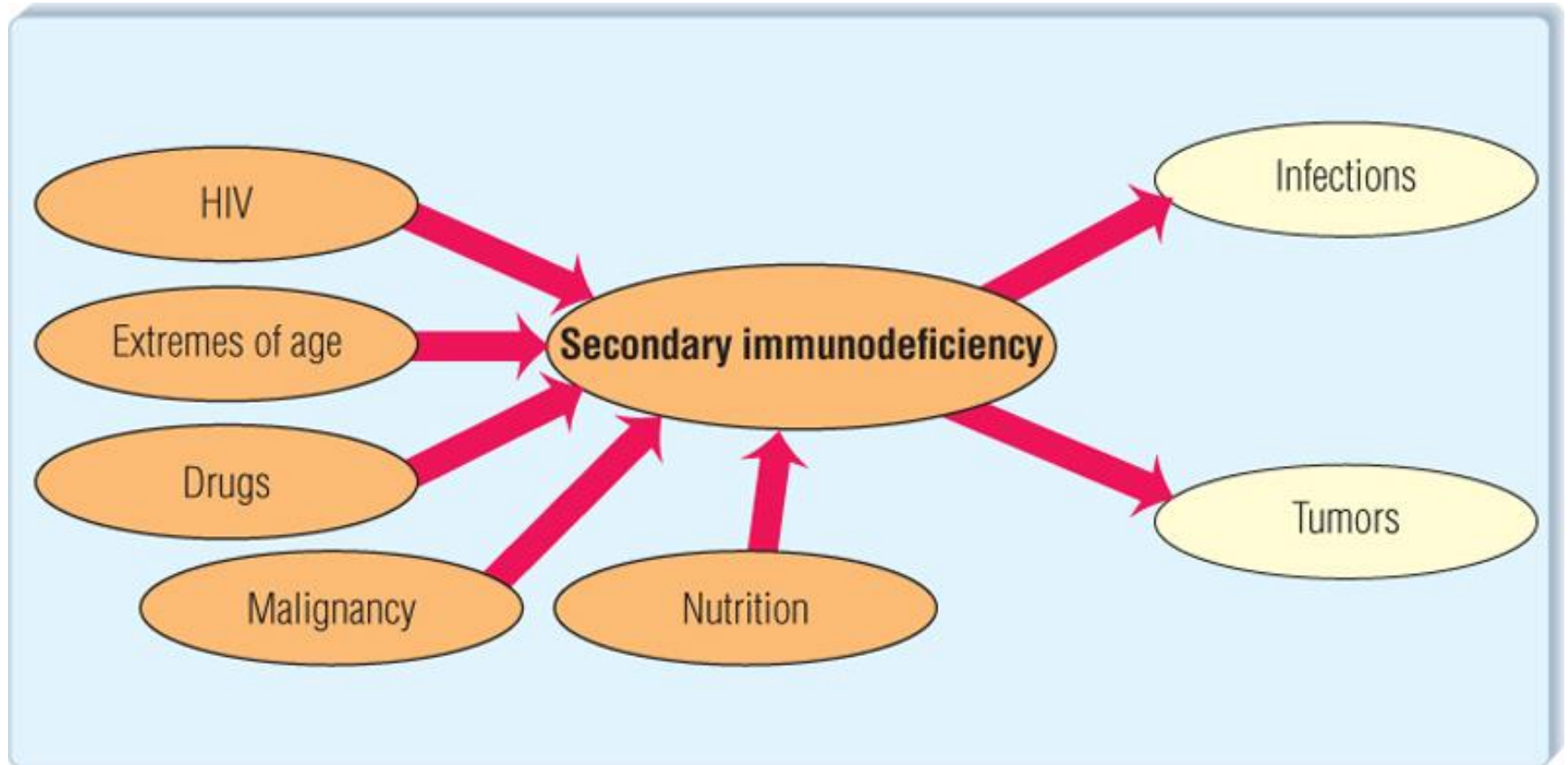
Treatment of primary immunodeficiencies

- SCID and other severe immunodeficiencies: bone marrow transplantation, gene therapy in some cases.
- Antibody deficiencies: immunoglobulin replacement
- Antibiotic prophylaxis

Causes of secondary immunodeficiency

- Metabolic - uremia, diabetes, malnutrition
- Iatrogenic – cytostatics, immunosuppressants
- Malignant tumors
- Viral infections - HIV, CMV, measles, infectious mononucleosis
- Splenectomy
- Stress
- Injuries, operations, general anesthesia

Secondary immunodeficiency



Immunodeficiency after splenectomy

- Disturbed phagocytosis, disturbed „blood filtration“, decreased production of antibodies.
- The most severe complication is hyperacute pneumococcal sepsis (OPSI syndrome) .
- Prevention: vaccination against Pneumococcus, Haemophilus infl. B, Meningococcus. PNC prophylaxis.

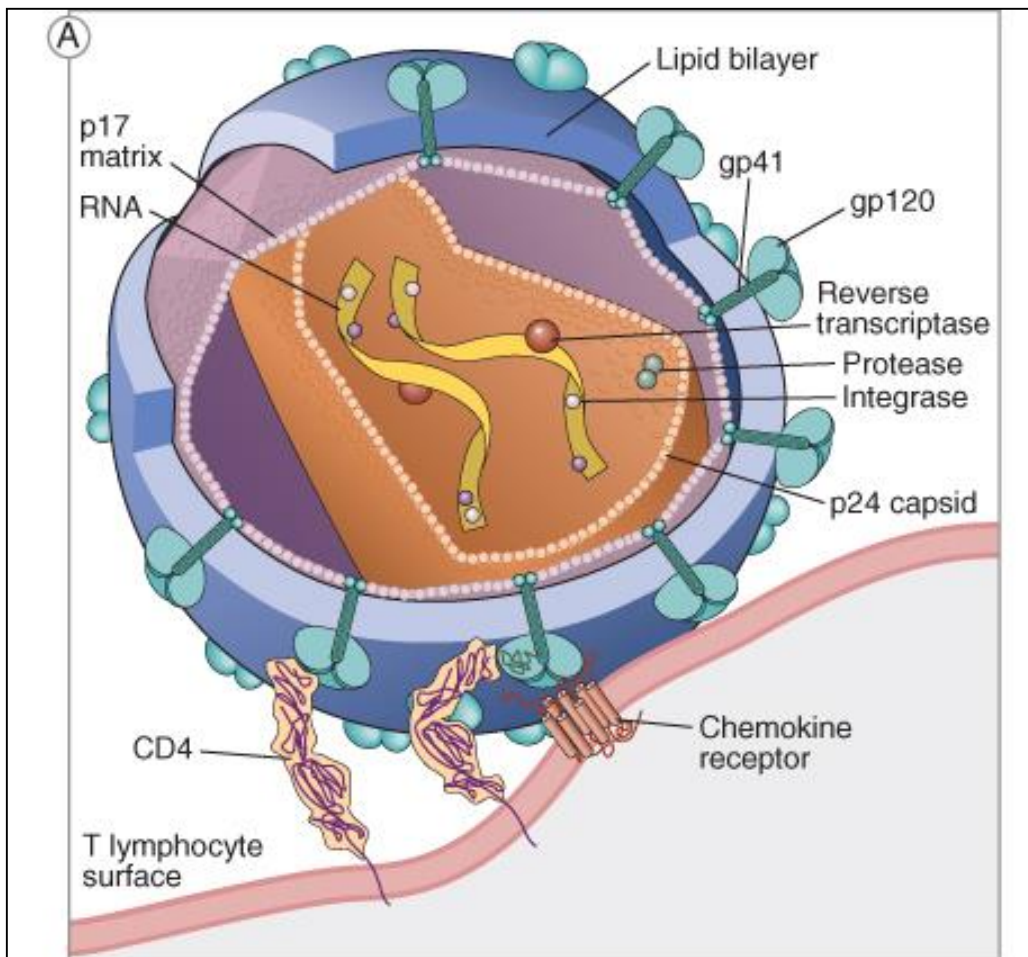
Secondary hypogammaglobulinemia

- **Decreased production of immunoglobulins**
 - **Chronic lymphatic leukemia**
 - **Lymphoma**
 - **Myeloma**
 - **B-cells targeted therapy, immunosuppressive therapy**
- **Loss of immunoglobulins**
 - **Nephrotic syndrome**
 - **Exudative enteropathy**

HIV disease

Ways of transmission

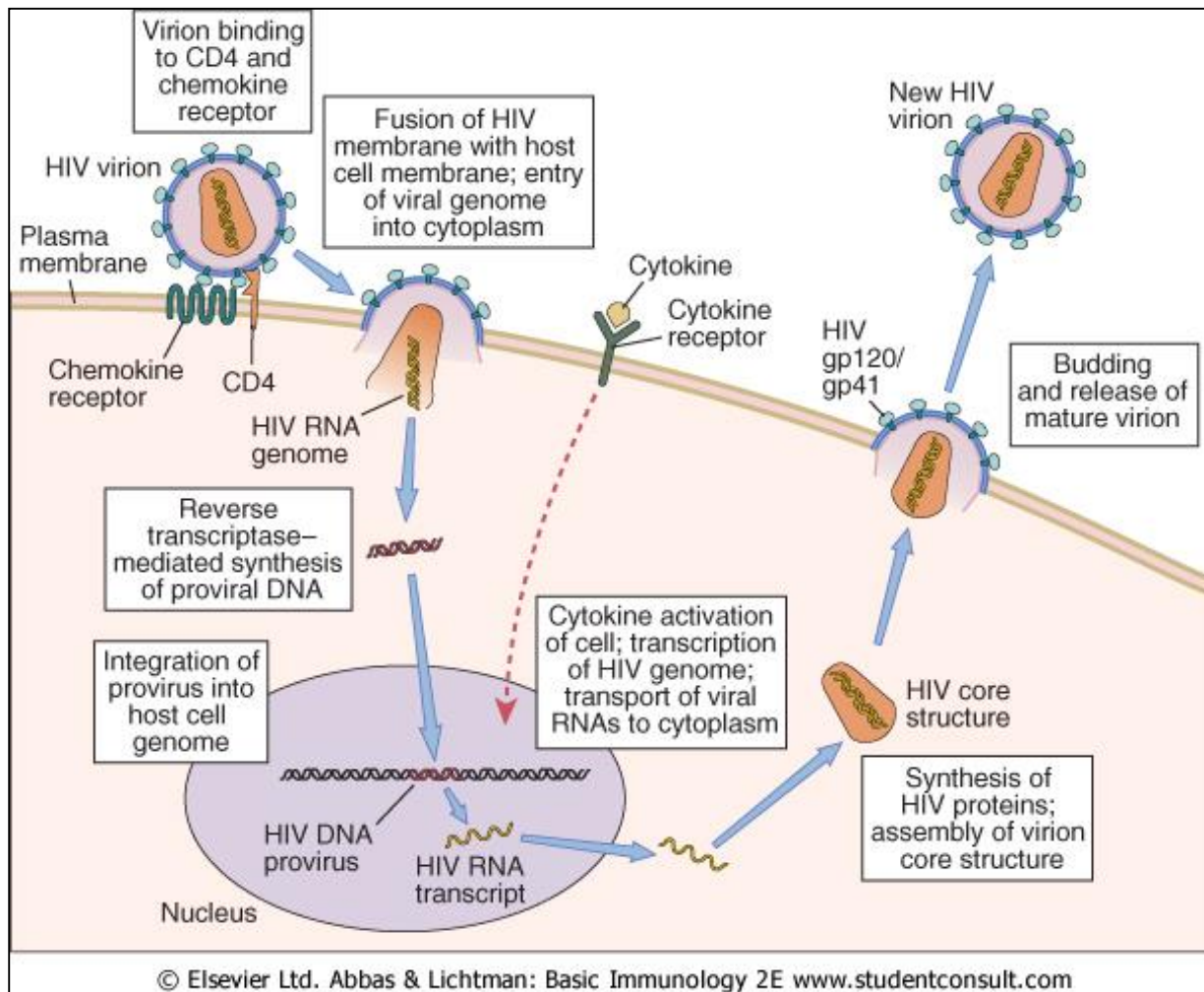
1. Sexual
2. Parenteral – intravenous drug addicts
previously blood products
3. Vertical – mother to child –
transplacental, during delivery,
by breastfeeding



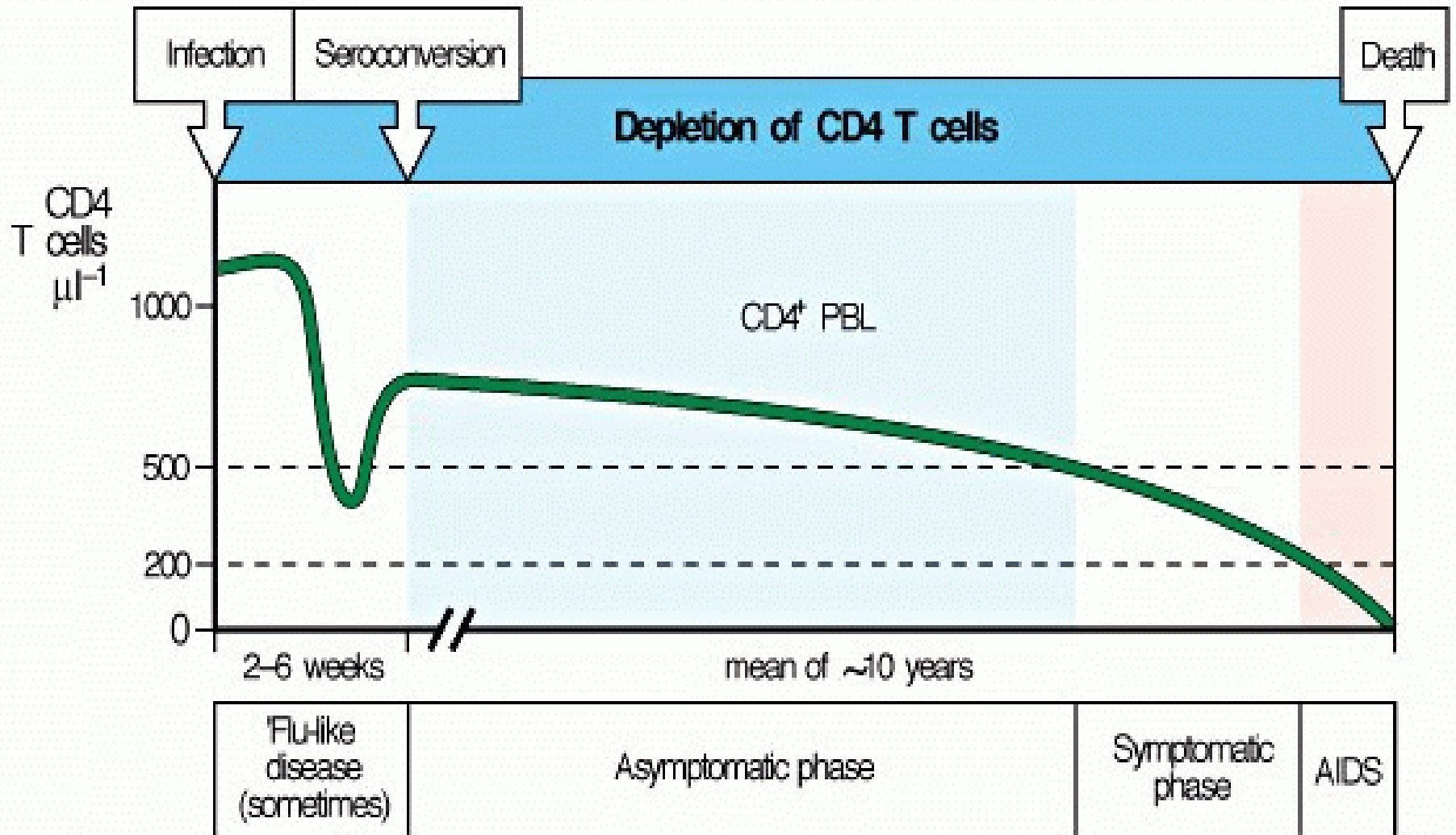
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HIV receptors

- CD4 – expressed on helper T lymphocytes, but also on macrophages. Binds to gp120.
- CCR5, CXCR4 – chemokine receptors. Are co-receptors necessary for majority of virus strains to enter the affected cells. Some (in CR approx. 5%) people are deficient for CCR5 – are relatively resistant to HIV infection. In infected patients, slow progression of the disease.



CD4+ cells number and progression of HIV disease



Classification of HIV disease (CDC) 3 clinical categories

A Asymptomatic disease

B „small“ opportunistic infections

**C „big“ opportunistic infections and
other states that define AIDS**

Clinical category A

- Acute (primary) HIV infection
- Asymptomatic HIV infection
- Persistent generalised lymphadenopathy (PGL)

HIV PRIMOINFECTION

- Acute retroviral syndrome,
(„mononucleosis-like syndrome“)
- Present in 50-70% patients
- 2-6 weeks after infection

Clinical presentaioon of HIV primoinfection

- Fever, lymphadenopathy, pharyngitis
- Rash
- Myalgia, arthralgia, diarrhoea, cephalea
- Thrush
- Neurologic symptoms
- Aphtous stomatitis

Perzistent generalized lympadenopathy



- More than 3 months
- 1/3 HIV-infected persons
- Lymph nodes 0,5-2,0 cm, painless

Clinical category B

- Fever $>38,5$ C more than 1 month
- Diarrhoea more than 1 month
- Oropharyngeal candidiasis
- Vulvovaginal candidiasis
(chronic or difficult to treat)
- Recurrent herpes zoster

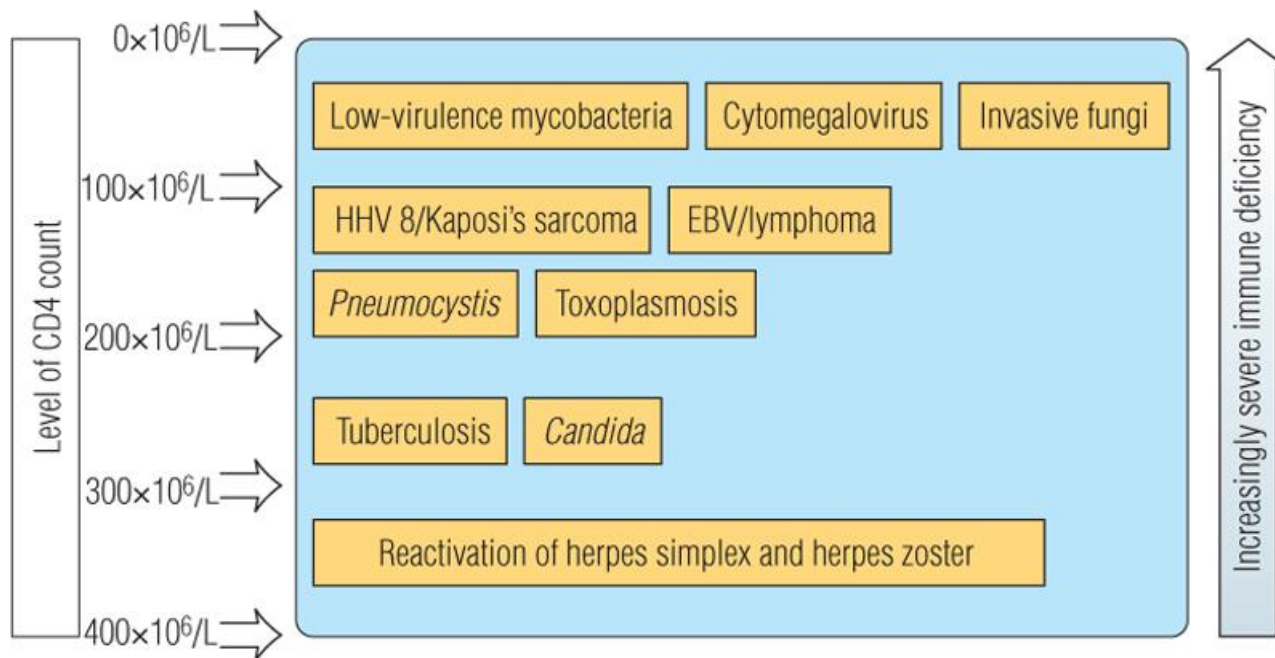
Clinical category C (AIDS)

- Pneumocystis pneumonia
- Brain abscess caused by Toxoplasma
- Esophageal, tracheal, bronchial or lung candidiasis
- Chronic anal herpes, herpetic bronchitis, pneumonia
- CMV retinitis, generalized CMV infection
- Progressive multifocal leukoencephalopathy
- Mycobacterial infections

Opportunistic Infections in AIDS Patients

- Pneumonia due to *Pneumocystis jiroveci* (*carinii*)
- *Toxoplasma* brain abscess
- Cytomegalovirus infection (retinitis, colitis)
- Mycobacterial infections
- Herpes virus and Varicella-Zoster infections

Type of oportunistic infections in HIV/AIDS depends on absolute CD4 count



Clinical category C (AIDS) - tumors

- Kaposhi sarcoma
- Brain lymphoma

Kaposhi sarcoma



Kaposiho sarkom



Kaposi sarkoma



Wasting syndrome



Treatment of HIV-disease

- Antiretroviral
 - **Nucleoside inhibitors of reverse transcriptase** – binding to the active center of reverse transcriptase
 - **Nonnucleoside inhibitors of reverse transcriptase** binding out of the active center of reverse transcriptase
 - **HIV protease inhibitors**
 - **Integrase inhibitors**
 - **Inhibitors of fusion (CCR5 blocking)**

Combination of anti HIV drugs is always used

- Prophylaxis of *Pneumocystis carinii* pneumonia (co-trimoxazol), antiviral and antimycotic antibiotics is sometimes used.

Diagnosis of HIV infection

- Detection of anti-viral antibodies
 - ELISA
 - Western blott
- Detection of antigen p 24