HIV INFECTION !

Human Immunodeficiency Virus (HIV)

- **Infects human cells and causes gradual loss of immune system function, and these immune alterations predispose to the opportunistic infections, neoplasms, and other conditions (wasting and dementia)**

The term

***Human Immunodeficiency Virus* syndrome**

is used to describe
the cellular and humoral immunodeficiency
and the numerous complications
that result from the HIV infection

Acquired immunodeficiency syndrome (AIDS)

- Is the spectrum of disorders resulting from very advanced HIV infection

1996 – HAART era

- the introduction of HIV therapy into clinical practice represented a significant step forward in the treatment of HIV infection
- the ability of HAART regiments have transformed HIV infection into

  a manageable chronic disease

  in many patients

HAART = cART = OBT = ART

Three-drug combinations

are currently recommended

for the initiation of treatment in all patients

HAART – Highly Active AntiRetroviral Therapy

cART - Combination AntiRetroviral Therapy

OBT - Optimalising Basic Treatment

ART - AntiRetroviral Therapy

ART

Enormous changes in prognosis of HIV/AIDS disease

- **maximally and durably supresses viral load**
- **restores immunological function**
- **improves quality of life**
- **dramatically reduces HIV-related morbidity and mortality**

Global summary of the AIDS epidemic 2014

Number of people living with HIV	Total	36.9 million [34.3 million – 41.4 million]
	Adults	34.3 million [31.8 million – 38.5 million]
	Women	17.4 million [16.1 million – 20.0 million]
	Children (<15 years)	2.6 million [2.4 million – 2.8 million]
People newly infected with HIV 2014	Total	2.0 million [1.9 million – 2.2 million]
	Adults	1.8 million [1.7 million – 2.0 million]
	Children (<15 years)	220 000 [190 000 – 260 000]
AIDS deaths in 2014	Total	1.2 million [980 000 – 1.6 million]
	Adults	1.0 million [760 000 – 1.8 million]
	Children (<15 years)	150 000 [140 000 – 170 000]

Czech republic 31.8.2016

- Czech citizens 2836
- Foreigners
  with long-lasting stay in CR 416
- Total number 3252
- Death due to AIDS 352

TRANSMISSION

HIV has been isolated from bodily fluids

With high/titer viremia

- **blood**
- **semen**
- **cervicovaginal secretion**

These bodily fluits have been implicated in the transmission of HIV

With low/titer viremia

- **saliva**
- **tears**
- **urine**
- **CSF**

These bodily fluits have not been implicated in the transmission of HIV

Modes of HIV transmission

HIV is transmitted through three primary routes:

1. **sexual**
2. **parenteral**
3. **vertical**

I. Sexual route

Sexual contact with an infected person is the predominant mode of transmission wordwide

1. Homosexual intercourse

- **Men who have sex with men**
- **Homosexual and bisexual men**

The main mode in North America, Europe and Australia

2. Heterosexual intercourse

- **The dominant mode (90%) wordwide**
- **As a risk factor for acquiring HIV has dramatically increased**

II. Parenteral route (exposure)

1. **Blood transfusion and blood products can be infected by HIV**

   - recipients are in risk acquiring of HIV

   - **hemophiliacs, plasma, clotting factors**
   - **whole blood, blood cellular components**
   - **recipients of tissue, organ transplants, semen**

Transfusion of infected blood
or blood components
as a risk factor for acquiring HIV has

dramatically decreased in incidence

secondary to the availability
of a screening of all blood products
since 1987

2. **Contaminated injection and medical equipments**

- **drug users, sportsman**
- **nosocomial**
- **health and laboratory workers**

The probability transmission of HIV infection

after skin puncture with infected materials

depends on multiple factors

- **high titer viremia of the patients**
- **amount of blood on the needle**
- **advanced HIV infection…**

Without antiretroviral therapy

is estimated to be 0.3 – 0.5 %

Postexposure Prophylaxis (PEP)

Prompt administration

of a combination regimen of AR drugs (PEP)

significantly decreases the likelihood

of HIV infection

following needle-stick injuries

III. Vertical route (mother-to-child)

Perinatal transmission may occur

1. **During pregnancy (in utero)**
2. **During delivery**
   (at birth, intrapartum)
3. **During breastfeeding**

No transmission

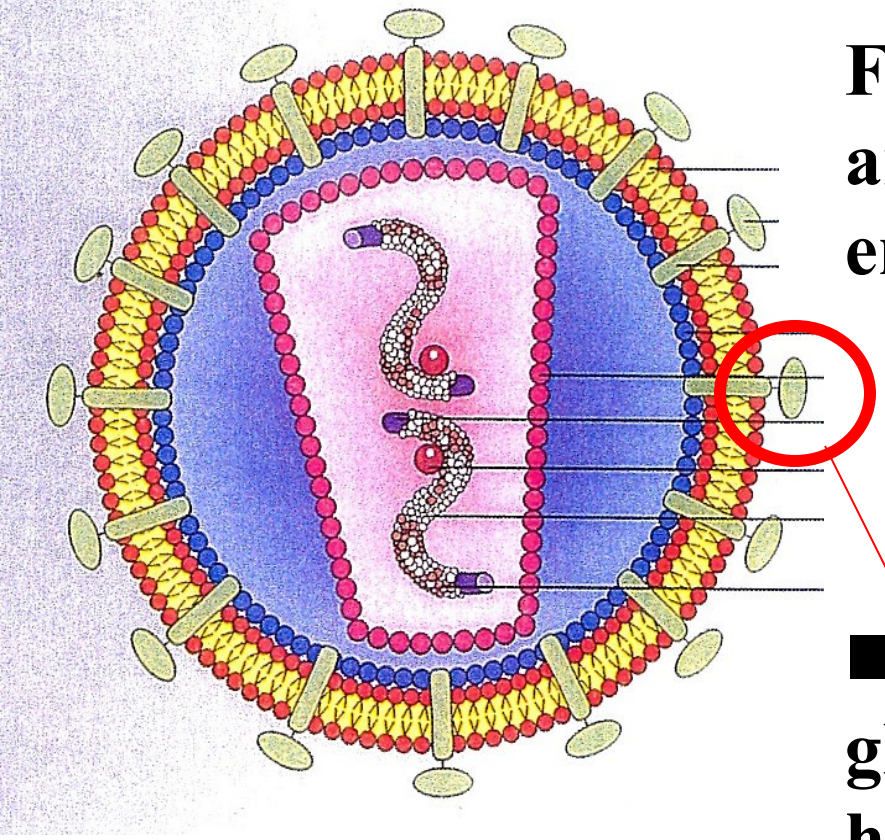
- **Household contacts** not sexually involved with infected persons **are not risk** for acquiring HIV

- **Family members** who shared bathrooms and eating utensils with HIV+ patients **did not become infected**

- **Mosquitoes do not transmit HIV**

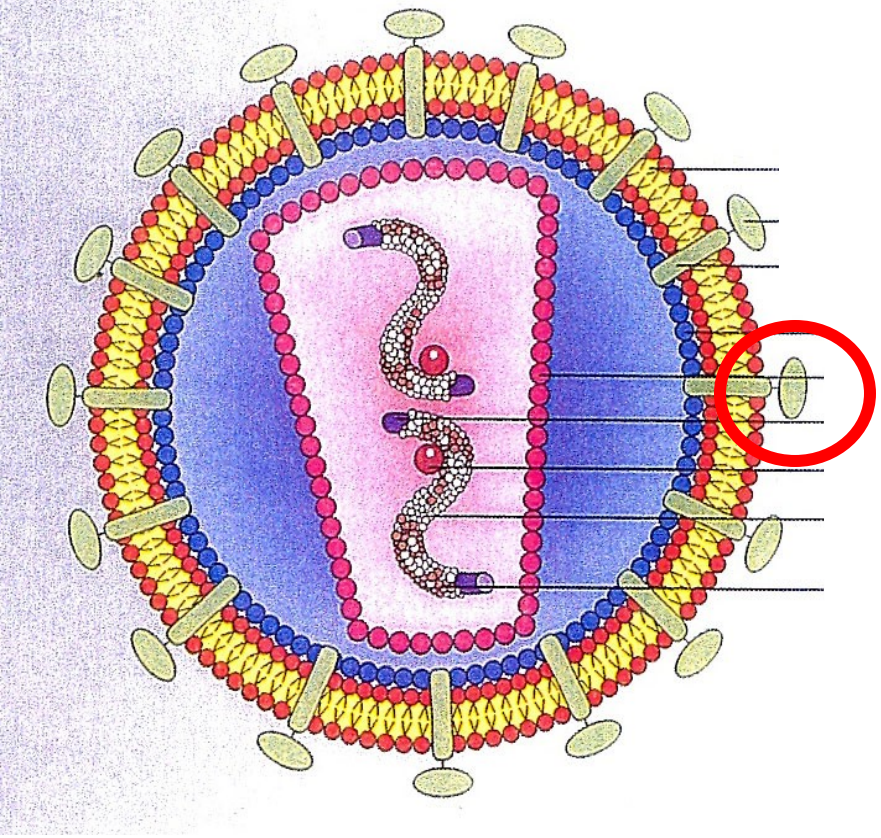
- **No cases of transmission from human bites have been reported.**
  Saliva contains neutralizing factors.

PATHOGENESIS



Free virus
and possibly virus-infected cells
enter the blood
during initial infection

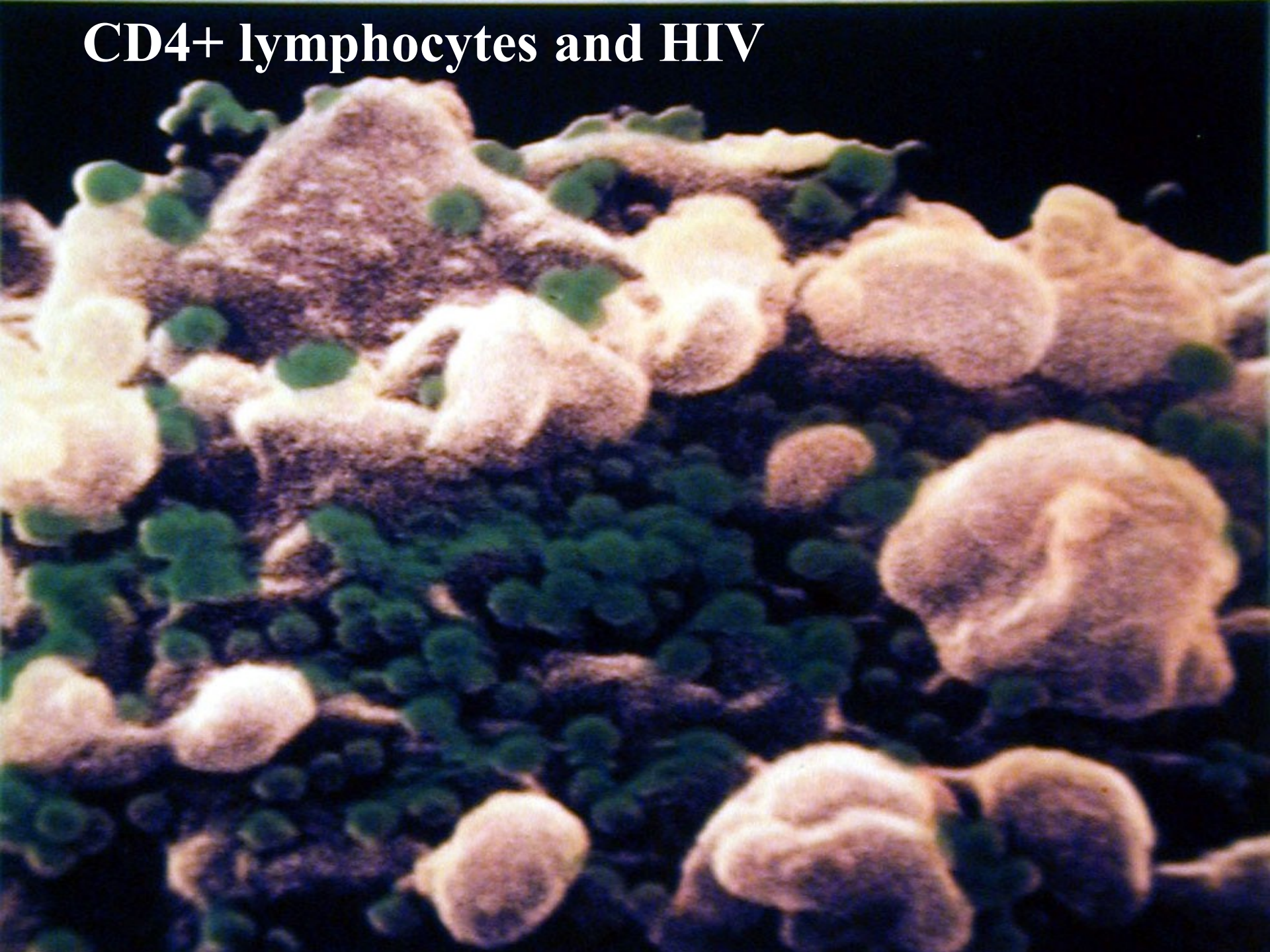
■ **The HIV envelope**
glycoprotein 120
have a high affinity
for the CD4 molecule (receptor)
on the surface of CD4 cells
(helper cells, Th lymphocytes)



- **Productive viral replication is lytic to infected T cells**

- **Loss of number of CD4 cells is basis of advanced infection**

CD4+ lymphocytes and HIV



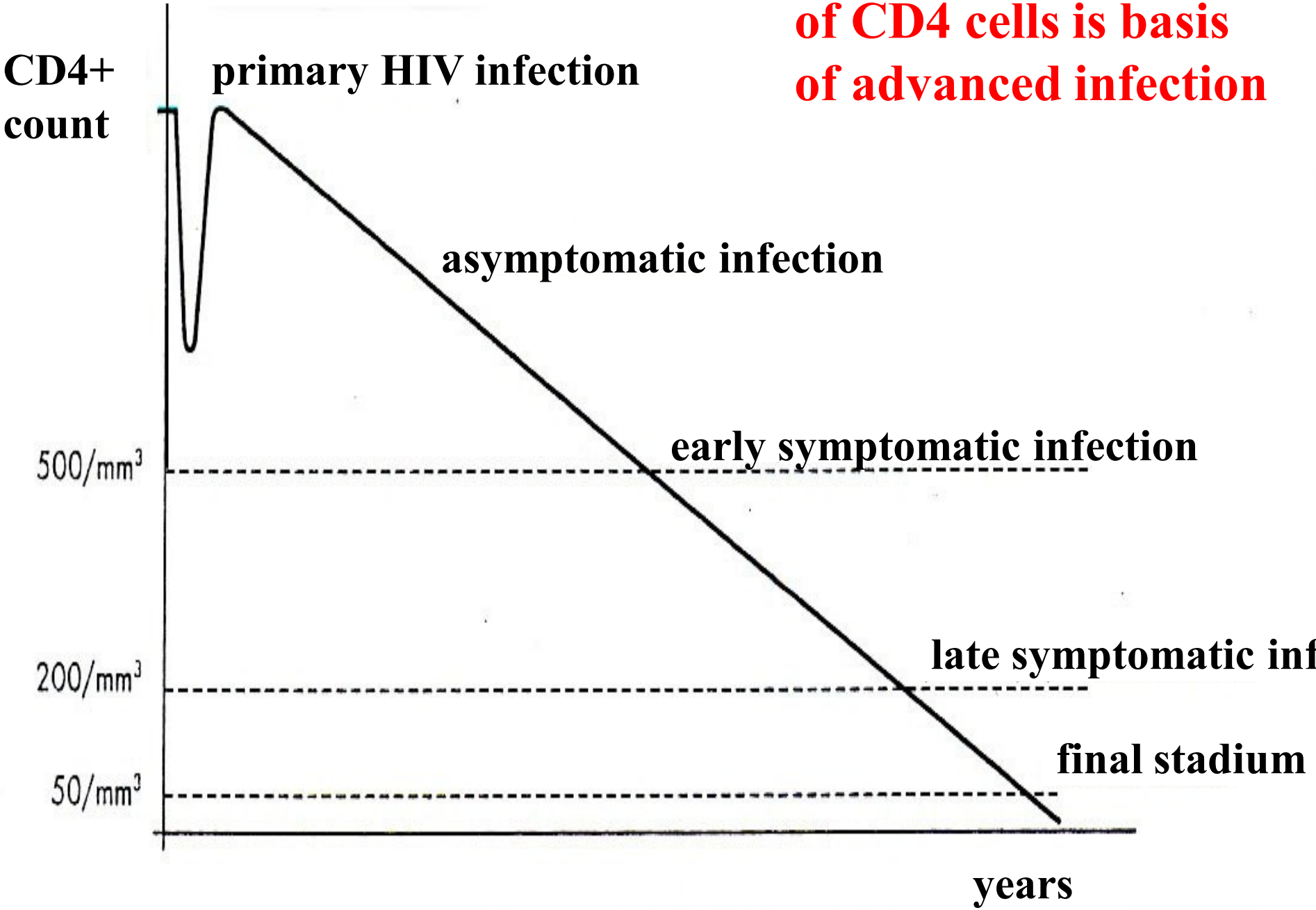
A decrease in function

as well as number of CD4 cells

is central

to the immune dysfunction

CD4+ lymphocytes depletion – gradual loss of number of CD4 cells is basis of advanced infection

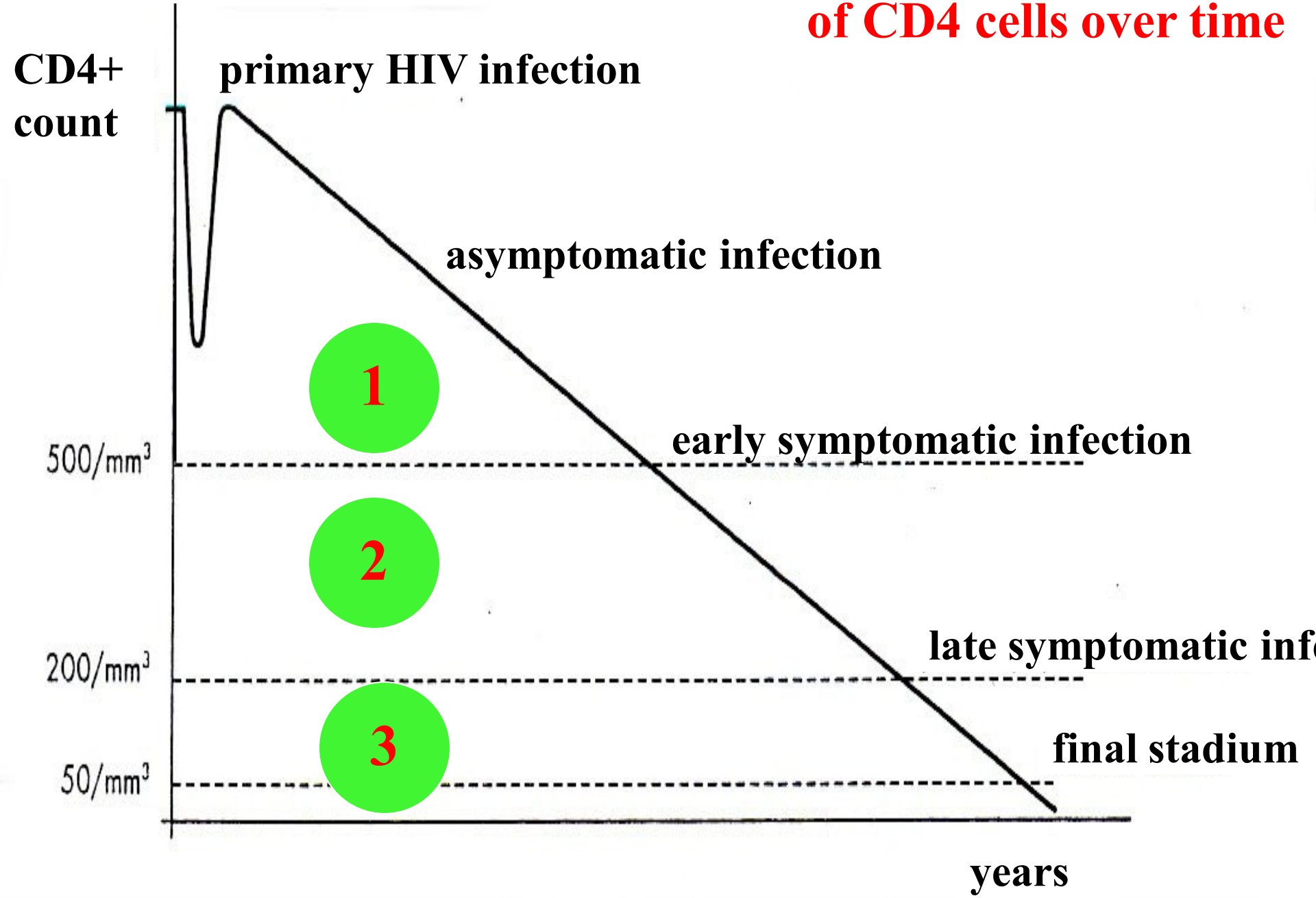


CLASSIFICATION OF HIV INFECTION

- **Criteria for HIV infection for adult person include:**
  - **laboratory categories**
  - **clinical categories**

Laboratory category	CD4+ T-cell count	%
1	≥ 500/mm^3	≥ 29 %
2	200 - 499/mm^3	14-28%
3	< 200/mm^3	<14%

CD4+ lymphocytes depletion – gradual loss of number of CD4 cells over time



Clinical categories – corresponding to clinical condition

A

- **acute primary HIV**
- **asymptomatic infection**
- **persistent generalized lymphadenopathy (PGL)**

is not typically associated with OI

Clinical categories – corresponding to clinical condition

Risk for OI begins

B • **symptomatic infection (not A or C condition)**

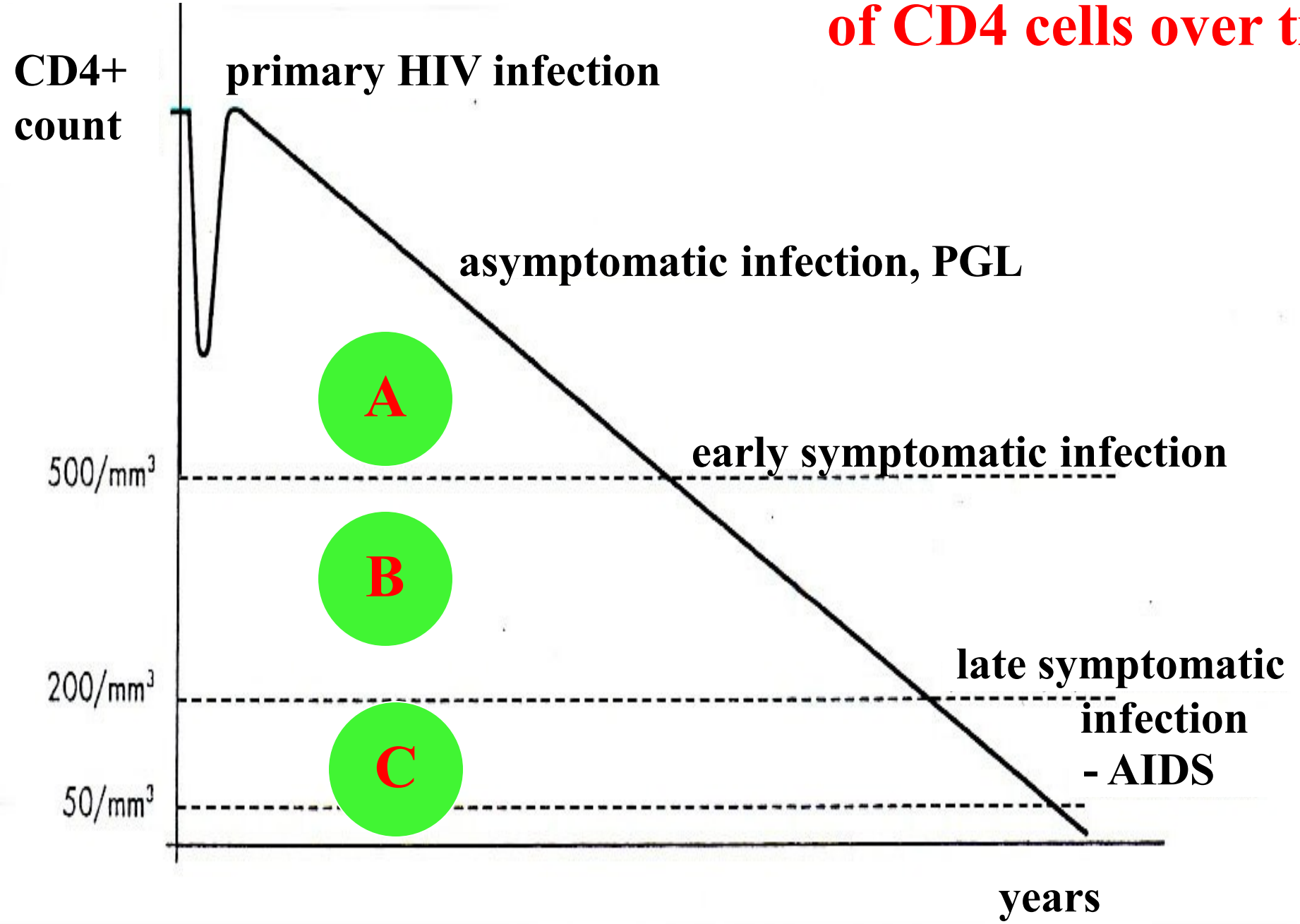
C • **AIDS indicator condition**

The AIDS syndrome is defined by various

- **opportunistic infections**
- **malignancies**
- **other conditions**

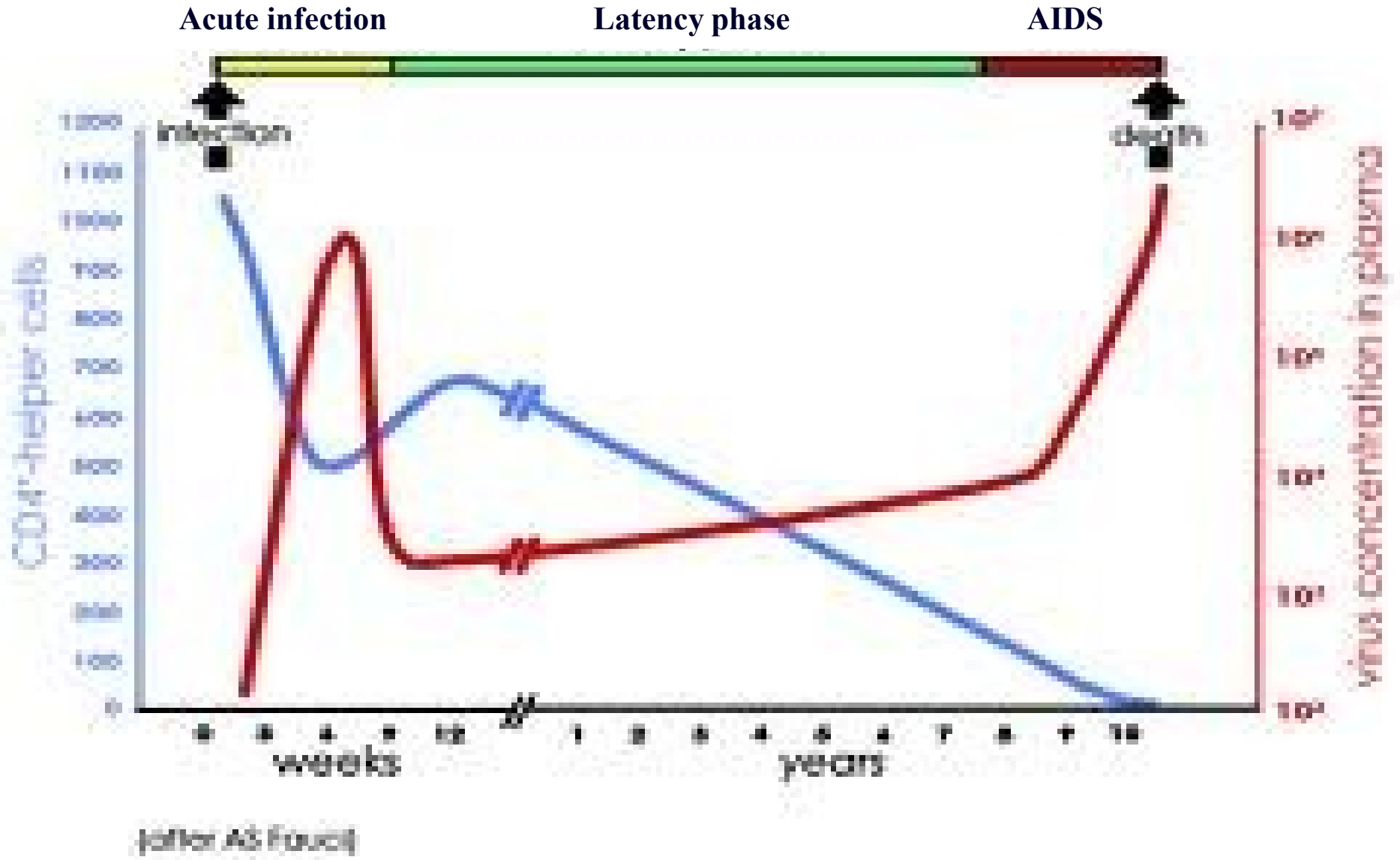
sumarized in the CDC definition.

CD4+ lymphocytes depletion – gradual loss of numb of CD4 cells over tim



Natural course of HIV infection (without treatment)

- Gradual loss of number of CD4 cells over time
- Gradual increase of number of viral copies (increase of viral load)



CLINICAL CATEGORY A

Category A

- Consists of one or more of the following conditions
  in an adolescent or adult
  with documented HIV infection

- Conditions listed in
  categories B and C must not have occured

Category A

Includes:

- **Acute (primary) HIV infection**
- **Asymptomatic HIV infection**
- **Persistent generalized lymphadenopathy (PGL)**

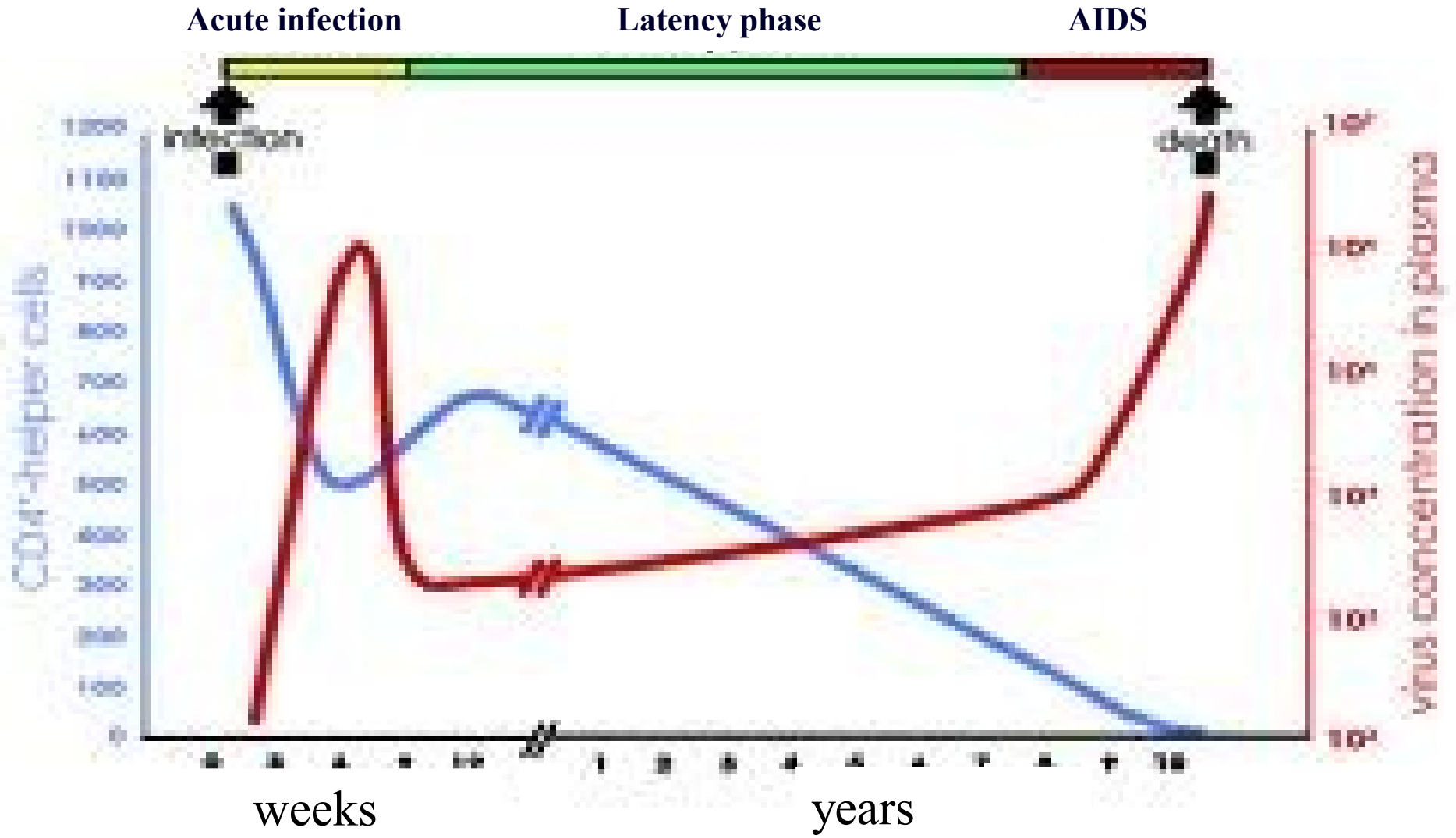
Acute primary HIV infection (mononucleosis-like syndrome, acute retroviral syndrom)

Occures:

- up to 70% of HIV-infected persons
- between 2 and 8 weeks after initial infection
- acute symptoms last 3 days to 3 weeks
- a variety of nonspecific signs and symptoms have been associated with the acute retroviral syndrome

Natural course of HIV infection (without treatment)

- Gradual loss of number of CD4 cells over time
- Gradual increase of number of viral copies (increase of viral load)



Signs and symptoms of primary HIV infection

- Fever 77%
- Lethargy/ fatigue 66%
- Rash 56%
- Myalgia 55%
- Headache 51%
- Pharyngitis 44%
- Cervical adenopathy 39%
- Arthralgia 31%

- Oral ulcer 29%
- Pain on swallowing 28%
- Axillary adenopathy 24%
- Weight loss 24%
- Nausea 24%
- Diarrhea 23%
- Night sweats 22%
- Cough 22%
- Anorexia 22%
- Abdominal pain 19%

- Oral candidiasis 17%
- Vomiting 12%
- Photophobia 12%
- Meningitis 12%
- Genital ulcer 7%
- Tonsillitis 7%
- Depression 7%
- Dizziness 6%

A variety

of nonspecific signs and symptoms

have been associated

with the acute retroviral syndrome

CLINICAL CATEGORY B

Category B
= symptomatic HIV infection

- Consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical category C
- Examples of conditions in clinical category B include:

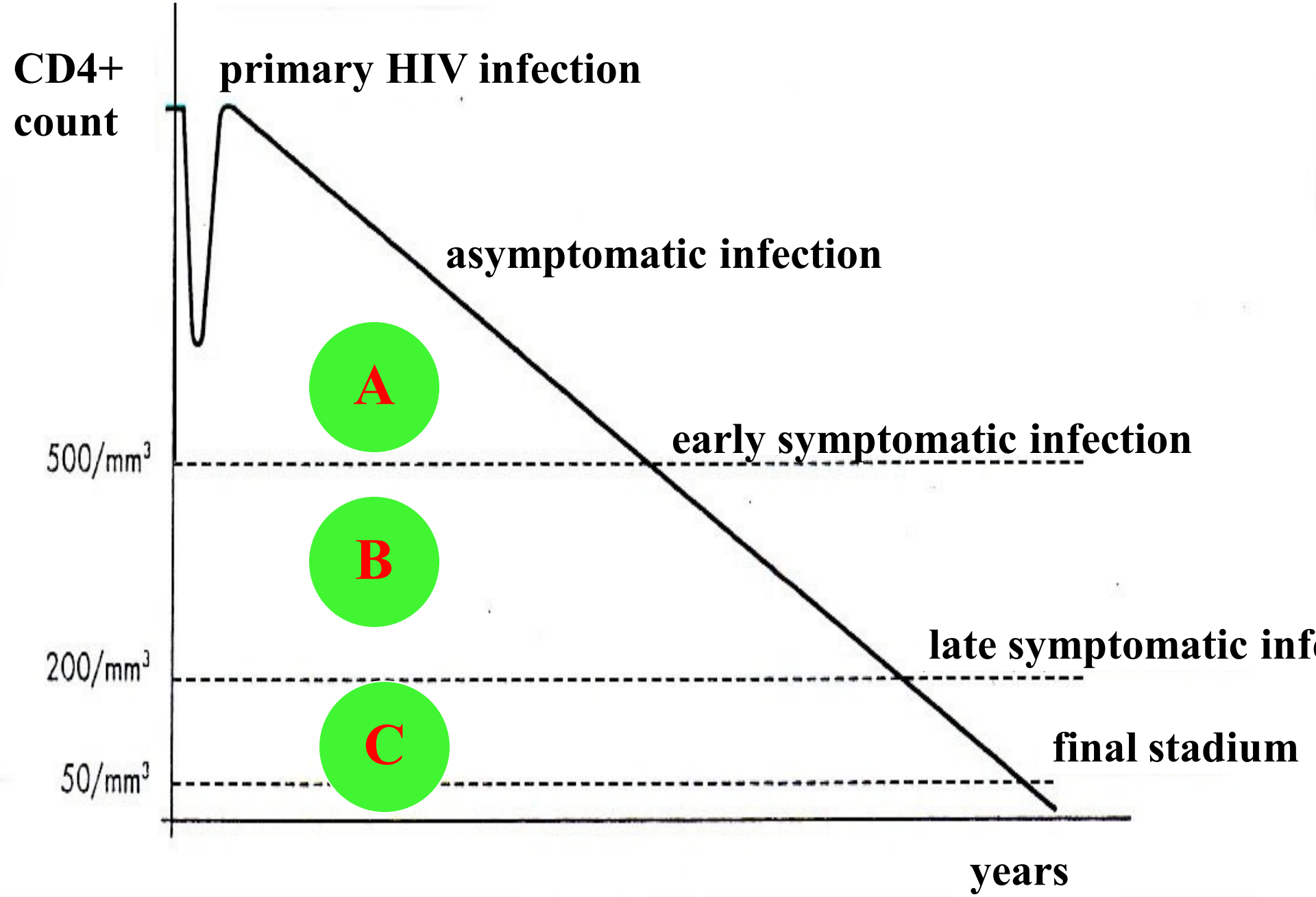
- Fever of >38.5 C > 1 month
- Diarrhea > 1 month

- Vulvovaginal candidosis
- Lymphoid interstitial pneumonitis (LIP)
- Cervical dysplasia or carcinoma in situ
- Pelvic inflammatory disease (PID)
- Listeriosis
- Bacillary angiomatosis
- Trombocytopenia
- Peripheral neuropathy

CLINICAL CATEGORY C

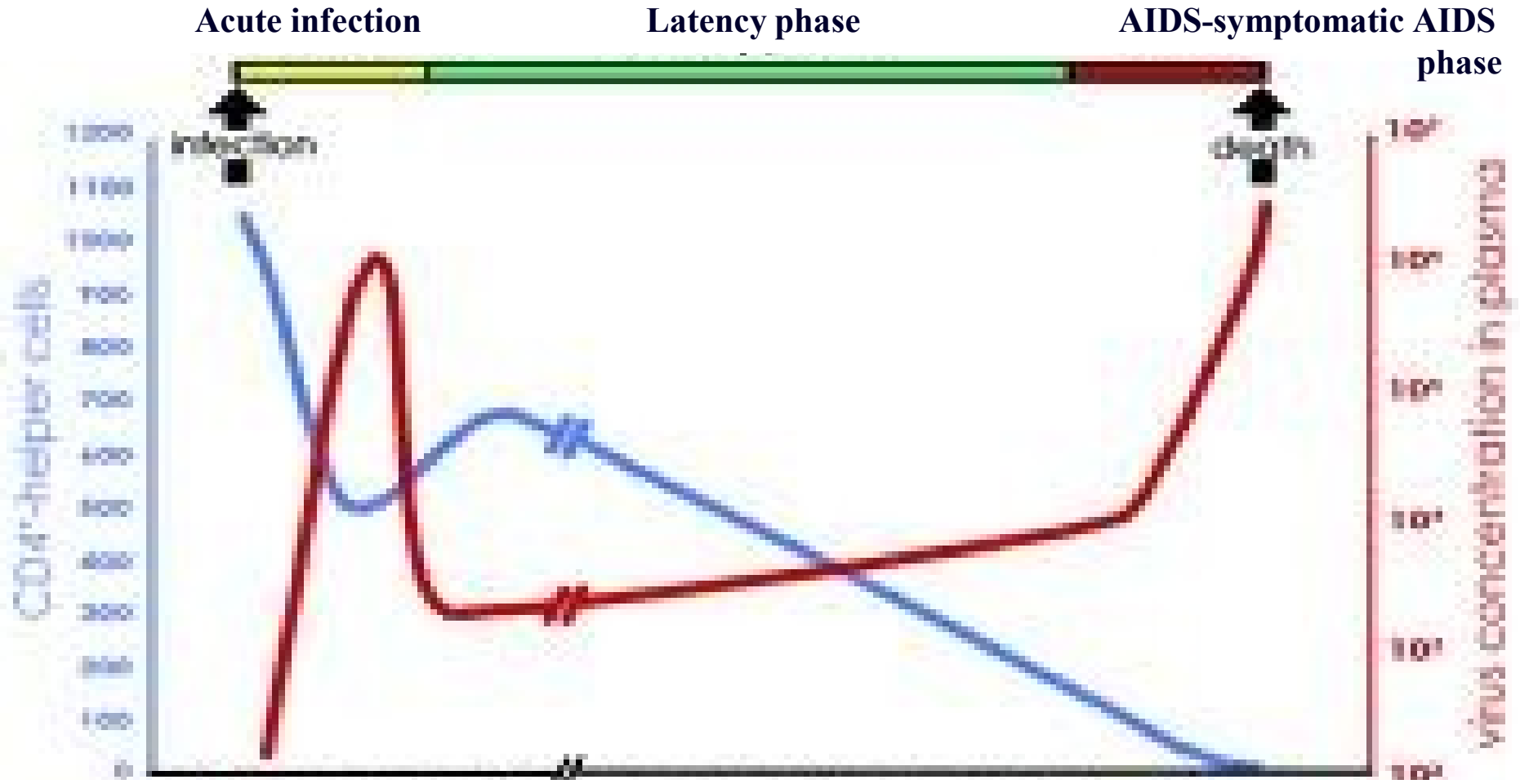
AIDS

CD4+ lymphocytes depletion



Natural course of HIV infection (without treatment)

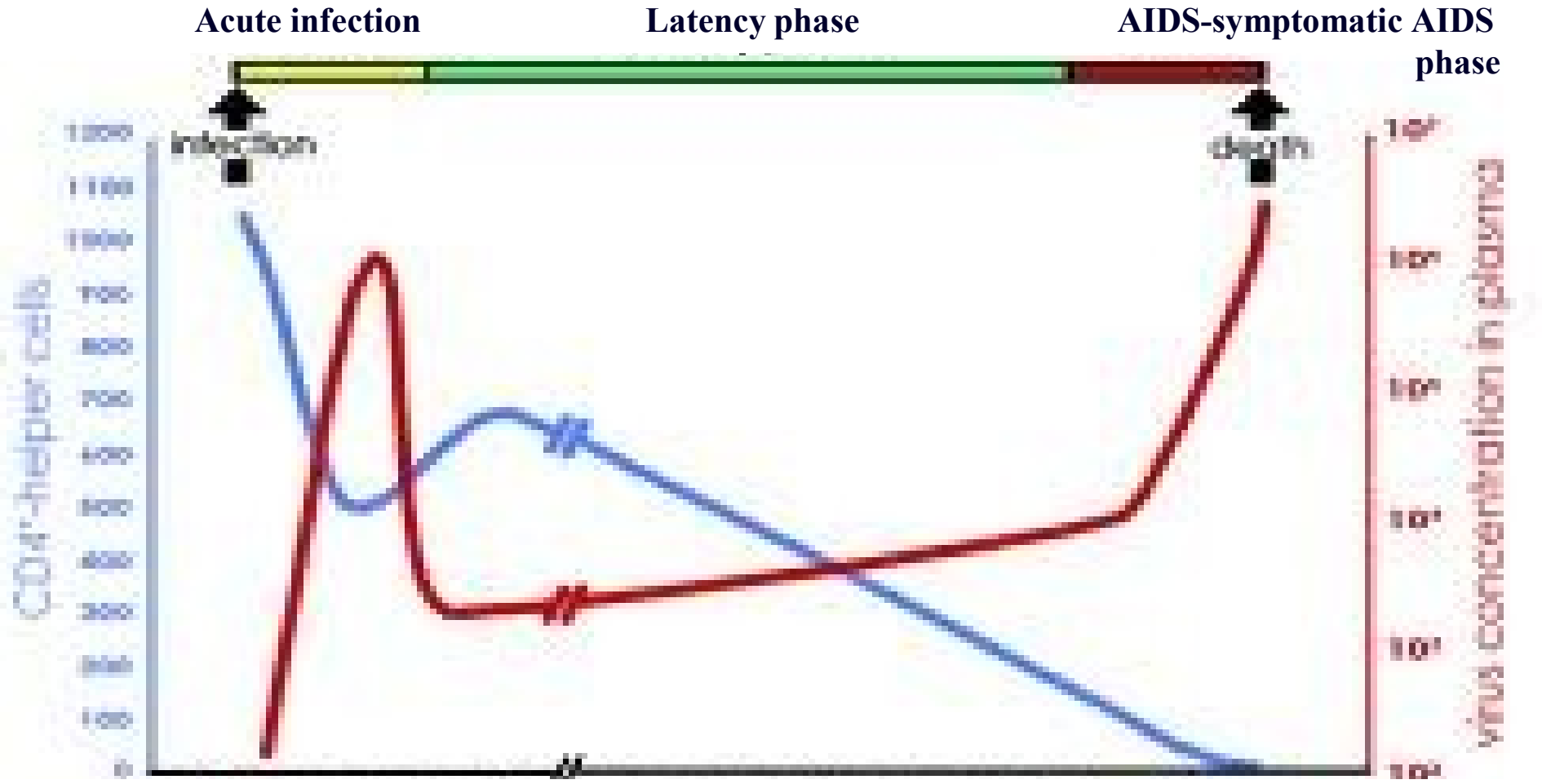
- Gradual loss of number of CD4 cells over time
- Gradual increase of number of viral copies (increase of viral load)



- **VL is extremely high** – possibly one million copies/ml or more
- **CD4 counts** usually **below 200** cells/mm3 and may fall **to zero**

Natural course of HIV infection (without treatment)

- **Gradual loss of number of CD4 cells over time**
- **Gradual increase of number of viral copies (increase of viral load)**



- Symptoms of very advanced infection include opportunistic infections, malignancies and other clinical conditions such as AIDS case definition

AIDS

- Is the **end stage** of long-standing, chronic infection with HIV

- Without antiretroviral therapy, approximately 50% of individuals develop AIDS **within 10 years** after HIV infection

The syndrome is defined by various

- opportunistic infections
- malignancies
- other conditions

sumarized in the CDC definition.

Category C - AIDS

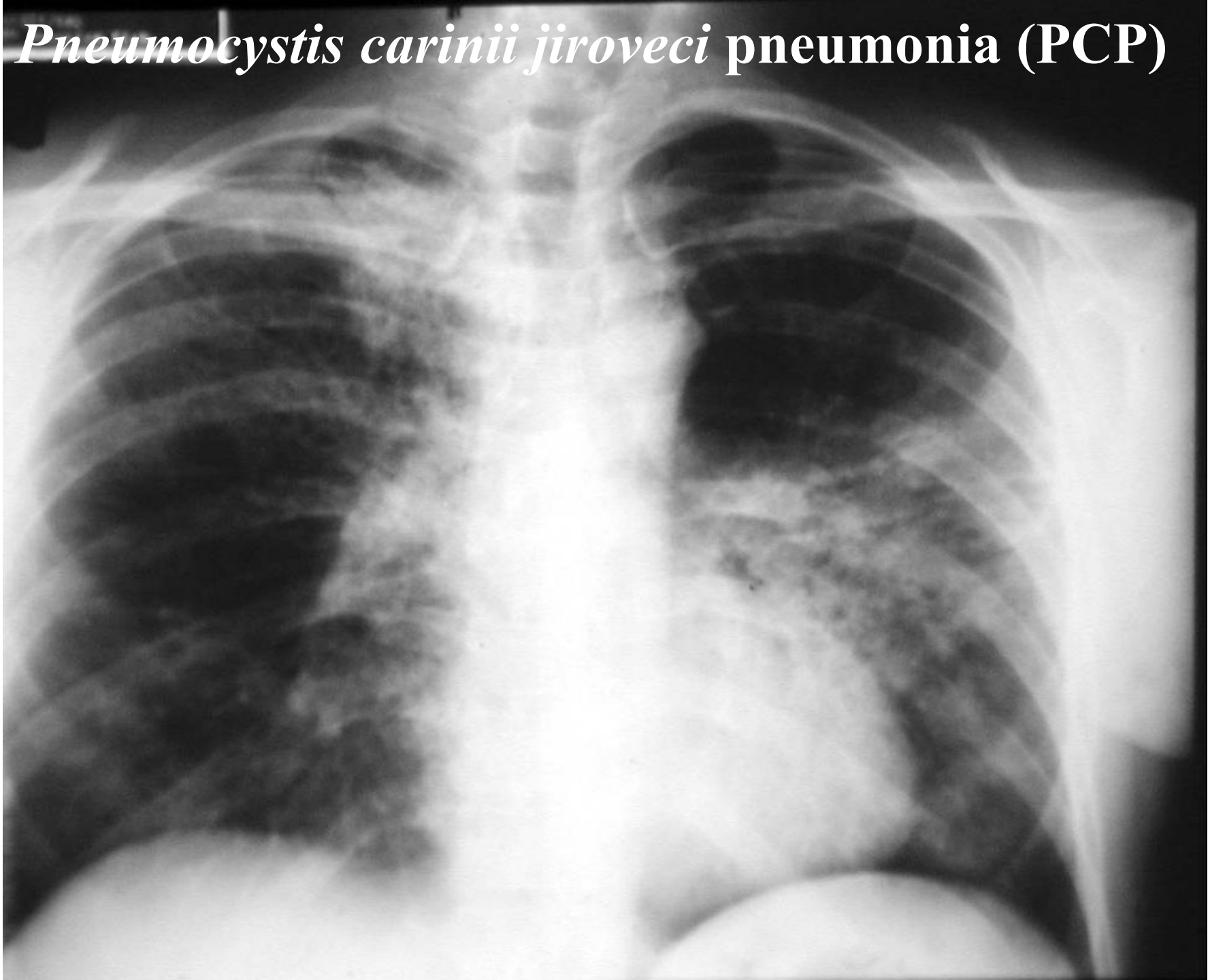
- Includes the following clinical conditions as listed in the AIDS case definition

- For classification purposes,
  once a category C conditions has occured,
  the person will remain in category C

Opportunistic infections

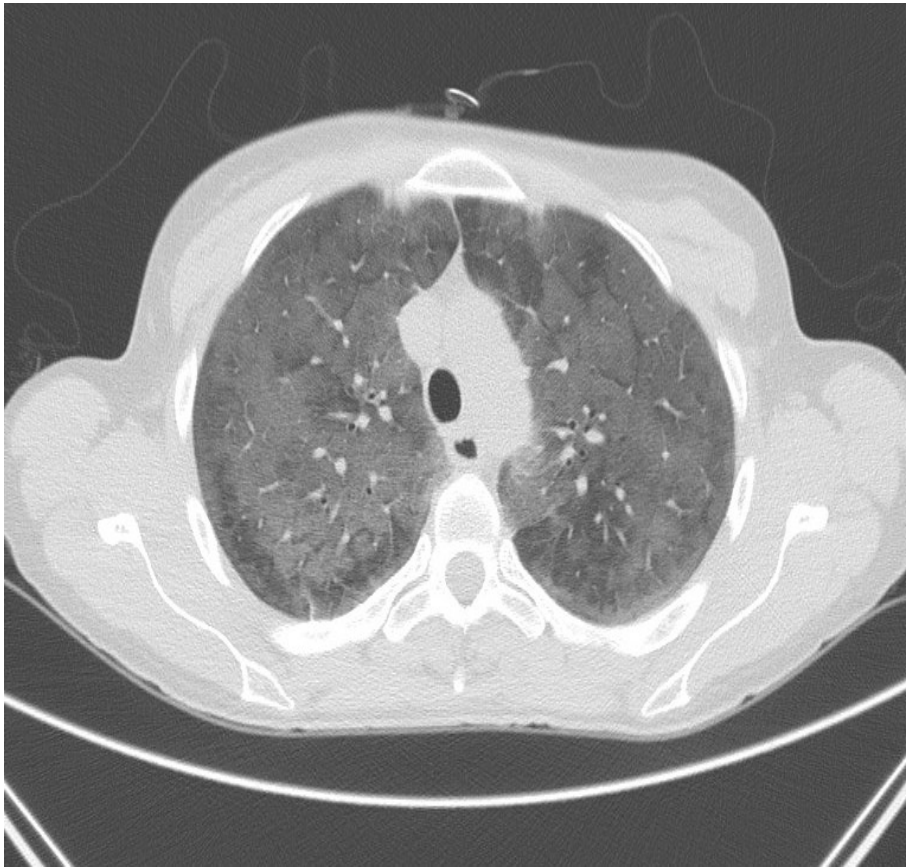
such as AIDS case definition

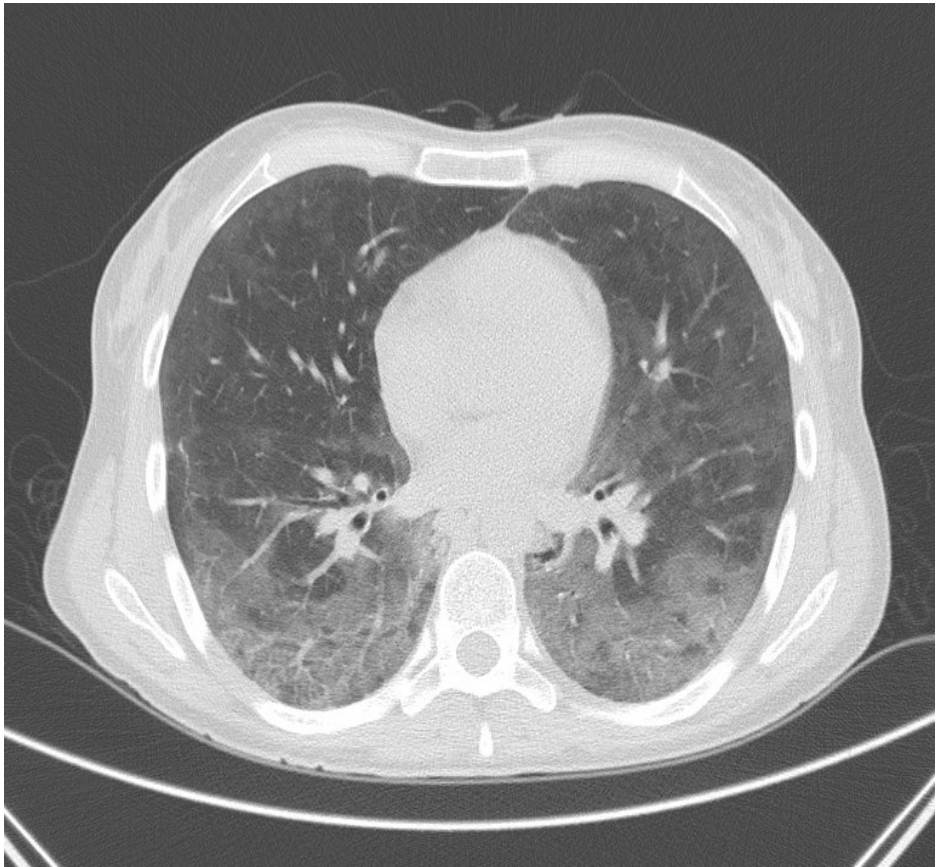
Pneumocystis carinii jiroveci pneumonia (PCP)



PCP – High-resolution CT scan (EP 20.11.2014)

- showing ground-glass appearance
- CD4+ lymfocyty 4/µl, MI……..IF……
- *Jirovecii* > 100 000 000 kopií DNA/rekaci





AIDS - OI

- Candidasis esophageal, tracheal, bronchial or pulmonary
- Herpes simplex with mucocutaneous ulcer > 1 month
- Herpes simplex esophagitis, bronchitis, pneumonia

AIDS - OI

- CMV retinitis
- Generalized CMV infection (in other organ than liver, spleen, nodes)

- Progresive multifocal leukoencephalopathy (PML)

AIDS - OI

- Recurrent pneumonia with > 2 episodes in 12 month
- Recurrent *Salmonella* bacteremia
- Chronic intestinal cryptosporidiosis (diarrhea > 1 month)
- Extrapulmonary cryptoccocosis

Extrapulmonary cryptoccocosis - CSF

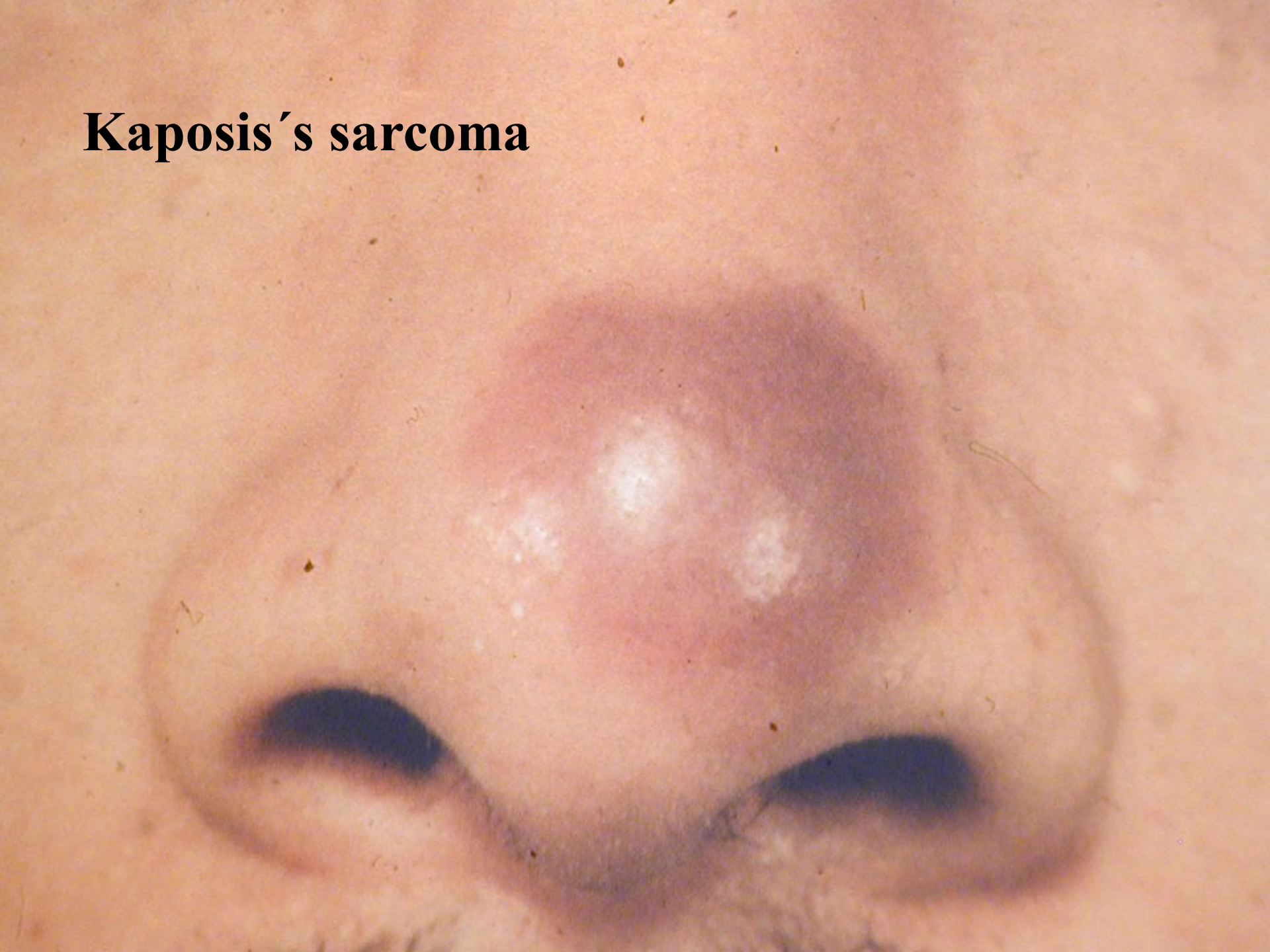
AIDS - OI

- **Diseminated or extrapulmonary histoplasmosis**
- **Disseminated coccidioidomycosis**
- **Tuberculosis (pulmonary or extrapulmonary)**
- **Disseminated or extrapulmonary *M. avium* or *M. kansasii* infection**

Malignancies – AIDS case definition

- Kaposi´s sarcoma
- Lymphoma
  - Burkitt´s
  - Non–Hodgkin lymphoma
  - Primary lymphoma in brain
- Invasive cervical cancer

Kaposis´s sarcoma



Other conditions - AIDS case definition

- HIV encefalopathia (dementia)
- Wasting syndrome („slim disease“)

Wasting syndrome („slim disease“)

HIV-associated wasting syndrome, „slim disease“

- Loss of body weight together with fever or diarrhea for more than 30 days
- In patient at the time of advanced infection
- In up to 50% of patients in Africa (less in industrialized countries)

- **the introduction of ART has decreased the incidence of OI and associated wasting**
- wasting still remains a common problem in clinical practice
- especially in middle income countries

LABORATORY TESTS

Main laboratory tests for dg.

- **Recommended for initial evaluation and follow-up of all patients**

1. **Anti-HIV** (antibodies to HIV)
   ELISA, WB
2. **Viral load** (the number of copies of RNA HIV-1)
3. **CD4+ lymphocyte count**

1. **Anti – HIV**
   - **enzyme-linked immunosorbent assay (ELISA)**
     - **antibodies to HIV**
     - **standard test**
     - **primary screening test for HIV infection**
   - **WB (Western Blot)**
     - **if the ELISA anti-HIV test is reactive, WB is done**
     - **more specific, less sensitive**

2. VL – viral load (viral detection)

- quantitative plasma RNA HIV-1
- the number of copies of

RNA HIV-1 per 1 ml plasma

- by technique PCR
- main virological marker
- the most reliable indicator of prognosis

Quantitative HIV RNA (VL) is useful for:

- Diagnosis acute HIV infection
- For predicting probability of transmission
- Predicting the rate of progression in chronically infected patiens
- For therapeutic monitoring

Viral load (VL)

- is very senstitive
- was developed for monitoring the progression of the disease and the effectiveness of antiretroviral therapy
- is not for establishing the diagnosis of HIV infection
- should be repeated from 3- to 4-month intervals during therapy
- In stabile patients

  it should be repeated every 6 mounths

ART

- **The objective of ART should be to maintain**

  the lowest VL for as long as possible

- **When an affective AR regimen is initiated in as asymptomatic patient with no previous ART, the VL should decrease to an undetectable level (< 50 copies/ml) within 24 weeks**

3. CD4+ Cell (lymphocyte) Count

This is a standard test:

- **to assess prognosis for progression infection**
- **to formulate the differential diagnosis in a symptomatic patient**
- **to make therapeutic decisions regarding antiviral treatment and prophylaxis for opportunistic pathogens**

CD4 Cell Count

- It was the most reliable indicator of prognosis until recently

- Number of copies RNA HIV (VL) is considered the most reliable indicator of prognosis currently

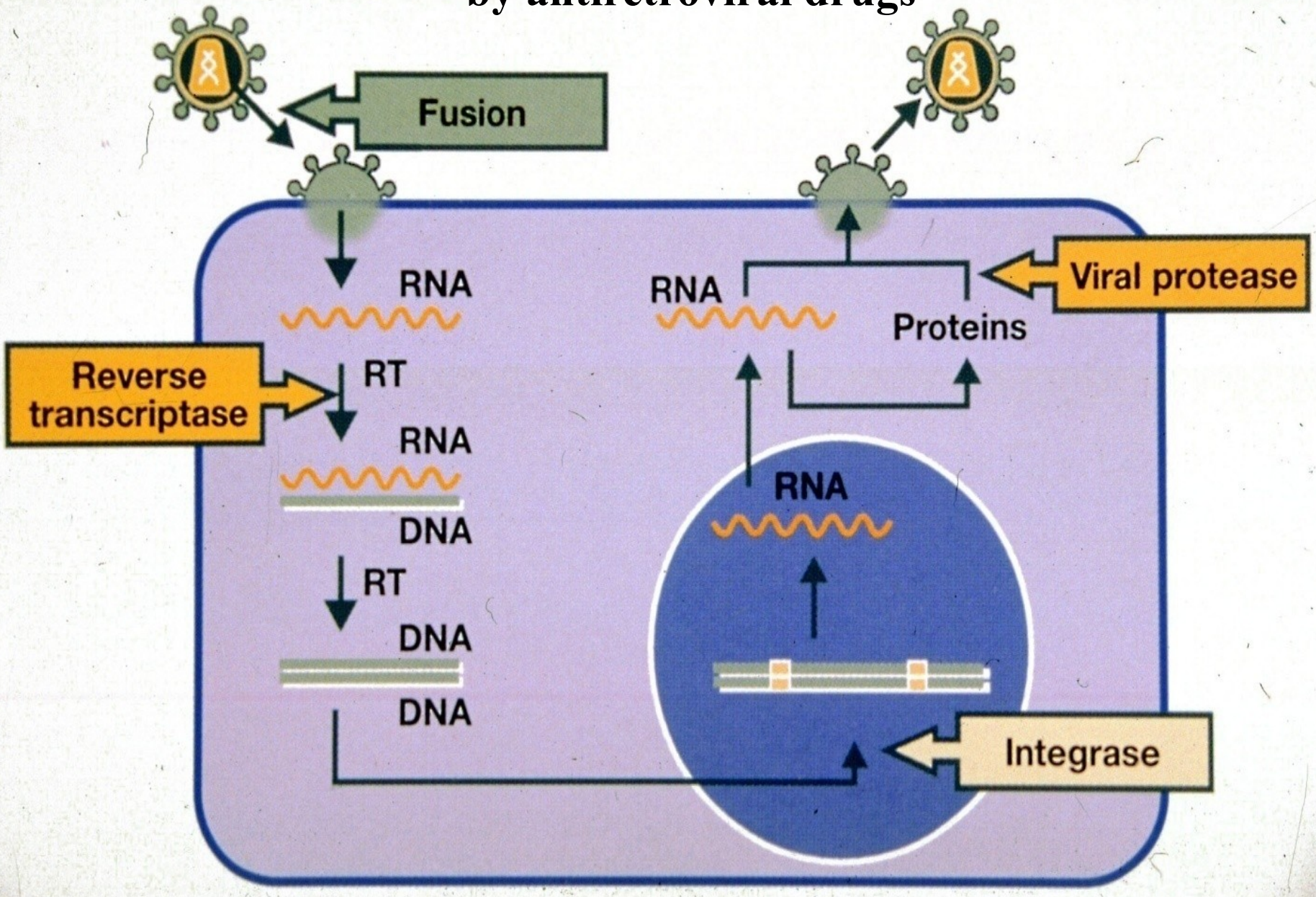
TREATMENT

The clasess of AR drugs

1. NRTs – nucleoside
   reverse transcriptase inhibitors
2. NNRTIs – non-nucleoside
   reverse transcriptase inhibitors
3. PIs – protease inhibitors
4. FI – fusion inhibitor
5. CCR5 inhibitor – coreceptor inhibitor
6. II - integrase inhibitors

HIV-1 life cycle

The main enzymes of HIV are blocked by antiretroviral drugs



NRTIs – nucleoside reverse transcriptase inhibitors

NRTIs block of enzyme reverse trascriprase

Generic name	Trade made
zidovudine (ZDV), azidothymidine (AZT)	Retrovir, Azitidin
didanosine (ddl)	Videx, Videx EC
zalcitabine (ddC)	Hivid
stavudine (d4T)	Zerit
lamivudine (3TC)	Epivir

Generic name	Trade made
abacavir (ABV)	Ziagen
ZDV+3TC	Combivir
ZDV+3TC+ABV	Trizivir
3TC+ABV	Kivexa
emtricitabin (FTC)	Emtriva
tenofovir (TDF)	Viread
FTC+TDF	Truvada

NNRTIs – non-nucleoside reverse transcriptase inhibitors

NNRTIs block of enzyme reverse transcriptase

Generic name	Trade made
nevirapine (NVR)	Viramune
delavirdine (DLV)	Rescriptor
efavirenz (EFV)	Stocrin, Sustiva
rilpivirine (RPV)	Edurant

PIs – protease inhibitors

PIs block of enzyme viral protease

Generic name	Trade made
saquinavir (SQV-hgc)	Invirase
saquinavir (SQV-sgc)	Fortovase
ritonavir (RTV)	Norvir
indinavir (IDV)	Crixivan
nelfinavir (NFV)	Viracept
amprenavir (APV)	Agenerase

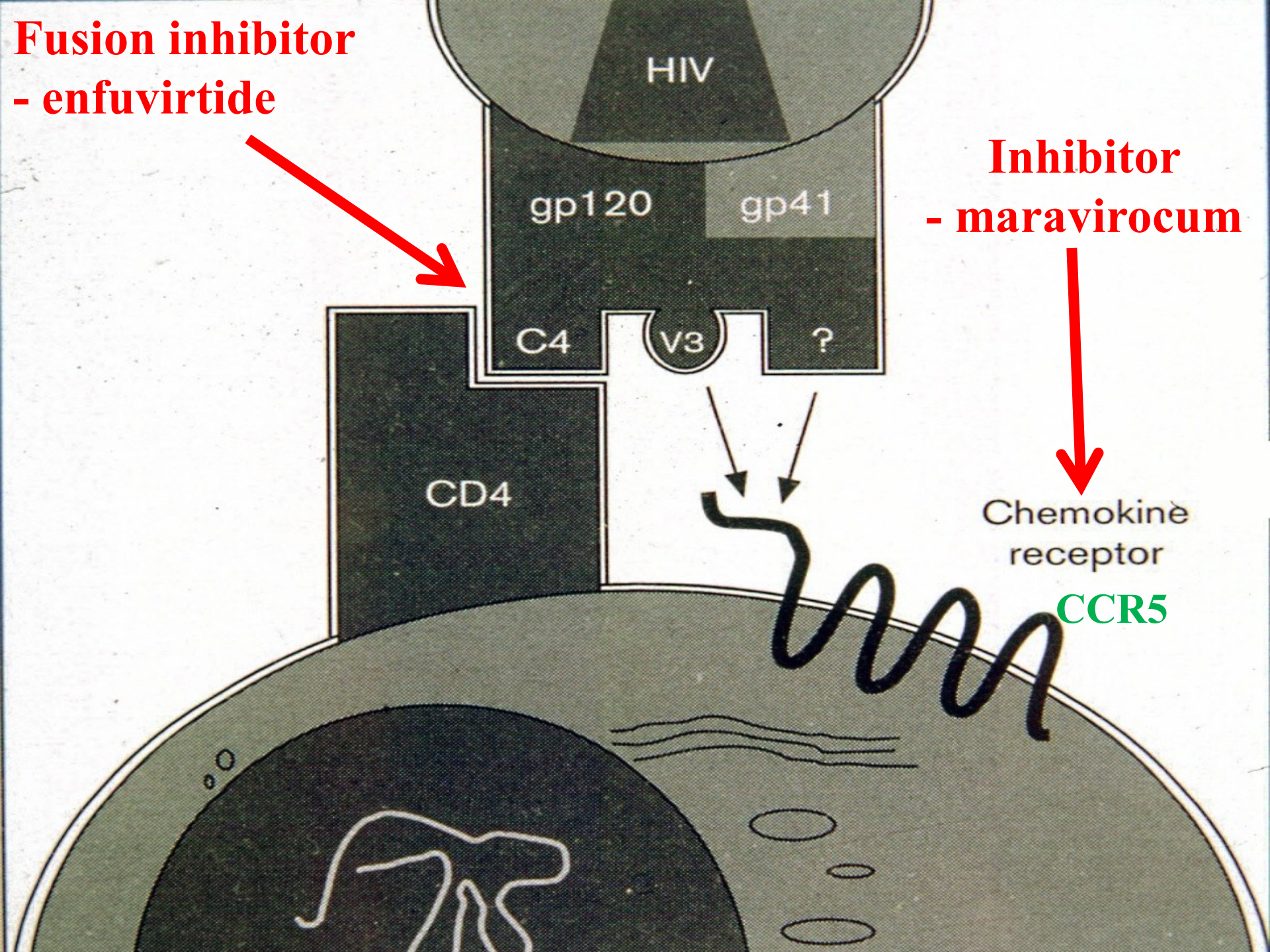
PIs – protease inhibitors

Generic name	Trade made
lopinavir/ritonavir (LPV/r)	Kaletra
atazanavir	Reyataz
fosamprenavir	Telzir
tipranavir	Aptivus
darunavir	Prezista

II – integrase inhibitor

II block of enzyme viral integrase

Generic name	Trade made
raltegravir	Isentress
elvitegravir	Stribild
dolutegravir	Tivicay


Fusion inhibitor
- enfuvirtide
HIV
gp120
gp41
C4
V3
?
CD4
Inhibitor
- maravirocum
Chemokinè
receptor
CCR5

- **Three-drug combinations are currently recommended for the initiation of treatment in all patients**

- **When HIV diagnoses is established regardless on CD4 lymphocyte count**

- **The most widely used combination is**

  two NRTIs with one II, PI or NNRTI

STR – single tablet regimen

- The most advanced way of treatment
- Complete ART for once-daily dosing
  - **in one pill**
- STR co-formulation for once-daily dosing is **the highest level of ART simplification** achieved so far

Co-formulations of drugs for STR

- **Atripla**
  - TDF/FTC/EFV
- **Eviplera**
  - TDF/FTC/RPV
- **Stribild**
  - TDF/FTC/EVG/COBI
- **Triumeq**
  - ABC/3TC/DTV
- **Genvoya**
  - TAF/FTC/EVG/c

cART (HAART, OBT) is very potent

BUT

is unable to completely eradicate the virus from the body !!!