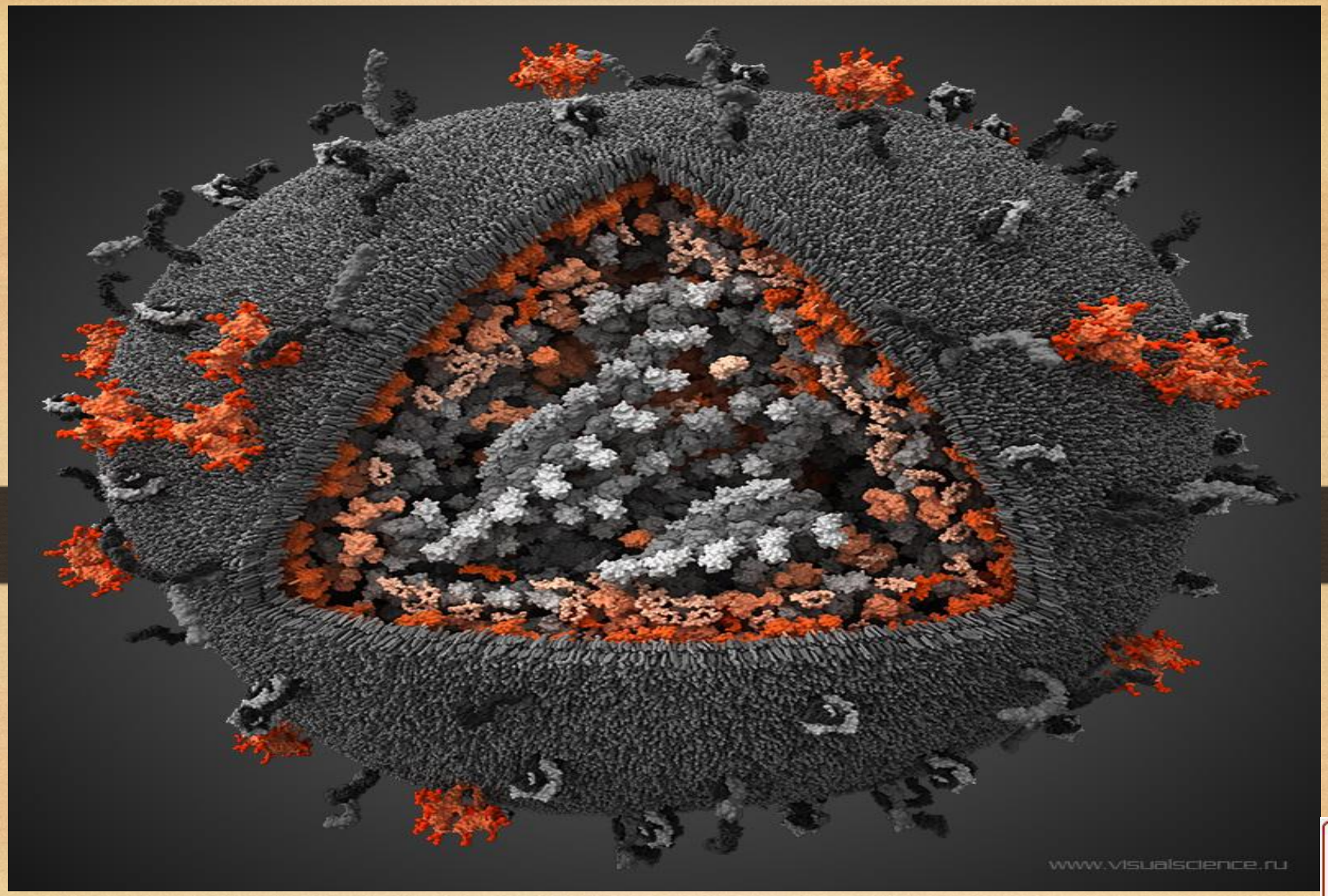


HIV/AIDS 1

Definitions

- **HIV (*human immunodeficiency virus*)** is a virus that attacks cells that help the body fight infection, making a person more vulnerable to other infections and diseases.
- **AIDS (*Acquired immunodeficiency syndrome*)** is the most advanced stage of HIV infection. To be diagnosed with AIDS, a person with HIV must have an AIDS-defining condition or have a CD4 count less than 200 cells/mm^3 (regardless of whether the person has an AIDS-defining condition).

HIV history

- **Pre-1980**

✓ HIV originated in Kinshasa, in the Democratic Republic of Congo around 1920 when HIV crossed species from chimpanzees to humans

✓ sporadic cases of AIDS were documented prior to 1970

✓ available data suggests that the current epidemic started in the mid- to late 1970s

✓ By 1980, HIV may have already spread to five continents (North America, South America, Europe, Africa and Australia).

HIV history

- **1980s**

- ✓ In **1981**, cases of a rare lung infection called *Pneumocystis carinii pneumonia (PCP)* were found in five young, previously healthy gay men in Los Angeles.
- ✓ At the same time, there were reports of a group of men in New York and California with an unusually aggressive cancer named *Kaposi's Sarcoma*.
- ✓ In December 1981, the first cases of PCP were reported in people who inject drugs.
- ✓ End of 1981 - there were 270 reported cases of severe immune deficiency among gay men - 121 of them had died.

HIV history

- **1980s**

- ✓ In June **1982,** a group of cases among gay men in Southern California suggested that the cause of the immune deficiency was sexual and the syndrome was initially called gay-related immune deficiency (or GRID).
- ✓ Later that month, the disease was reported in haemophiliacs and Haitians leading many to believe it had originated in Haiti.
- ✓ In September, the CDC used the term 'AIDS' (acquired immune deficiency syndrome) for the first time, describing it as AIDS cases were also being reported in a number of European countries.

HIV history

- **1980s**

- ✓ In January **1983**, AIDS was reported among the female partners of men who had the disease suggesting it could be passed on via heterosexual sex.
- ✓ In May, doctors at the Pasteur Institute in France reported the discovery of a new retrovirus called Lymphadenopathy-Associated Virus (or LAV) that could be the cause of AIDS.
- ✓ In April **1984**, the National Cancer Institute announced they had found the cause of AIDS, the retrovirus HTLV-III. In a joint conference with the Pasteur Institute they announced that LAV and HTLV-III are identical and the likely cause of AIDS.

HIV history

- **1980s**

- ✓ In March **1985**, the U.S Food and Drug Administration (FDA) licensed the first commercial blood test, ELISA, to detect antibodies to the virus.
- ✓ In May **1986**, the International Committee on the Taxonomy of Viruses said that the virus that causes AIDS will officially be called HIV (human immunodeficiency virus) instead of HTLV-III/LAV.
- ✓ In February **1987**, the WHO launched The Global Program on AIDS.
- In March, the FDA approved the first antiretroviral drug, zidovudine (AZT), as treatment for HIV.
- In April, the FDA approved the western blot blood test kit, a more specific HIV antibody test.
- In July, the WHO confirmed that HIV could be passed from mother to child during breastfeeding.
- In October, AIDS became the first illness debated in the United Nations (UN) General Assembly.

HIV history

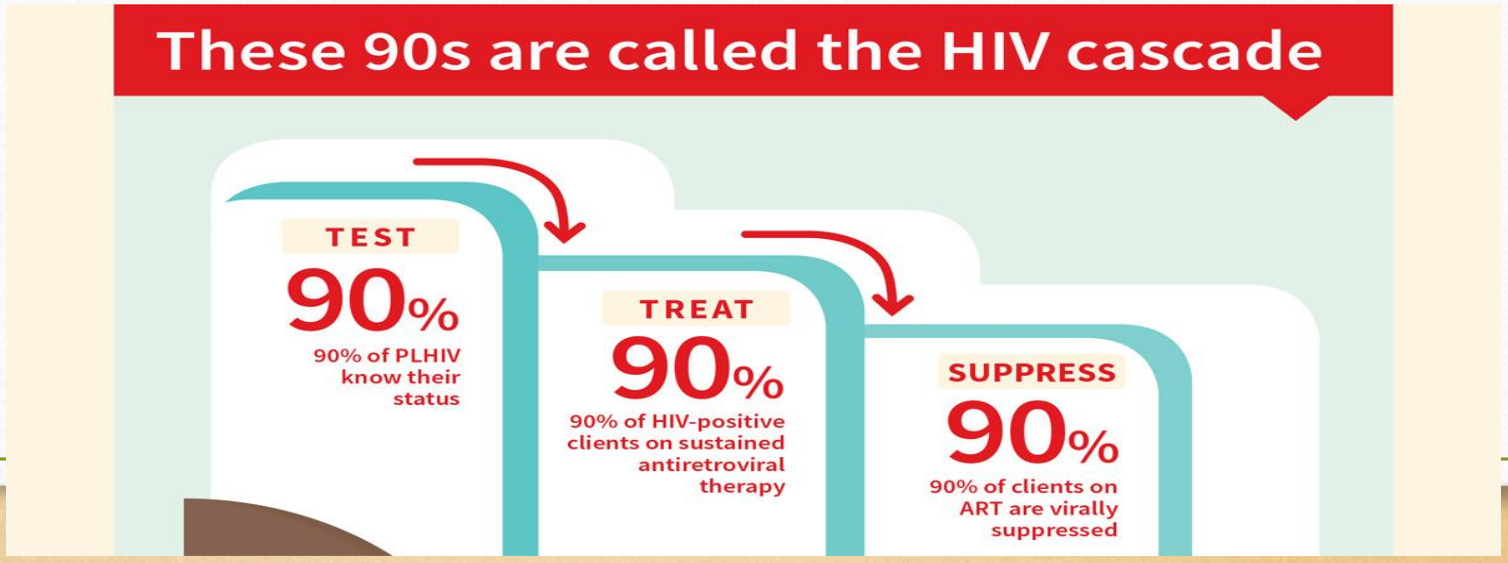
- **1990s**

- ✓ In **1996**, 11th International AIDS Conference highlighted the effectiveness of HAART leading to a period of optimism.
- ✓ The FDA approved - the first home testing kit; a viral load test to measure the level of HIV in the blood; the first non-nucleoside transcriptase inhibitor (NNRTI) drug (nevirapine); and the first HIV urine test.
- ✓ In July **2012**, the FDA approved PrEP for HIV-negative people to prevent the sexual transmission of HIV.

HIV history

- **2000s**

✓ In **2014** - UNAIDS launched the 90-90-90 targets which aim for 90% of people living with HIV to be diagnosed, 90% of those diagnosed to be accessing antiretroviral treatment and 90% of those accessing treatment to achieve viral suppression by 2020.



2019

- 81% of people with HIV - know their HIV status

↓

- 82% of people with HIV status had access to ART

↓

- 88% of those who benefited from ART - obtained virological suppression

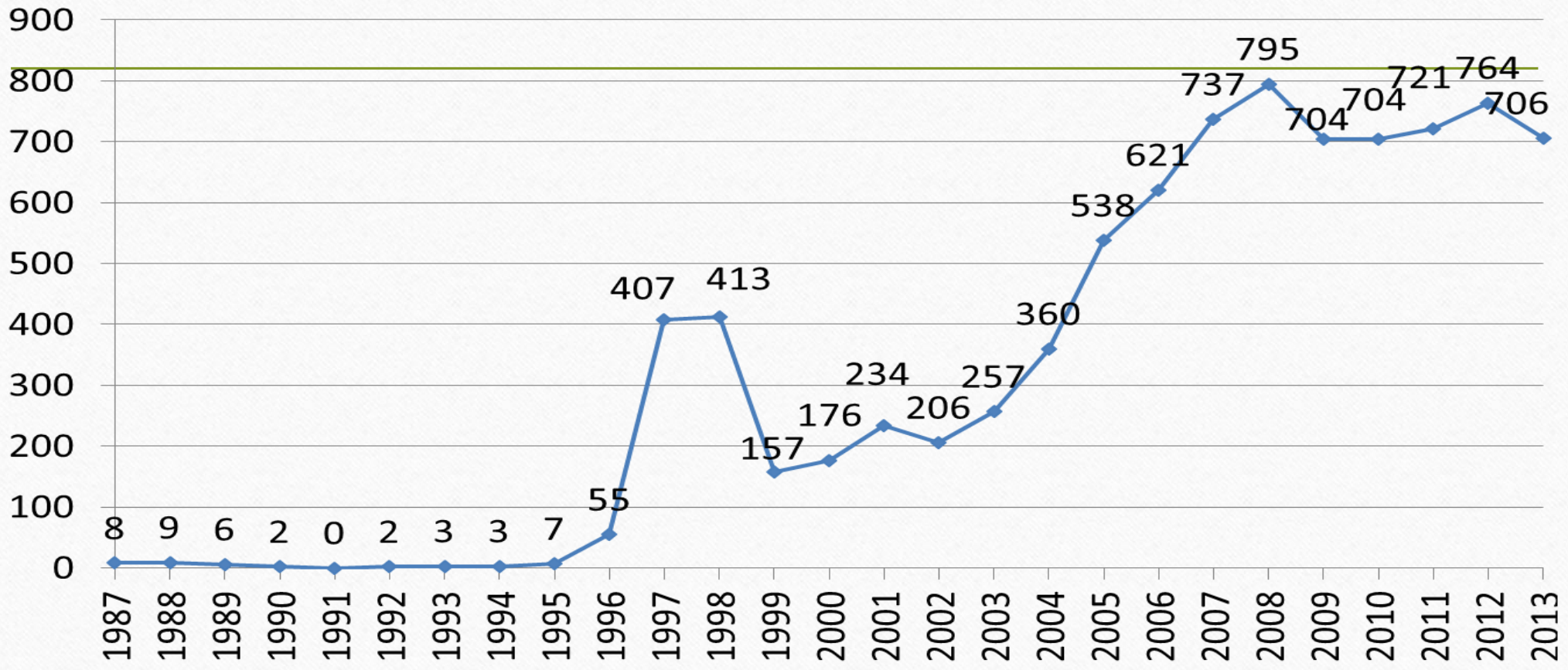
Summary of the global HIV epidemic (2019)

	People living with HIV in 2019	People newly infected with HIV in 2019	HIV-related deaths in 2019
Total	38.0 million [31.6 million – 44.5 million]	1.7 million [1.2 million – 2.2 million]	690 000 [500 000 – 970 000 million]
Adults	36.2 million [30.2 million – 42.5 million]	1.5 million [1.1 million – 2.0 million]	600 000 [430 000 – 840 000]
Women	19.2 million [16.4 million – 22.2 million]	790 000 590 000 – 1.1 million]	300 000 [220 000 – 420 000]
Men	17.0 million [13.8 million – 20.4 million]	870 000 630 000 – 1.2 million]	390 000 [280 000 – 560 000]
Children (<15 years)	1.8 million [1.3 million – 2.2 million]	150 000 [94 000 – 240 000]	95 000 [61 000 – 150 000]

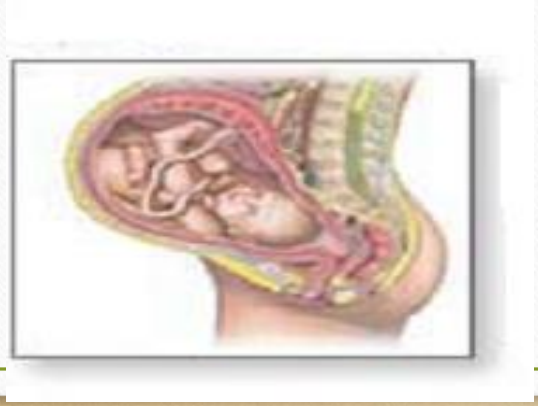
Source: UNAIDS/WHO estimates

World Health Organization

R.Moldova
1987-2013 (www.aids.md)



Modes of HIV/AIDS Transmission



Percent infection by transmission route….

Transmission route	%
Sexual intercourse	70-80
Mother-to-child-transmission	5-10
Blood transfusion	3-5
Injecting drug use	5-10
Health care – eg: needle stick injury	<0.01

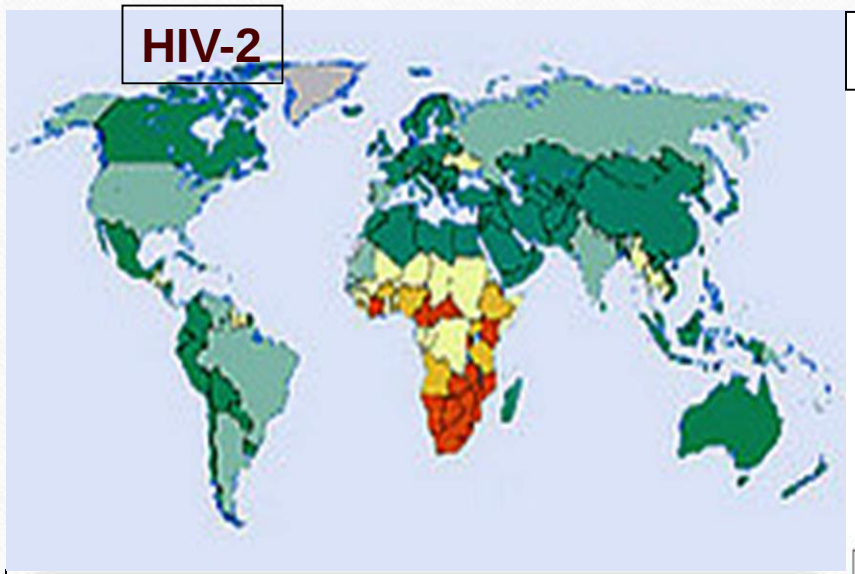
HIV is a retrovirus - family of lentiviruses

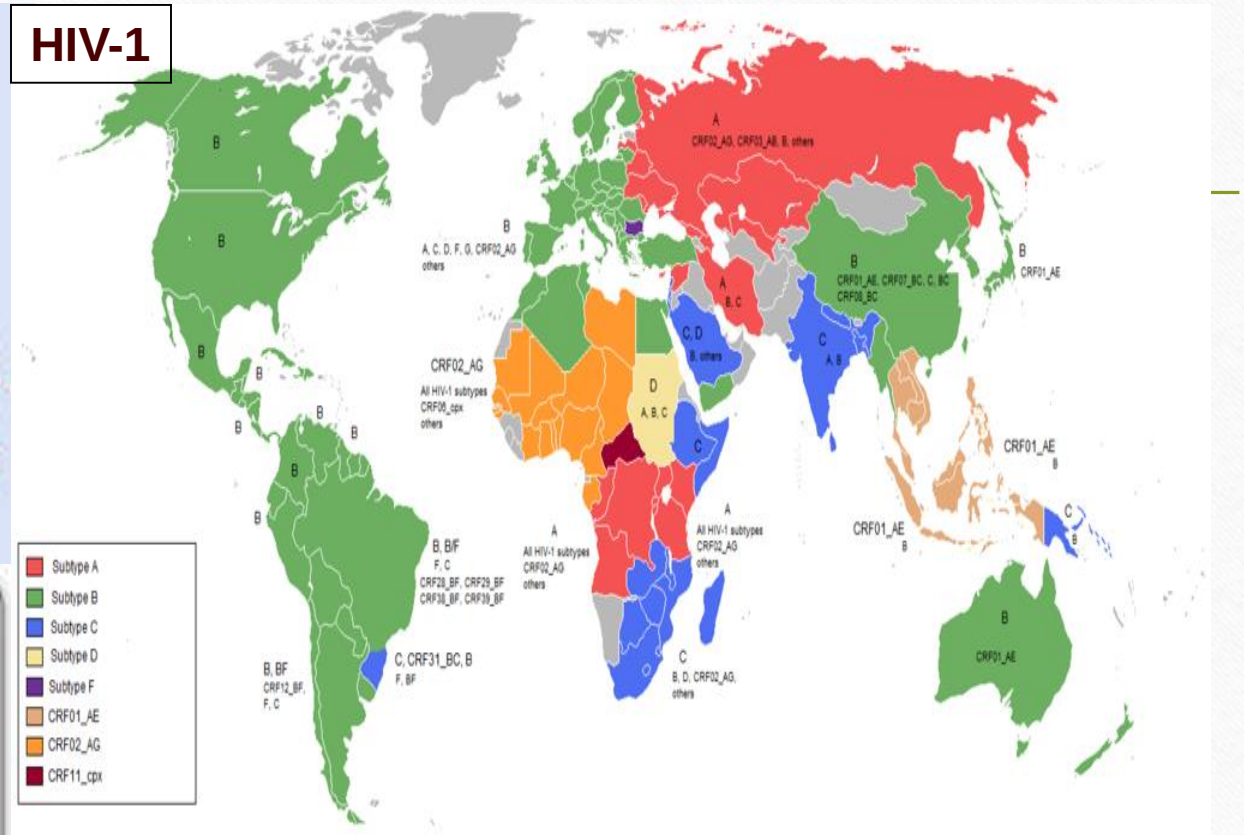
Lentivirus Serotypes

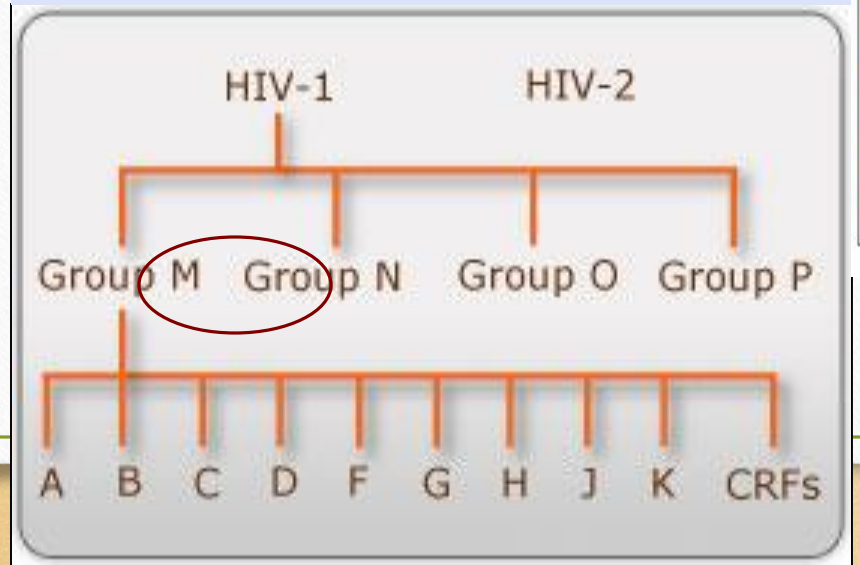
1. **Bovine** serogroup
   Bovine immunodeficiency virus
2. **Equine** serogroup
   Equine infectious anemia virus
3. **Feline** serogroup
   Feline immunodeficiency virus
4. **Ovinecaprine** serogroup
   Caprine arthritis-encephalomyelitis virus
   Maedi/visna virus
5. **Primate** serogroup
   Human immunodeficiency virus
   Simian immunodeficiency virus

Comparison of HIV species

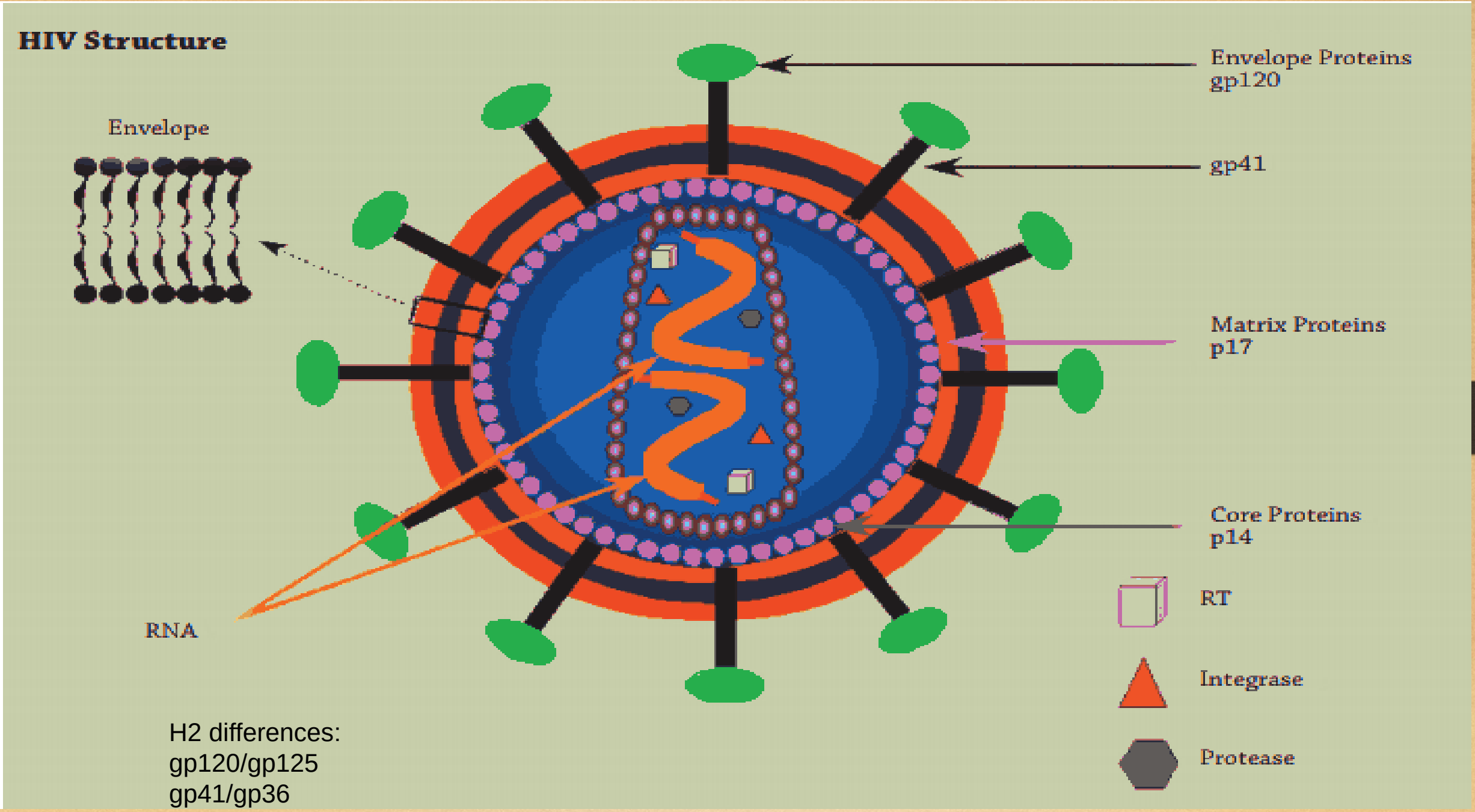
Species	Virulence	Transmittability	Prevalence	AIDS
HIV-1	High	High	Global	more quickly
HIV-2	Lower	Low	West Africa	more slowly



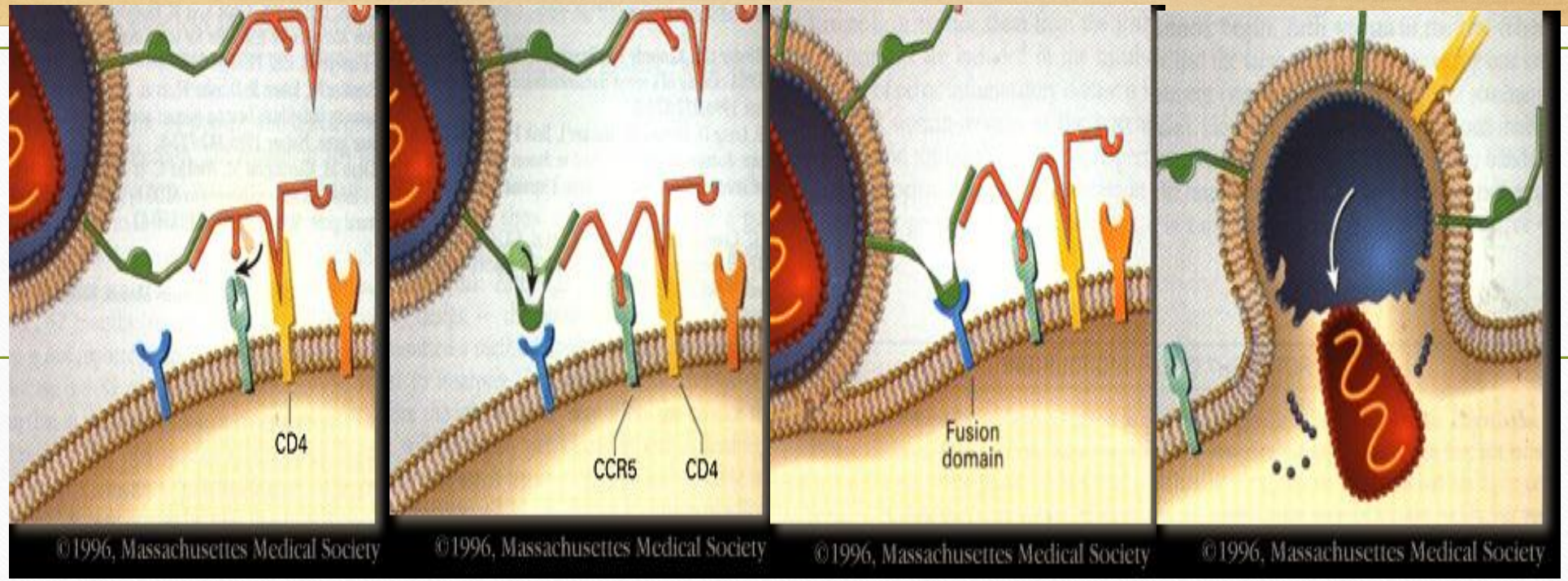




group M >90%
group O (outlier) - west-central Africa
group N & P - extremely rare, Cameroon
CRFs = "circulating recombinant forms"



H2 differences:
gp120/gp125
gp41/gp36



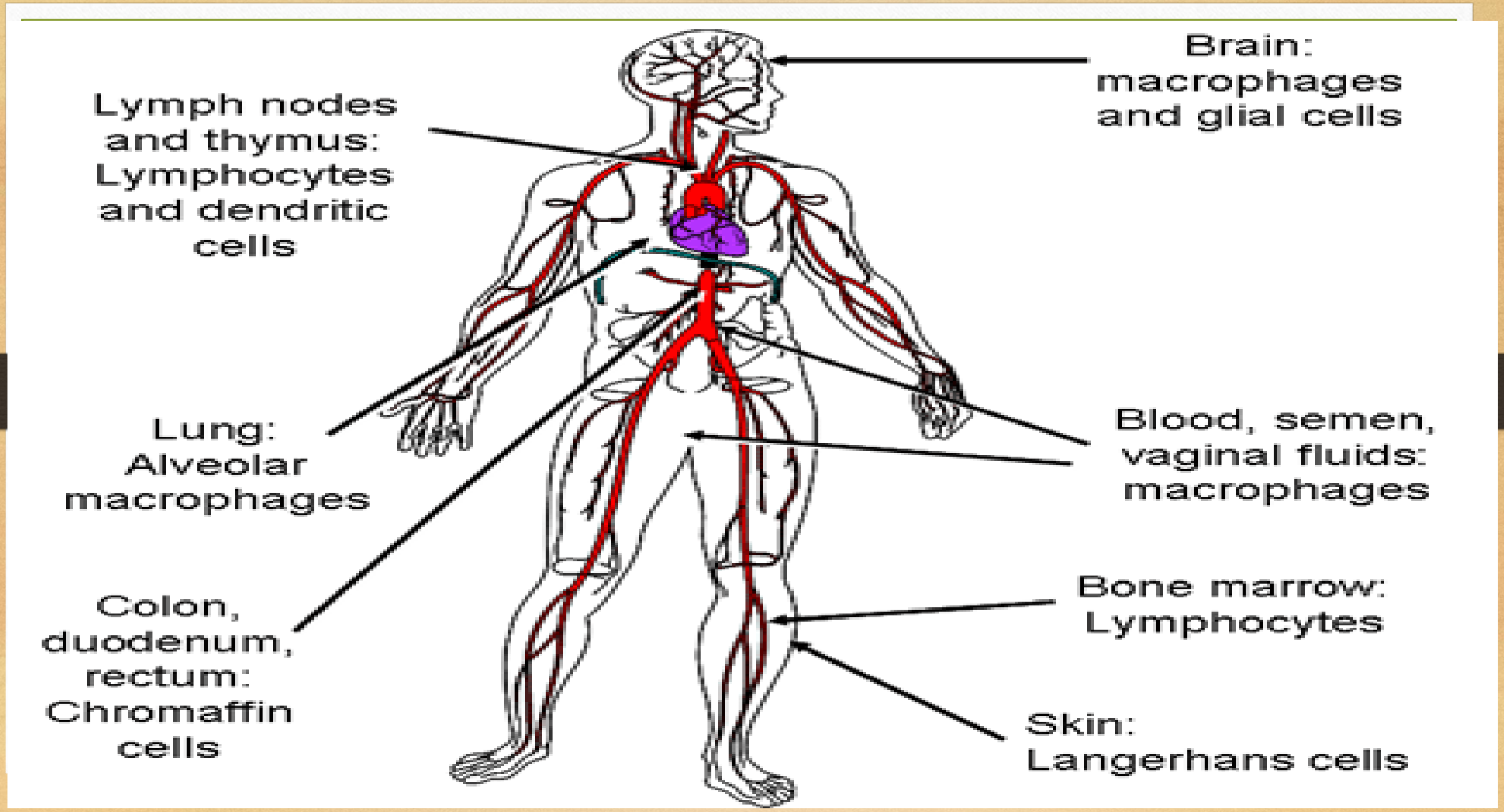
1. gp120 interacts with CD4 receptor
2. interacts with chemokine receptors:
   - CXCR4 (expressed only on T lymph, SI)
   - CCR5 (monocytes & lymphocytes, NSI)
3. gp41 interacts with fusion domain
4. surface HIV then fuses with the cell
5. the viral nucleoid enters into the cell

Half-life of HIV in various HIV-infected compartments

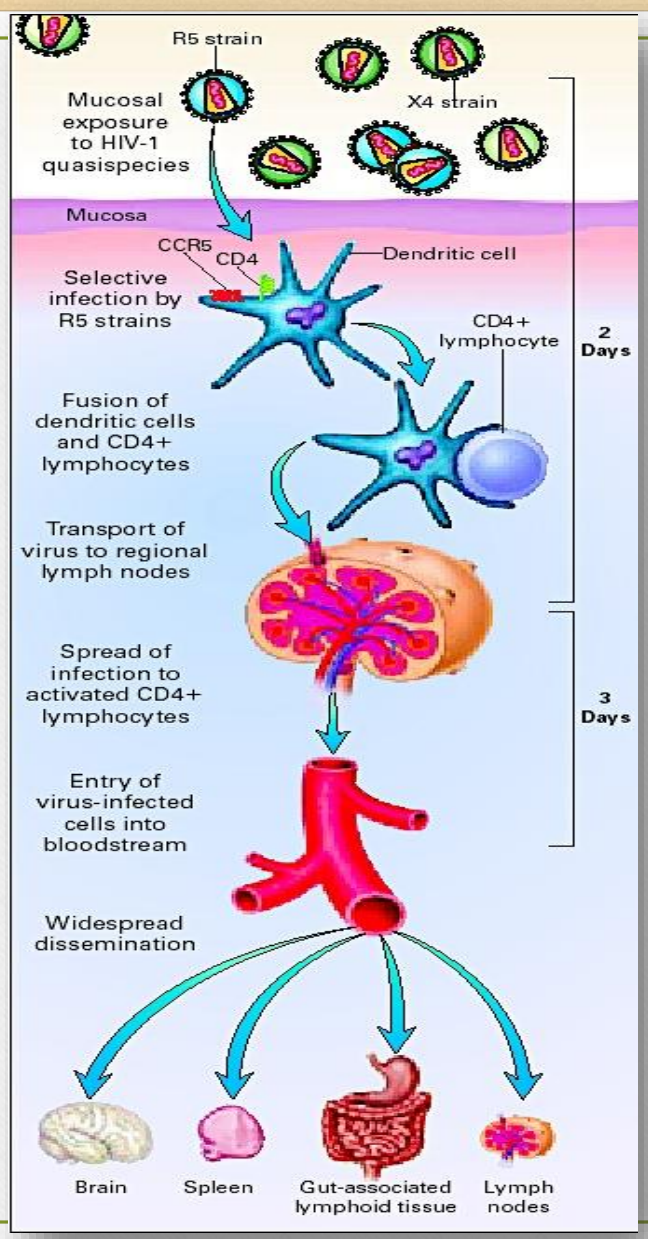
Free virus	0.25 day (6 hours)
Actively infected CD4 cells	1 day
CD4 cells with un-integrated virus	6 days
Macrophages	14 days
Follicular dendritic cells	14 days
Latently infected CD4 cells	240 days

- HIV - fully replicate in activated CD4 T cells.
- **Resting and quiescent CD4 T cells do not produce infectious HIV.**
- Monocytes, macrophages & dendritic cells - don`t produce many HIV

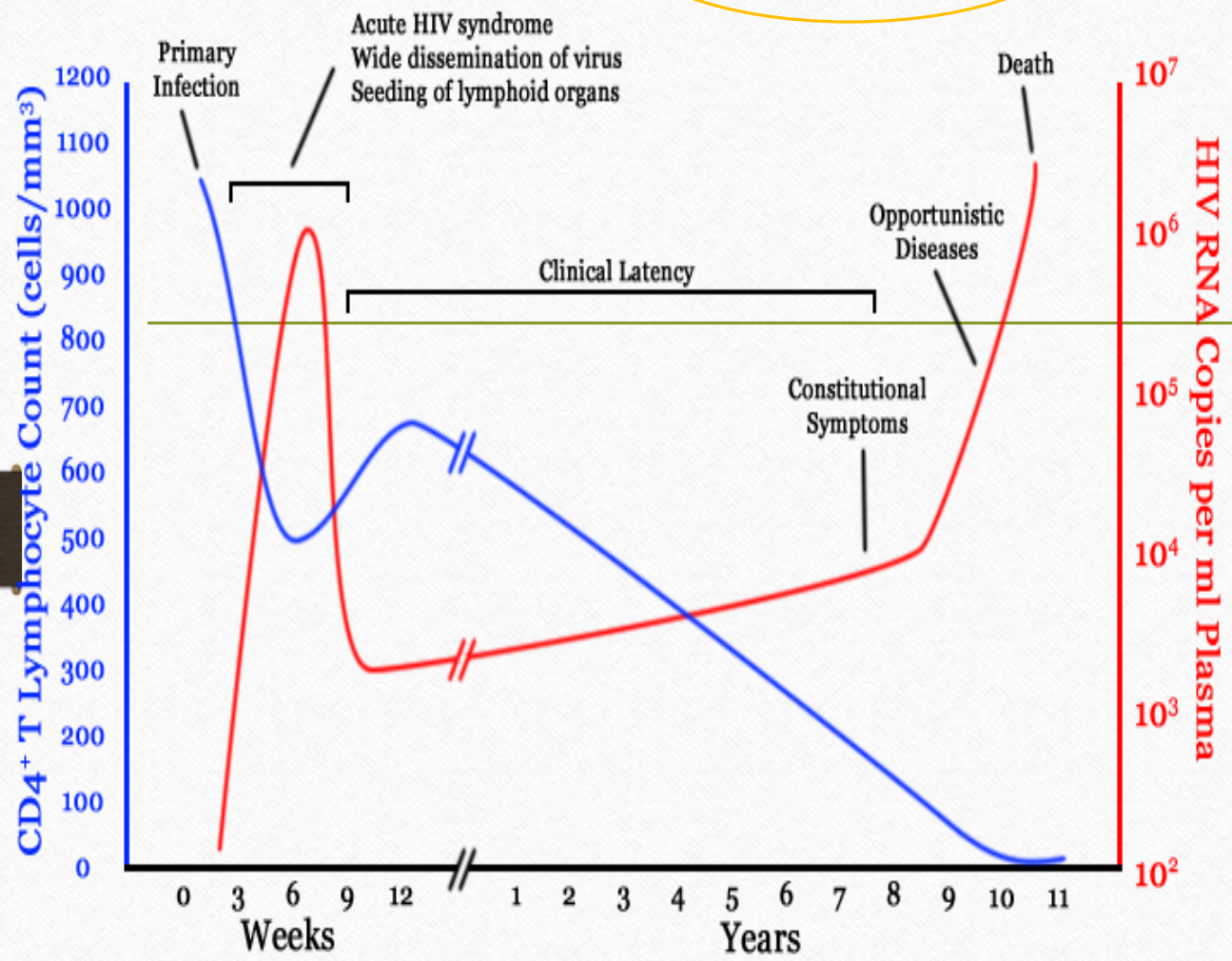
HIV target cells



- day 0
- day 0-2
- day 4-11
- day >11



- mucosal exposure (sexual)
- the virus is collected by dendritic cells and transported to the lymph nodes
- HIV replicates in CD4, and is spread into the blood
- the virus invades other organs



Course of HIV infection

- Day 0
  - The individual is exposed to HIV, and infection begins.
- Day 8
  - Virus is detectable by RNA RT-PCR.
  - The viral load more than doubles each day.
  - CD4 and total WBC counts begin to decrease.
- 2-4 weeks
  - Earliest antibodies – can be detected by newer assays.
  - The viral load peaks and begins to decline.
- 20-24 weeks
  - The viral load drops to the lowest also known as the set point.
  - Seroconversion is complete and chronic HIV infection begins.

http://aids.gov/

Recent infection = 6-month period after infection occurs.

Early infection = both acute and recent infection, after which inf. is defined as chronic.

HIV lifecycle

- **Each replication cycle only lasts 1 to 2 days.**
- It has several stages and different HIV drugs are active at different stages.
- HIV drugs are called inhibitors because they inhibit or stop parts of the cycle.

HIV lifecycle

1. HIV first has to attach to a CD4 cell.

2. The proteins on the outer surface of HIV (called gp41 and gp120) connect with receptors on the surface of the CD4 cell (usually the CD4 receptor and the CCR5 coreceptor).

- HIV drugs that block this process are called **entry inhibitors**. This family of drugs block attachment to gp41 or gp120 on the CD4 receptor or block the coreceptor CCR5.
- **Monoclonal antibodies** (mAbs) can also block this stage.

HIV lifecycle

3. After HIV attaches to the CD4 cell, it is absorbed into the main body of the cell.

HIV first loses its outer shell.

This leaves viral capsid with HIV and three key enzymes (a type of protein) that HIV uses to replicate.

- The first enzyme is called RT. This stands for reverse transcriptase.
- RT changes the single strand of HIV (called RNA) into a double strand to fit in with human DNA. Two different types of RT inhibitors (RTIs) block this process: (I) **nucleoside/tide (NRTIs/NtRTIs)**, and (II) **non-nucleoside (NNRTIs)**.

HIV lifecycle

4. The new double-stranded HIV crosses into the central nucleus of the CD4 cell. This is where HIV is integrated into human DNA.

- Drugs that block this process are called **integrase inhibitors**, abbreviated to INIs or INSTIs.

5. The CD4 nucleus then starts producing raw material to make new HIV. These long strands of new HIV particles need to be cut up and assembled as new virus.

- The enzyme involved in the cutting and assembling process is called protease. The HIV meds that block this process are called **protease inhibitors**.

HIV lifecycle

6. The newly formed virus then has to leave the cell.

- Although there are currently no HIV drugs that block this stage, several drugs are in development

✓ **Budding inhibitors** stop new HIV from leaving of the CD4 cell.

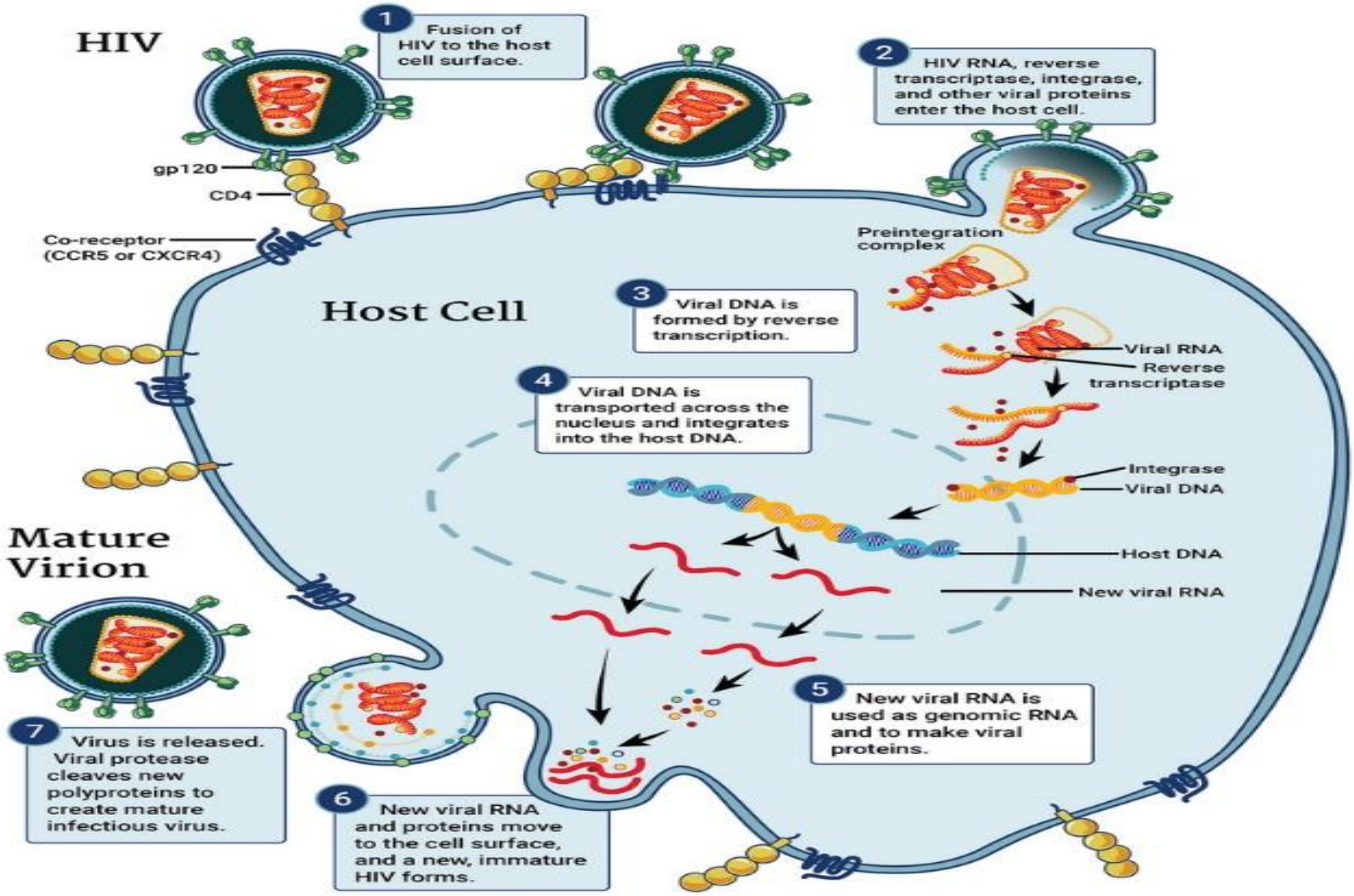
✓ **Maturation inhibitors** block the final assembly process.

7. The newly released viruses (called virions) go on to infect new CD4 cells – to repeat the process over again.

8. The old CD4 cell then dies.

This continuous process happens millions of times every day when not on ART.

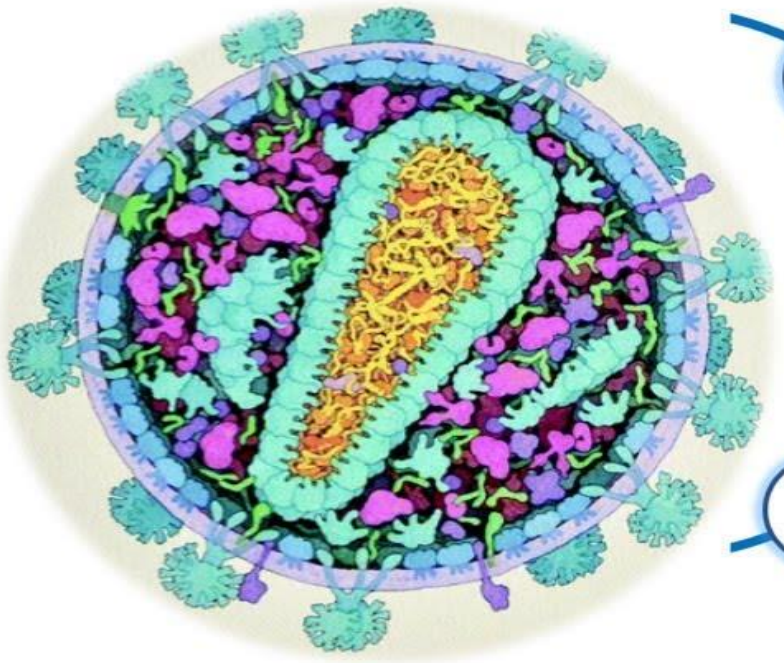
Without ART, HIV is one of the most active and rapidly reproducing virus.


HIV
gp120
CD4
Co-receptor
(CCR5 or CXCR4)
1 Fusion of HIV to the host cell surface.
2 HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.
Preintegration complex
Host Cell
3 Viral DNA is formed by reverse transcription.
Viral RNA
Reverse transcriptase
4 Viral DNA is transported across the nucleus and integrates into the host DNA.
Integrase
Viral DNA
Host DNA
New viral RNA
5 New viral RNA is used as genomic RNA and to make viral proteins.
6 New viral RNA and proteins move to the cell surface, and a new, immature HIV forms.
Mature Virion
7 Virus is released. Viral protease cleaves new polyproteins to create mature infectious virus.

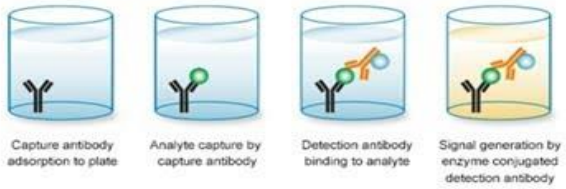
Main types of HIV drugs

Abbreviation	Full names
NRTIs/NtRTIs ("nukes")	Nucleoside/tide reverse transcriptase inhibitors or nucleoside/tide analogues
NNRTIs ("non-nukes")	Non-nucleoside reverse transcriptase inhibitors
PIs	Protease inhibitors
INIs (or INSTIs)	Integrase (strand transfer) inhibitors
CCR5 inhibitors	CCR5 inhibitors are a type of entry inhibitor
Fusion inhibitors	Fusion inhibitors are a type of entry inhibitor
mAbs	Monoclonal antibodies block HIV entering the T-cell

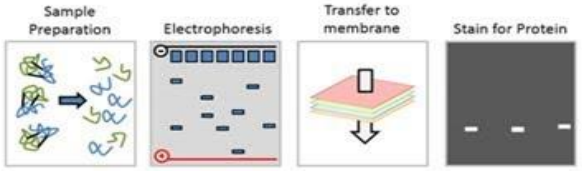
What is the diagnosis for HIV?



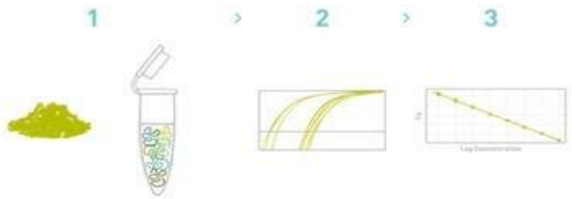
1 ELISA



2 Western Blot



3 qPCR



Ab HIV1+ HIV2

ELISA → reactive results → +/- **confirmed** by **Western blot.**

Western blot identifies Ab against 8 proteins:

p18, p24, p31, gp41, p51, p55, p65/66, gp120/p160.

CDC require Ab against **any two** of:

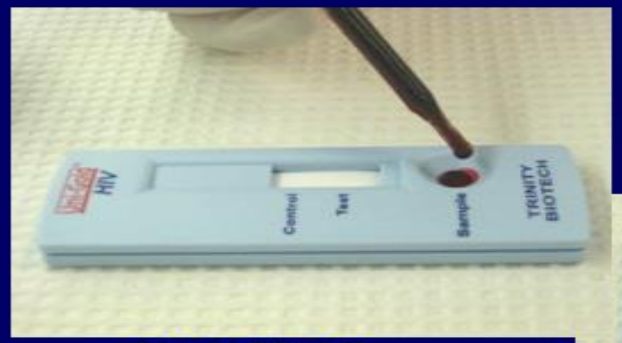
p24, gp41, gp120/160.

Indeterminate speciments = reactivity to HIV protein(s), but not fulfilling the criteria for a positive result

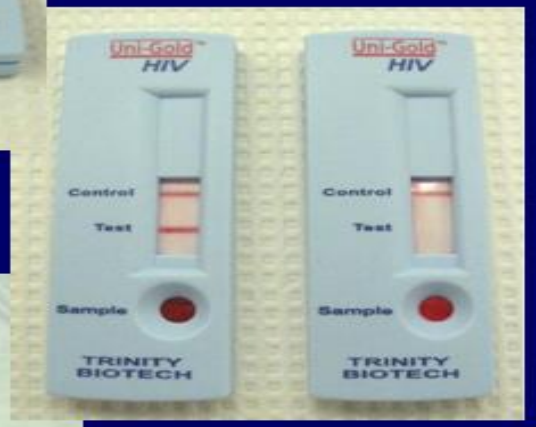
Negative Western blot = no detectable bands

Virological tests detect:

- HIV **DNA / RNA / total nucleic acid**
- p24 antigen.



Uni-Gold Recombigen



Reveal G2

Multispot HIV-1/HIV-2

OraQuick Advance

CDC

Diagnostic lab test for HIV infection

A- Tests to diagnose HIV infections:

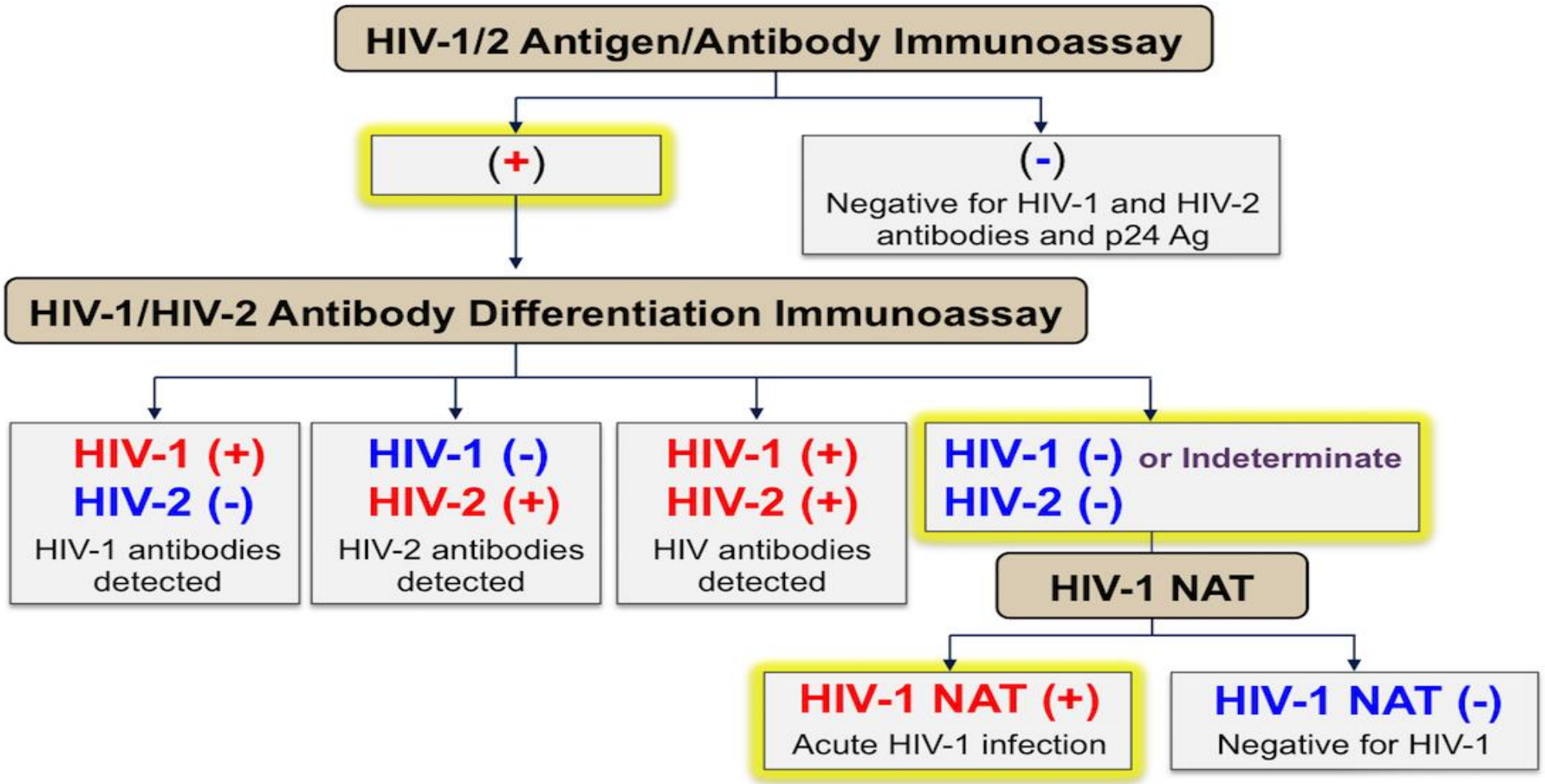
1- Screening
2- Confirmatory

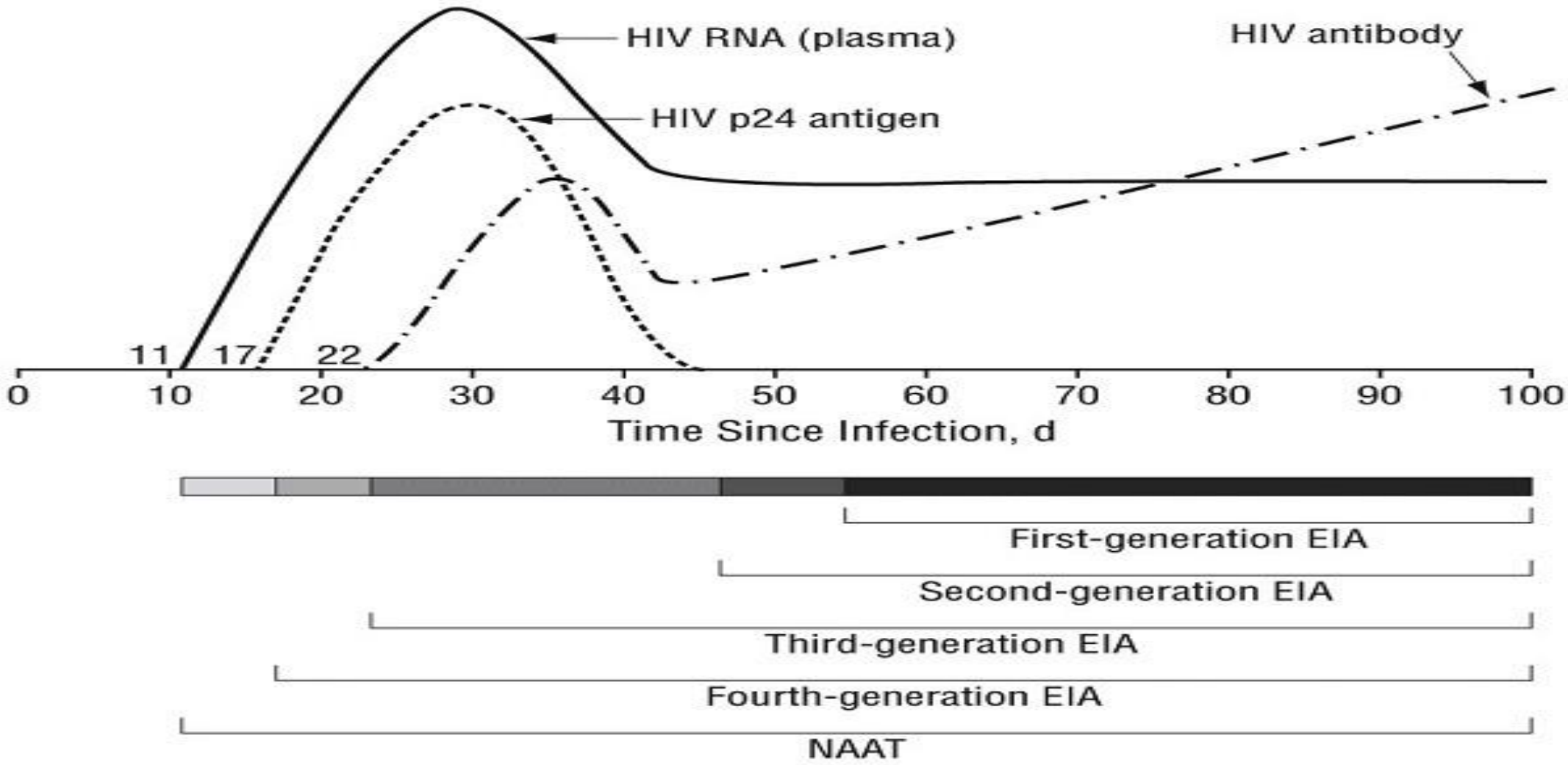
B- Tests for follow up the disease:

1- Viral load by Quantitative PCR
2- Th-cells count (CD4+)

C- Tests for the complication of the disease:

1- TB infection
2- HBV
3- HCV
4- Toxoplasma
5- Liver function tests
6- UTIs
7- Others.


HIV-1/2 Antigen/Antibody Immunoassay
(+)
(-)
Negative for HIV-1 and HIV-2 antibodies and p24 Ag
HIV-1/HIV-2 Antibody Differentiation Immunoassay
HIV-1 (+)
HIV-2 (-)
HIV-1 antibodies detected
HIV-1 (-)
HIV-2 (+)
HIV-2 antibodies detected
HIV-1 (+)
HIV-2 (+)
HIV antibodies detected
HIV-1 (-) or Indeterminate
HIV-2 (-)
HIV-1 NAT
HIV-1 NAT (+)
Acute HIV-1 infection
HIV-1 NAT (-)
Negative for HIV-1



Nucleic acid amplification testing (NAAT) is performed to detect HIV RNA.
Enzyme immunoassay (EIA) detect HIV antibody (2- and 3-generation EIA)
HIV antibody/antigen (fourth-generation EIA).

Diagn. tests 4th generation have a 2-3 week window period:

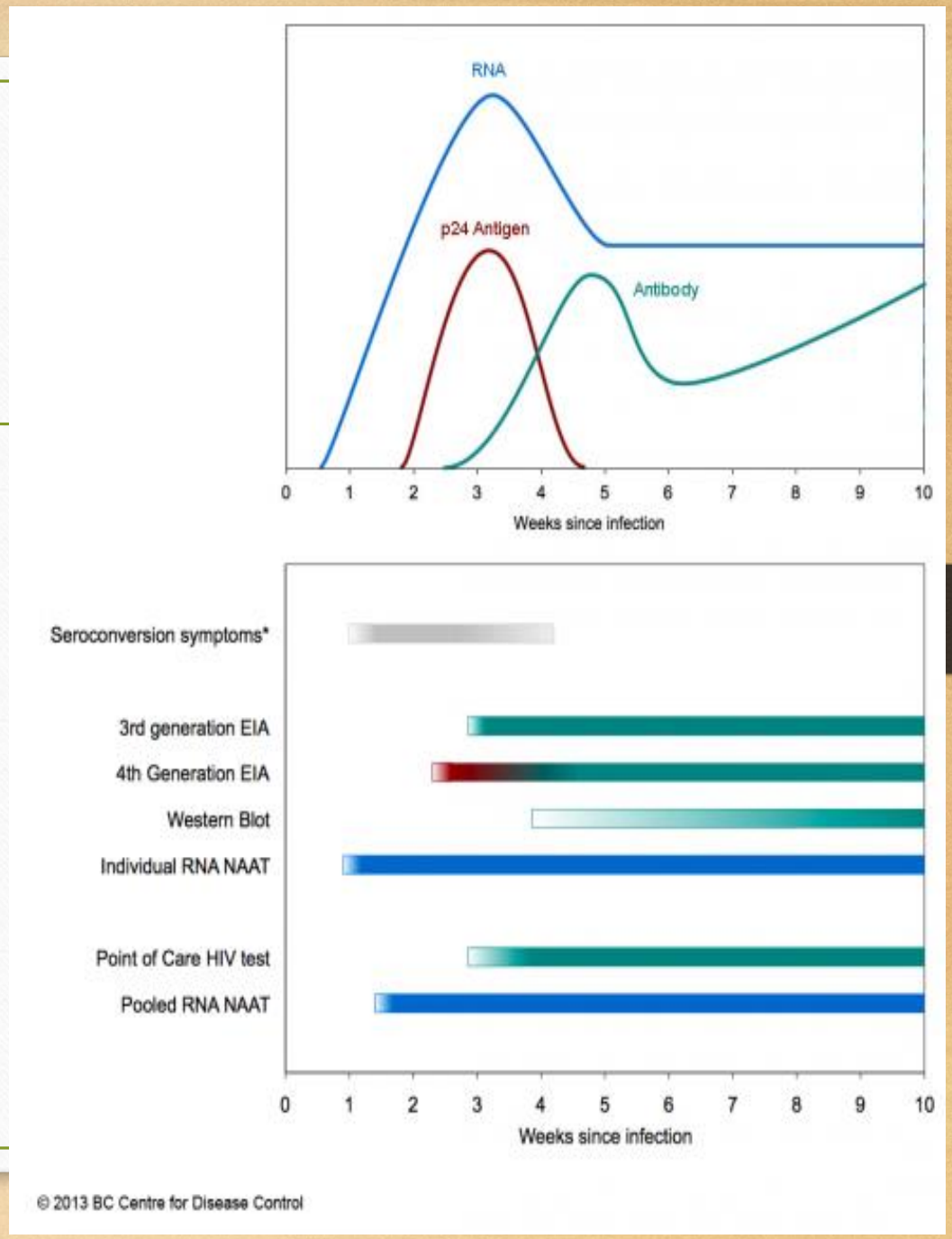
95% = detectable Ab by 4 to 6 weeks,
99% = by 3 months (as detected by Western Blot).

Pregnant women and male partners

- **At first antenatal care visit**
- **Re-test in third trimester or peripartum**

For the Group of risk & HIV-neg in serodiscordant couples:

- **offer re-testing every 6–12 mo**



Pediatric HIV infection

- **maternal Ab → cross placenta → may persist for up to 18 mo**
- **HIV in infants <18 mo → Virologic assays**

Definitive exclusion of HIV infection in non-breastfed infants:

- **2 or more neg virologic tests: one obtained at age ≥1 mo & one at ≥4 mo, or**
- **2 neg HIV Ab tests from separate specimens obtained at age ≥6 months**.

- Virologic diagnostic: **2- 4 weeks after cessation of ARV prophylaxis for infants**
- **A pos virologic test →confirmed by repeat virologic test on a second specimen**

HIV testing indications

Clinical signs or symptoms suggesting HIV infection
- Fever of unknown origin - Oral candidiasis - Chronic and/or recurrent skin problems (prurigo nodularis, psoriasis, etc.) - Unexplained lymphomegaly with or without fatigue or weight loss
Diagnoses suggesting increased risk for HIV infection
- Diagnosis of sexually transmitted diseases - Diagnosis of hepatitis B or C - Recurrent pneumonia - Tuberculosis - Opportunistic infections - Cervical or anal cancer - Lymphoma, Kaposi's sarcoma
Self-reported risk behaviors
- Injection drug users - Men who have sex with men - Unprotected vaginal or anal sex with a partner that might be infected with HIV - Unprotected vaginal or anal sex with more than one partner
Pregnant women
Occupational exposure

Natural History of HIV Infection

- **Rapid Progressors**

  5– 10%, AIDS 1-2 years

- **Intermediate Progressors**

  80-90%, Asymptomatic 5-8 years

- **Slow Progressors**

  5-10%,Good immune responses

  10-15 years, Rare

- **Long term non-progressors**
  - **HIV → AIDS = 8 - 10 years**
    - **~ 10% pts = 2 - 3 years**

WHO immunological classification for established HIV infection, 2007				
HIV-associated Immuno-deficiency	**Age-related CD4 values**			
	<11 months %CD4+	12–35 months %CD4+	36 –59 months %CD4+	**>5 years & adults absolute number or %CD4+**
None or not significant	>35	>30	>25	**>500**
Mild	30-35	25-30	20-25	**350-499**
Advanced	25-29	20-24	15-19	**200-349**
Severe *AIDS*	**<25**	**<20**	**<15**	**<200 or <15%**

WHO clinical staging for established HIV infection, 2007 :

- *Clinical stage 1*
- *Clinical stage 2*
- *Clinical stage 3*
- ***Clinical stage 4 = AIDS***

Adults and adolescents[a]	Children
Clinical stage 1	
Asymptomatic Persistent generalized lymphadenopathy	Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2	
Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Seborrhoeic dermatitis	Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) Herpes zoster Lineal gingival erythema Recurrent oral ulceration Papular pruritic eruption Fungal nail infections Extensive wart virus infection Extensive molluscum contagiosum Unexplained persistent parotid enlargement
Clinical stage 3	
Unexplained severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for longer than 1 month Unexplained persistent fever (intermittent or constant for longer than 1 month) Persistent oral candidiasis Oral hairy leukoplakia Pulmonary tuberculosis Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10^9/l) and/or chronic thrombocytopaenia (<50 x 10^9/l)	Unexplained moderate malnutrition[b] not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) Unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one 1 month) Persistent oral candidiasis (after first 6 weeks of life) Oral hairy leukoplakia Lymph node tuberculosis Pulmonary tuberculosis Severe recurrent bacterial pneumonia Acute necrotizing ulcerative gingivitis or periodontitis Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 10^9/l) or chronic thrombocytopaenia (<50 x 10^9/l)

Clinical stage 4[c]	
HIV wasting syndrome	Unexplained severe wasting, stunting or severe malnutrition[d] not responding to standard therapy
Pneumocystis (jirovecii) pneumonia	*Pneumocystis (jirovecii)* pneumonia
Recurrent severe bacterial pneumonia	Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site)	Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)	Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis	Extrapulmonary tuberculosis
Kaposi sarcoma	Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)	Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month)
Central nervous system toxoplasmosis	Central nervous system toxoplasmosis (after the neonatal period)
HIV encephalopathy	HIV encephalopathy
Extrapulmonary cryptococcosis, including meningitis	Extrapulmonary cryptococcosis, including meningitis
Disseminated nontuberculous mycobacterial infection	Disseminated nontuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis	Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis	Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)	Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
Lymphoma (cerebral or B-cell non-Hodgkin)	Lymphoma (cerebral or B-cell non-Hodgkin)
Symptomatic HIV-associated nephropathy or cardiomyopathy	HIV-associated nephropathy or cardiomyopathy
Recurrent septicaemia (including nontyphoidal *Salmonella*)	
Invasive cervical carcinoma	
Atypical disseminated leishmaniasis	

Additional: penicilliosis -Asia, HIV rectovaginal fistula -south Africa, reactivation trypanosomiasis -Latin America

Primary HIV infection

30% → asimptomathic

70% → acute retroviral syndrome

Diagnosis:

Exposure previous 2- 8 weeks (5–29 days)

&

clinical symptomatology

&

HIV detectabil in plasma
(p24 Ag+ or HIV-VL >1000 /mL)

&

serological test neg or weakly positive
ELISA neg or slightly poz & Western Blot ≤ 1 band

ART should be recommended while awaiting serologic confirmation.

Transient: Leucopenia, lymphopenia, trombocitopenia, ↓CD4 ↑CD8 , reversing T CD4+/T CD8+, Hypertransaminazemia

Clinicians should include acute HIV inf. in the dif. diagn. for *anyone* with:

- **flu- or mono-like illness, especially when the patient:**
  - **Presents with a rash**

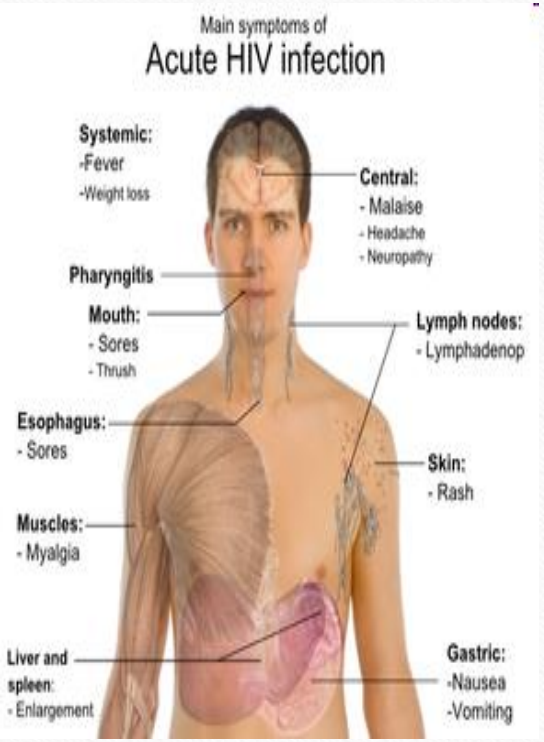
  - **Requests HIV testing**
  - **Reports recent risk for HIV infection**
  - **Presents with a newly diagnosed sexually transmitted infection**
  - **Presents with aseptic meningitis**
  - **Is pregnant or breastfeeding**
  - **Is currently on pre- or post-exposure prophylaxis (PrEP or PEP)**

Acute retroviral syndrome →mild disease, self-limiting

Main sympt. of acute HIV-1 inf.

Symptom	Frequency
Fever (38-40ºC) lymphadenopathy	80%
Rash (48-72h = 5-8d)	51%
Oral ulcers	37%
Arthralgia	54%
Pharyngitis	44%
Loss of appetite	54%
Weight loss >2.5 kg	32%
Malaise	68%
Myalgia	49%
Fever and rash	46%

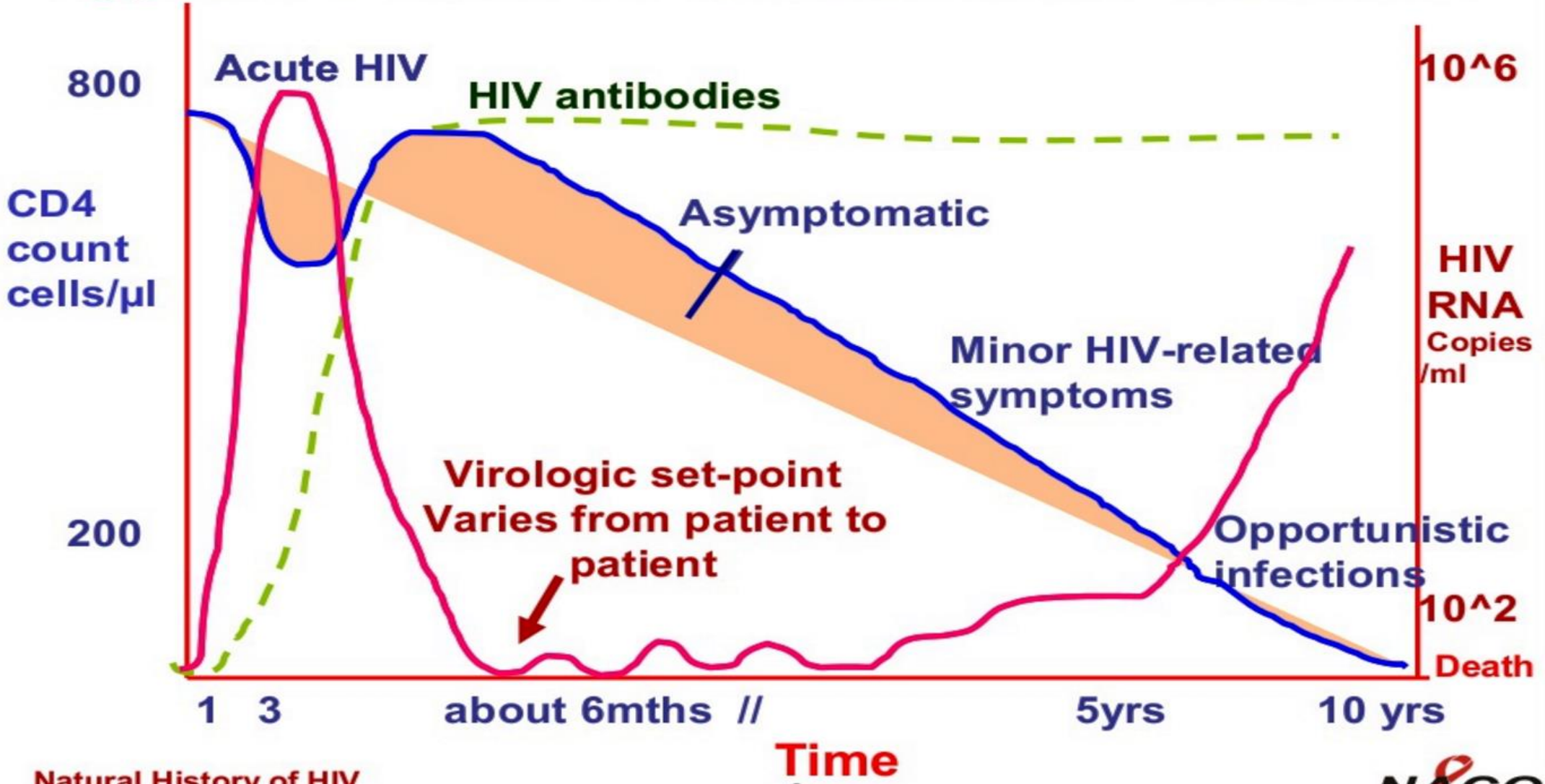
more severe sympt. during acute inf. and a longer duration = more rapidly to AIDS



Clinical syndroms:
- **Monolike**
- **Pseudoflu**
- **GI**
- **Neurolog.**

Duration 1- 4 weeks

Typical Course of Untreated HIV Infection



Natural History of HIV

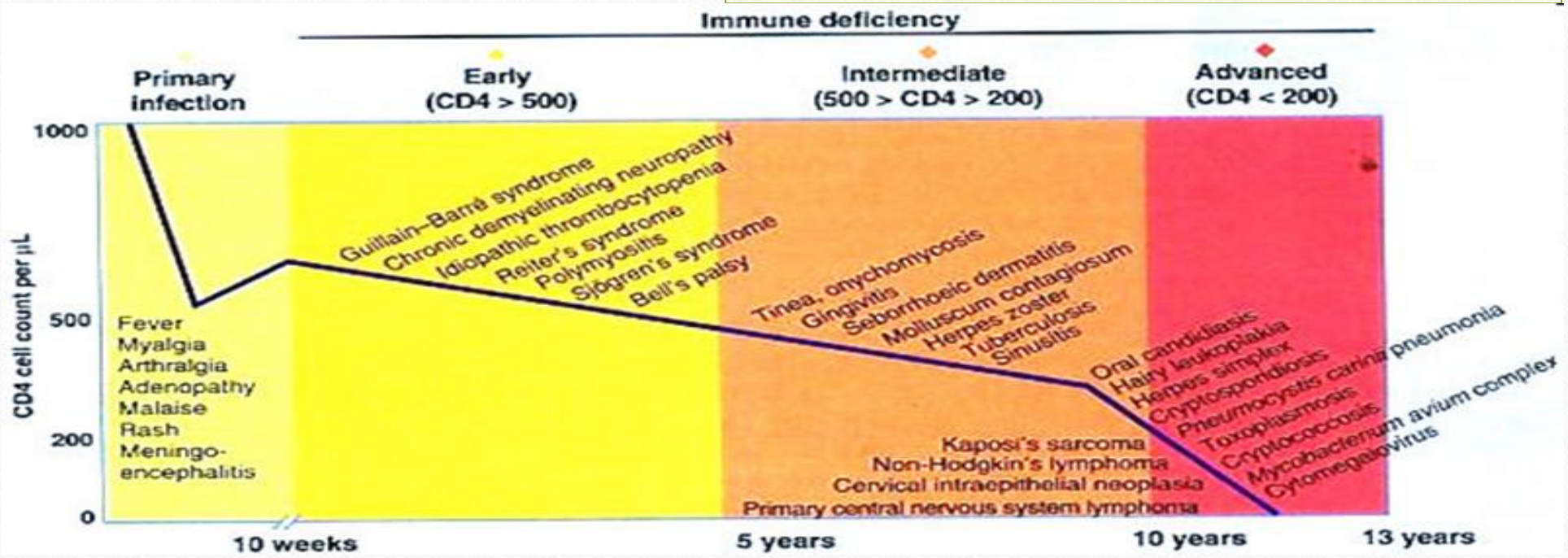
NACO

HIV doesn't kill anybody directly
HIV weakens the body's ability to fight disease.

"opportunistic" = take advantage of the weakened immune system

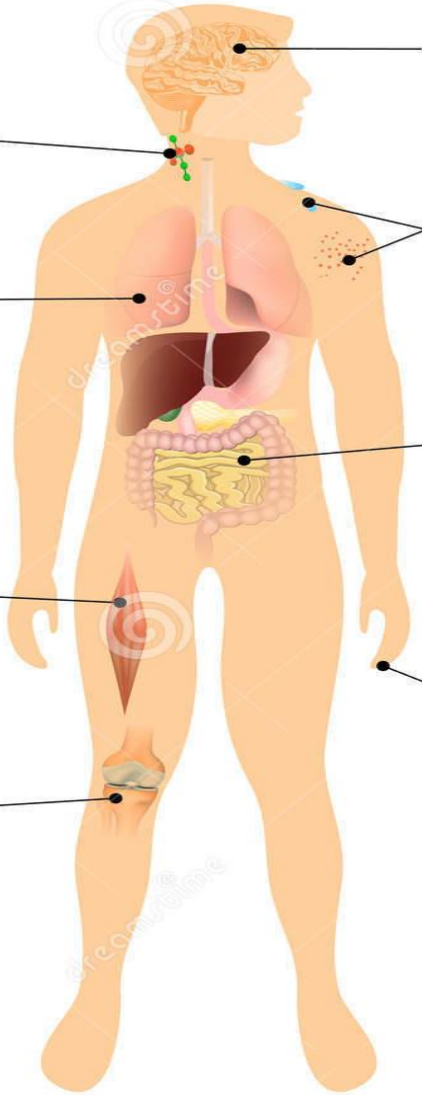
OIs = occur when *CD4 < 200* cells/mm^3.

OIs = most common cause of death



CD4/CD8 cell ratio = better picture of disease progression,
Normal ratio is about 1 to 1.5. Disease progression CD4/CD8 ratio <1

Symptoms of HIV infection



Lymph node
(swelling)

Respiratory system
- dry cough
- pneumonia
- sore throat

Muscle
- pain

Joints
- pain

Headache
and difficulty
concentrating

Skin
- rashes
- fever
- night sweats

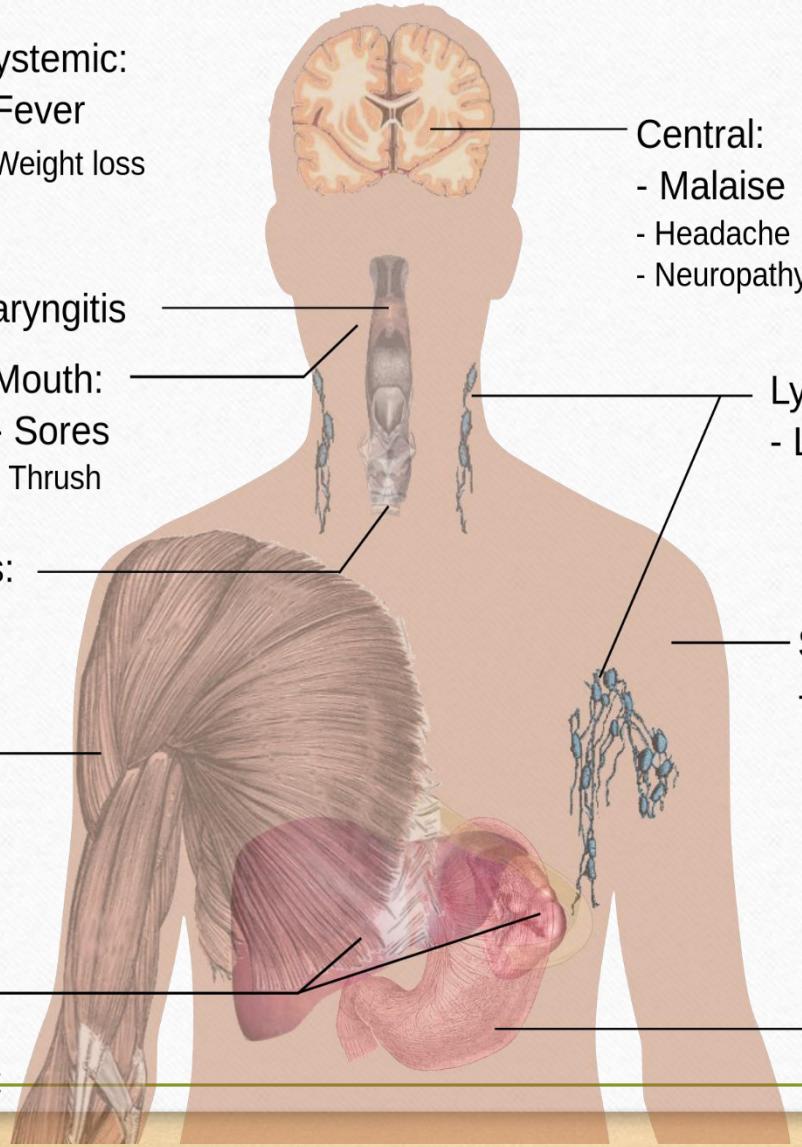
Digestive system
- nausea
- vomiting
- diarrhea

Nail
(thickening
and curving)

Weight loss
and fatigue

Main symptoms of

Acute HIV infection



Systemic:
- Fever
- Weight loss

Central:
- Malaise
- Headache
- Neuropathy

Pharyngitis

Mouth:
- Sores
- Thrush

Lymph nodes:
- Lymphadenopathy

Esophagus:
- Sores

Skin:
- Rash

Muscles:
- Myalgia

Liver and spleen:
- Enlargement

Gastric:
-Nausea
-Vomiting

Main symptoms of

AIDS

Central
- Encephalitis
- Meningitis

Eyes
- Retinitis

Lungs
- Pneumocystis pneumonia
- Tuberculosis (multiple organs)
- Tumors

Skin
- Tumors

Gastrointestinal
- Esophagitis
- Chronic diarrhea
- Tumors