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).

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 patogens

- 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 late).

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
- Clinical manifestation usually begins at 6-12 months
- Severe and complicated respiratory tract infections.
- Very low levels of all immunoglobulin isotypes.
- B-cells not detected.

Common variable immunodeficiency (CVID)

- Both sexes affected.
- Clinical manifestation initiates 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 derivates)!

T-cell Deficiences

-Early onset of clinical manifestation.

-Increased susceptibility to viral, fungal, mycobacterial, and protozoal infections.

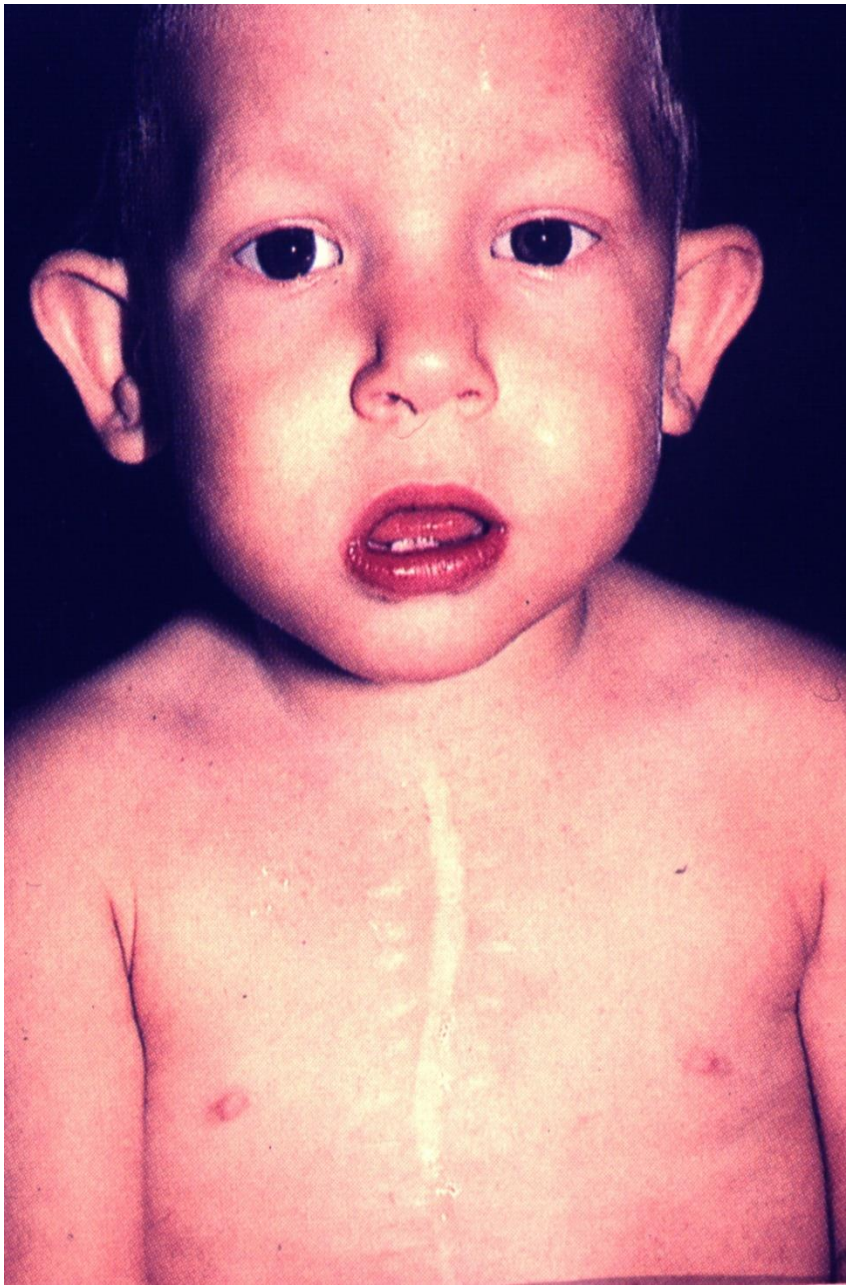
- Respiratory system most frequently affected, but also other systems can be involved.

DiGeorge syndrome

- Defect in embryonic development of the 3rd and 4th pharyngeal pouches.
- Cardiovascular defects (e.g Fallot´s tetralogy, intrrupted aortic arch..)
- Hypoparathyroidism → hypocalcemia → seizures
- Thymic hypoplasia → T cell deficiency
- Typical facies: hypertelorism, micrognatia, low-set, posterior rotated ears.

DiGeorge syndrome

DiGeorge syndrome

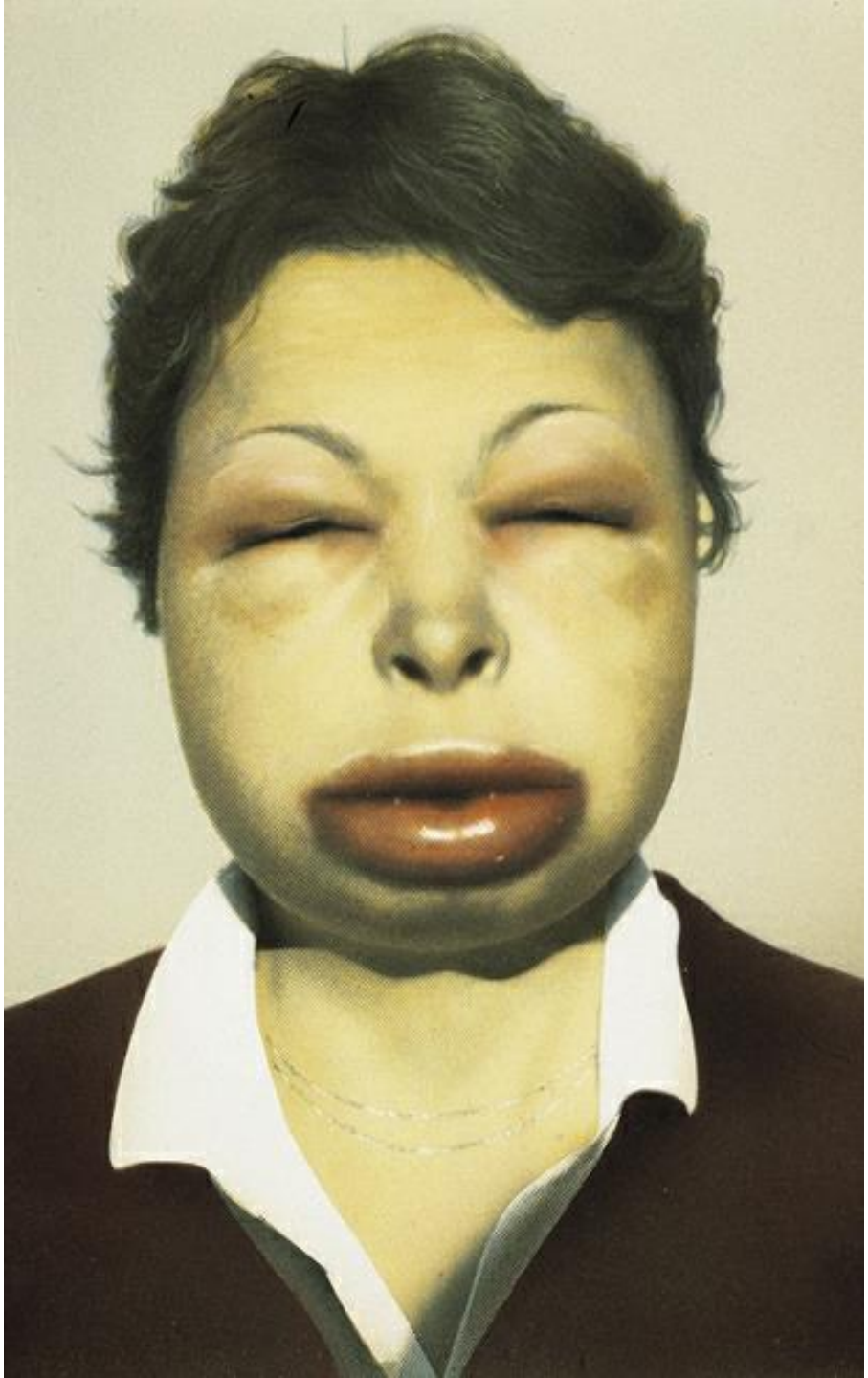


Complement deficiencies

- 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.

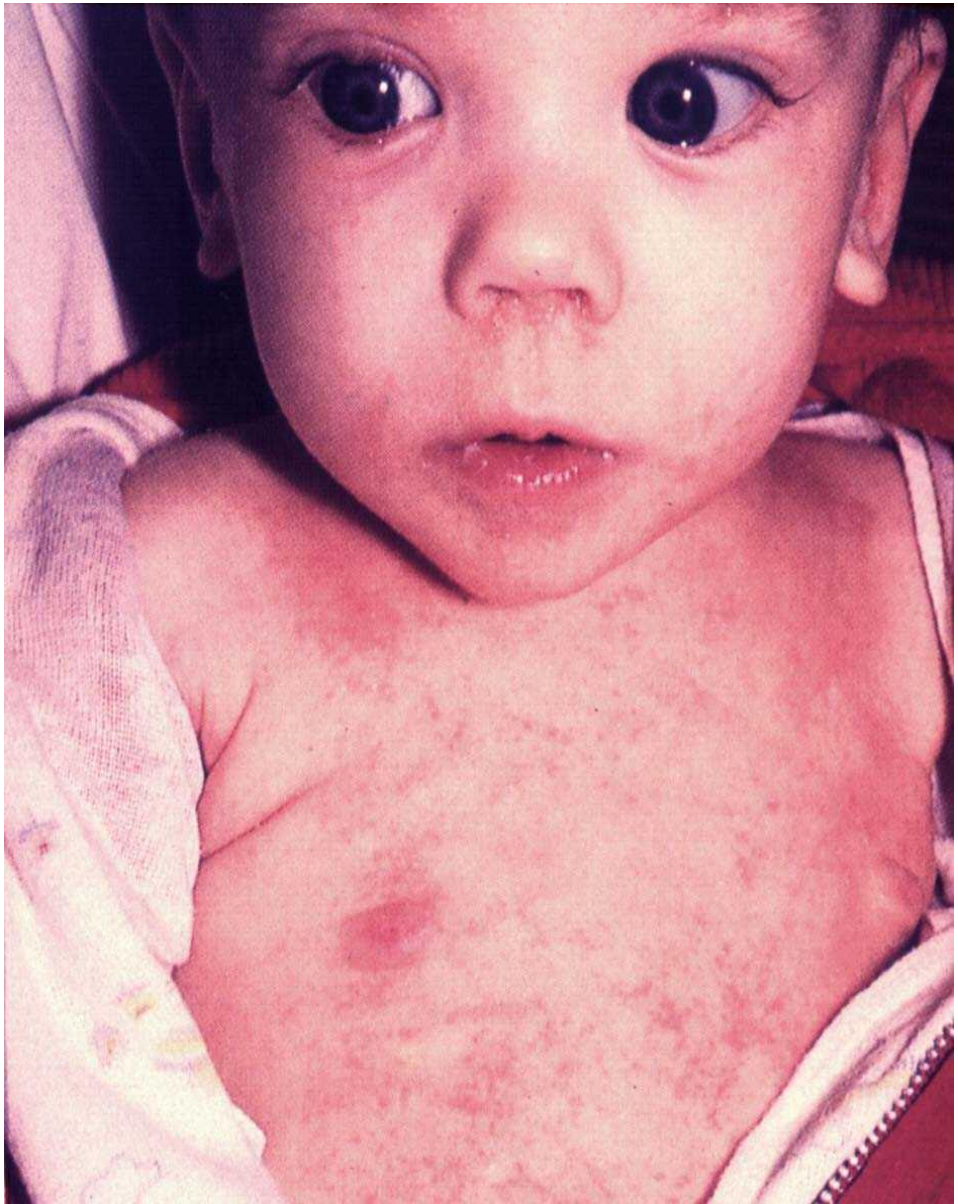
Chronic granulomatous disease

- 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).

Wiskott-Aldrich syndrome

- X-linked disease
- Thrombocytopemia $\rightarrow$ bleeding tendency
- Severe eczema
- Immunodeficiency
- Severe allergic and autoimmune manifestations
- B-cell lymphomas

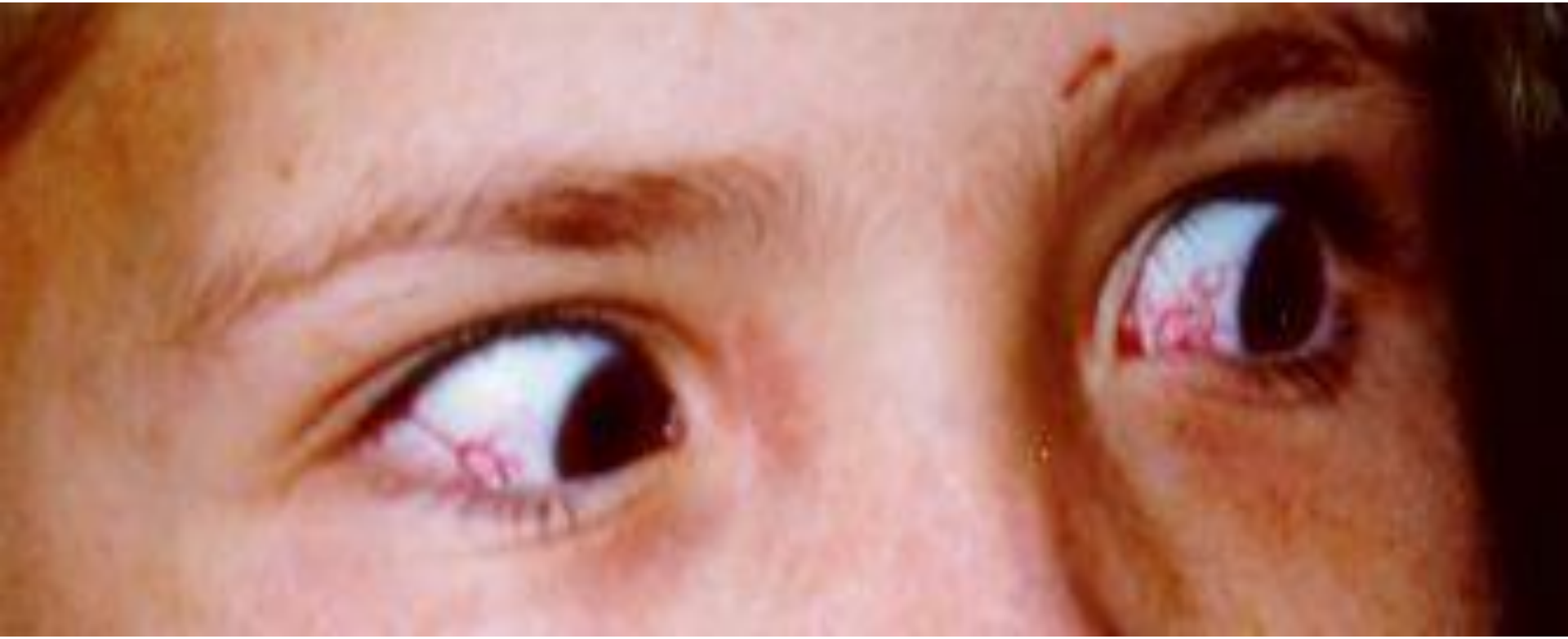
Wiskott-Aldrich syndrome



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



Treatment of primary immunodeficiencies

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

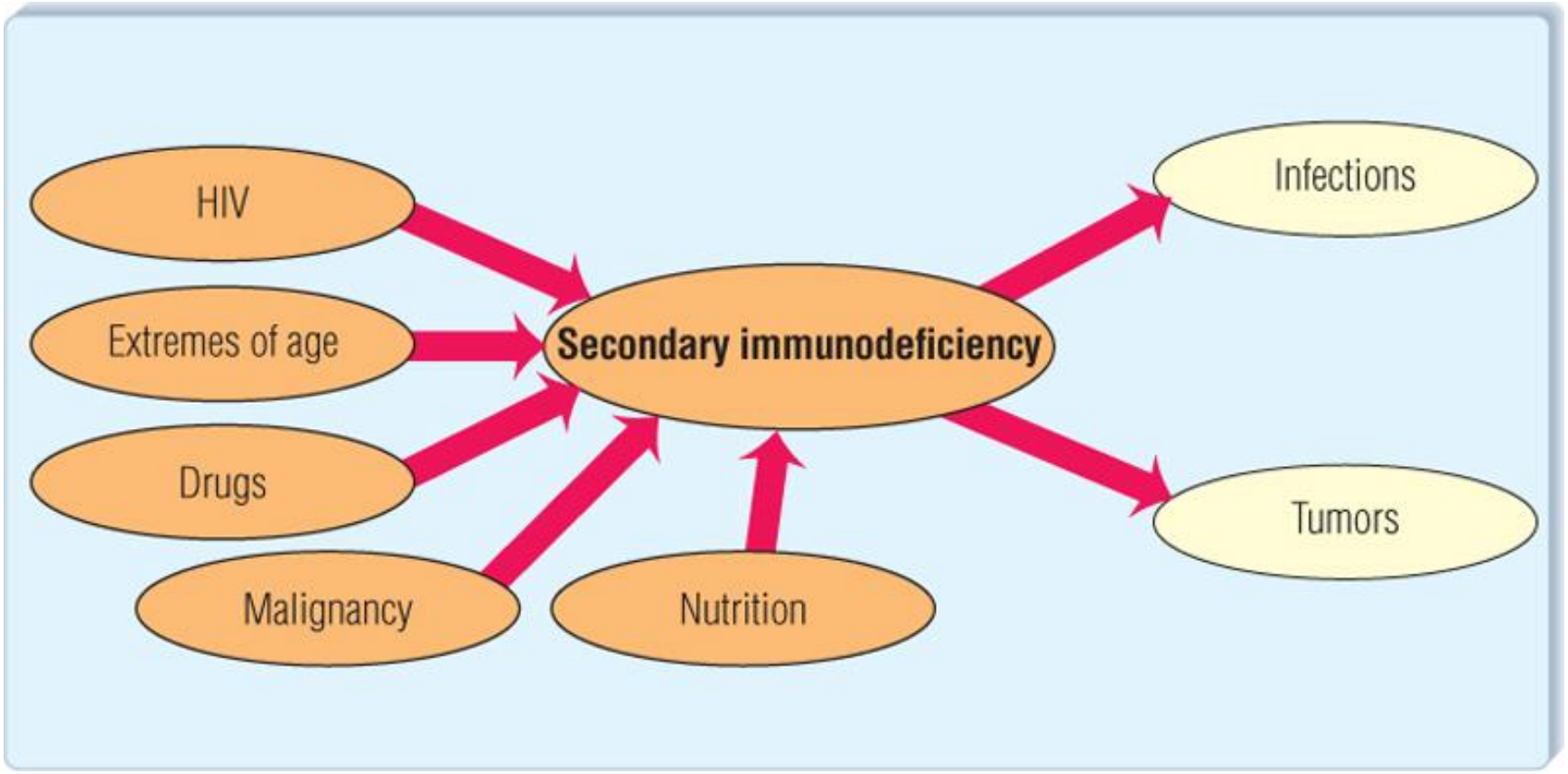
Clinical use of non-specific immunoglobulin derivates

- Types of derivates:
  - „Normal immunoglobulin“ - for intramuscular use. Used very rarely at present because only low dose can be given..
  - Intravenous immunoglobulins, subcutaneous immunoglobulins - can be used in high doses
- Indications:
  - Replacement treatment in patients with antibody deficiencies
  - Prophylaxis of infections against which there is no specific immunoglobulin derivate (hepatitis A)
  - High doses of i.v. immunoglobulins are used in autoimmune diseases, systemic vasculitic diseases.

Causes of secondary immunodeficiency

- Metabolic - uremia, diabetes, malnutrition
- Iatrogenic – cytostatics, immunosuppresants
- Malignat tumors
- Viral infections - HIV, CMV, measles, infectious mononucleosis
- Splenectomy
- Stress
- Injuries, operations, general anestesia

Secondary immunodeficiency



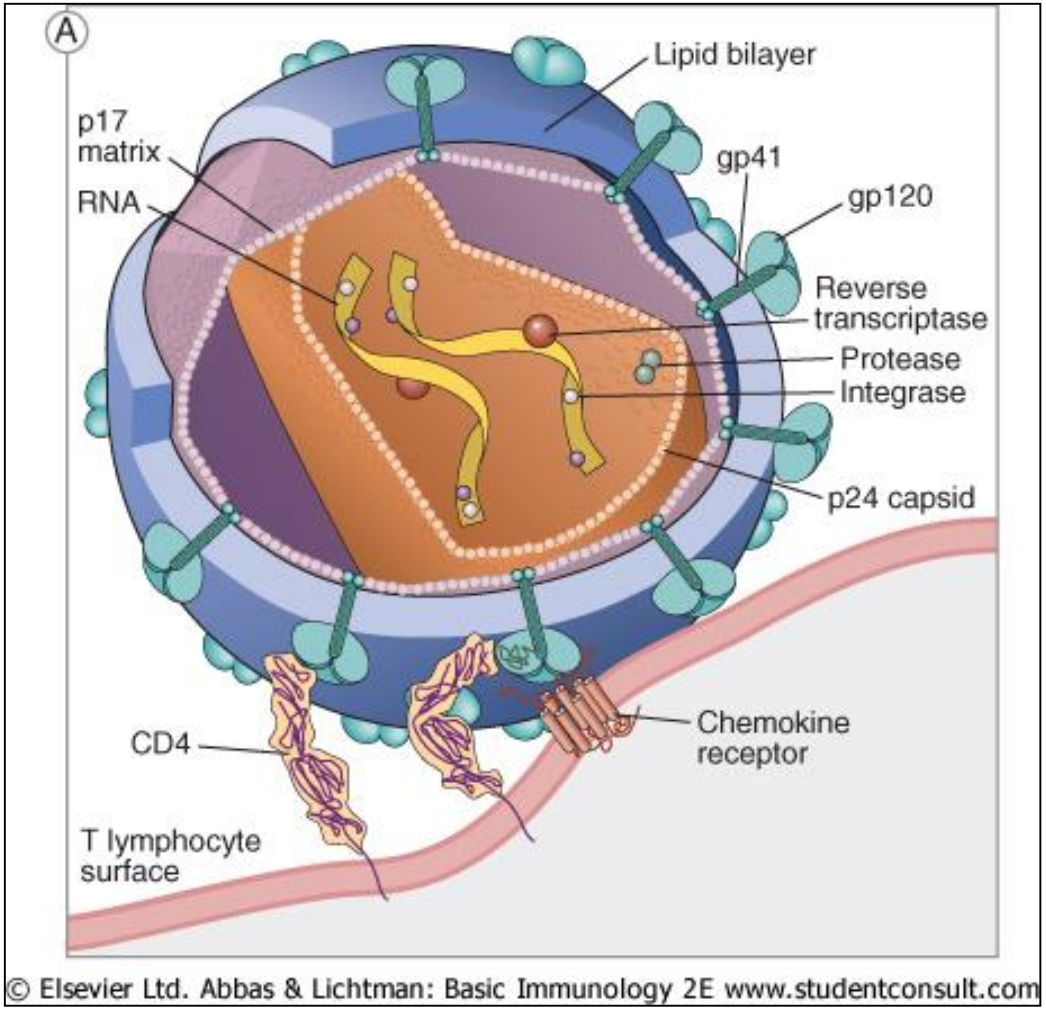
Imunodeficiency after splenectomy

- Disturbed phagocytosis, decreased production of antibodies.
- The most severe complication is hyperacute pneumococal sepsis.
- Prevention: vaccination against Pneumococcus, Haemophilus infl. B, Meningococcus. PNC prophylaxis.

Secondary hypogammaglobulinemia

- **Decreased production of immunoglobulins**
  - **Chronic lymphatic leukemia**
  - **Lymphoma**
  - **Myeloma**
- **Loss of immunoglobulins**
  - **Nephrotic syndrome**
  - **Exudative enteropathy**

HIV disease



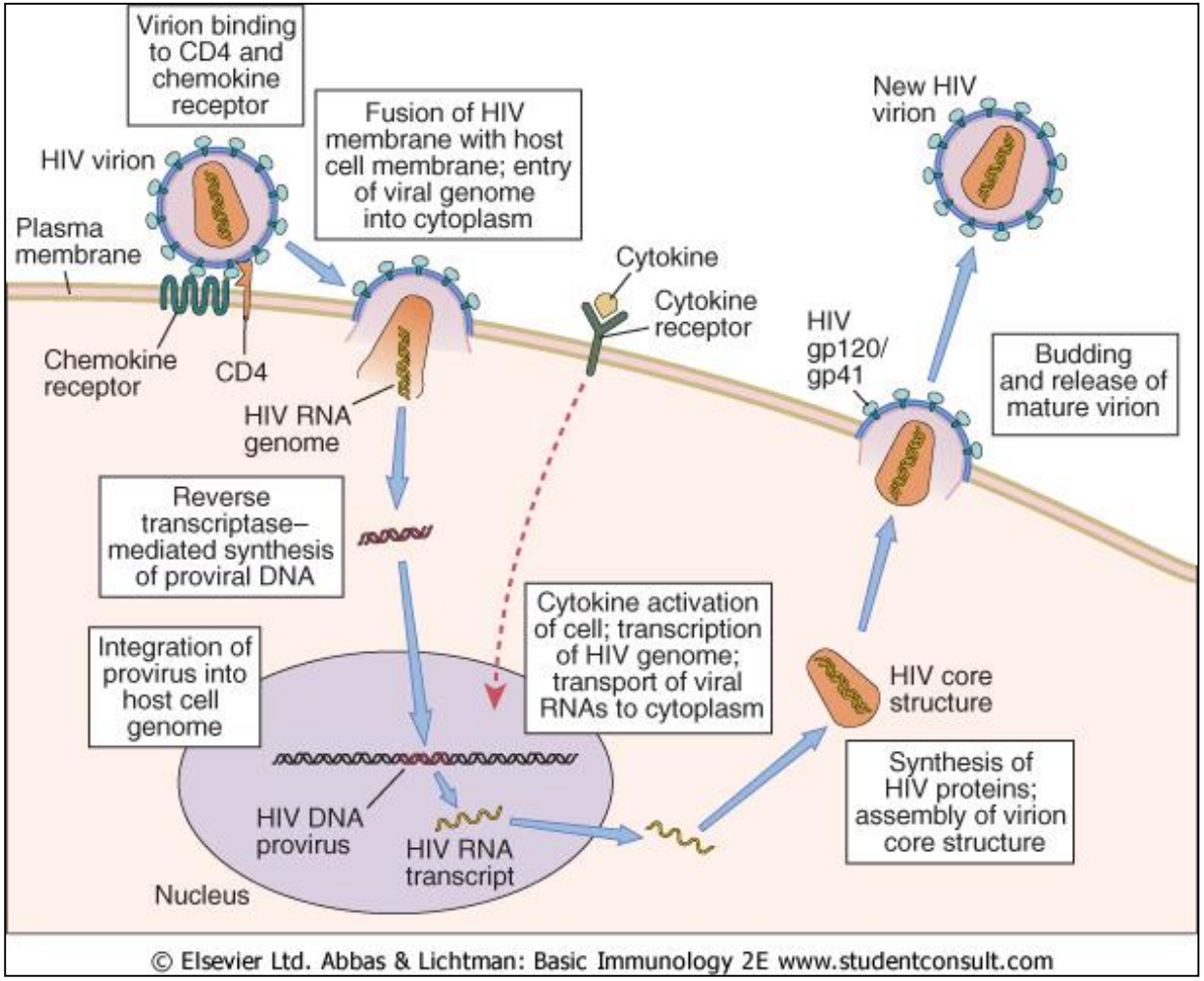
Ways of transmission

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

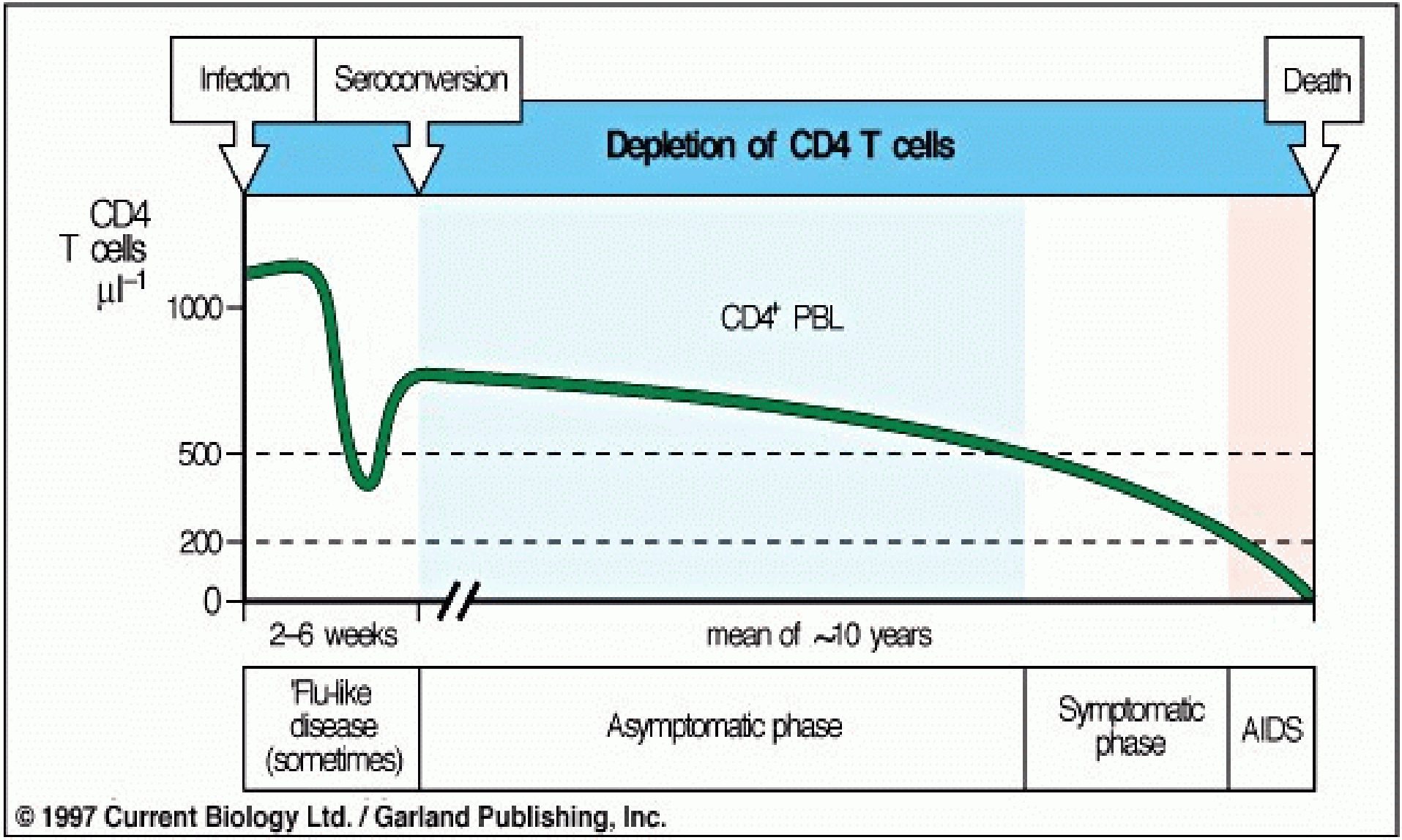
HIV receptors

- 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 resistent to HIV infection. In infected patients, slow progression of the disease.



CD4+ cells mumber and progression of HIV disease



Classification of HIV disease (CDC)

3 clinical categories

A Asymptomatic disese

B „small“ opportunistic infections

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

Clinical category A

- Accute (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, lympadenopathy, 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

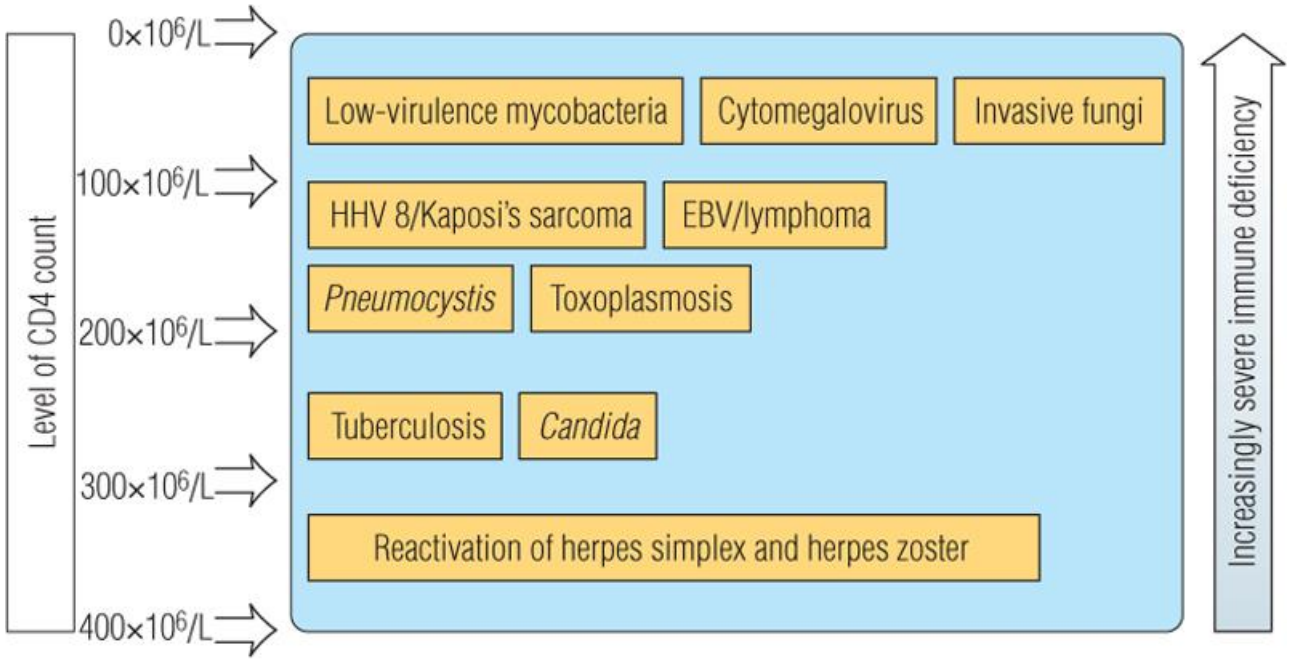
Clinical category C (AIDS)

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

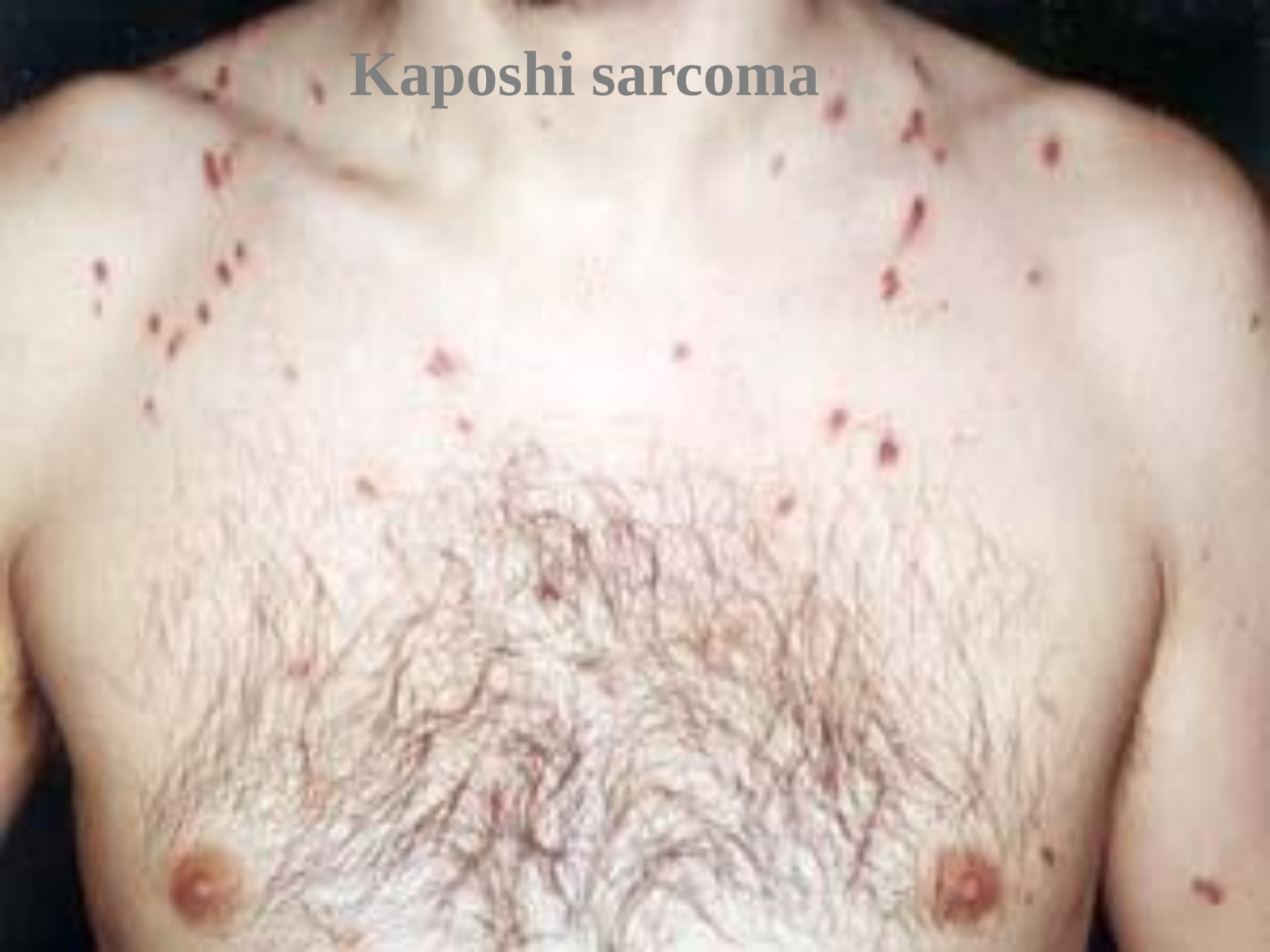
Type of oportunistic infections in HIV/AIDS depends on absolute CD4 count



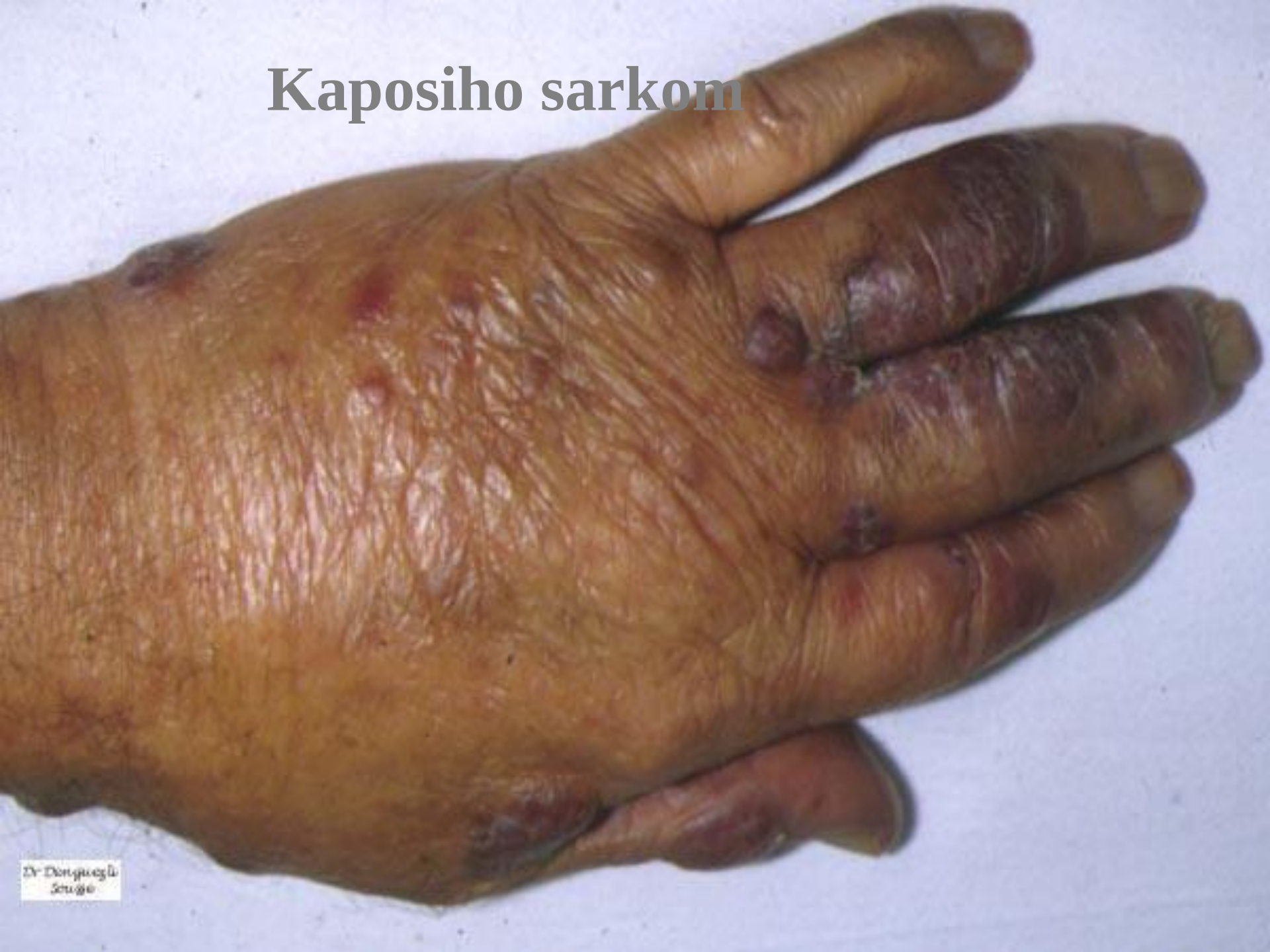
Clinical category C (AIDS) - tumors

- Kaposhi sarcoma
- Brain lymphoma

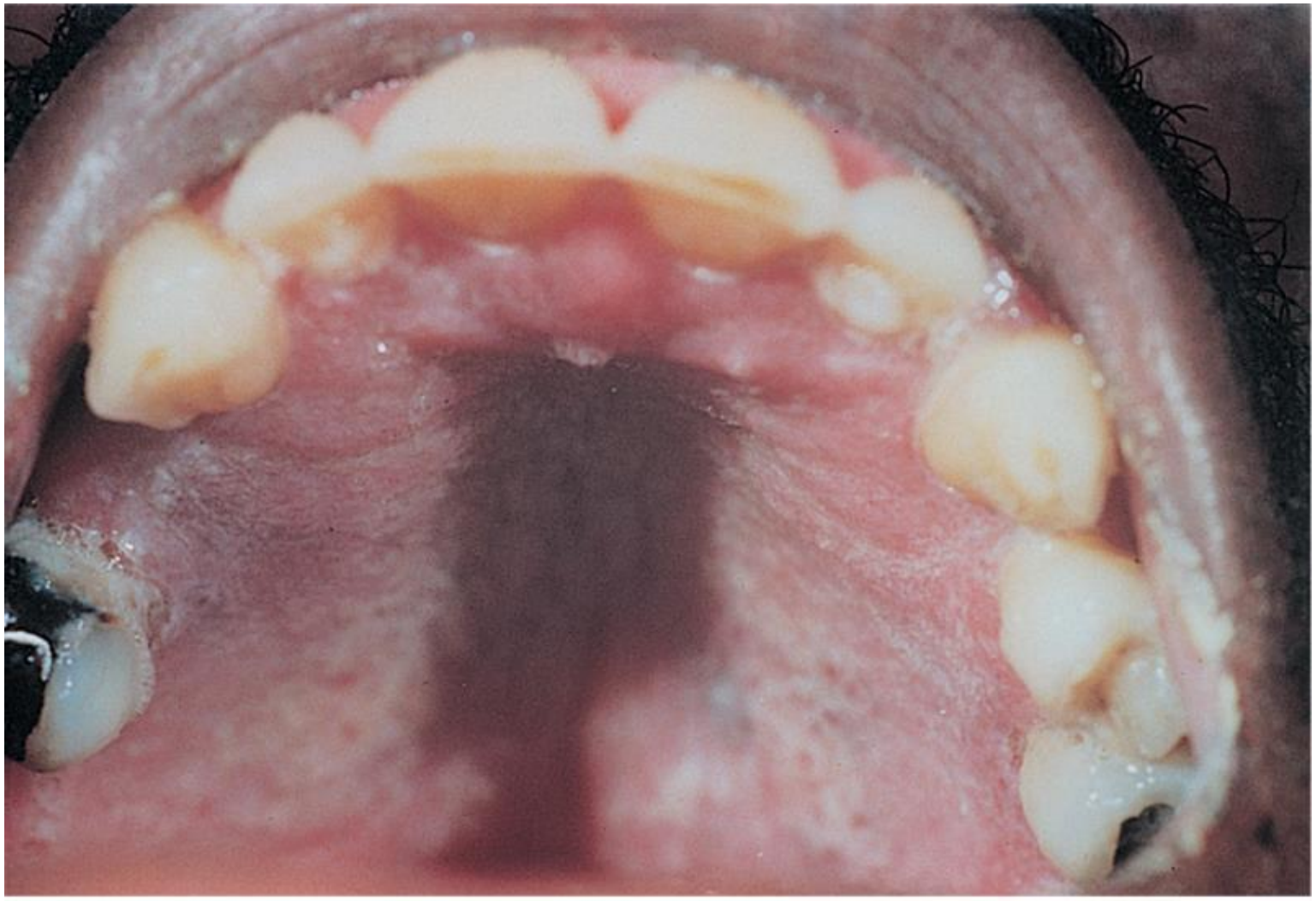
Kaposhi sarcoma



Kaposiho sarkom



Kaposi sarkoma



Wasting syndrome

Treatment of HIV-disease

- Antiretroviral
  - **Nucleoside inhibitors of reverse transcriptase: azidothymidin (syn. zidovudin), didanosin, zalcitabin, stavudin, lamivudin**
  - **Nonnucleoside inhibitors of reverse transcriptase: Nevirapin, delavirdin, efavirenz**
  - **HIV protease inhibitors: Saquinavir, ritonavir, indinavir**
  - **Integrase inhibitors**
  - **Inhibitors of fusion (CCR5 blocking)**

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

Strategy of treatment

- **HAART - Highly Active Anti Retroviral Therapy**

- **Mega-HAART**

Diagnosis of HIV infection

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