HIV- INFECTION

Identification. HIV-infection is slowly progressing viral disease of man (It is lethal disease at present!!) with the parenteral mode of transmission described by a specific damage of the immune system of the patient with development immunodeficiency which clinical appears by opportunistic infections, malignant neoplasms and various autoimmune effects.

Historical reference

- 1981- CDC-center for Disease (USA) registered among homosexuals increase morbidity of pneumocytosis and Kaposi's sarcoma on a background of oppression at them cellular immunity

- 1982 - D.Frensis isolated AIDS into a separate clinical syndrome

- 1983 - L.Montenje isolated both a virus of the HIV type1 and in 1986 - the HIV – type 2

- 1983 - R. Gallo isolated the HIV – type 1 (repeatedly)

- 1984- the similar virus is found out in monkeys in Asia (SIV - simian immunodeficience virus)

Presence of the HIV - 1 is revealed in samples of blood, since the 50th years. Disease probably has arisen in Africa, and then was distributed all over the world.

HIV- infection in world (2007)

Quantity of people living with HIV

Common — 33.2 million (30.6 – 36.1 million)
Adults — 30.8 million (28.2 – 33.6 million)
Women — 15.4 million (13.9 – 16.6 million)
Children to 15 years old- 2.1 million (1.9 – 2.4 million)

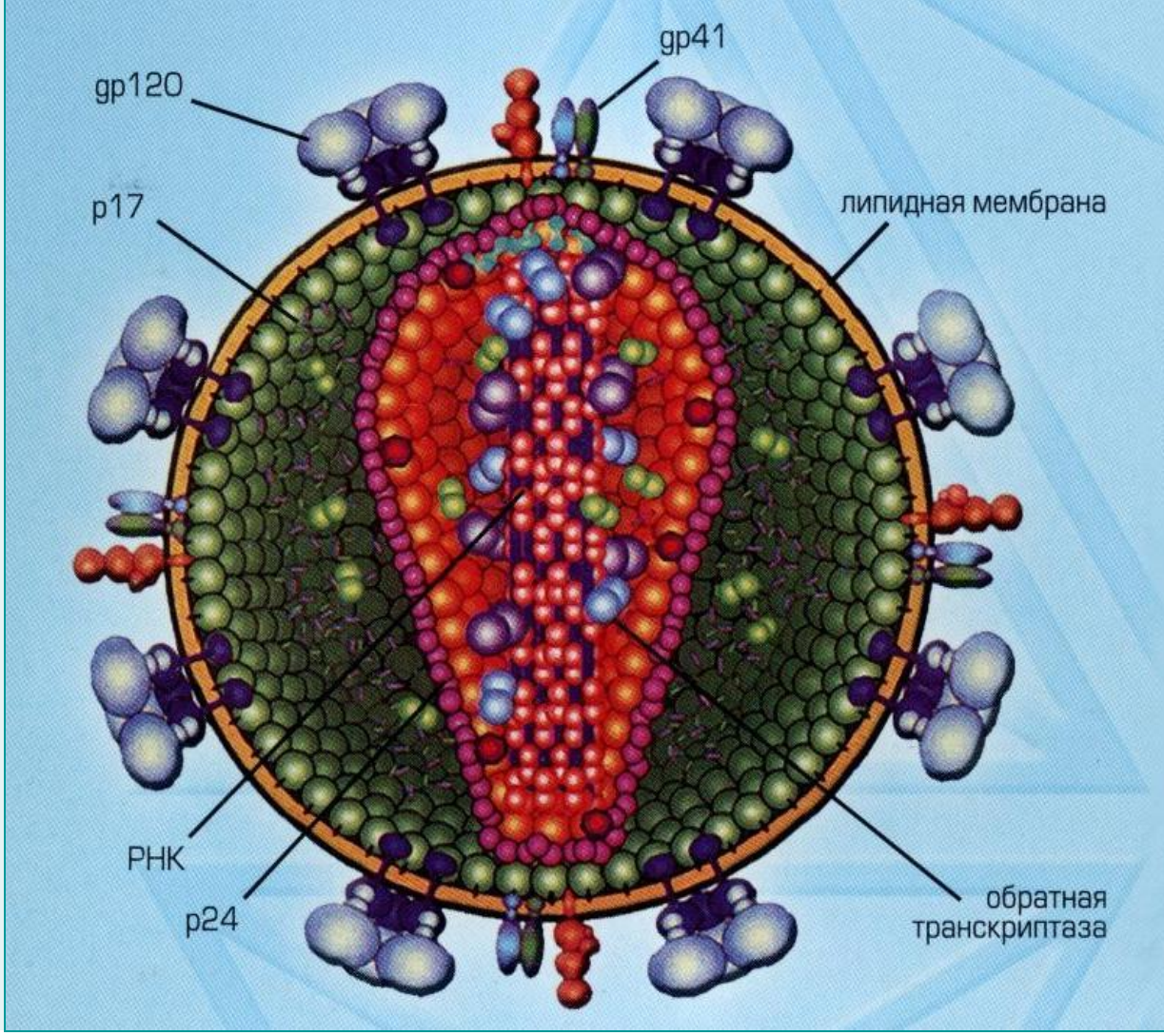
Quantity of people infected VIH in 2007.

Common— 2.5 million (1.8 – 4.1 million)
Adults— 2.1 million(1.4 – 3.6 million)
Children to 15 years old— 420,000 (350,000 — 540,000)

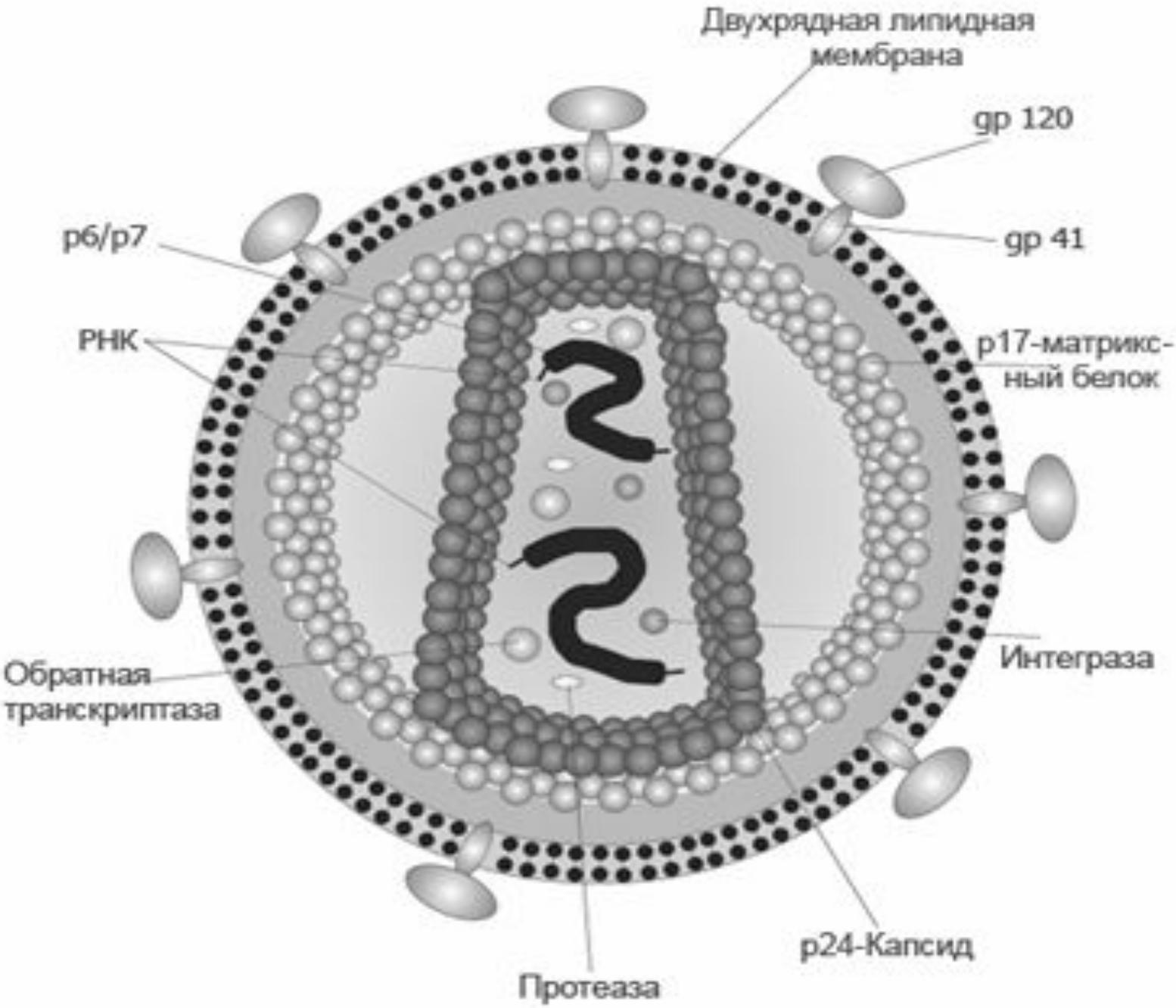
Quantity deaths from HIV- infection in 2007.

Common — 2.1 million (1.9 – 2.4 million)
Adults— 1.7 million (1.6 – 2.1 million)
Children to 15 years old — 290,000 (270,000 – 320,000)

ETIOLOGY: the virus by a size 100 - 140 nm the **Family Retroviridae Subfamily Lentivirus**. It has got a spherical **Nucleocapsid** containing two filamentlines **RNA (+)**, **own a return transcriptase (revertase)**, **own a intergrase**, **own a protease** and is surrounded by the bilayer proteinous envelope (**p18 , p24**), under which there is a matrix frame **(p17)**.



The outside envelope consists of **phospholipids** and **glycoproteins**. It has numerous glycoproteins bulges on a surface (**gp 160** = gp120 + gp 41) **gp120 -** contacts to protein CD4 of cell-targets and **gp 41 –** intensifies this link.


Двухрядная липидная мембрана
gp 120
gp 41
p6/p7
РНК
p17-матрикс-ный белок
Интеграза
Обратная транскриптаза
p24-Капсид
Протеаза

Therefore virus is capable to penetrate only into those cells, on which surface there are the proteins: CD-4, CCR-4, XCR-5, galactozylceramid

The variability of a virus is very large because of presence revertase (The VIH in the life cycle is declined to mutations in 5 times more, than a virus of a influenza)

Stability of the virus in the external environment is low:

- at desiccation is perished through 3 - 7 days (at 25dg.C)

- in the moist environment is survived about 15 days (at 25 dg.C)

- in a blood is survived by years!!!

- in the frozen plasma is survived till 10 years!!!

- at warming up to 56 dg.C is inactivated through 30 min.

- at boiling is inactivated in 5 minutes

- it is sensitive to all disinfectants and fat-solvents , but is steady to radiation!!!

EPIDEMIOLOGY

Pandemic of a HIV- infection annually carries of millions human lives and for its not exists: of international boundaries, groups of hazard, social, material, religious differences!!!

Today 45 million was infected and 41 million died.

The source - is infectious man in any period of illness, but particularly during primary clinical manifestations and in a stage AIDS (acquired immunodeficiency s-me)

It is found out in : BLOOD, LYMPH, SEMEN, less – milk, a vaginal secretion, the least- saliva, tears, sweat of the patient.

Modes of TRANSMISSION:

Main mode of transmission in world is sexual (80 %)

- **the homosexual links (especially passive) most are dangerous – because more traumatic (a rectum has a single-layer epithelium) + presence of a semen**

- **heterosexual of links are more dangerous to the women - because more area injury epithelium and high concentration of the viruses in a semen (at unprotected vaginal contact)**

Vertical mode of transmission (30 - 40%) :

- **intrauterine - hazard of infection of a fetus 7- 11 %**
- **perinatal - hazard of infection of the child 11- 22 %**
- **breast-feeding - hazard of infection of the child 12- 20 %**

The parenteral mode of transmission:

- any biological tissue past testing on HIV is not absolutely safe!!!

- intravenous drug addicts infect in Asia in 70 % of cases, in to Europe in 44 % (free-of-charge output syringes)

The risk of an infection at one trauma of the doctor of the surgical profile operating ill with HIV infection makes - 0.34 % (at VHB - it makes 34 %!!)

The risk of an infection at **one contact** with the **source** of a VIH infection:

-blood and its components	90%
-intravenous drug addicts	30%
-vertical mode of transmission	30%
-unprotected anual contact	1%
-unprotected vaginal contact	0,1%

VIH - is not transmitted by :

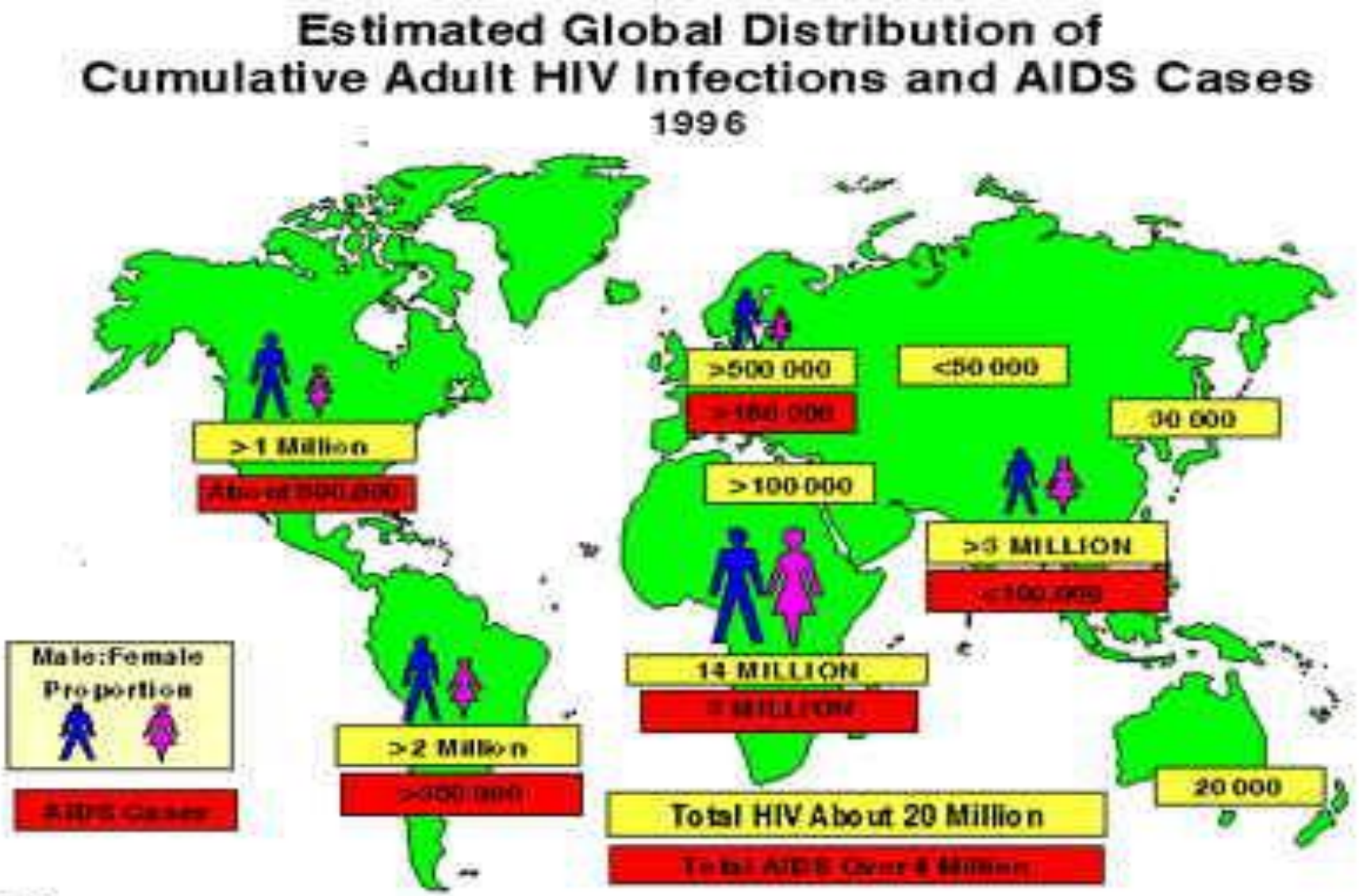
- at touches, embraces, hand shakes, kisses (if in a saliva there is not impurity of a blood)

- at joint residing in one apartment, through tableware, clothes, nutrition, linen, subjects communal of use, toies and etc.

- through air (even at sneeze and cough)

- at bathing in water, through sports equipment (which are not polluted by a blood)
- through stings of insects and animals.

Susceptibility to VIH - general. In each country HIV has epidemiological features. In USA - relation infectious of the male/ female 9:1- main path of transmission - homosexual links, in Africa one is 1:1 – heterosexual of links Today 45 million was infected and 41 million died.



PATHOGENY

Infectious the dose can makes only 10 viruses!!

1. **Infiltration into an organism through a injury skin or mucous as free viruses or inside monocytes of the donor and dissemination in all bodies and systems.**

2. **Detection of cell-targets having on the surface reseptors СД4, galactozylceramid or coreceptors CCR4, XCR5:**

monocytes, macrophages, lymphocytes, neuroglia, colonocytes, cell-pancreas, thymus, spleen

3. **Fixation of a virus to a surface cell-targets with the help gp120 and intensifying of an adhesion with the help gp 41 (neuroglia cells infection through galactozylceramid as on their surfaces have not detected СД4)**

- In process attachment of the virus to cell-targets and its confluence by cell membrane together with primary receptor (molecula СД4) take part and coreceptors :

- receptor a-chemokines CCR5 is coreceptor lymphotropic strains VIH-1 in process its attachment to T- lymphocytes

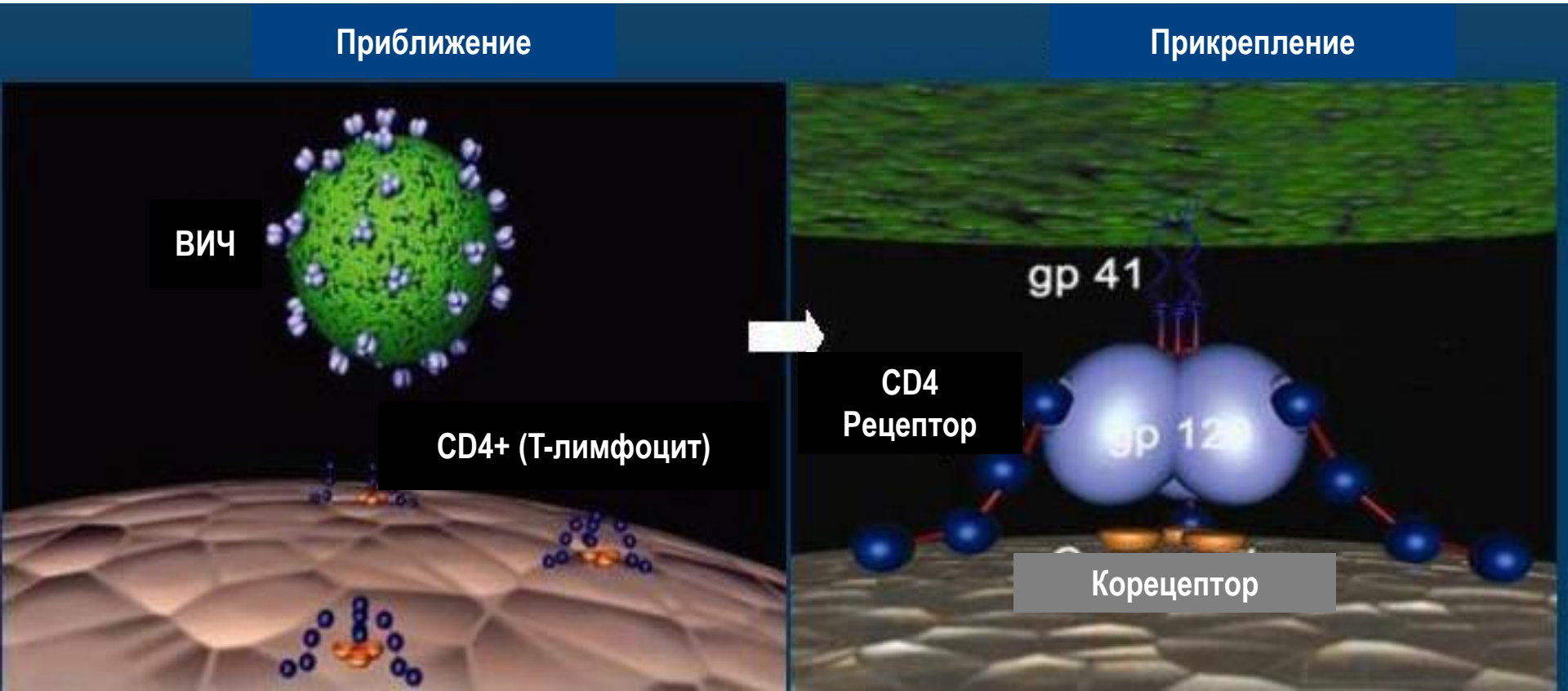
- receptor в-chemokines XCR4 - is by coreceptor macrophagotropic strains VIH-1 in process its attachment to macrophages

- primary receptor of virus VIH-1 in nervous tissue (microglia and the endothelium of brain vessels) is galactozylceramid - capable connect with gp120.

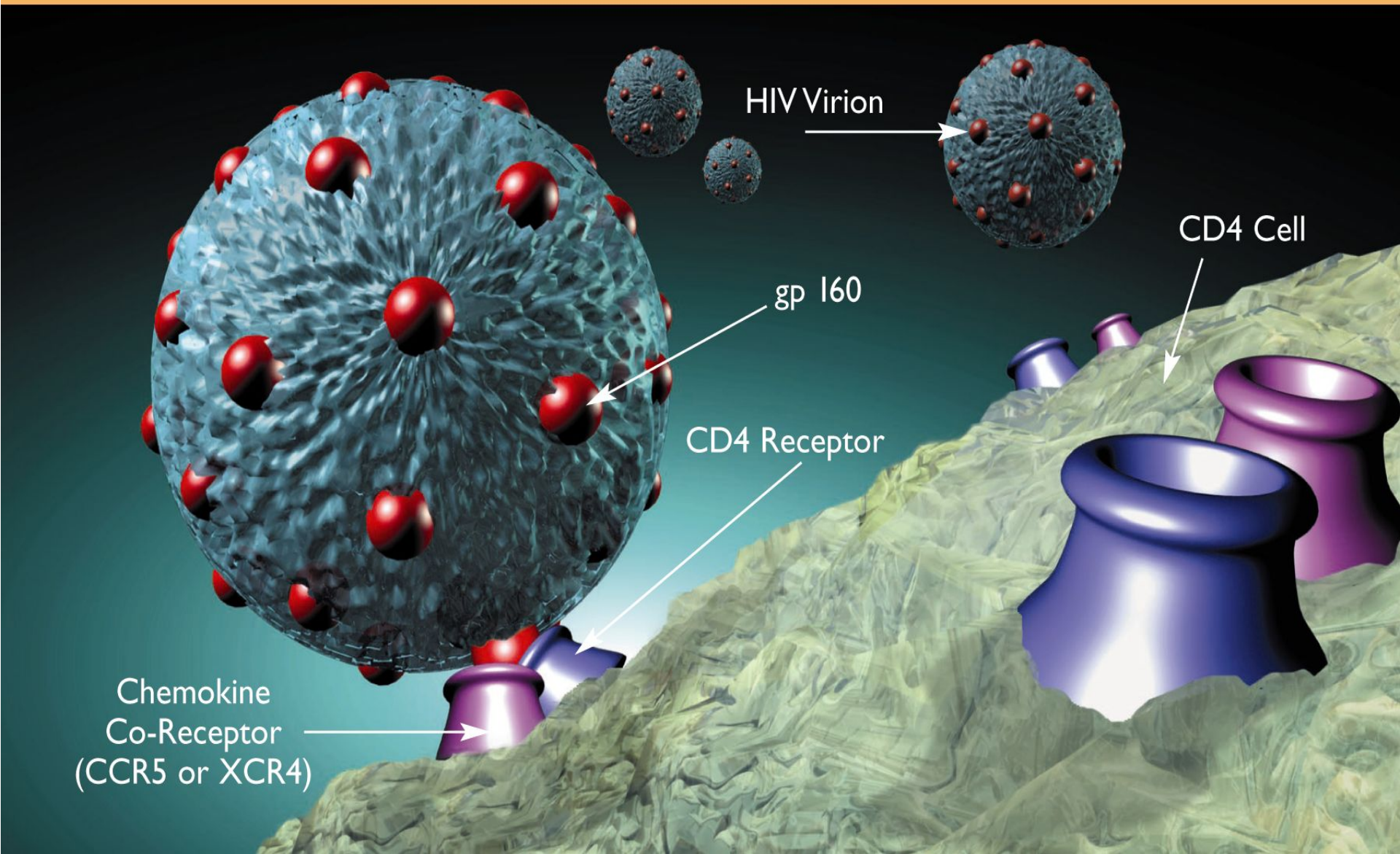
Vital cycle of the VIH

Penetration VIH in the cell CD4

Stage 1. Attachment

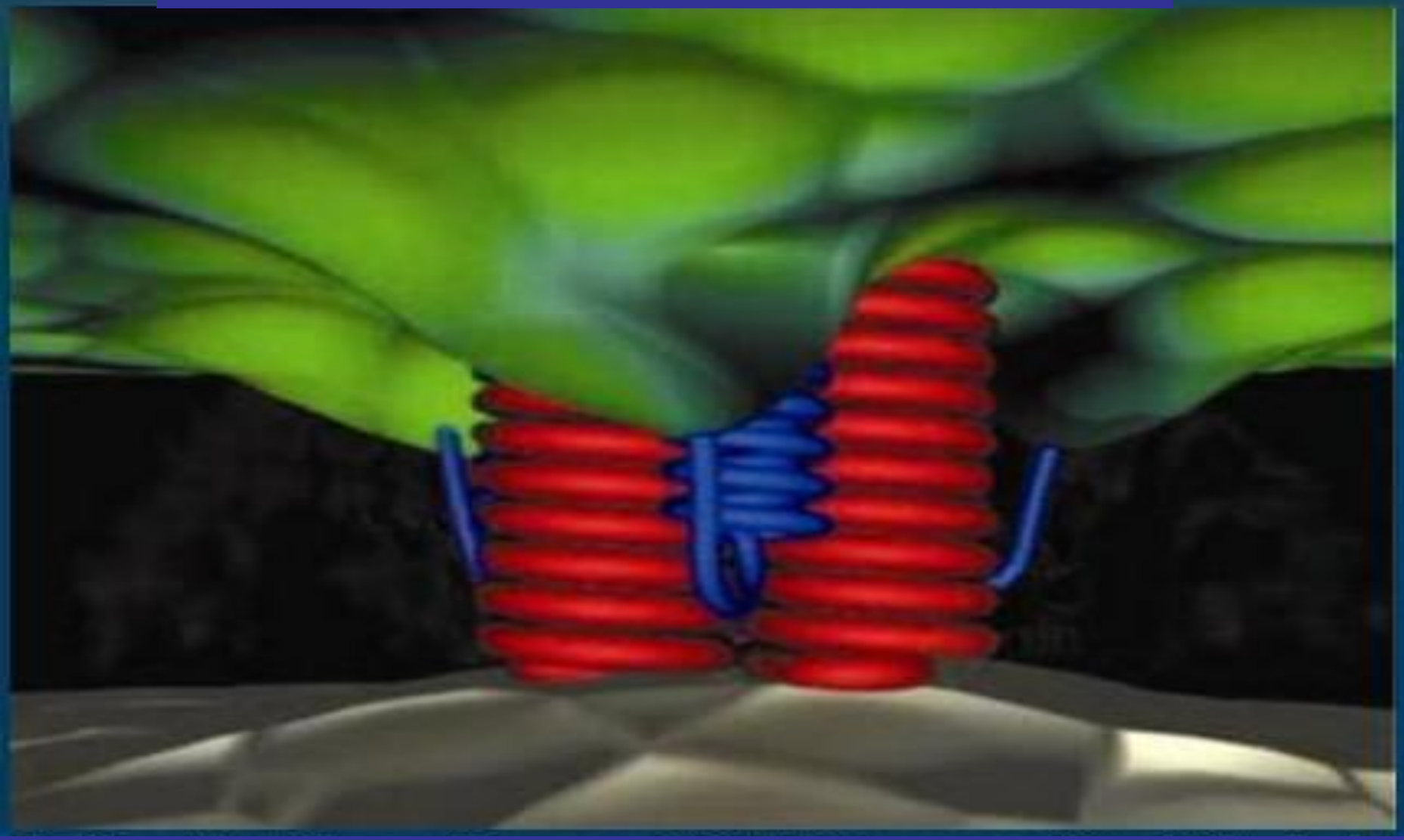


Attachment


HIV Virion
CD4 Cell
gp 160
CD4 Receptor
Chemokine
Co-Receptor
(CCR5 or XCR4)

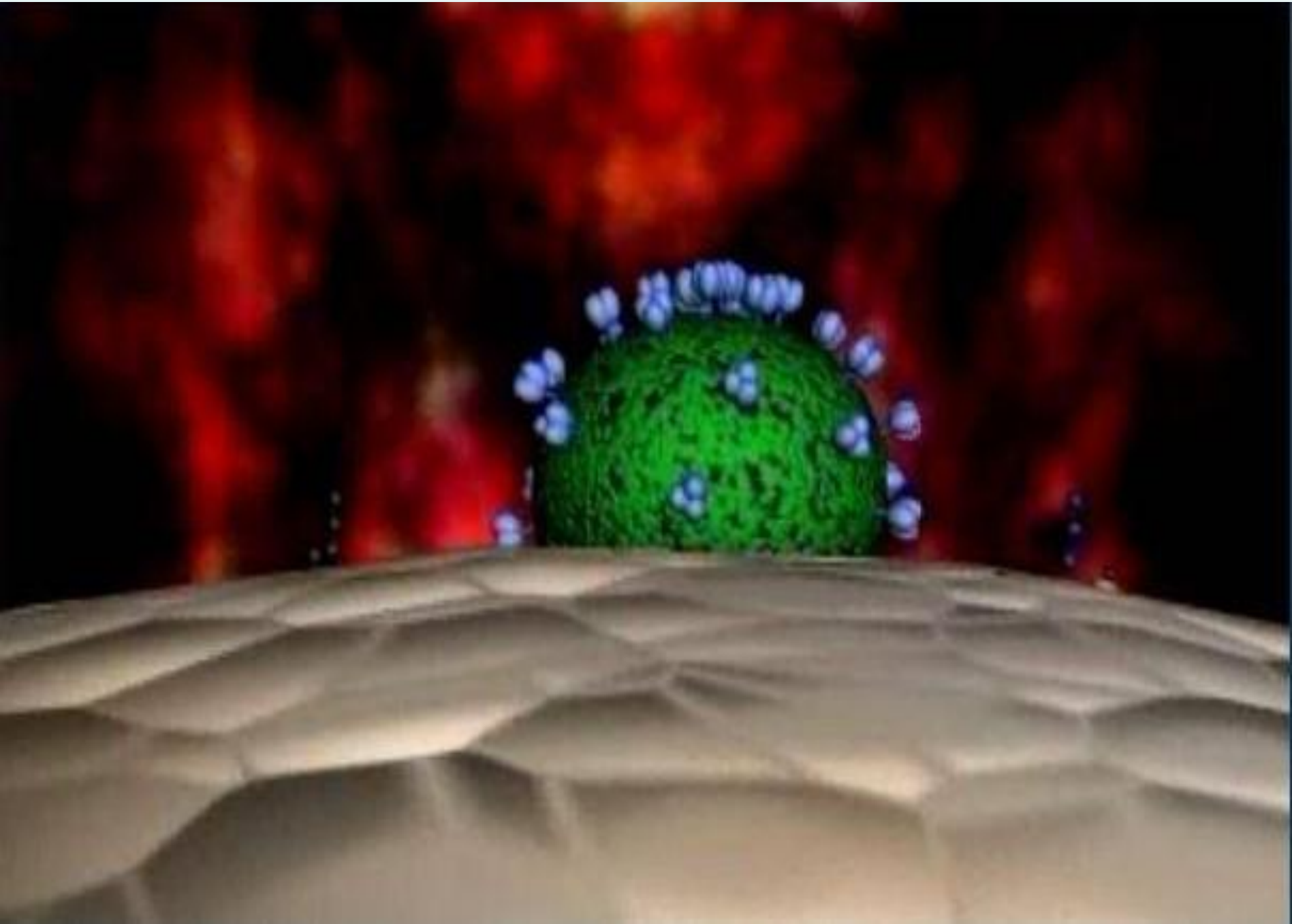
Stage 3. Confluence

Внедрение и «зацепление»



После внедрения gp41 «скручивается» и
сцепляет мембраны вируса и клетки

Penetration VIH in the cell CD4



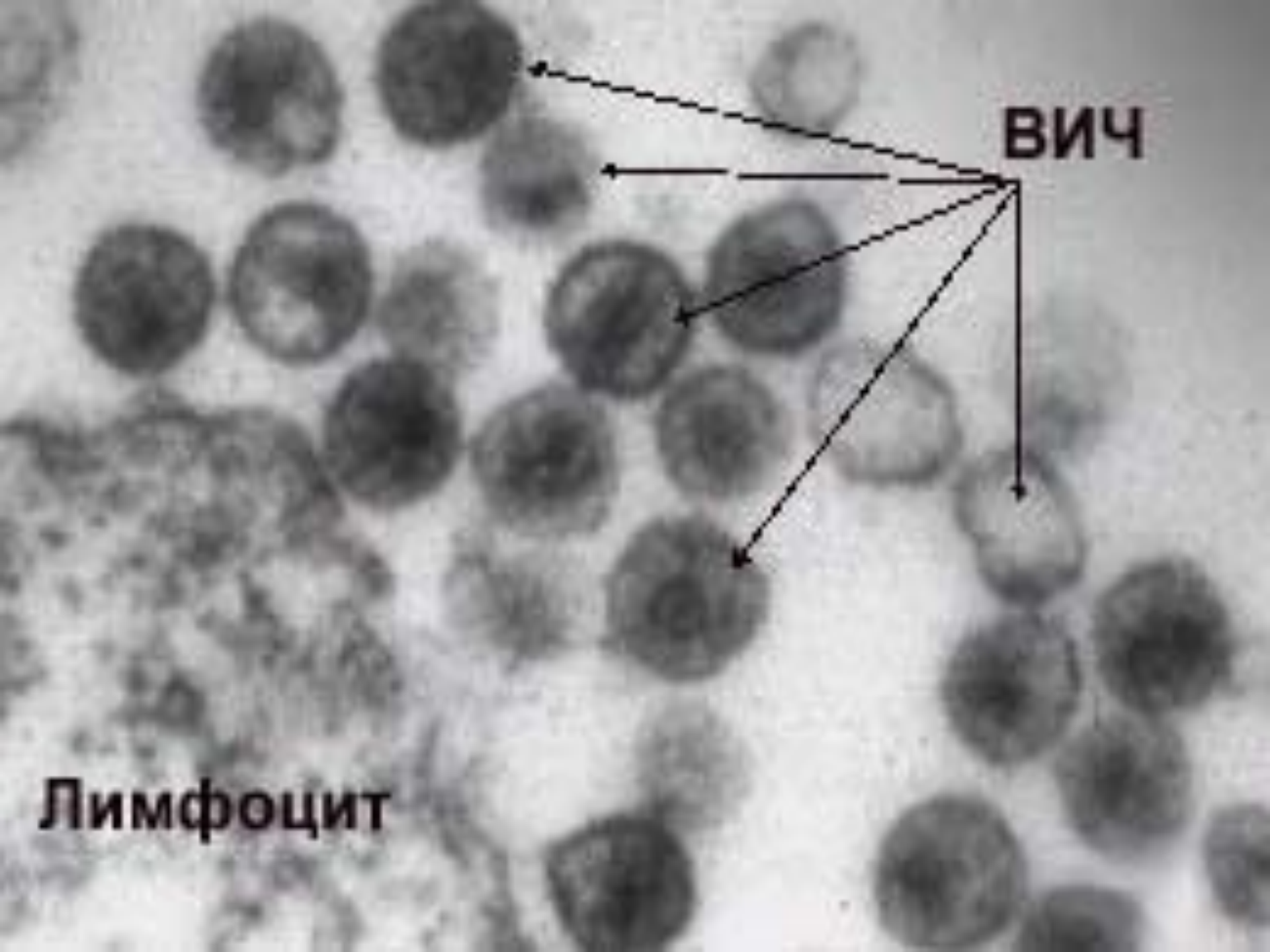
4. Destroy by enzymes of a cell of the envelope of a virus and Infiltration of a nucleocapsid in cytoplasme of host, where on to basis viral RNA with the help revertase occurs synthesis viral DNA, which then with the help own integrase is introduced in DNA nucleus of cell - targets, being transmuted there in provirus and can be in such a state many months or years.

Were inside a core of a cell - provirus permanently induces replication new viruses that frequently not clinical appears, but causes seroconversion !

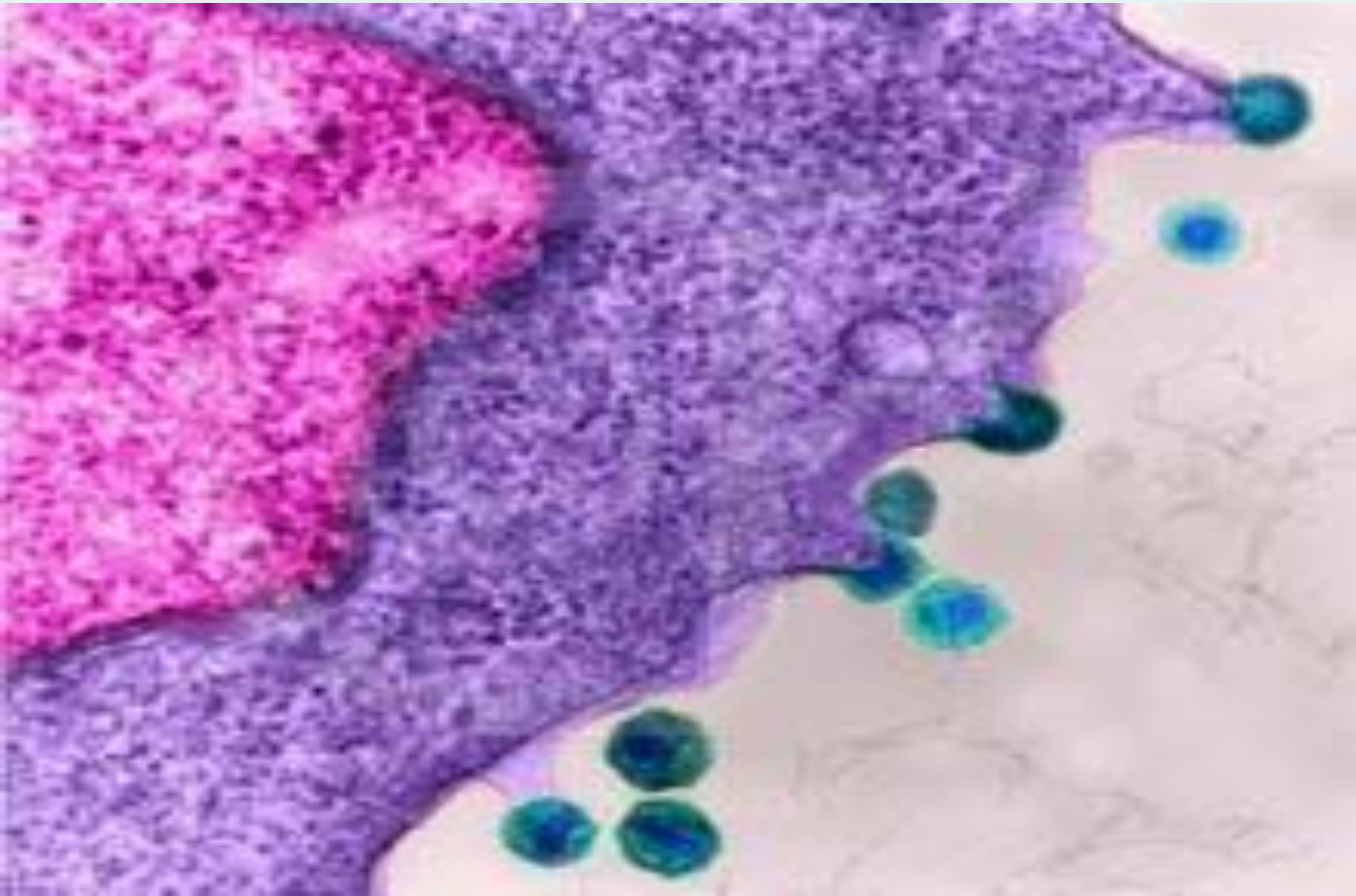
5. The maximal induction the viruses is registered in a stages primary clinical manifestations and AIDS.

6. The antigenrecognition and antigenpresentation function of macrophages and monocytes is oppressed simultaneously with increase of formation by them of various mediators (pyrogens, cachexins, tumornecrossis of the factor etc.)

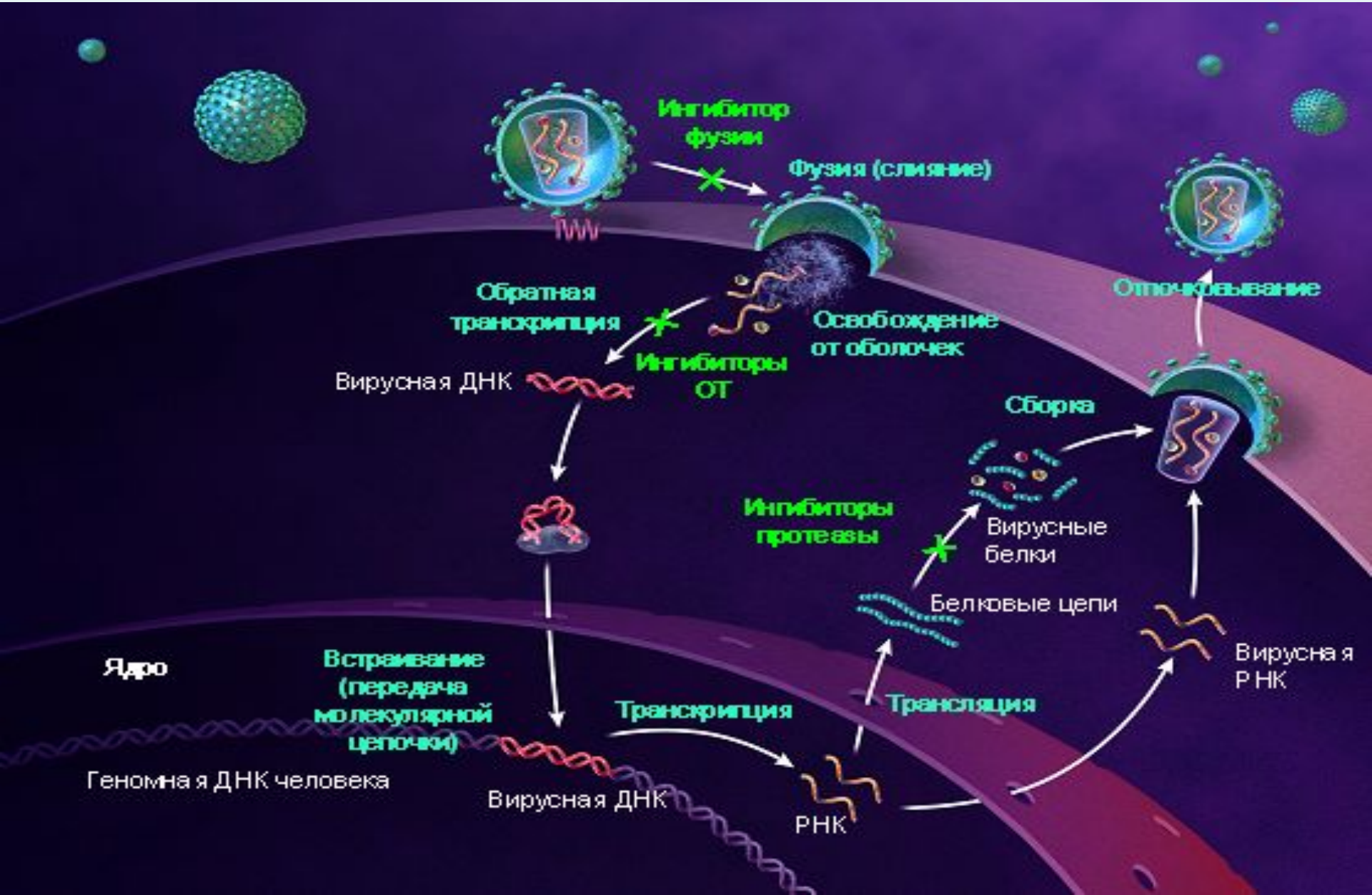
7. The considerable injury of the population СД4-lymphocytes fulfilling key role in immune processes, that result is violation of cooperation immune cells, loss by them of ability to the adequate answer on allogenic and autoantigenic exposures, that promotes clinical manifestation of the opportunistic infections and neoplasms


ВИЧ
Лимфоцит

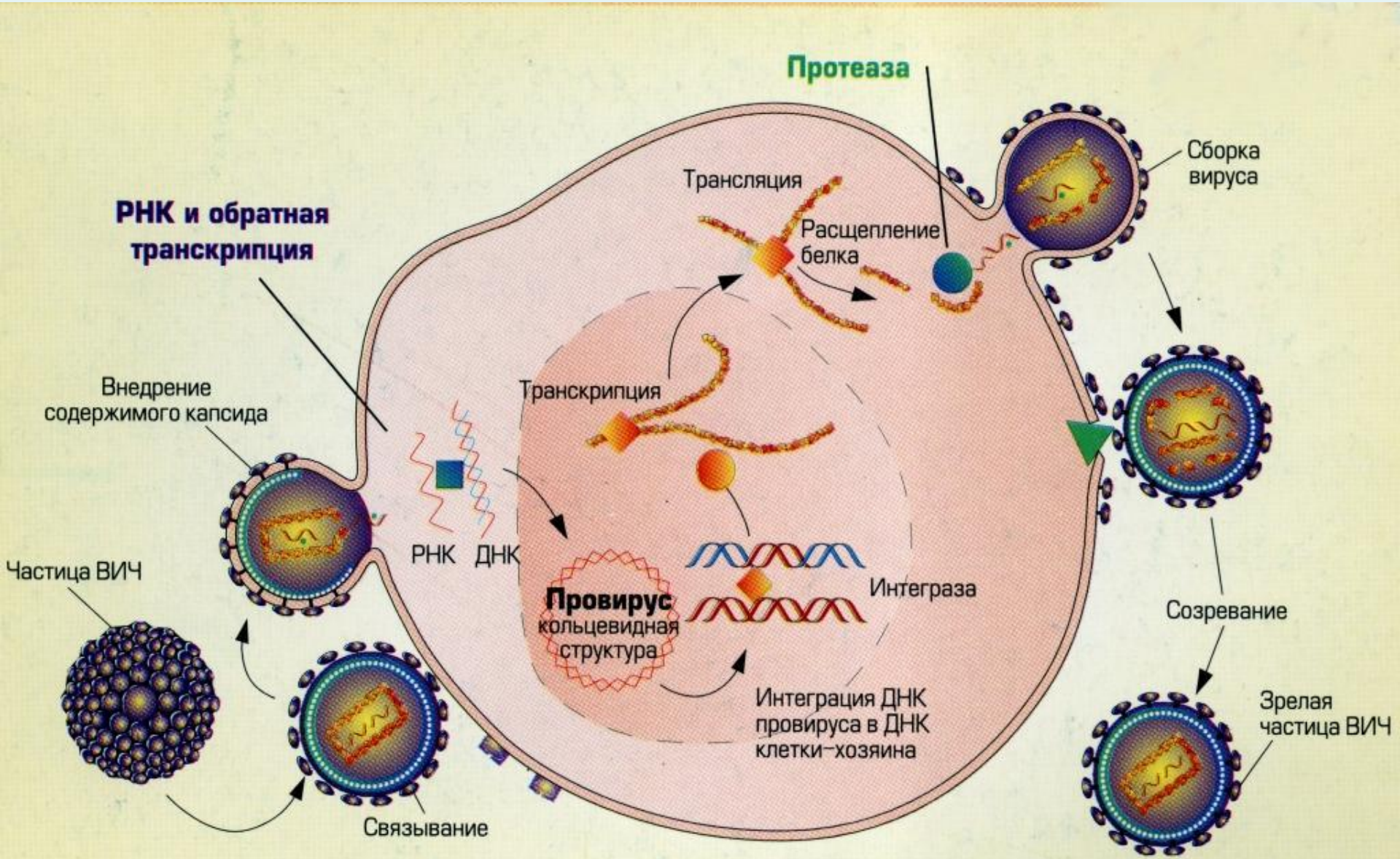
Viruses of an immunodeficiency (HIV) join to glycoproteins to receptors on a surface lymphocytes. СЭМ x 110.620. Conditional colors.



Vital cycle of the VIH and targets for medicine



Vital cycle of the VIH



8. The polyclonal activation of B-lymphocytes is cause increase in a blood of all classes immunoglobulins (high level of antibodies in a blood) that results in exhausting and this link immunity

9. Decrease of immune cells occurs because of:

- direct destroy by a virus in during reproduction
- derivation gp 41 of the complexes between damage and undamage of cells
- blockade gp120 receptors uninfected cells with by loss of function activity with subsequent by destroy them Тк - lymphocytes
- injury of the cell- precursors in marrow
- intensifying apoptose infected of cells

10. Occurs anergy of a skin and mucous, are depressed inflammatory responses.

11. Under influence of manifold co-factors or superinfections, toxic effects (narcotics) begining the intensive replication of viruses (in the end of secondary latent period) with mass destruction immune cells, that results in appearance AIDS-indicator diseases, make progress which even on a background of specific treatment results in death of the patients

PATHOMORFOLOGY

(the manifestations are diversiform)

- lymphadenopathy with involution of a glandular tissue
- demyelination and sponge degeneration of the nervous tissues

- vasculites and glomerulonephrites, hepatitises etc.
- manifold manifestations of AIDS - indicators

Incubation period:

- virologic from 2 to 4 weeks
- immunological from 8 to 12 weeks
- AIDS-incubation from 2 to 10 years and more

Acute retroviral a syndrome

CLASSIFICATION HIV-infection (WHO June 2006 г)

Clinical stage 1

- asymptomatic
- persistic a generalized lymphadenopathy

Clinical stage 2

- losses of mass of a body less than 10 kg
- activation herpes VZV the last 5 years
- minimal dermo-mucous damage (seborrheas a dermatitis, prurigo, mycotic affection nails, relapsing damage of an oral cavity, cheilitis
- repeated infections URT (including bacterial sinusitises)

Clinical stage 3

- losses of mass of a body more than 10 kg
- diarrhea more than 1 month of a vague etiology
- fever more than 1 month of a vague etiology
- candidiasis of an oral cavity
- hairy a leukoplakia of an oral cavity
- pulmonary tuberculosis on an extent of the last year
- severe bacterial infections (pneumonia, purulent myosites etc.)

Clinical stage 4:

- Wasting syndrome, due to HIV
- pneumocystis carinii pneumonia, pneumonia recurrent
- toxoplasmosis of brain
- cryptosporidias, isosporiasis – chronic intestinal, 1-month duration
- cryptococcosis extrapulmonary (meningitis)
- CMV - infection (excepting a damage of a liver, spleen, lymphatic nodi), CMV-retinitis (with loss of vision)
- HSH - infection with a damage of a skin or mucous by duration more than 1-month or with a damage visceral bodies of any duration
- progressive multifocal leukoencephalopathy
- anyone a endemic mycosis (disseminated or extrapulmonary) (histoplasmosis, coccidioidomycosis etc.)
- candidiasis of bronchi, trachea or lungs, oesophageal candidiasis

- visceral leishmaniasis
- extrapulmonary a tuberculosis
- atypical mycobacteriosis disseminated or extrapulmonary)
B - cellular malignant lymphoma – brain, Burkitt`s sarcoma
- Kaposi*s sarcoma
- encephalopathy, HIV-related

CLINIC ACUTE RETROVIRAL of a SYNDROME:

- high fever	96 %
- adenopathy	74 %
- pharyngitis	70 %
- eruption on a skin and mucous	70 %
- myalgia -	54 %
- diarrhea -	32 %

- headache - 32 %
- nausea and vomiting - 27 %
- hepatospleenmegaly - 14 %
- lowering mass of a body - 13 %
- candidiasis of an oral cavity - 12 %

- neurologic manifestations - 12 %
(aseptic meningitis, meningocephalitis, peripheral neuropathy, paresis, s-m Гийена - Барре, psychosis)

All these manifestations are stipulated only HIV and after 3-6 months (even without any treatment) disappear and for the patient is starting the secondary latent period from 2 up to 15 and more than years.

Acute retroviral a syndrome- eruption on a skin

Острая лихорадочная фаза ВИЧ-инфекции: сыпь. Сыпь состоит из отдельных беспорядочно разбросанных пятен и папул; локализуется на руках и туловище. Помимо лихорадки у больного выявлены увеличенные лимфоузлы, язва на мошонке и гиперемические пятна на небе

(seborrheas a dermatitis

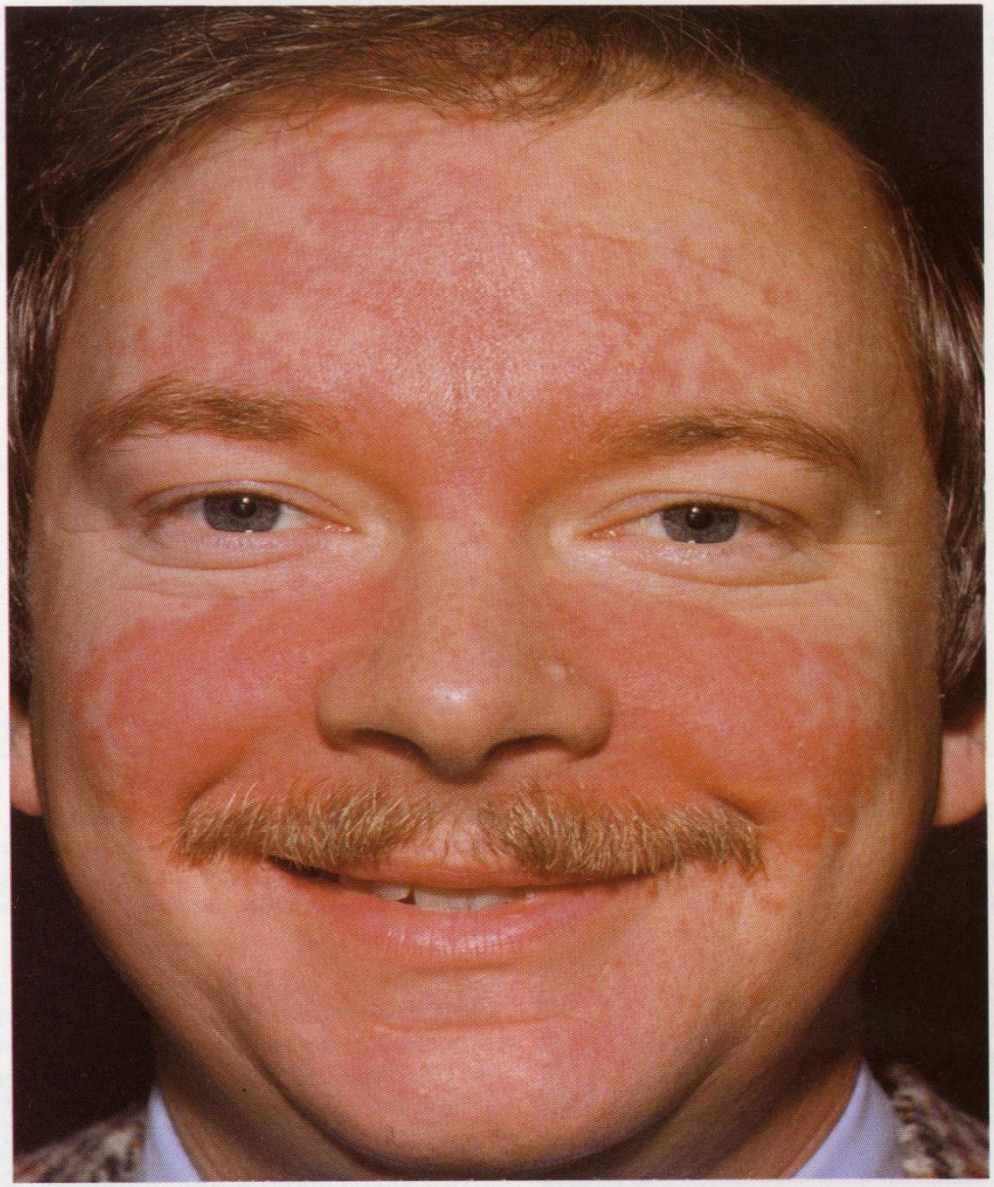


Рисунок 3-15. Себорейный дерматит. Поражены верхняя губа, щеки, носогубные складки, брови, надпереносье и лоб. Такие же высыпания — эритема и желтовато-оранжевые чешуйчатые бляшки — обнаружены за ушами и на груди

seborrheas a dermatitis

Рисунок 3-16. Себорейный дерматит на фоне ВИЧ-инфекции. На левой щеке, носу, переносице и бровях — красные шелушащиеся бляшки, напоминающие псориатические (это состояние известно как себопсориаз). У больного — СПИД. Недавно он перенес инсульт. Левая половина лица парализована, поэтому высыпаний на ней гораздо больше

candidiasis of a tongue

LABORATORY DIAGNOSIS HIV:

The data epidanamnesis , parenteral anamnesis and sexual behaviour, presence HIV for the pregnant woman

1.ELISA - detection in a blood of antibodies against a virus

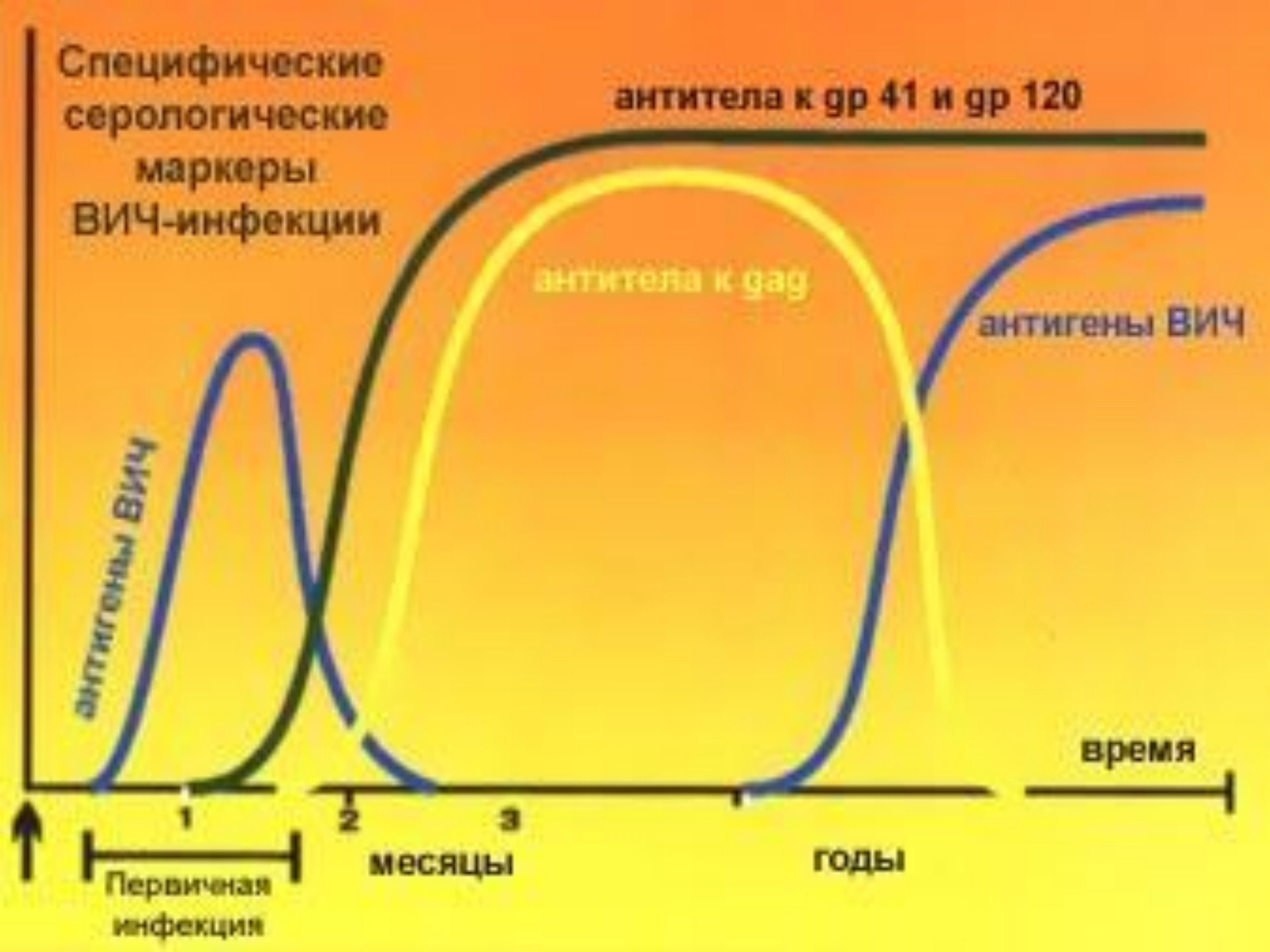
2. Immunoblotting (detection in blood of antibodies against major antigenes HIV- from 4 up to 6)

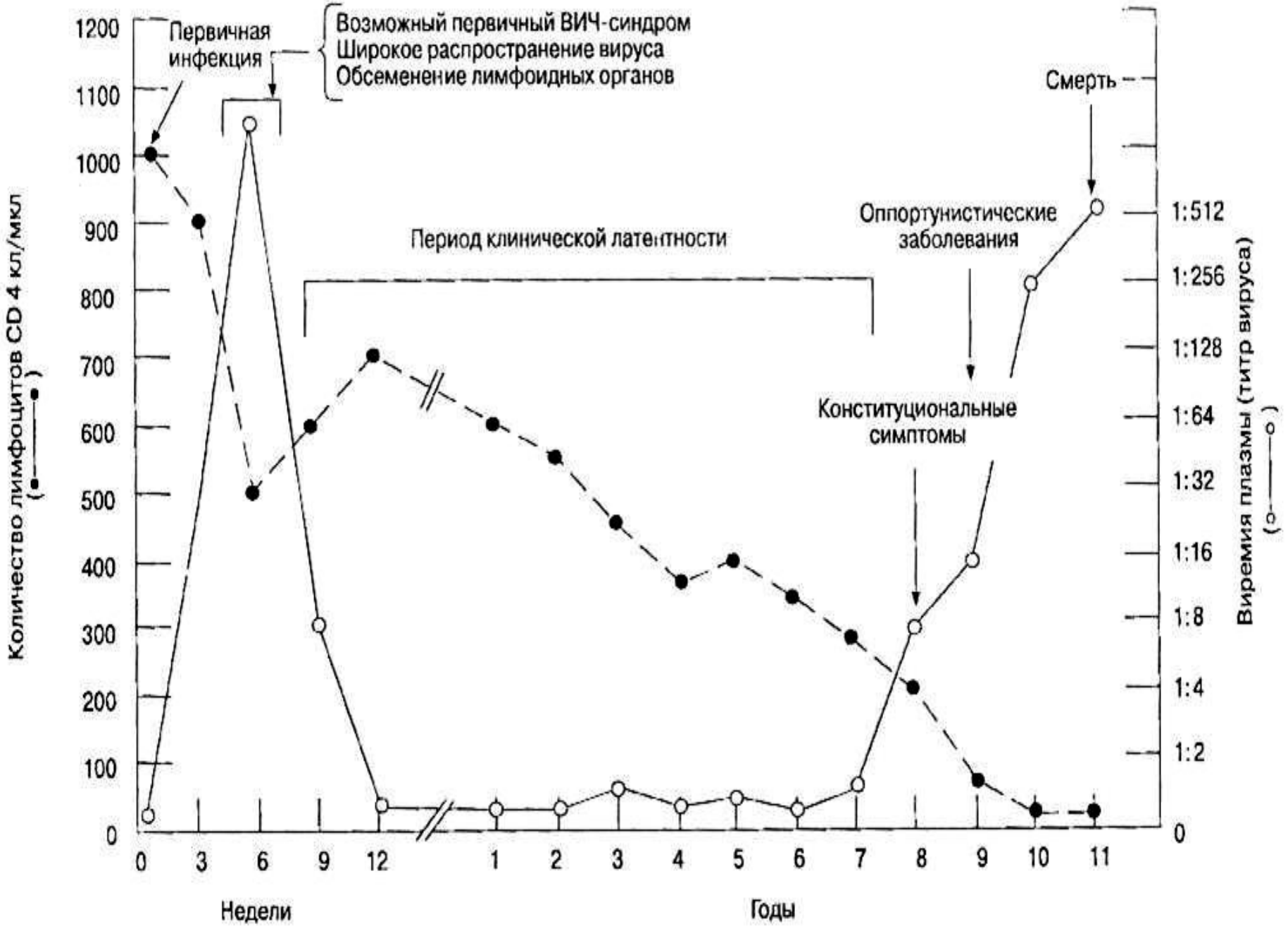
3. PCR - detection in a blood of virus RNA

4. Virologic research (cultivation HIV on cultures of tissues)

5. Immunogram (quantity СД4 of cells)

6. Manifold bacteriological, virologic, parasitologic, mycotic, histological and tool methods research for revealing of indicator diseases


Специфические серологические маркеры ВИЧ-инфекции
антитела к gp 41 и gp 120
антитела к gag
антигены ВИЧ
антигены ВИЧ
время
1
2
3
месяцы
годы
Первичная инфекция


Возможный первичный ВИЧ-синдром
Широкое распространение вируса
Обсеменение лимфоидных органов
Первичная инфекция
Смерть
Оппортунистические заболевания
Период клинической латентности
Конституциональные симптомы
Количество лимфоцитов CD 4 кл/мкл
Виремия плазмы (титр вируса)
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
1:512
1:256
1:128
1:64
1:32
1:16
1:8
1:4
1:2
0
0 3 6 9 12 1 2 3 4 5 6 7 8 9 10 11
Недели
Годы

ANTIRETROVIRAL TREATMENT (ART)

ART is a reception of specific drugs, which operating on various components HIV, prevent it to develop and to be multiplied

ART - does not cure of a HIV-INFECTION completely, but improves quality of life and allows essentially slows down development AIDS

ART - allows sharply to lower quantity of a virus in organism and longer to save effective operation the immune system

ART - will be carried out continuously and all life!!!

ART - is assigned only at lowering quantity СД4 lymphocytes from 350 and is lower in 1 mcl. of a blood (It is often starting from 2-nd clinical stage of the disease)

GROUPS ANTIRETROVIRAL of DRUGS:

1. Nucleozid`s inhibitors return transcriptasa-
   (d4T, AZT, ddl, 3TC …)

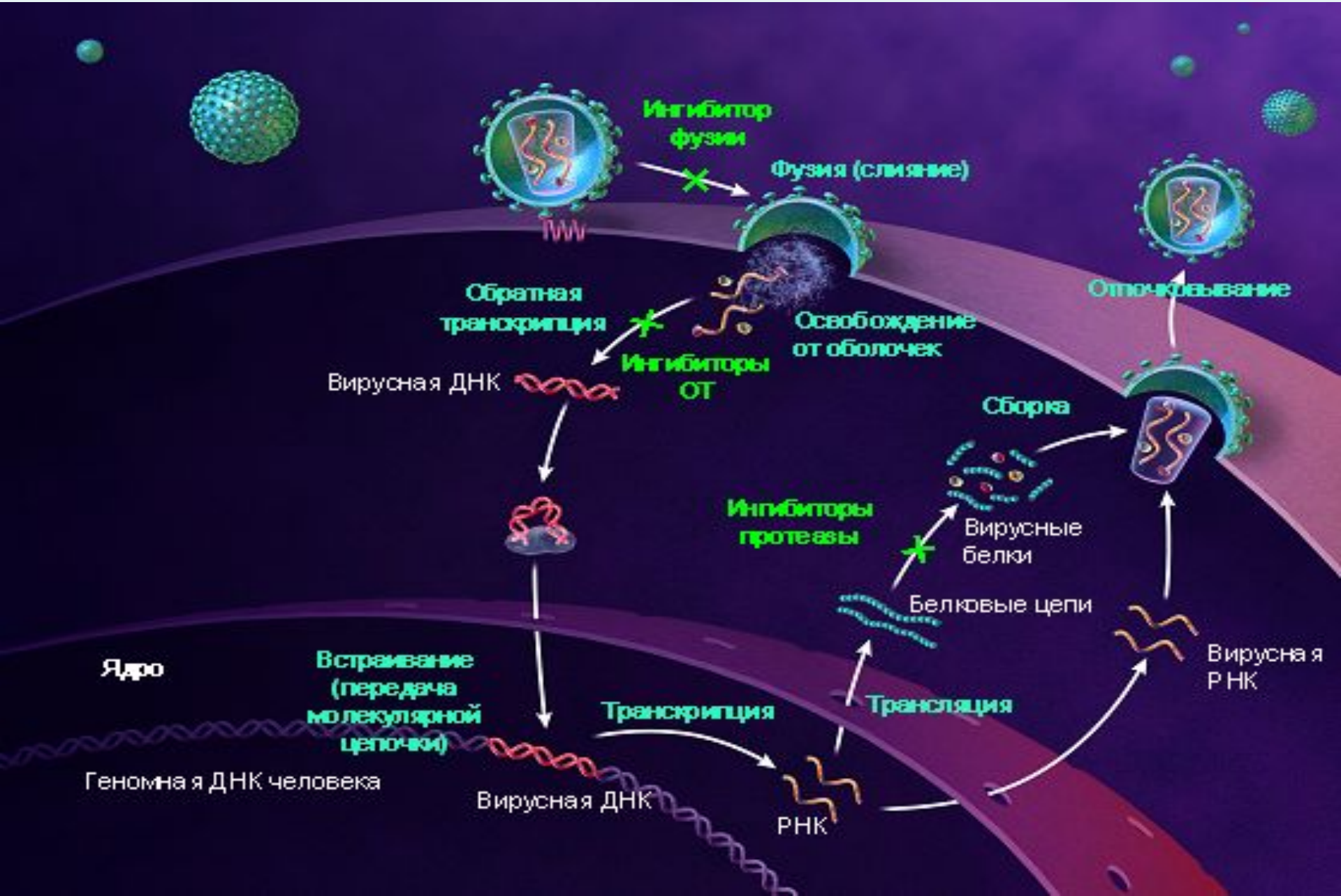
2. Unnucleozid`s inhibitors return transcriptasa -
   (EFV, NVP …)

3. Inhibitors of a protease: (NFV, Ipv/rtv, IDV, RTV, SQV …)

Triple therapy (on one drug from each of the listed above groups with replacement on the following triple combination will be used only at appearance of stability to the first group!!!

The mechanism of operation of drugs from each of groups represented on the following slide

Vital cycle of the VIH and targets for medicine

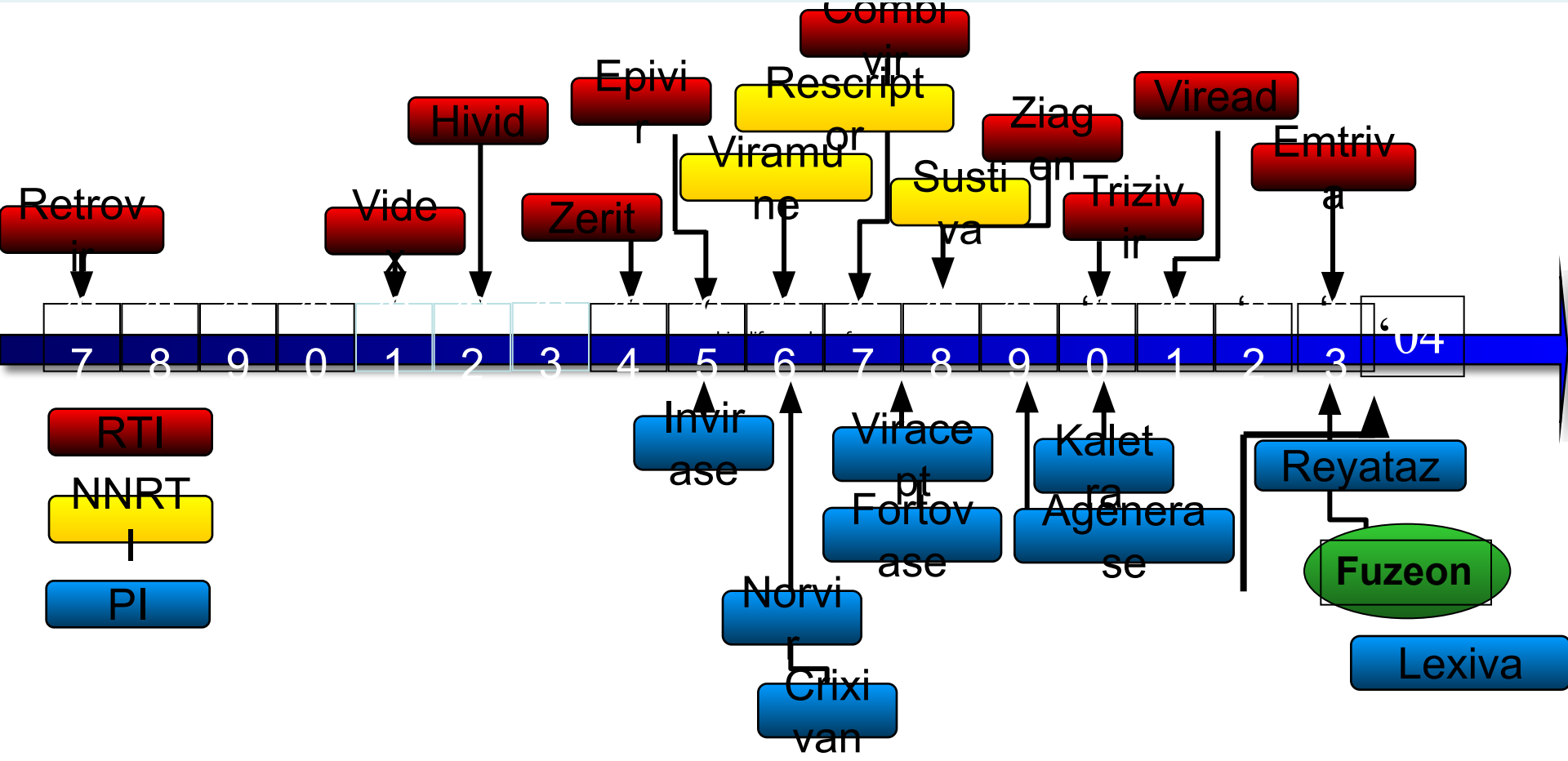


GROUPS ANTIRETROVIRAL of DRUGS:

НИОТ	ННИОТ	ИП	ИФ
Zidovudine(AZT) Stavudine (d4T) Lamivudine(3TC) Didanosine (ddI) Abacavir (ABC) Emtricitabine (FTC)	Efavirenz (EFV) Nevirapine (NVP)	Indivavir(IDV) Ritonavir(RTV) Нелфинавир (NFV) Saquinavir(SQV) Фосампренавир (FPV) Lopinavir(LPV/r) Atazanavir(ATV) Типранавир (TPV) Дарунавир (DRV)	ИФ Энфувиртид (ENF) CCR5 Маравирок
НтИОТ			**ИИ**
Tenofovir (TDF)			Ральтегравир

История антиретровирусных препаратов

С 1987 по 1995 использовались 4 АРВ препарата класса НИОТ. Во второй половине 90-х годов начали использоваться ННИОТ препараты. С 1995 было начато применение ингибиторов протеаз.



1) Nucleoside Reverse Transcriptase Inhibitors

Emtriva

Eg : Emtricitabine
200 mg once a day

Epivir

Eg : Lamivudine or 3TC
300-mg tablet once a day
150 mg tablet twice a day

Videx EC

Eg : Didanosine or ddI
400 mg enteric coated capsules

Retrovir

Eg : Zidovudine or AZT
100 mg and 300 mg capsules
10 mg/mL IV solution
10 mg/mL oral solution

Viread

Eg : Tenofovir
300 mg tablets
once a day

Zerit

Eg : Stavudine or d4T
15, 20, 30 and 40 mg capsules
1 mg/mL oral solution

2) Non-Nucleoside Reverse Transcriptase Inhibitors

Sustiva

Eg : Efavirenz

50, 100 and 200 mg capsules

Viramune

Eg : Nevirapine

200 mg tablets

50 mg/5 mL oral suspension.

hiv_life_cycle.asf

3) Fusion Inhibitor

Fuzeon

Eg : Enfuvirtide

90 mg

4) Protease Inhibitors

Fortovase

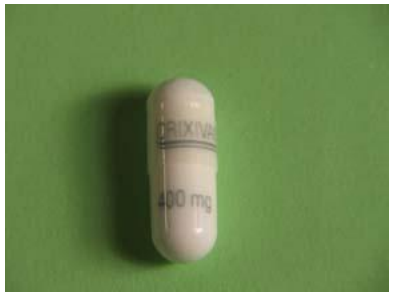
Eg : Saquinavir 200 mg soft gel capsules

Norvir

Eg : Ritonavir100 mg capsules 600 mg/7.5 mL oral sol.

Invirase

Eg : Saquinavir 1,000 hard gel twice daily



Crixivan

Eg : Indivavir 200, 333 and 400 mg every 8 hours.

Kaletra

Eg : Lopinavir or Ritonavir 200 mg lopinavir 50 mg ritonavir.

Reyataz

Eg : Atazanavir sulfate 200-mg capsules

1)Truvada

- Emtricitabine / Emtriva 200 mg
- Tenofovir / Viread

2)Combivir

- Lamivudine / Epivir 150 mg
- Zidovudine / Retrovir

3)Epzicom

- Lamivudine 300 mg
- Abacavir

hiv_life_cycle.asf

4)Trizivir

- Zidovudine / Retrovir 300 mg
- Lamivudine / Epivir 150 mg
- Abacavir / Ziagen 300 mg

TYPICAL the SCHEME ART AT HIV For the ADULT:

1. AZT (zidovudin) +3TC (lamivudin) + Kaletra (Lopinavir/ Ritonavir)

2. AZT +3TC + EFV (ifavirens)

3. d4T (stavudin) +ddL (didanosin) + Kaletra (Lopinavir / Ritonavir)

4. d4T + ddL + EFV (ifavirens)

Other schemes of treatment in a case are stipulated thouse decrease of effect or excessive toxic operation ART:

- oppression of the function of a marrow
- neurotoxicity or peripheral neurotoxicity
- hepatotoxicity

- appearance of an exanthema or enanthema
- syndrome of the diarrhea
- pancreatitis
- lowering and violation of vision

Because of a toxicity many patients interrupt treatment!!

The efficiency of treatment depends on the mode of treatment. If the patient in currents of year has accepted of drugs:

- It is more than 95 % - efficiency makes 78 %
- 90 - 95 % - efficiency 45 %
- 80 - 90 % - efficiency 33 %
- 70 - 80 % - efficiency 29 %

- It is less than 70 % - efficiency only 18 %!!!

Снижение смертности с появлением ВААРТ

Palella et al, N Engl J Med 2000

PROPHYLAXIS (there is no specific prophylaxis!!!)

- revealing groups of hazard and their testing (with permissions of the patient!!!)
- careful research of all biological tissues obtained from the man on HIV (donors)
- usage of medical gloves
- usage of masks,shields, glasses, aprons- for protection of a skin and mucous
- usage of a «scoop» technique dressing disperser hood on a needle of a utilised squirt
- at transmission during operation of the tool from hands in hands to utillize « a neutral field » - little table, tray
- washing hands, disinfection of tools, ware, linen, equipments

-usage of special containers at a transportation of test tubes with anyone biological by materials obtained from the patient

- emergency prophylaxis ART injured medical personal during contact to the patients

- struggle about distribution of narcotic resources

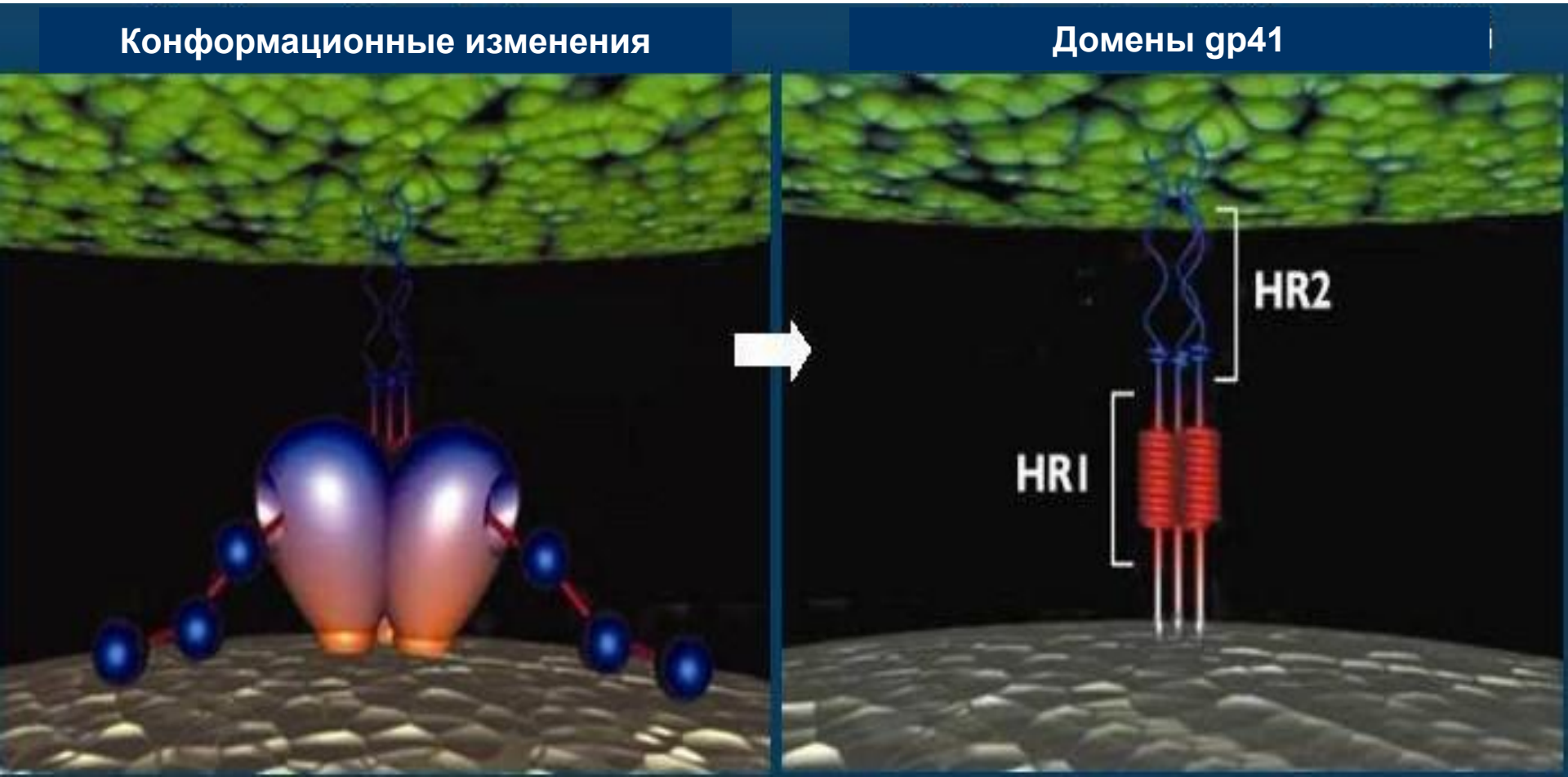
- carrying out by the pregnant woman ART before labor

- obligatory usage of condoms at random sex links

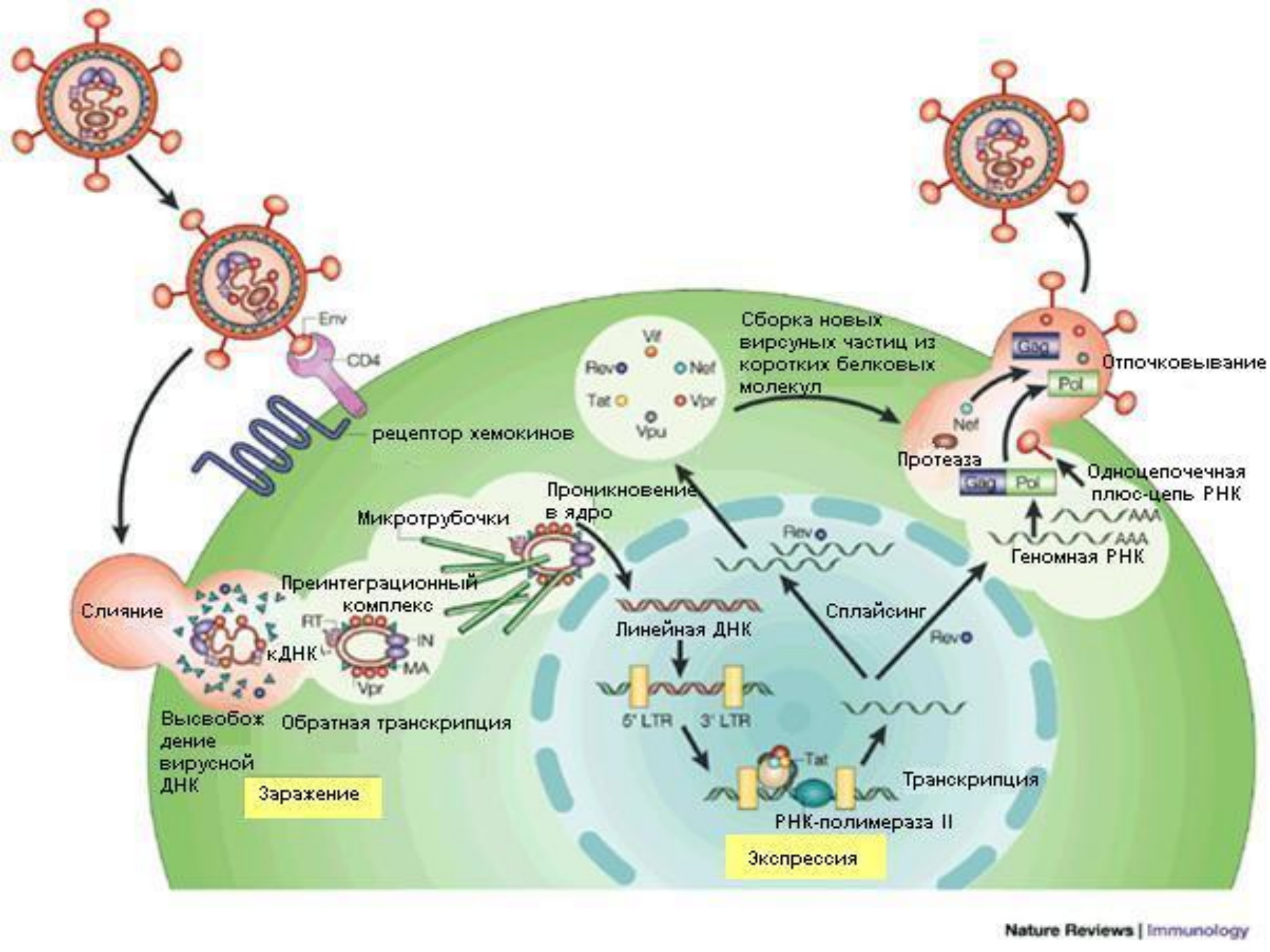
- sanitary enlightenment since school age, connection public and religious the figures to the given operation

ENDING OF THE LECTURE

Stage 2. Attachment with coreceptors



Хронический язвенный герпес: поражение перианальной области.
Крупные, чрезвычайно болезненные язвы соседствуют с саркомой Капоши


Env
CD4
рецептор хемокинов
Vif
Rev
Nef
Tat
Vpr
Vpu
Сборка новых вирсуных частиц из коротких белковых молекул
Gag
Pol
Отпочковывание
Nef
Протеаза
Gag
Pol
Одноцепочечная плюс-цепь РНК
AAA
AAA
Геномная РНК
Rev
Проникновение в ядро
Микротрубочки
Преинтеграционный комплекс
RT
IN
MA
Vpr
Слияние
кДНК
Высвобождение вирусной ДНК
Обратная транскрипция
Заражение
Линейная ДНК
Сплайсинг
Rev
5' LTR
3' LTR
Tat
Транскрипция
РНК-полимераза II
Экспрессия

This lung is as solid as liver because of Pneumocystis carinii pneumonia (PCP). There is diffuse consolidation. PCP is typical of

immunocompromised patients, particularly those with AIDS.

1

Нуклеозидные ингибиторы обратной транскриптазы
ZDV, ddI, d4T, 3TC, ABC,TDF,
2 Не-нуклеозидные ингибиторы обратной транскриптазы
NVP, EFV