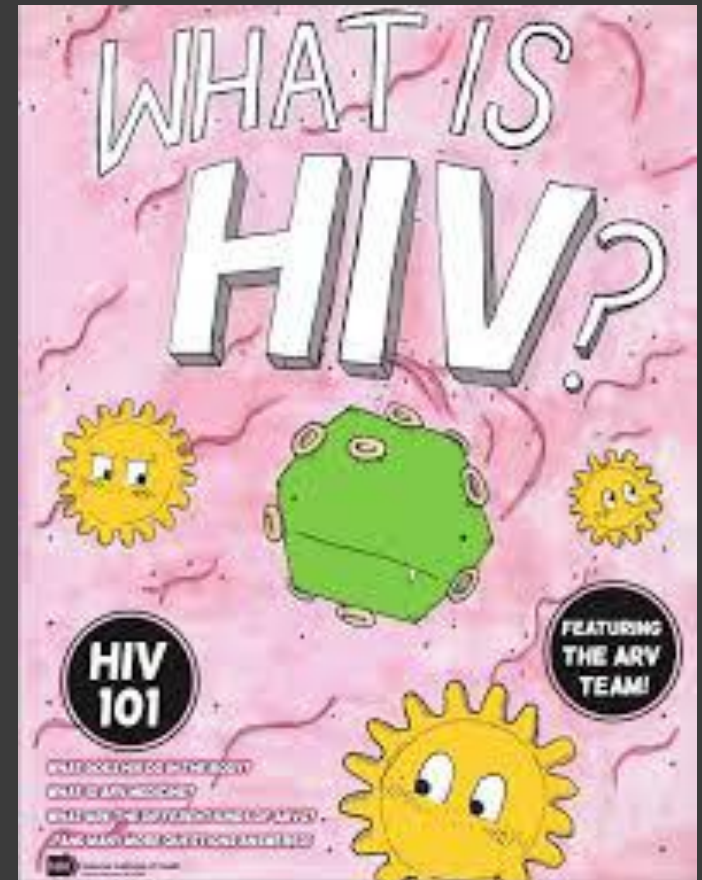


# Human Immunodeficiency Virus (HIV) Infection and Acquired Immunodeficiency Syndrome (AIDS)



Асо. проф. Биљана Поповска  
Јовичић

# History

1980. - **GRID** (**G**ay **R**elated **I**mmunodeficiency),

1984. - **AIDS** (**A**cquired **I**mmunodeficiency **S**yndrom).

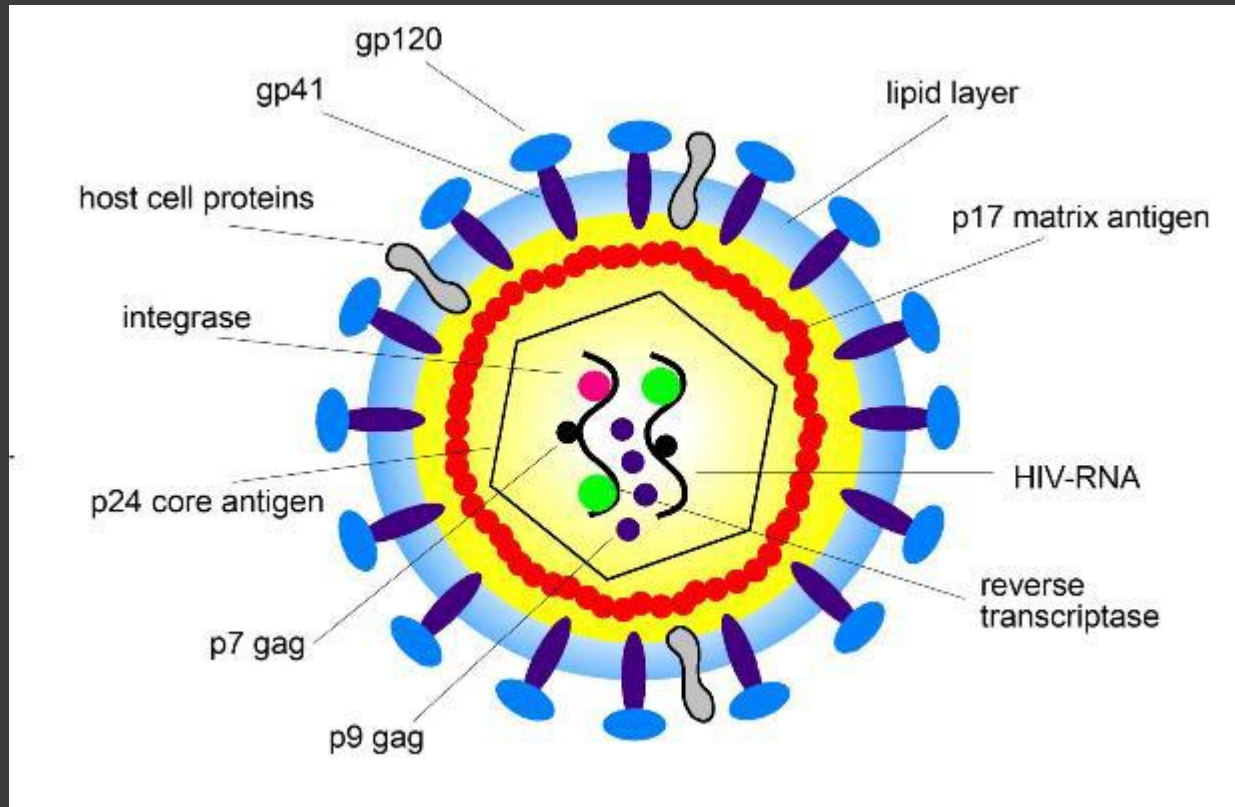
## Etiology Acquired Immunodeficiency Syndrome

1983. - **LAV** (**L**ymphadenopathy **A**ssociated **V**irus),

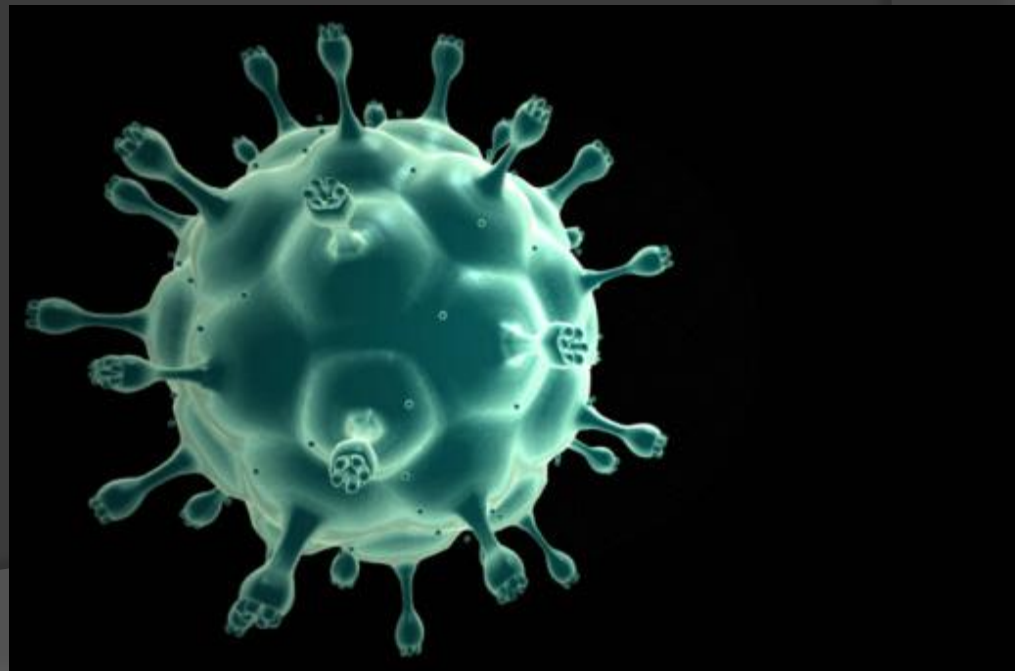
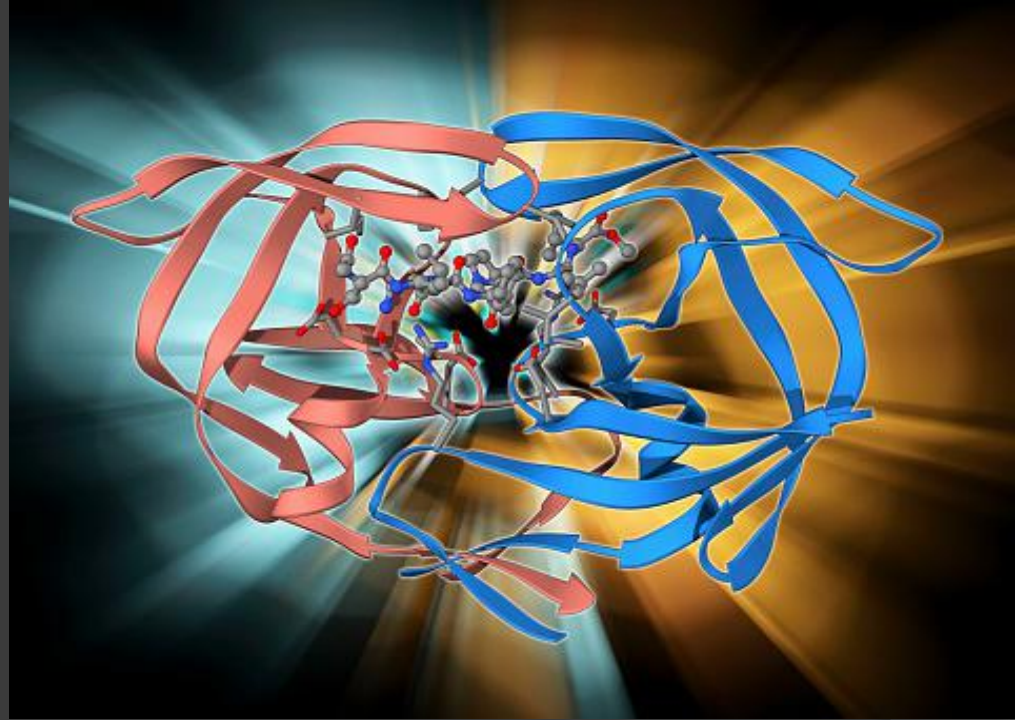
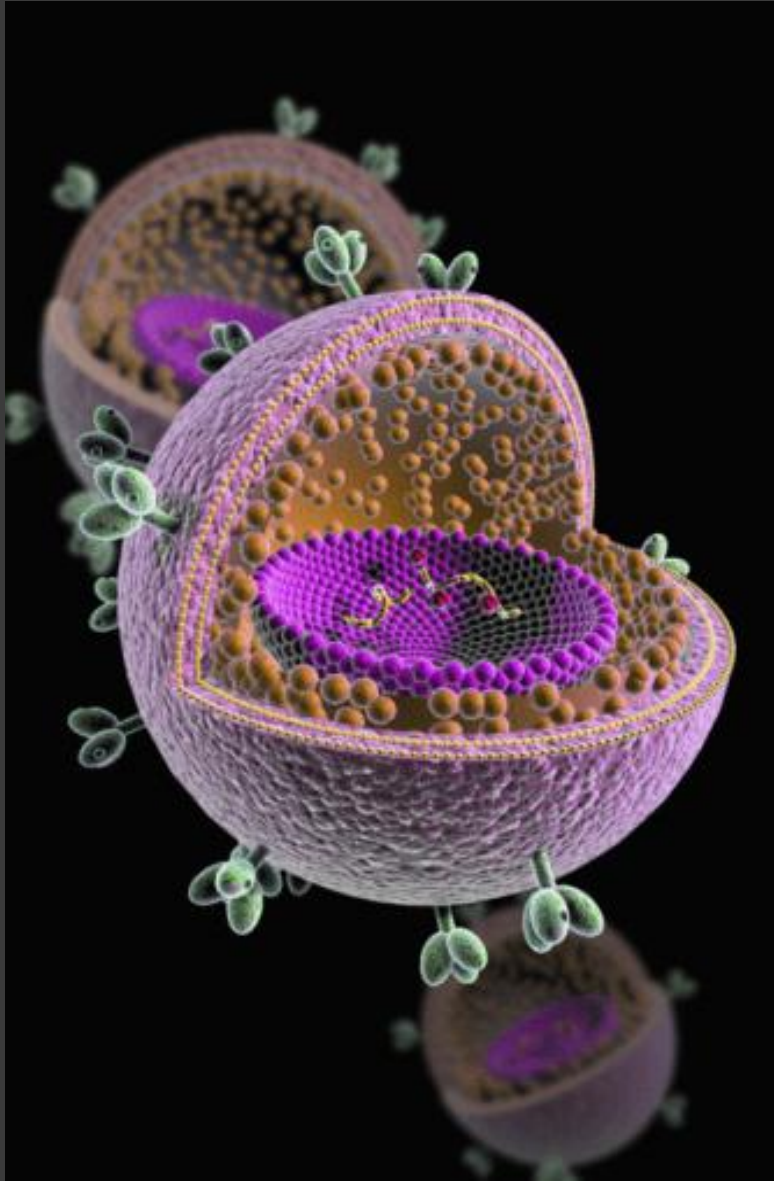
1984. - **HTLV III** (**H**uman **T**-**L**ymphotropic **V**irus type **III**),

1986. - **HIV** - 1 (**H**uman **I**mmunodeficiency **V**irus).

# HIV (RNA вирус, Retroviridae)

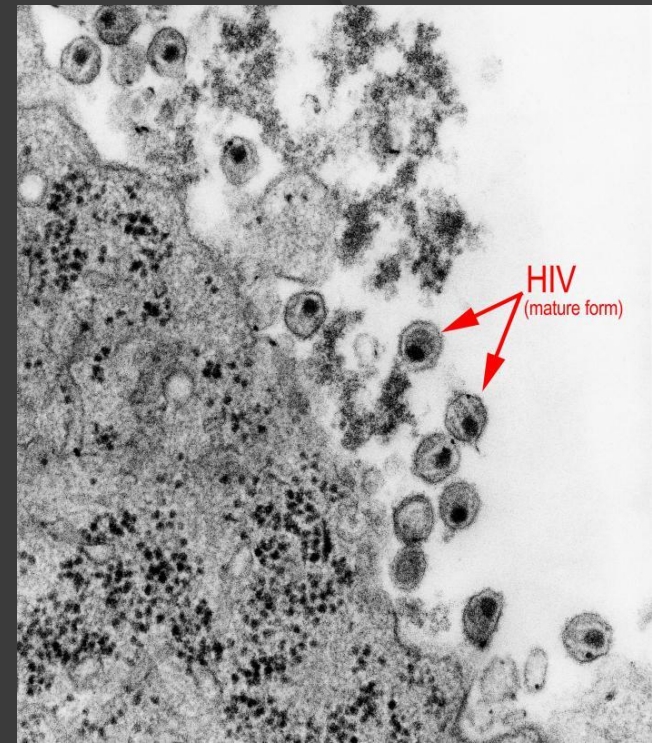
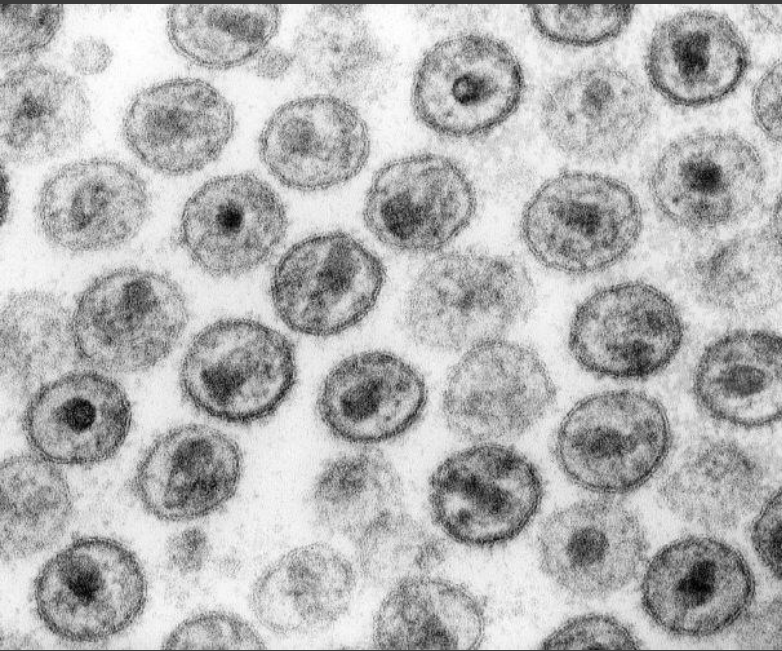


Shape and structure of the HIV-1 virus

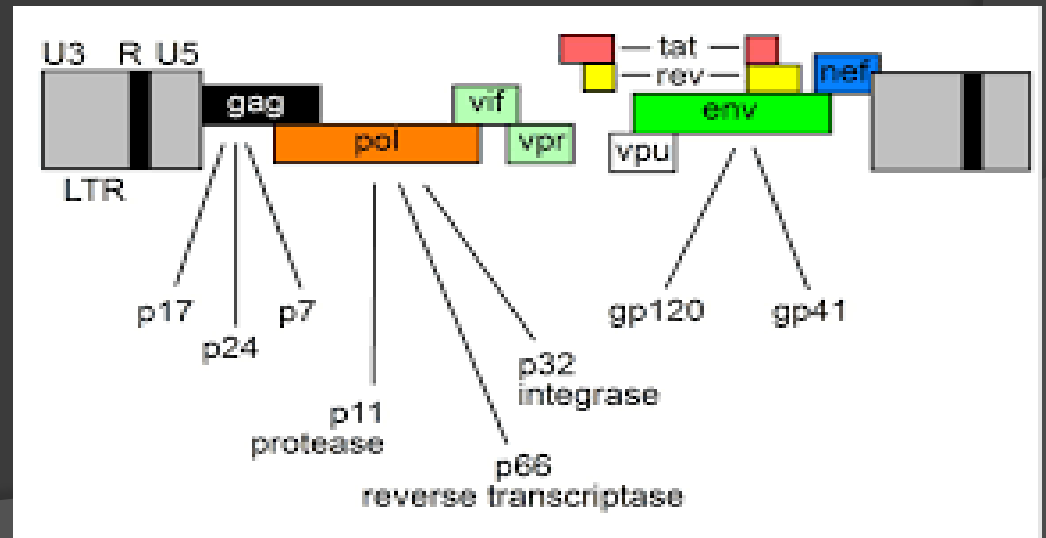




*The image of HIV taken with electronic microscope*



*Genom HIV*



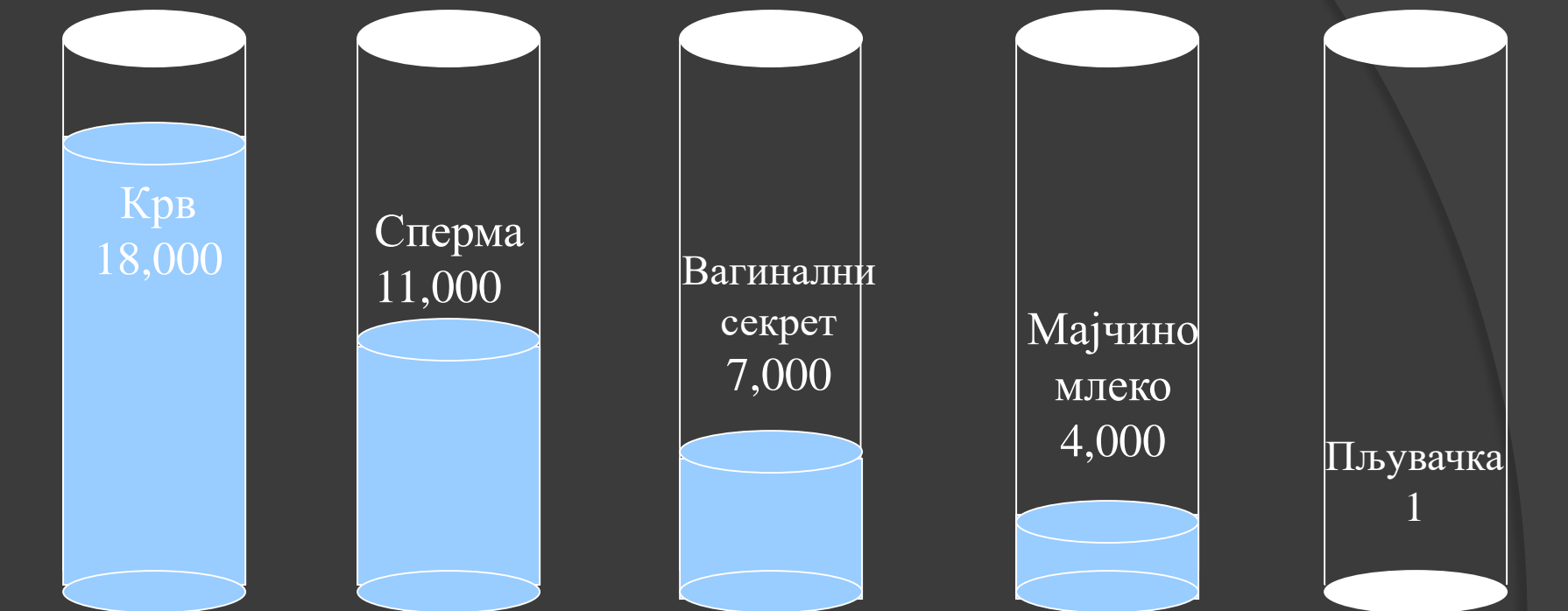
# Epidemiology

The reservoir of HIV and the source of infection is an HIV-infected person, HIV has been proven in:

- blood,
- semen,
- tears,
- saliva,
- breast milk,
- vaginal secretions,  
cerebrospinal fluid.

**The bodily fluids through which HIV can be transmitted are:**

- **blood,**
- **semen,**
- **vaginal secretions, and**
- **breast milk.**

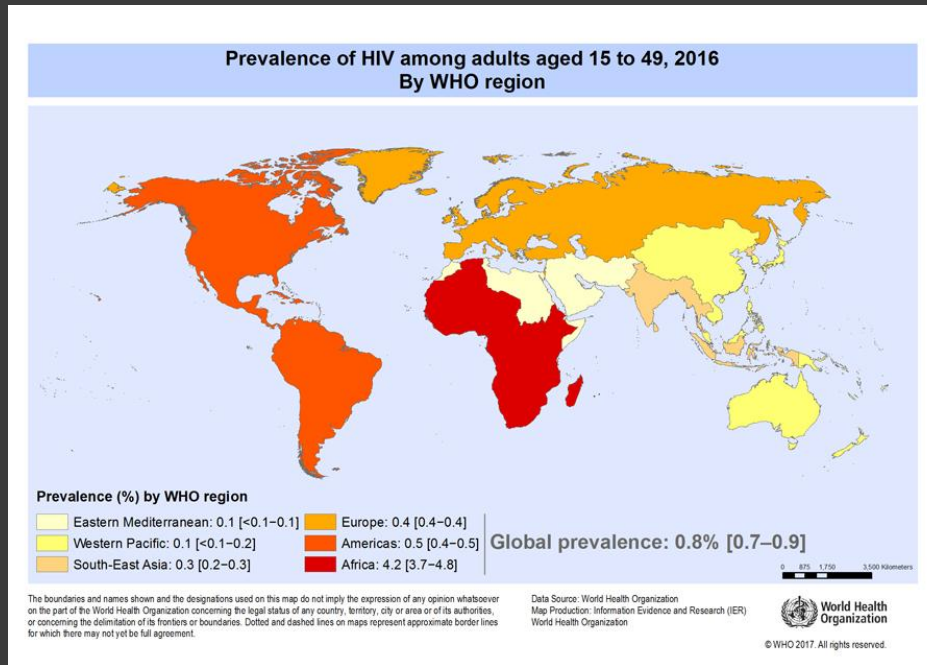


Average number of HIV particles in 1 ml of certain body fluids in HIV-infected individuals

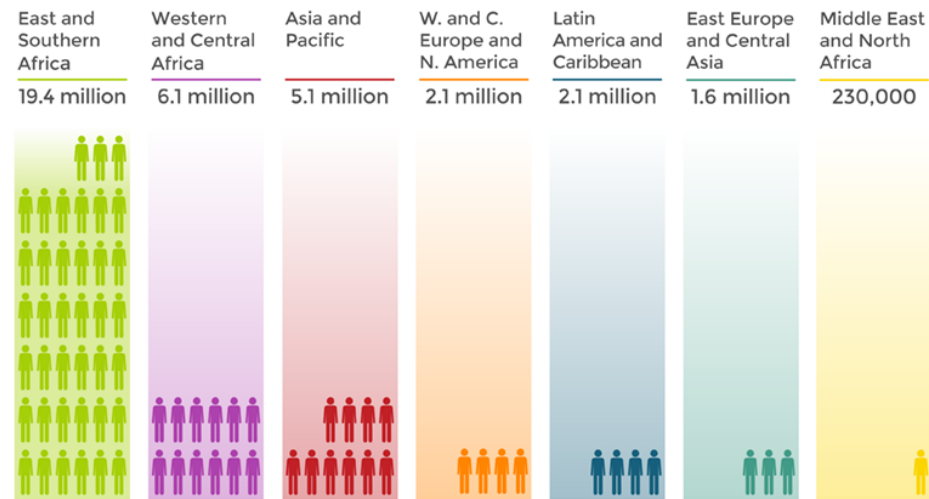
Certain established routes of transmission of HIV infection

- Blood and blood products,
- Sexual transmission,
- Mother-to-child transmission.

# Global HIV infection

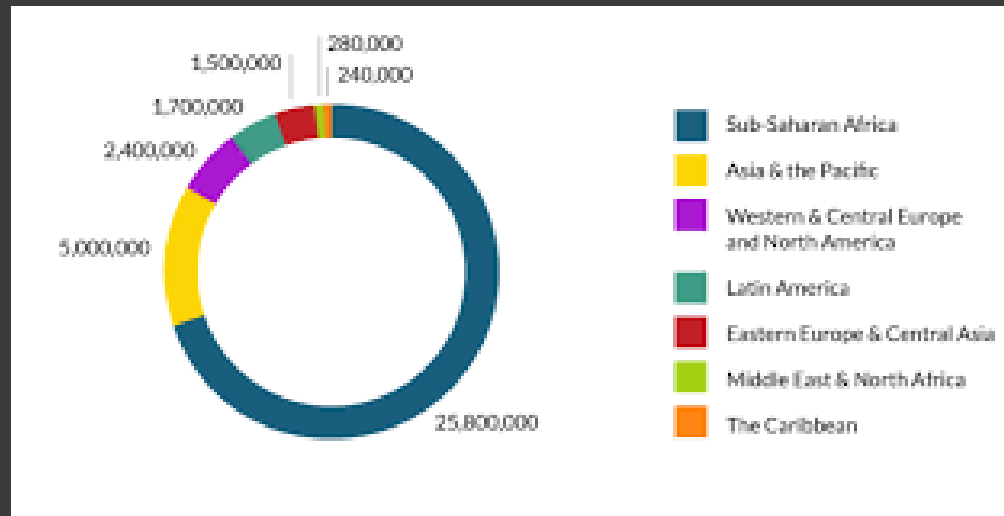


## Number of people living with HIV in 2016



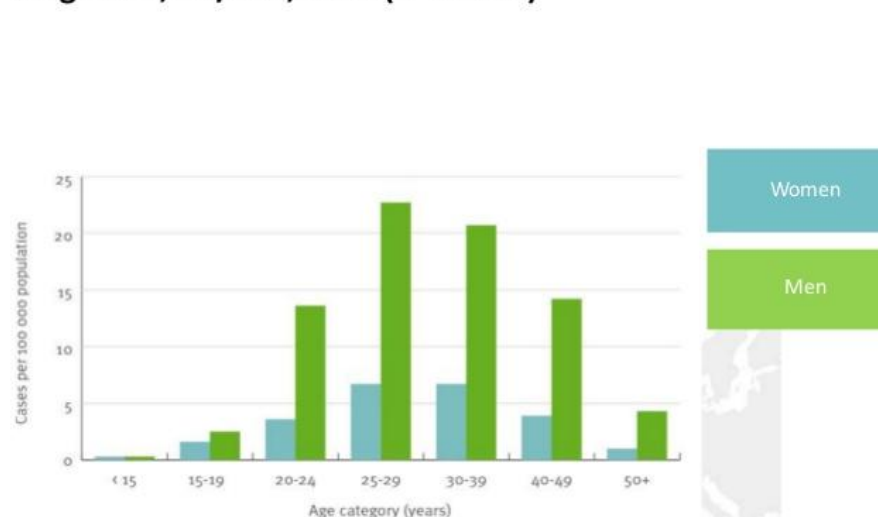


# The incidence of HIV infection in certain regions of the world



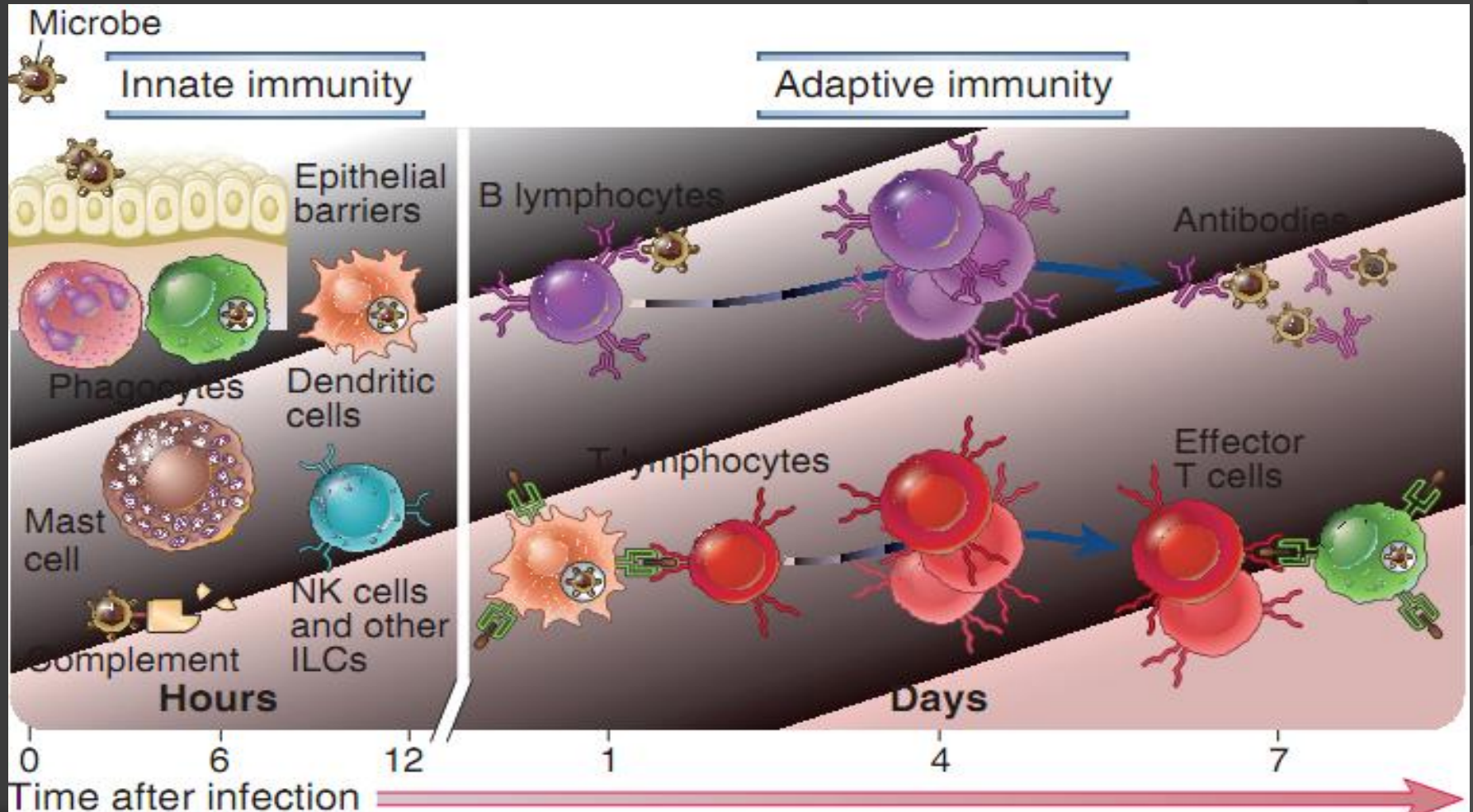
## HIV infection prevalence by gender and age in Europe

Age- and gender-specific rates of new HIV diagnoses, EU/EEA, 2015 (n=29 639)

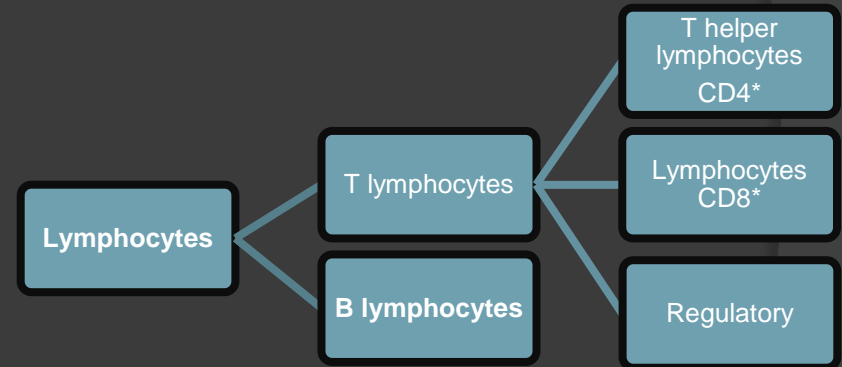
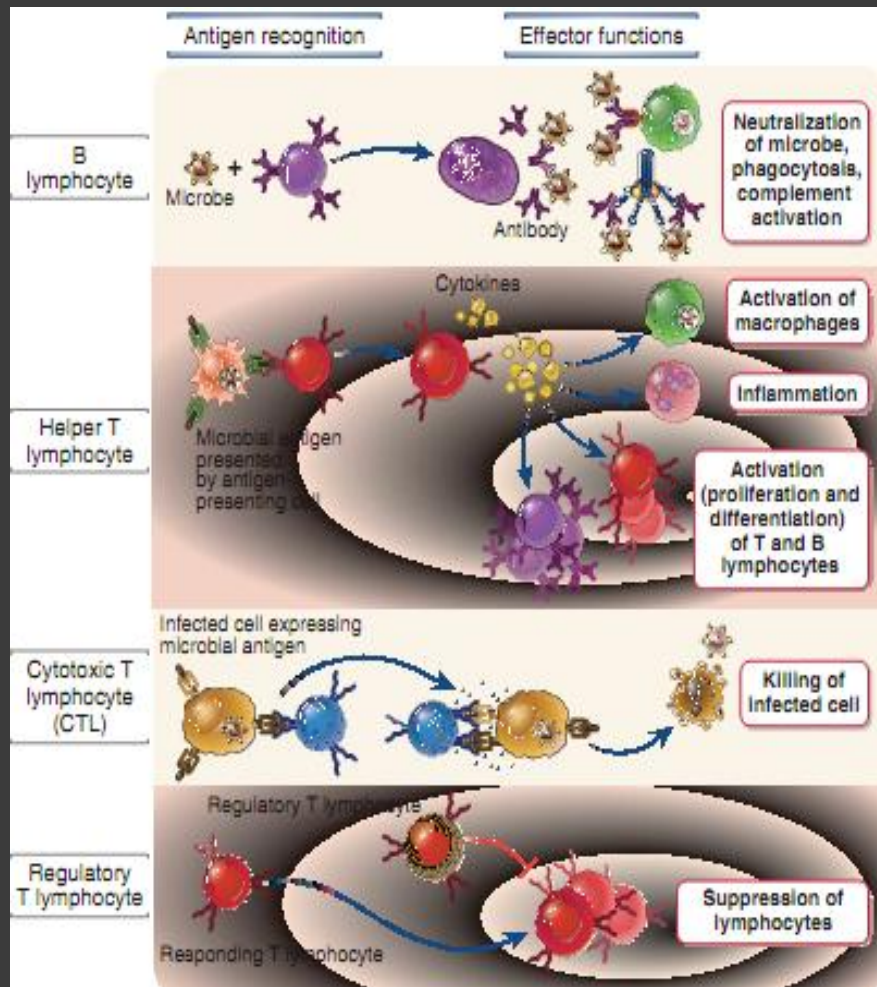


# Pathogenesis of HIV infection

Immunocompetent cells of nonspecific and specific immunity

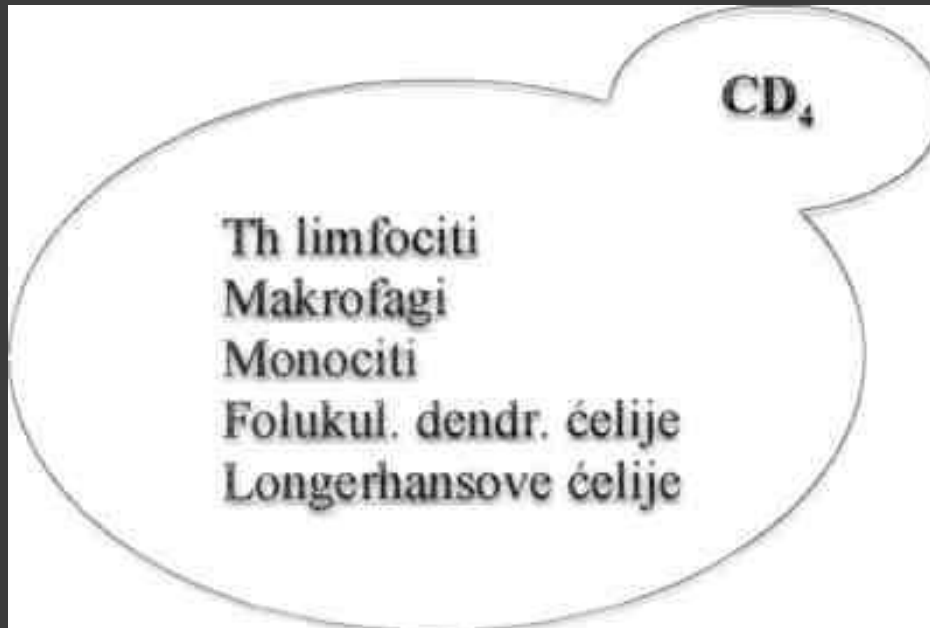


# Different classes of lymphocytes of specific immunity



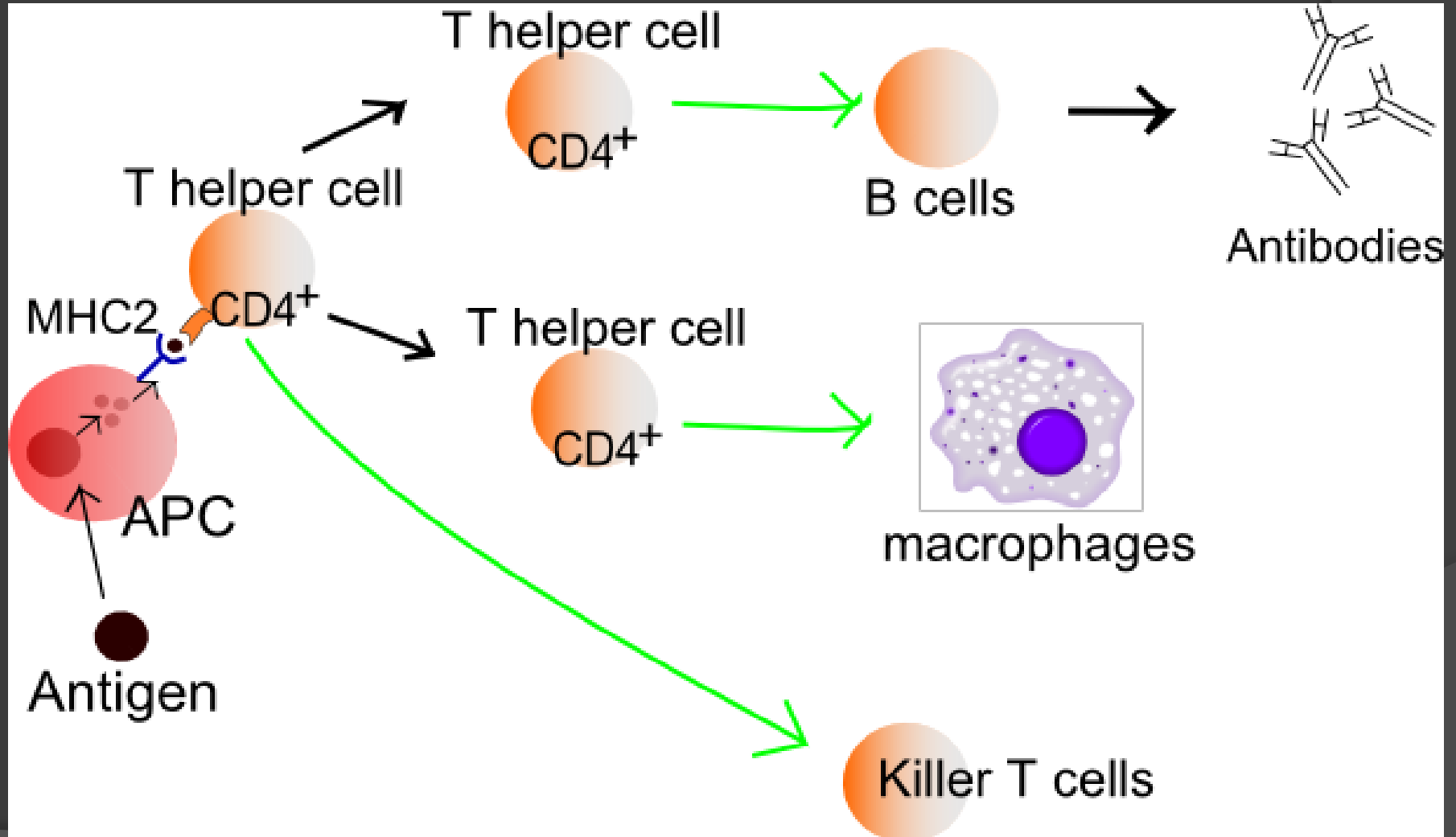
## Target cells affected by HIV

After entering the body, HIV infects cells that have the CD4 molecule on their surface, the CD4 molecule functions as a specific receptor for HIV.



The Th lymphocyte is the main target cell affected by HIV.

# The role of helper CD4 lymphocytes

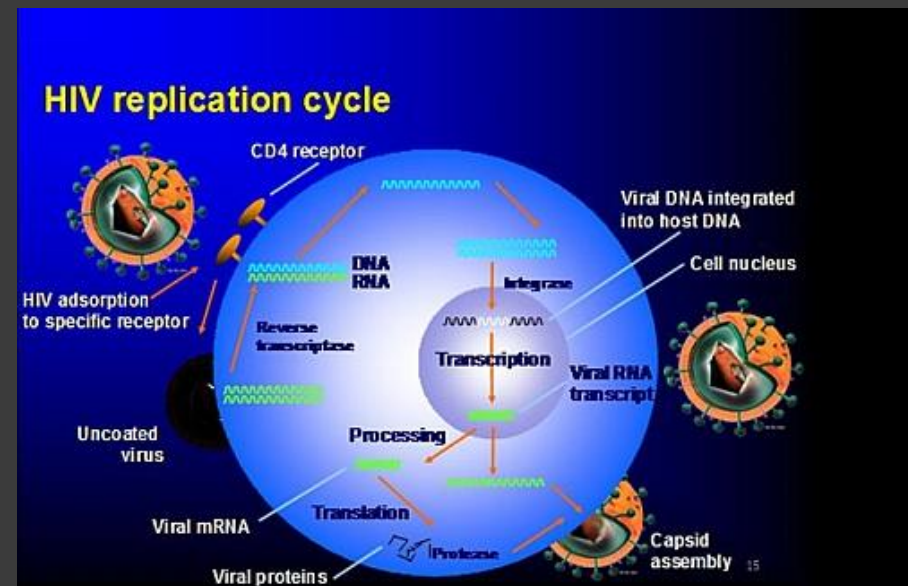




## The effect of HIV on Th (CD4) lymphocytes

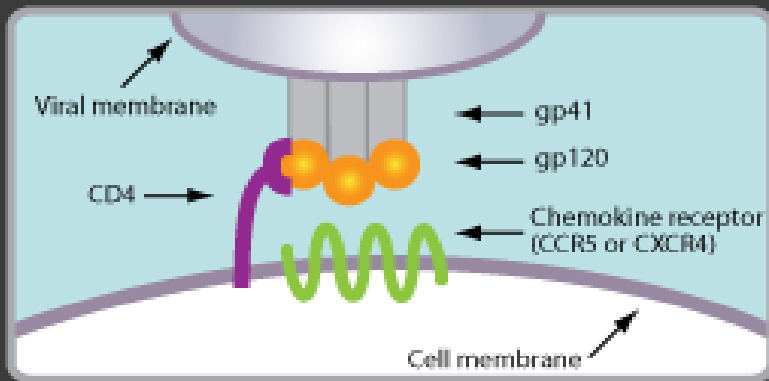
### Stages in the action of HIV on Th lymphocytes

- Binding of HIV (gp 120) to the CD4 receptor,
- Penetration of the viral genome (RNA) into a susceptible cell,
- Integration of the viral genome into the host cell genome,
- After the latency phase, HIV replication begins,
- Release of HIV from the cell (by budding),
- Death of the susceptible cell (Th)



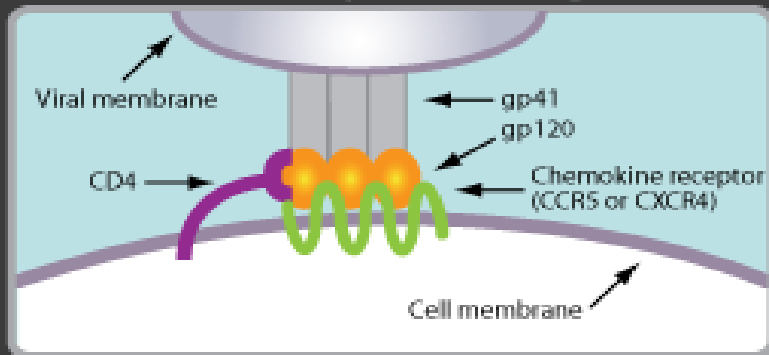
# Binding of HIV virus to target cell

## Attachment to CD4



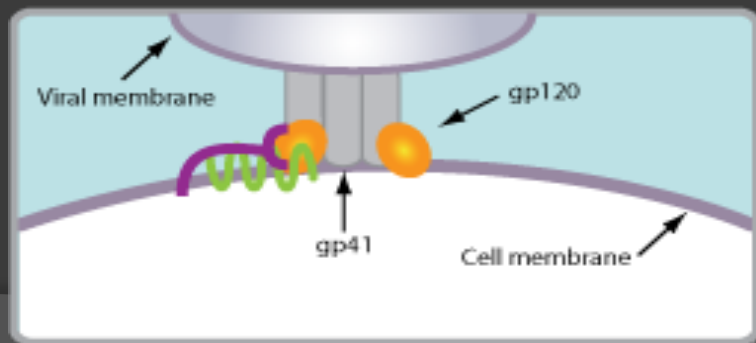
✓ Binding of gp120 of HIV virus to the CD4 receptor of T lymphocytes

## Co-Receptor Binding

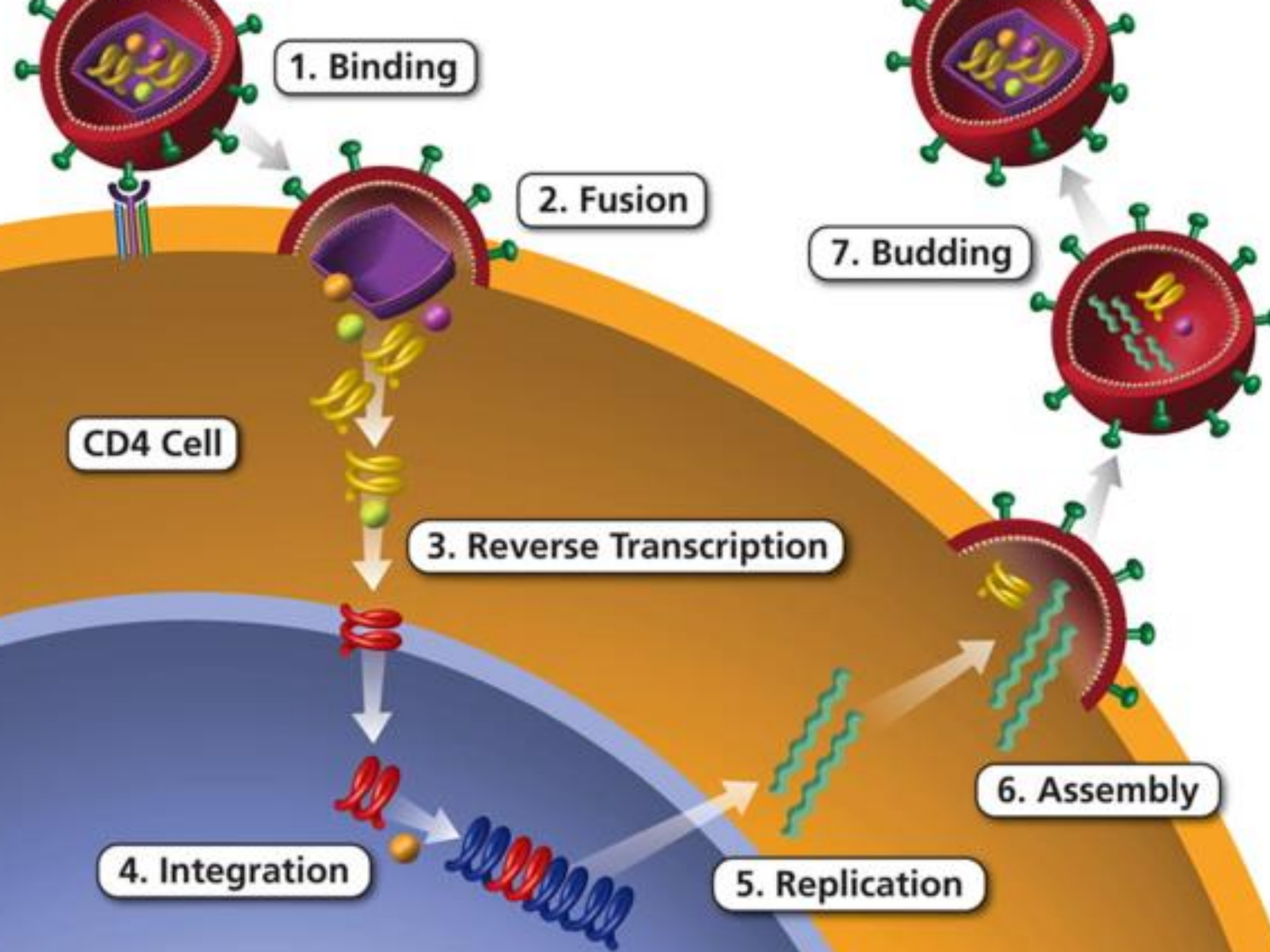


✓ Binding of gp 120 of HIV virus to chemokine receptors of host cells

## Virus-Cell Fusion



✓ Insertion of gp 41 into T lymphocyte membrane and fusion of virus and host cell membrane



## Effects of HIV on Th lymphocytes

1. Decrease in the absolute number of Th (CD4) lymphocytes in the blood (quantitative Th lymphocyte deficiency)
2. Impairment of Th (CD4) lymphocyte function (qualitative Th lymphocyte deficiency)

HIV infection is based on immunodeficiency resulting from quantitative and qualitative Th lymphocyte deficiency (cellular type of immunodeficiency)

## Effect of HIV on macrophages, monocytes and dendritic cells

- Dendritic cells are the first in line to spread the infection to naive T lymphocytes,
- Macrophages and monocytes can also be infected with HIV, but show resistance to cytolysis (they are less susceptible to HIV infection),
- Therefore, macrophages and monocytes become the main reservoir of HIV in the body, HIV infection is transmitted to the CNS through infected macrophages and monocytes, via HEB.



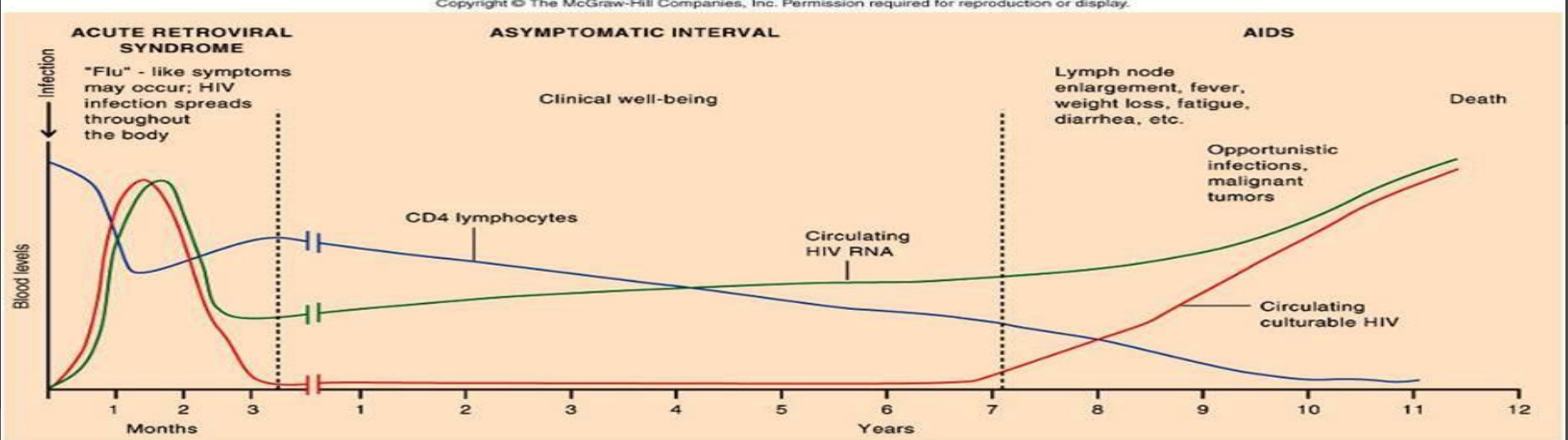
# The natural course of HIV infection

Acute HIV infection

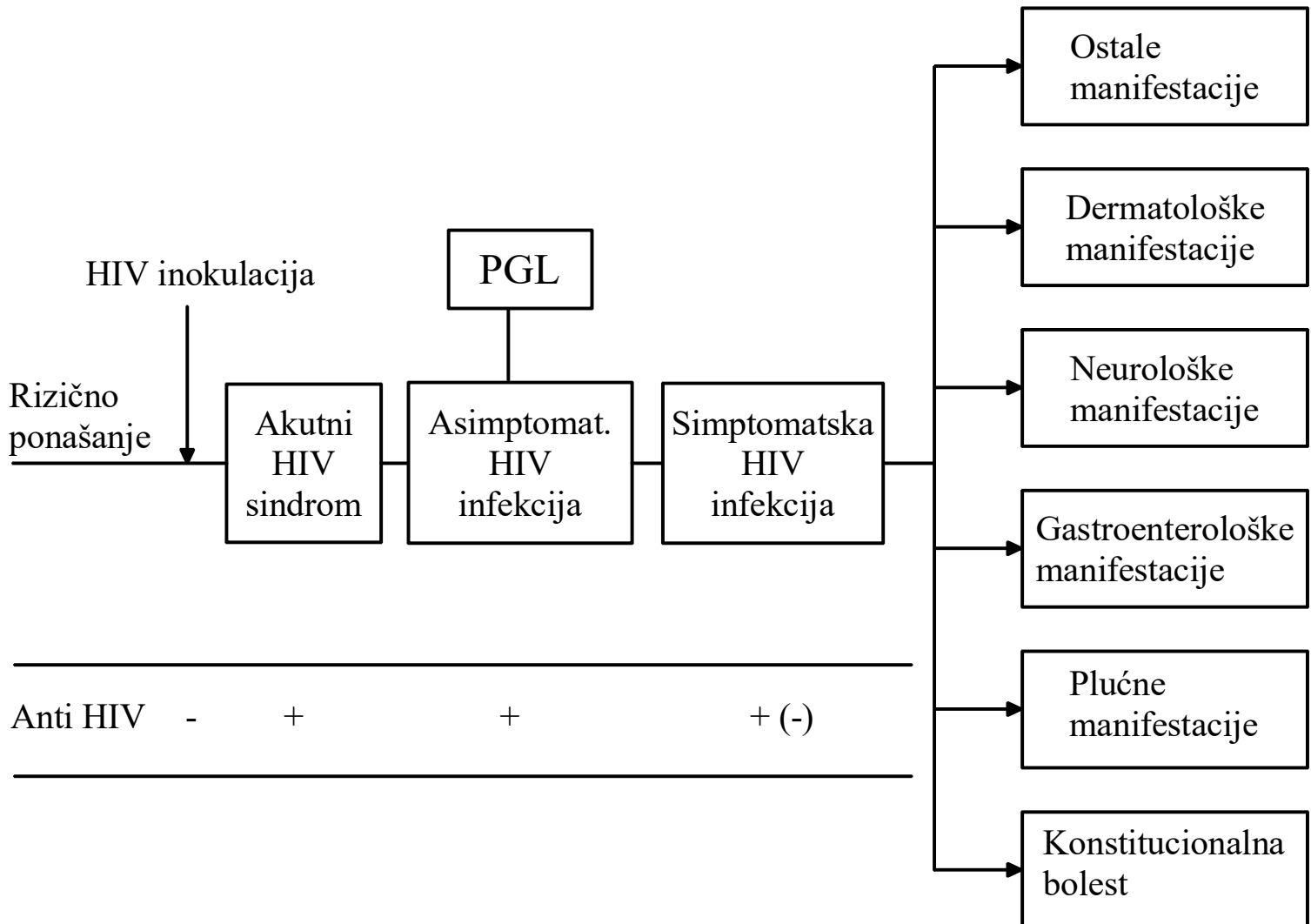
Asimtomatic HIV infection

AIDS

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## the natural course of HIV infection



## Opportunistic infections

Microorganisms whose control and elimination requires a preserved immune response (cellular immune response).

### PARASITES:

Toxoplasma gondii  
Cryptosporidium,  
Isospora belli.

### BACTERIA:

Mikrobakterije,  
Salmonelle.

### ВИРУСИ:

Herpes simplex virus,  
Varicella-zoster virus,  
Cytomegalovirus,  
JC papova virus,  
Humani papiloma virus.  
Parvovirus B19

### FUNGI:

Candida species,  
Pneumocystis jirovecii,  
Cryptococcus neoformans,  
Histoplasma capsulatum.

Cellular type of immunodeficiency is responsible for the development of opportunistic infections in HIV-infected individuals.

## Opportunistic tumors

- Opportunistic tumors
- Kaposi's sarcoma,
- Non-Hodgkin's lymphoma,
- Cervical intraepithelial neoplasia,
- Cervical cancer.

The cellular type of immunodeficiency is responsible for the development of opportunistic tumors in HIV-infected individuals.

# Клиничке манифестације HIV инфекције

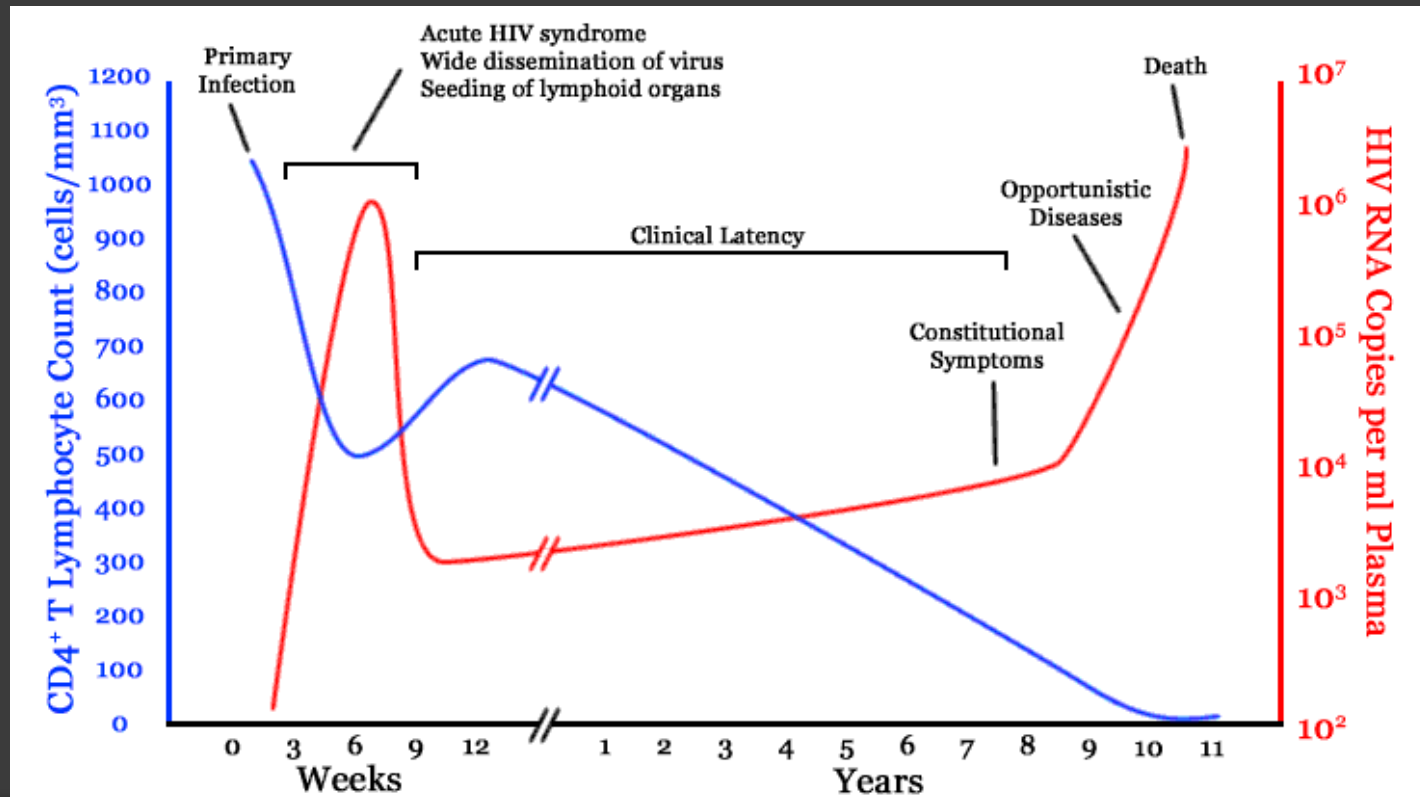
## Акутни HIV синдром

- Јавља се 3-6 недеља након примарне инфекције HIV-ом код мање од 50% инфицираних,
- Клинички се презентује у виду:
  - ✓ синдрома инфлуенце,
  - ✓ мононуклеозног синдрома или
  - ✓ серозног менингитиса.
- Болест траје 2-3 недеље и спонтано пролази,
- Акутни HIV синдром се поклапа са сероконверзијом.



## Asymptomatic phase of HIV infection

- Corresponds to the incubation period of AIDS (average 11 years),
- It occurs without symptoms,
- The physical examination is normal (possibly PGL can be found), The number of CD4 lymphocytes progressively decreases



## PGL (Перзистентна генерализована лимфаденопатија)

- Diagnostic criteria for PGL

Lymphadenopathy in 2 or more non-inguinal regions for more than 3 months, Lymph node diameter greater than 1 cm.

- Other characteristics of PGL

Lymph nodes are mobile, painless, up to 2×2 cm in diameter, Lymphadenopathy is symmetrical, bilateral,

**Histological findings:** reactive hyperplasia of the lymph nodes (as a consequence of the immune response to local replication of HIV in the lymph tissue).



## Symptomatic phase of HIV infection

### A. ("Wasting syndrome")

Diagnostic criteria:

- Fever lasting more than 3 months,
- Malaise,
- sweating,
- Diarrhea lasting more than a month,
- Weight loss (more than 10%).

It is necessary to exclude other pathological conditions (opportunistic infections or tumors) that can cause similar symptoms.

*Конституционална болест ("Wasting syndrome")*





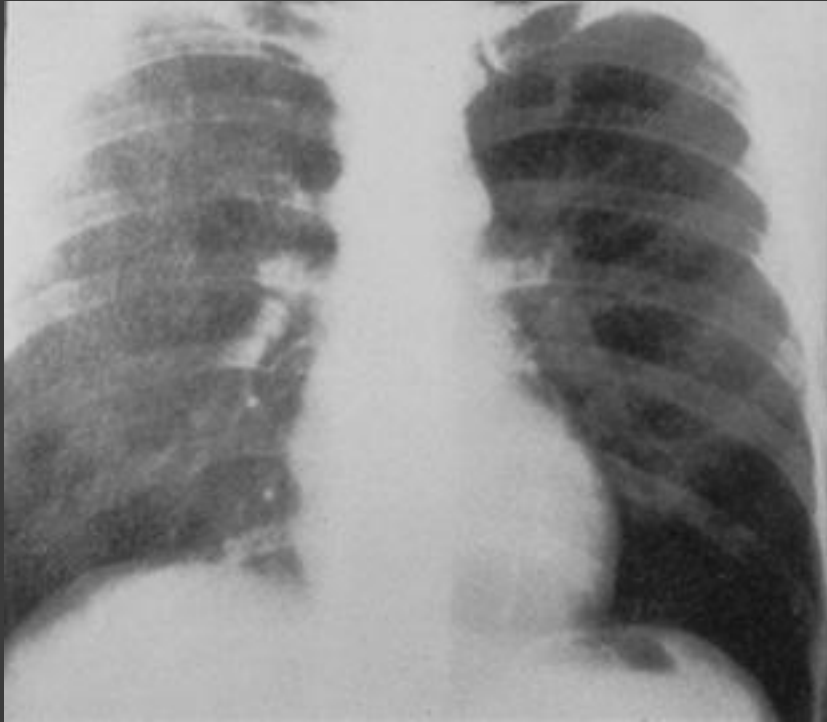
## **B. Pulmonary manifestation**

### **Pneumocystis Jirovecii Pneumonia (PJP)**

- Occurs in more than 80% of all AIDS patients,
- In 60% of patients it occurs as an initial opportunistic infection,
- Clinical picture: low fever, dry cough, dyspnea, night sweats.
- If untreated, ARDS develops, X-ray findings: bilateral interstitial infiltrates,

**Diagnosis: identification of the causative agent in bronchoalveolar secretions or biopsy material (lung tissue).**

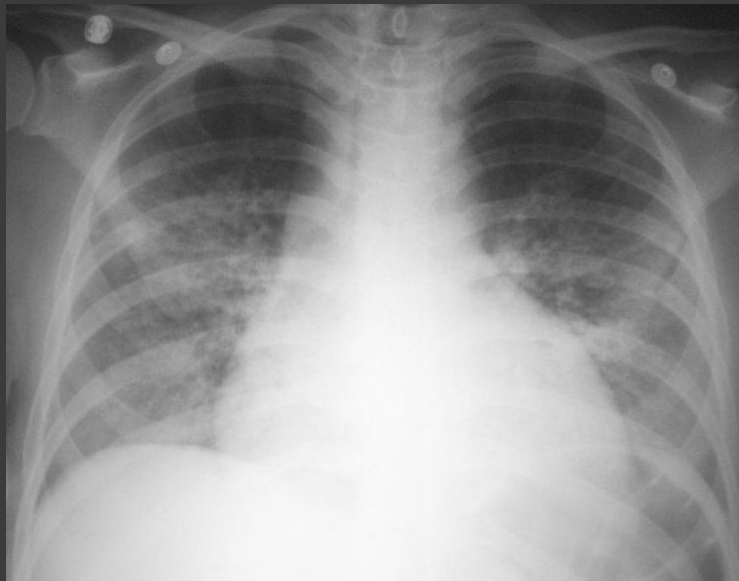
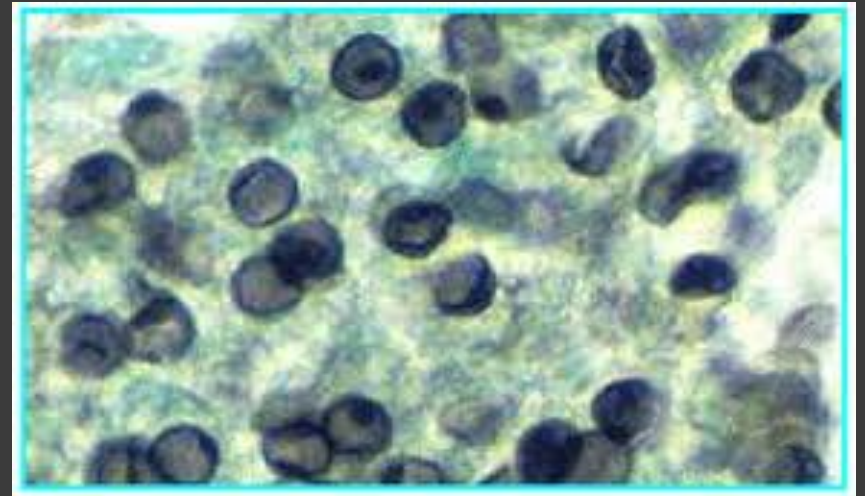
## *Pneumocystis Pneumonia (PJP)*



initial



advanced



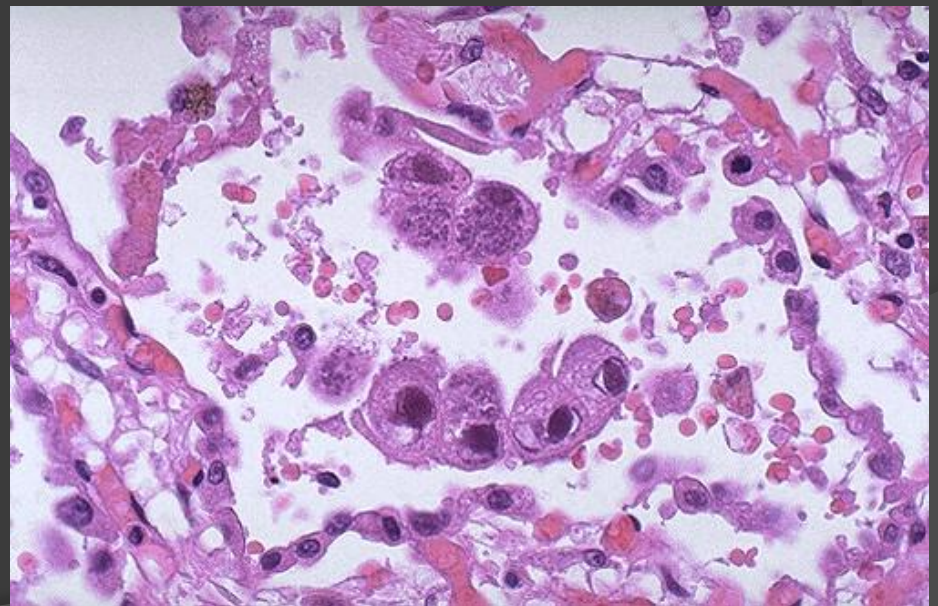
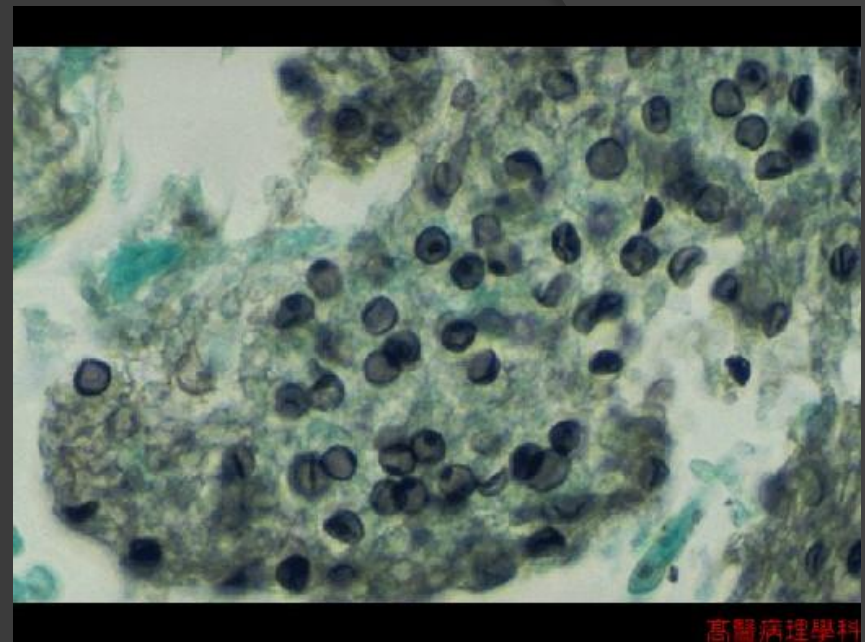
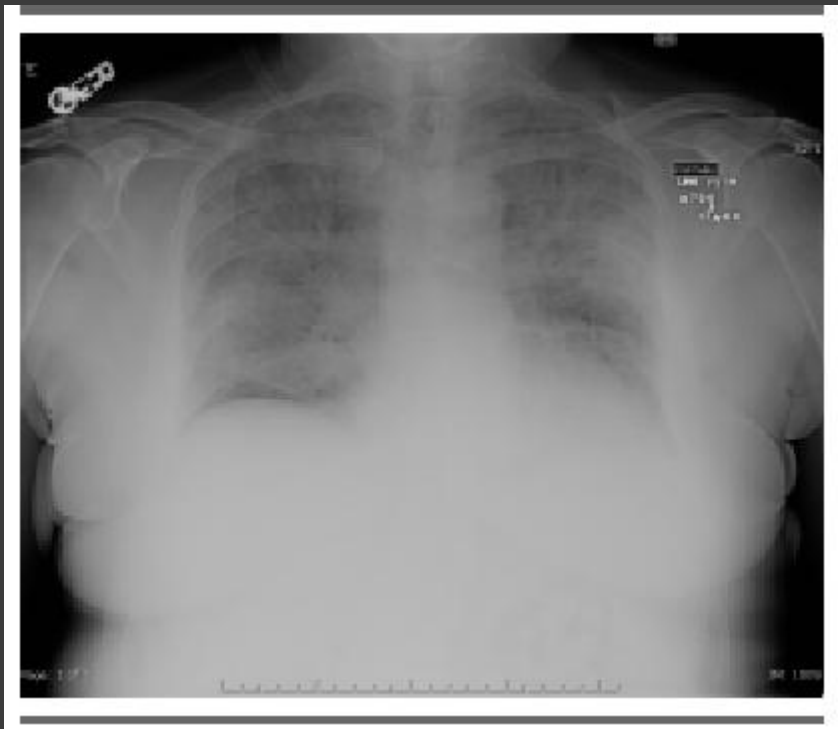
*Pneumocystis Pneumonia*

## Cytomegalovirus Pneumonitis (CMVP)

- Clinically, it is difficult to distinguish from PJP,
- Most often occurs in association with PJP,
- Diagnosis: PCR CMV DNA of bronchoalveolar lavage, lung biopsy (finding of giant cells in the lung tissue).

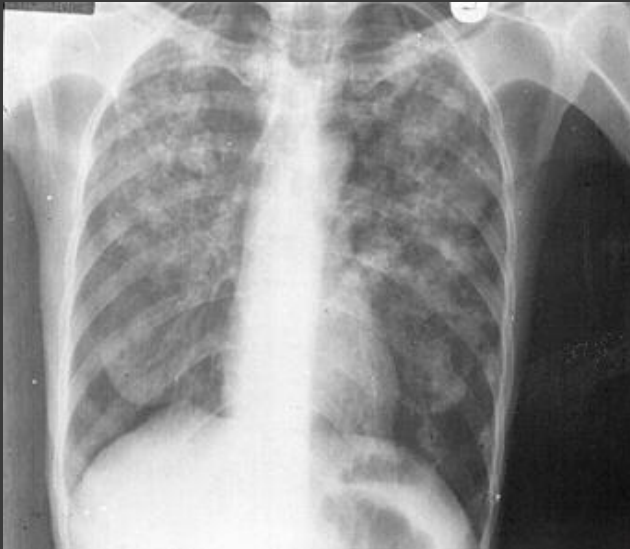


## *Cytomegalovirusni pneumonitis (CMVP)*



## Pulmonary tuberculosis

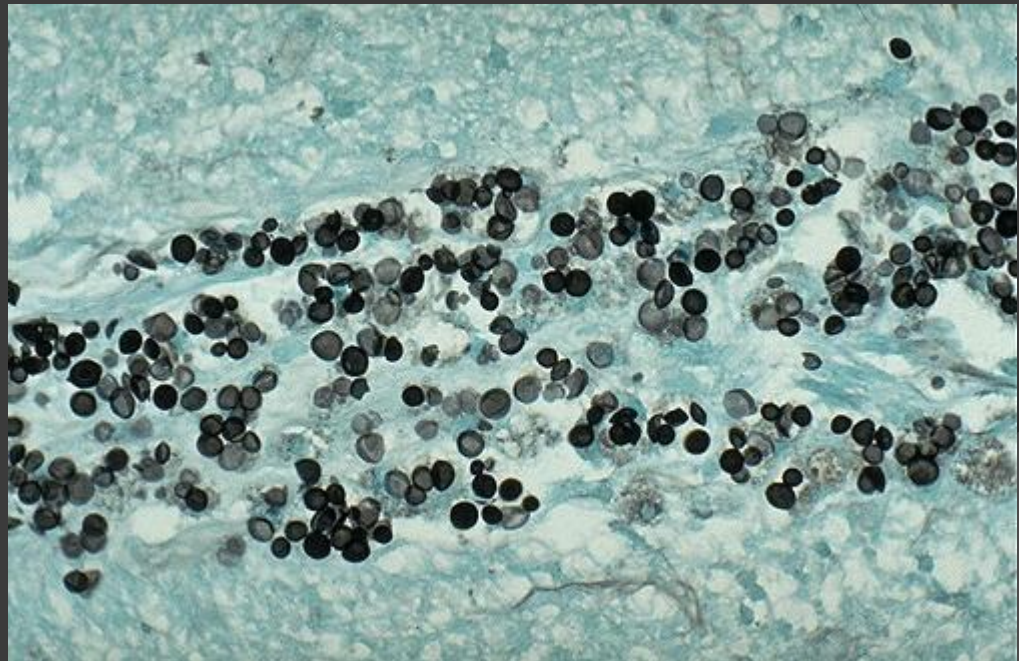
It occurs more often in people infected with HIV, It occurs due to the reactivation of latent TB foci in the lungs early in the course of HIV infection.



## Cryptococcus neoformans pneumonia (CNP)

- It has features of interstitial pneumonia, Less commonly it presents as massive pneumonia with effusion

Histological findings in the lungs





## Lymphocytic interstitial pneumonia (LIP)

The causative agent of this pneumonia is HIV,

It occurs more often in children than in adults,

Clinically and radiologically it presents similarly to PJP



Medscape®

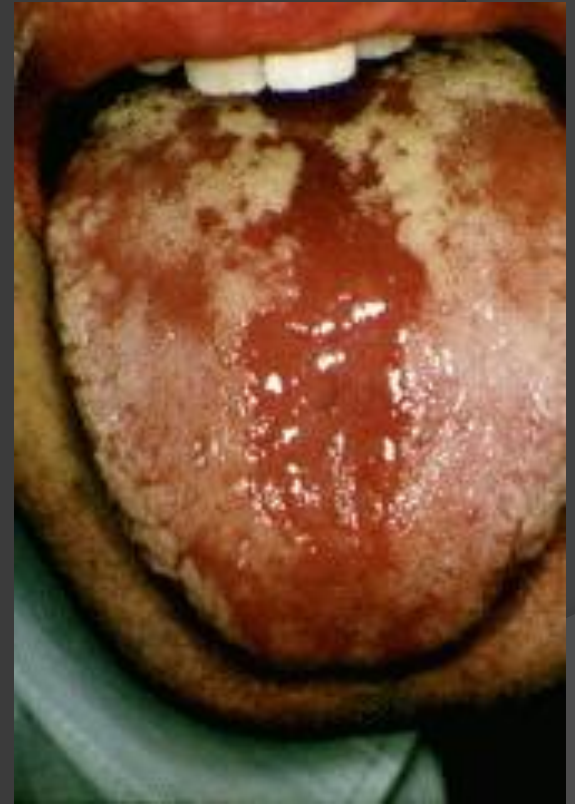
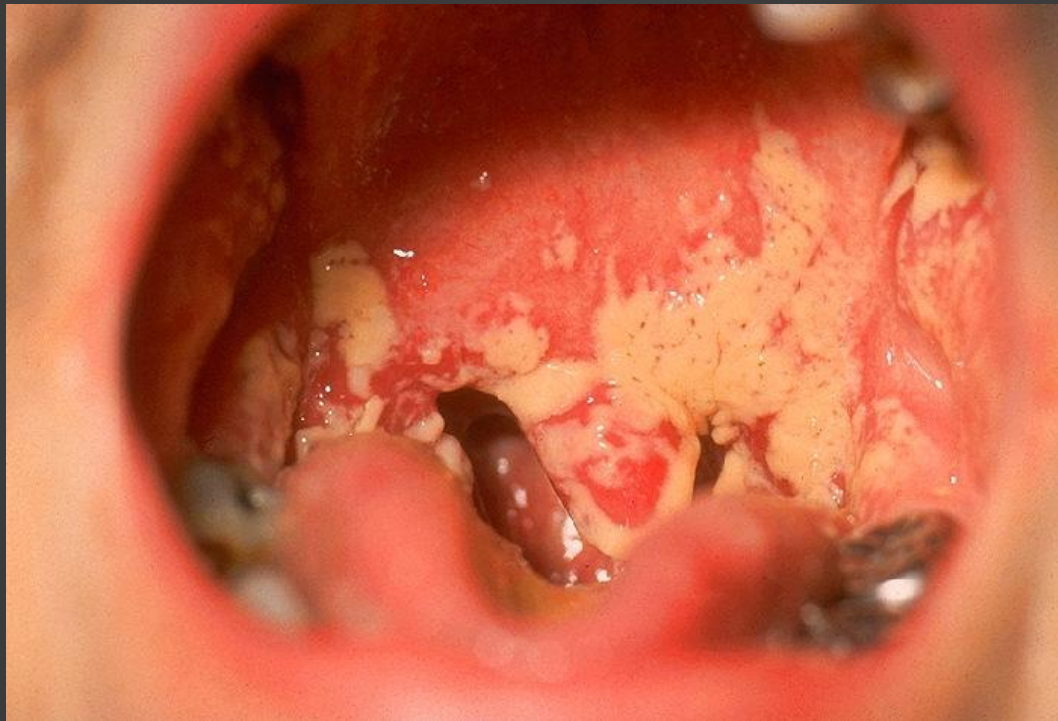
<http://www.medscape.com>



## C. Gastrointestinal manifestations

1. Oropharyngeal lesions OROPHARYNGEAL  
CANDIDIASIS
2. Causative agent: *Candida albicans*
3. Clinical forms:
  - ✓ Pseudomembranous type of candidiasis,
  - ✓ Erythematous type of candidiasis,
  - ✓ Hyperplastic type of candidiasis.

## Pseudomembranous type of oropharyngeal candidiasis



## Erythematous type of oropharyngeal candidiasis



## ORAL HAIRY LEUKOPLAKIA

- Cause: EBV? It presents as whitish vertical folds on the sides of the tongue.



Figure 2 - Oral hairy leukoplakia – this finding can also be a feature of iatrogenic immunosuppression

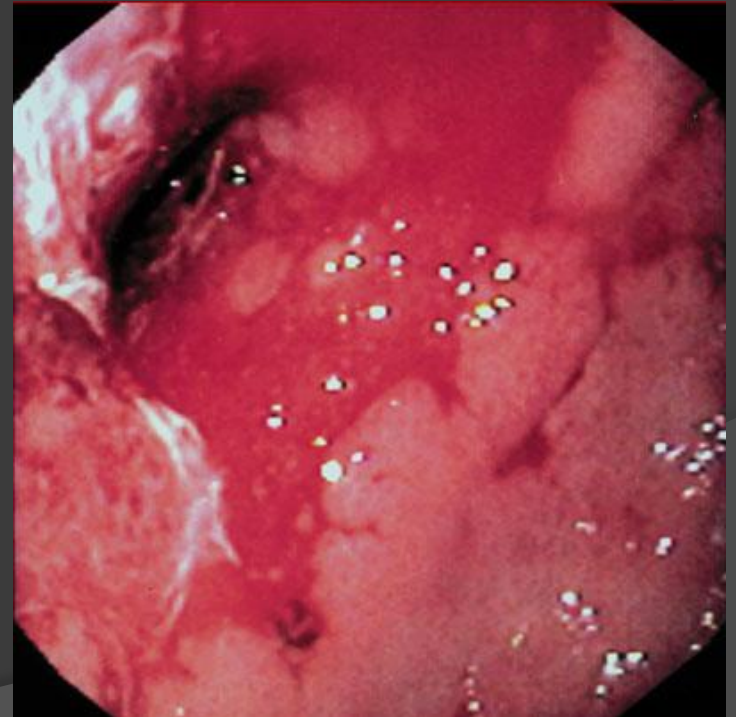
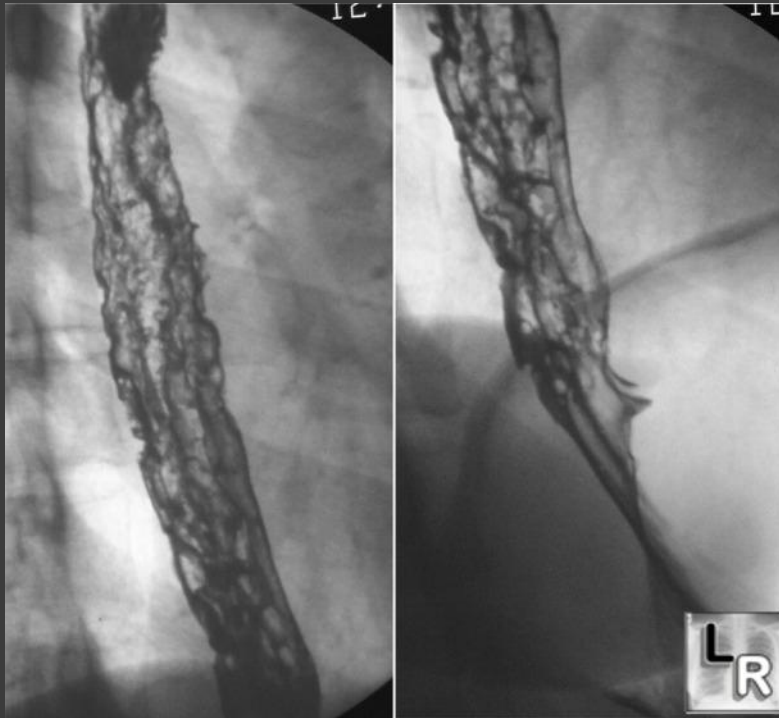




## 2. Esophagitis

Etiology: *C. albicans*, CMV, HSV, Symptoms: retrosternal pain, dysphagia,

Diagnosis: esophagoscopy with biopsy.





## Diarrheal syndrome

### SYMPTOMS:

- ✓ Diarrhea,
- ✓ Abdominal pain,
- ✓ Weight loss,
- ✓ Signs of malnutrition.

### ETIOLOGY:

- ✓ Cryptosporidium,
- ✓ Isospora belli,
- ✓ CMV,
- ✓ HIV,
- ✓ Other pathogens (Shigellae, Salmonellae, Giardia, Entamoeba histolytica, ...)

#### 4. Kaposi's sarcoma

It most commonly occurs in the oral cavity and lower parts of the gastrointestinal tract.



## D. Neurological manifestations

### 1. Meningitis

Most common causative agent: **Cryptococcus neoformans**,

Clinical course subacute: fever, headache, meningeal signs, later impaired consciousness to coma,

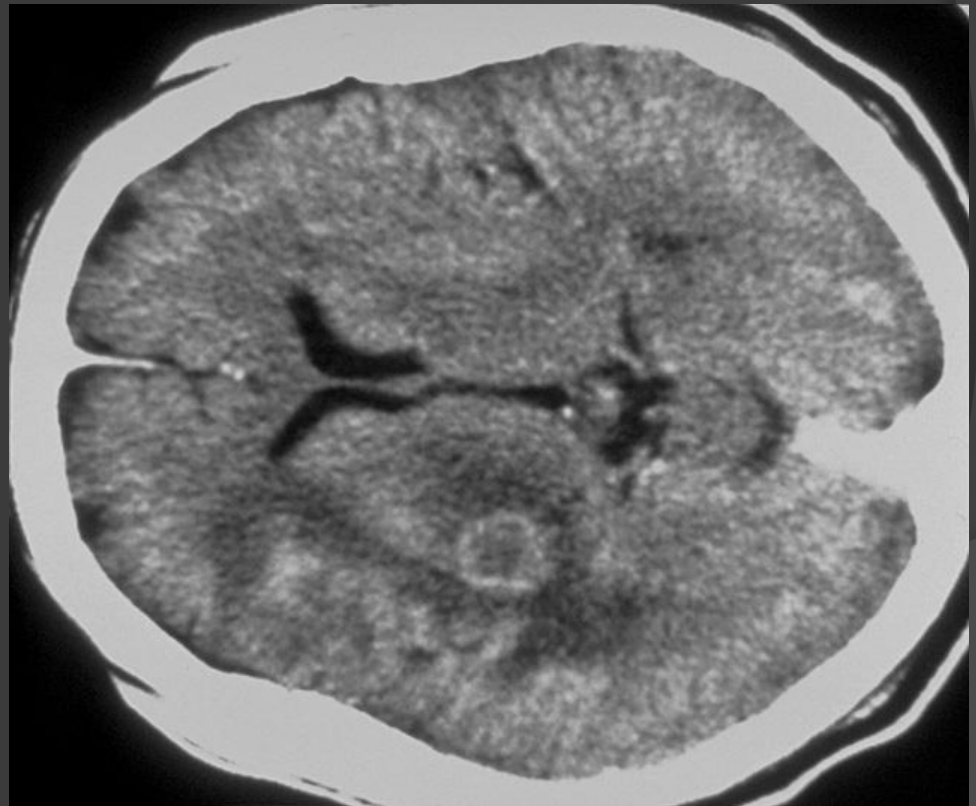
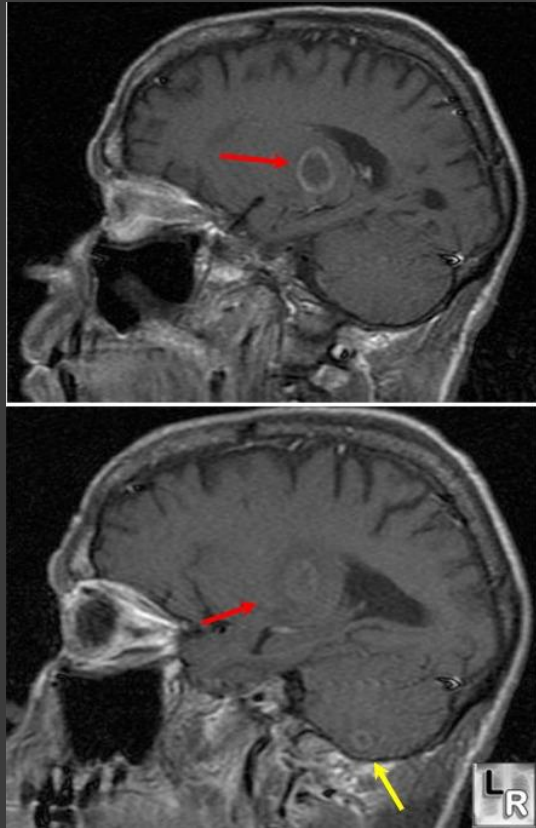
**CSF findings:** moderate pleocytosis, elevated proteins, decreased sugar,

**Diagnosis:** microscopic examination of CSF, CSF culture on selective medium or detection of cryptococcal antigen in CSF.

## 2. Toxoplasma brain abscess

**Causative agent:** *Toxoplasma gondii*, Clinical picture: focal neurological deficits, ataxia, impaired consciousness,

**Diagnosis:** CT or MRI of the brain (multiple abscesses in the form of hypodense zones).

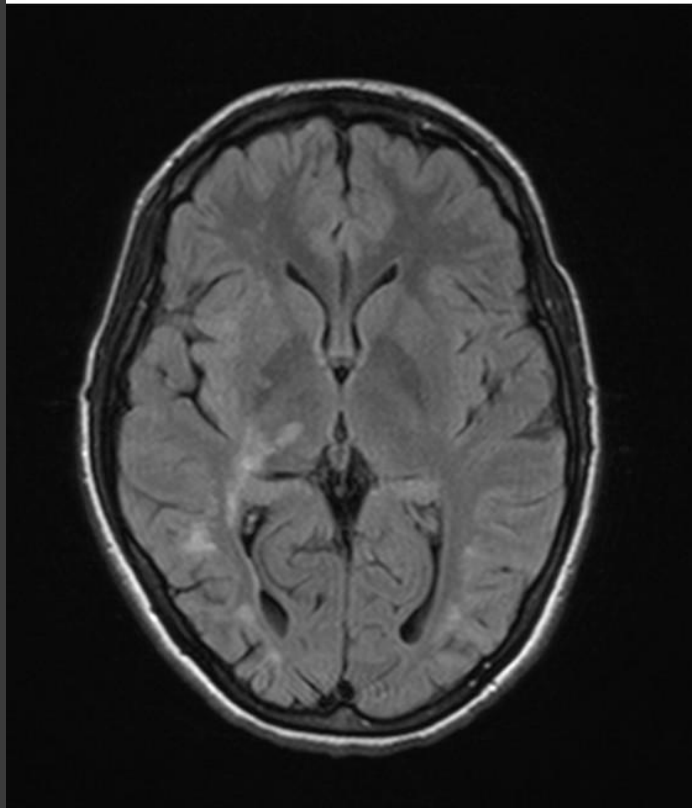


### 3. Progressive Multifocal Leukoencephalopathy (PML)

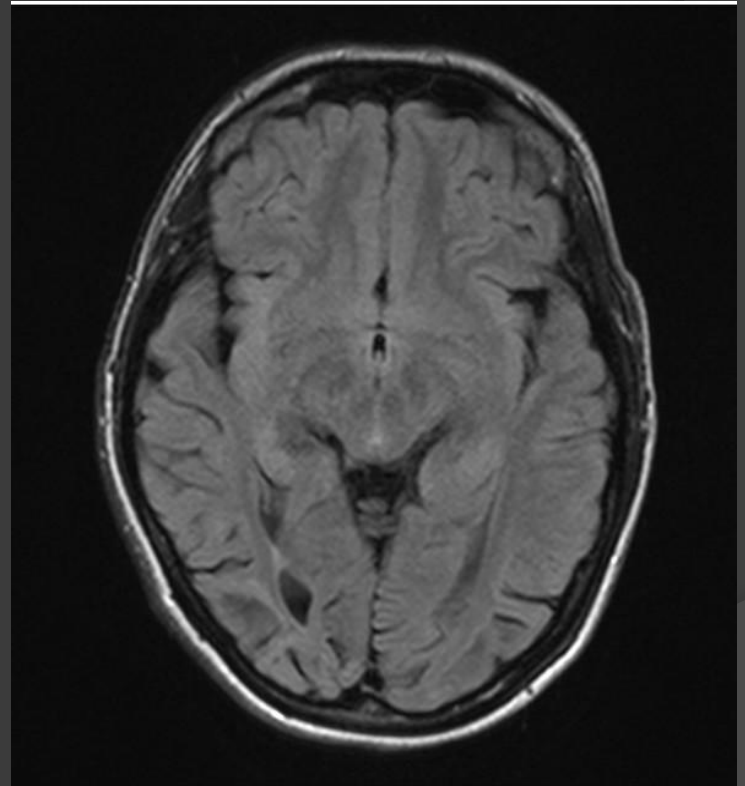
**Causative agent:** JC papova virus,

**Clinical picture:** speech disorder up to aphasia, visual impairment up to blindness, hemiparesis, ataxia,

**Diagnosis:** PCR of JC virus from cerebrospinal fluid, CT or MRI of the brain (multifocal hypodense zones).



Before ART



After ART

#### 4. Cytomegalovirus retinitis

Untreated, it leads to blindness.





## 5. AIDS Dementia Complex (ADC)

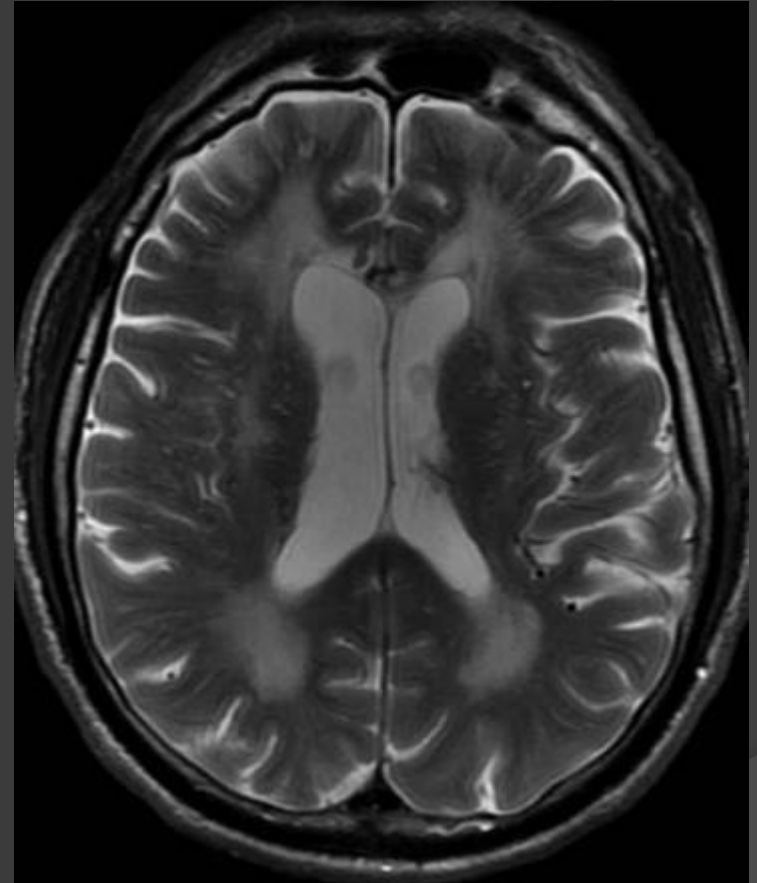
It occurs as a result of the direct effect of HIV on the brain parenchyma,

The clinical picture is dominated by mental disorders and neurological disorders,

**Mental disorders:** thought disorders, mental retardation, loss of interest in the environment, apathy, depression, intellectual reduction to dementia,

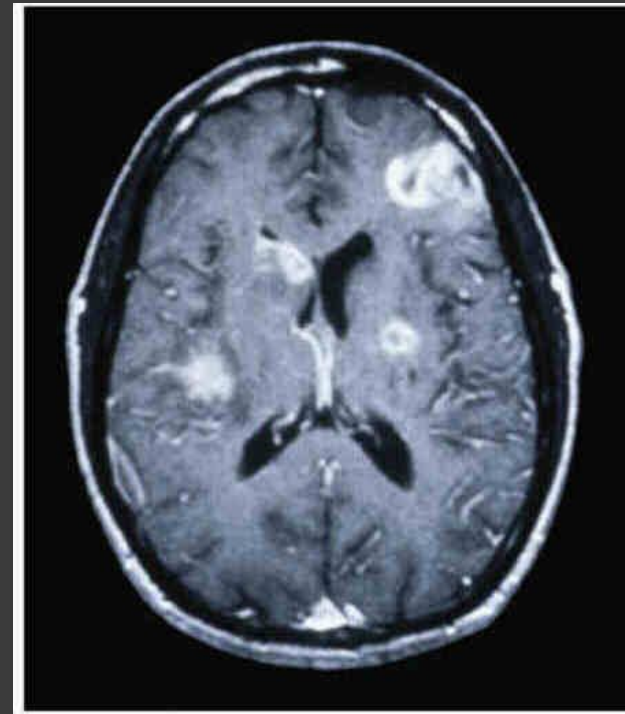
**Neurological disorders:** unsteadiness in gait, uncoordinated movements, tremor, slow speech, incontinence, paraparesis.

**Diagnosis:** CT or MRI of the endocranium (diffuse brain atrophy).



## Kaposi's sarcoma and non-Hodgkin's lymphoma

Often cause space compression syndrome.



## E. Dermatological manifestations

### Infections

#### **S. aureus:**

Folikulitis,  
Bulozni impetigo,  
Ektima,  
**Apsces,**  
Celulitis.



#### **S. pyogenes:**

Bulozni impetigo,  
Celulitis.



## 2. Erythemosquamous dermatoses

seborrheic dermatitis, Psoriasis.



## Classification system for HIV infection according to CDC criteria

categories			
	A	B	C
Categories by CD4+ T lymphocyte count/mm3	Asymptomatic, PGL or acute HIV infection	Symptomatic (not A or C)	AIDS "Indicative diseases"
1. > 500 (> 29%)	A <sub>1</sub>	B <sub>1</sub>	C <sub>1</sub>
2. 200-499 (14-28%)	A <sub>2</sub>	B <sub>2</sub>	C <sub>2</sub>
3. < 200 (< 14%)	A <sub>3</sub>	B <sub>3</sub>	C <sub>3</sub>

## Category C

Cervical carcinoma,  
invasive CMV- any organ except liver, spleen, and lymph nodes  
HSV infection, chronic mucocutaneous or visceral  
Histoplasmosis, extrapulmonary HIV wasting syndrome  
HIV encephalopathy (ADC)  
Isosporiasis  
Cryptococcosis,  
extrapulmonary Candidiasis of esophagus, trachea, bronchi, or lungs  
Cryptosporidiosis  
Kaposi's sarcoma  
NHL Microbacteriosis – *M. avium* or *M. kansasii*, disseminated.  
*M. tuberculosis*, extrapulmonary and/or disseminated and pulmonary Microsporidiosis  
Nocardiosis Pneumocytoma,  
pulmonary PML  
Salmonella sepsis  
Toxoplasmosis,  
visceral Strongyloidiasis,  
extraintestinal Pneumonia,  
recurrent bacterial

## Diagnosis of HIV infection and AIDS

Clinical picture,

Epidemiological data,

Laboratory analyses (immunological and virological analyses).



## Detection of HIV antibodies (anti HIV)

1. Anti HIV usually appears **between 4 weeks and 6 months** after infection, The most common method for their detection is an enzyme-linked immunosorbent assay (ELISA).

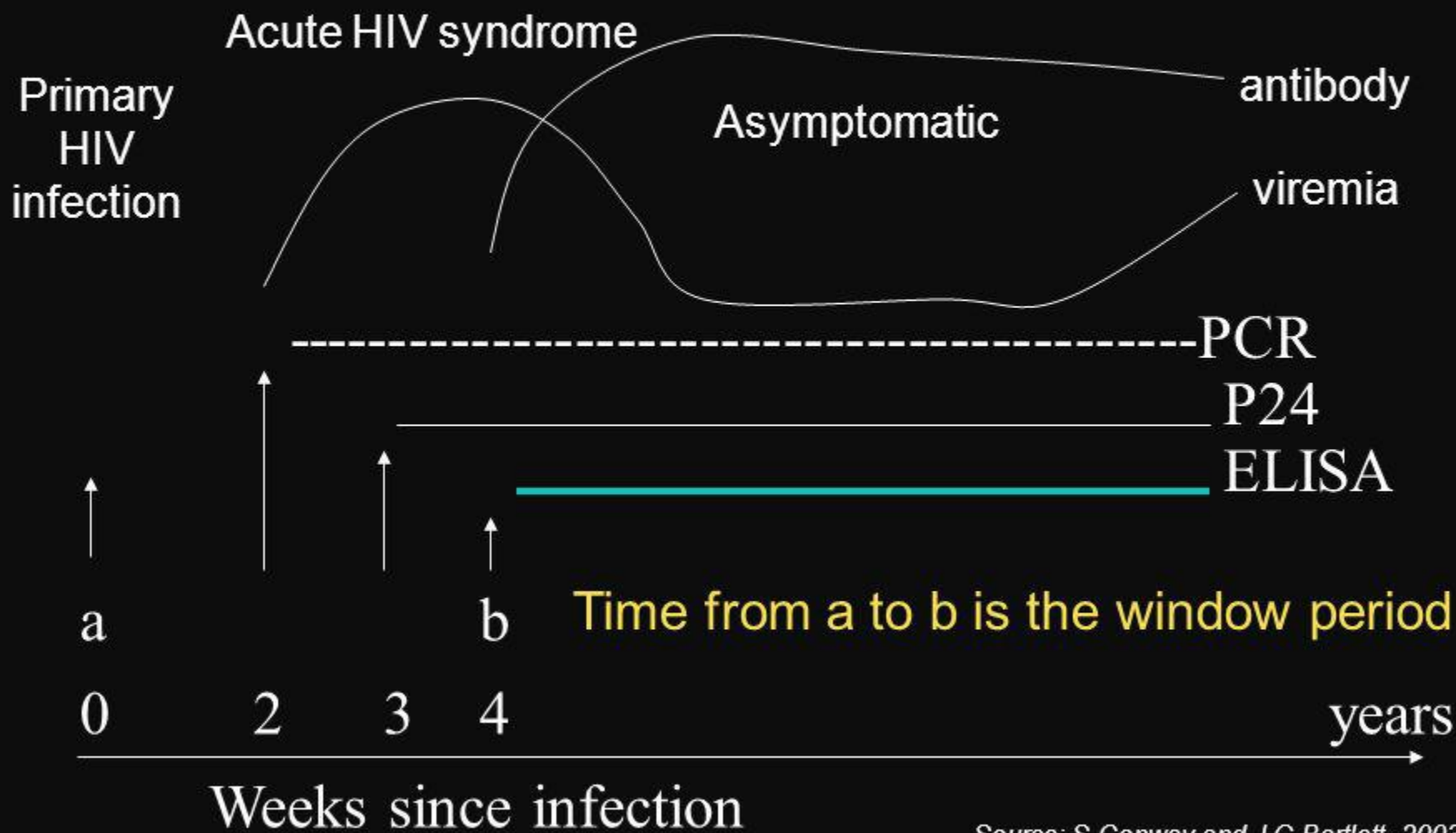
## **Western blot test (confirmatory test).**

2. Detection of HIV antigen (HIV-p24) HIV-Ag appears 2-3 weeks after infection, A positive HIV-Ag test indicates HIV infection, A negative HIV-Ag test does not rule out HIV infection.

3.Detection of HIV genetic material PCR (Polymerase Chain Reaction).

4.Virus isolation (by cultivation) HIV can be isolated from:  
Peripheral blood lymphocytes, Lymph nodes, Brain

# Window Period: Untreated Clinical Course



Source: S Conway and J.G Bartlett, 2003

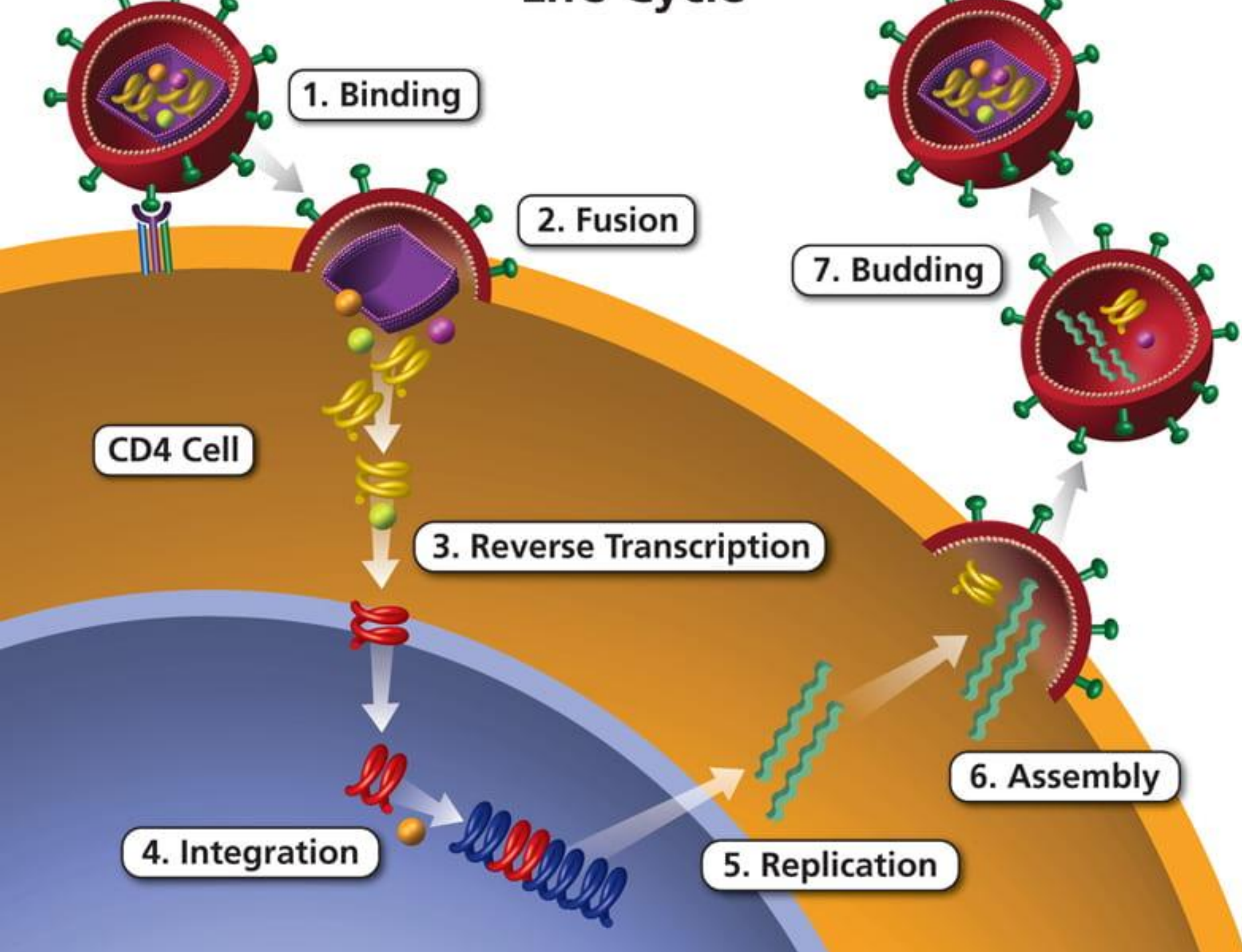
## Therapy of HIV infection

1. Antiretroviral therapy (anti-HIV therapy),
2. Therapy and prophylaxis of opportunistic infections i
3. Opportunistic tumor therapy.

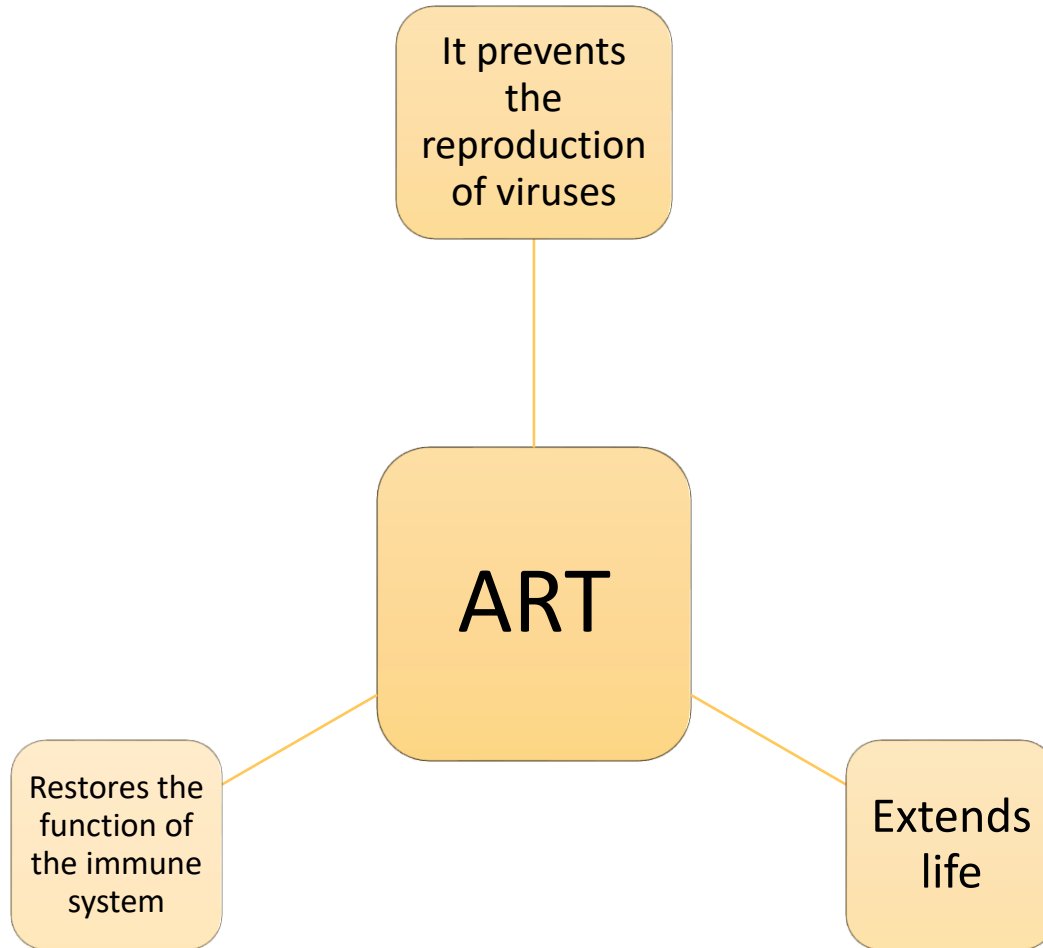
# Комбинована антиретровирусна терапија HAART (eng. **H**ighly **A**ctive **A**nti**R**etroviral **T**reatment)

1. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)
2. Non-nucleoside reverse transcriptase inhibitors (NNIRTs)
3. Protease inhibitors (PIs)
4. Integrase inhibitors (IIs)
5. CCR5 antagonists
6. Fusion inhibitors

NIRT	NNIRT	IP	II	CCR5 антагонисти	Инхибитори фузије
Zidovudin	Nevirapin	Sakvinavir	Raltegravir	Maraviroc	Enfuvirtide
Abacavir	Efanvirenz	Fosamprenavir	Elvitegravir		
Didanosin	Entravirine	Indinavir	Dolutegravir		
Lamivudin	<b>Doravirin</b>	Ritonavir	<b>Bictegravir</b>		
Емтрицитабине		Атазанавир			
Tenofovir		Lopinavir			
		Darunavir			









UNDETECTABLE EQUALS UNTRANSMITTABLE

## MODERN ATTITUDES REGARDING ANTIRETROVIRAL THERAPY

- ⦿ Antiretroviral therapy should be included in all HIV positive patients.
- ⦿ Two most important problems of antiretroviral therapy are: resistance and toxicity.

# Therapy opportunistic infections

<b>P. carinii</b>	TMP-SMX 20 mg/kgTT/dn	P.O ili i.v.	Pentamidin Dapson	3 weeks
<b>Candida</b>	Fluconazol	P.O.	Itraconazole	2 weeks
<b>T. gondii</b>	pirimetamin-sulfadiazin 50 nig+6 g/dn	P.O.	Klindamicin + Pirimetamin	4÷6 weeks
<b>C neoformans</b>	Amfotericin B 0,6 mg/kgTT/dn	i.v.	Flukonazol	4÷6 weeks
<b>HSV</b>	Aciklovir 1000 mg/dn 5 mg/kgTT/8 <sup>h</sup>	P.O. i.v.	Valciklovir Famciklovir	2÷4 weeks
<b>VZV</b>	Aciklovir 4g 10mg/kgTT/8 <sup>h</sup>	P.O. i.v.	Valciklovir Famciklovir	2÷3 weeks
<b>CMV</b>	Ganciklovir 5 mg/kgTT/12 <sup>h</sup>	i.v.	Foskarnet	2-3 weeks
<b>M. tuberculosis</b>	Tuberkulostatici	P.O.		12 monts
<b>M. avium intracelulare</b>	Klaritromicin+ Etambutol+ Rifabutin	P.O.	Azitromicin+ Etambutol+ Rifabutin	8 weeks

## Therapy of opportunistic tumors

- Antiretroviral therapy,
- Radiotherapy,
- Chemotherapy.



Thank you!

Hiv Infection &

**AIDS**