

- **ORIGINAL ARTICLE**

Pneumocystis carinii Pneumonia and Mucosal Candidiasis in Previously Healthy Homosexual Men — Evidence of a New Acquired Cellular Immunodeficiency

Michael S. Gottlieb, M.D., Robert Schroff, Ph.D., Howard M. Schanker, M.D., Joel D. Weisman, D.O., Peng Thim Fan, M.D., Robert A. Wolf, M.D., and Andrew Saxon, M.D.

***N Engl J Med* 1981; 305:1425-1431 December 10, 1981**

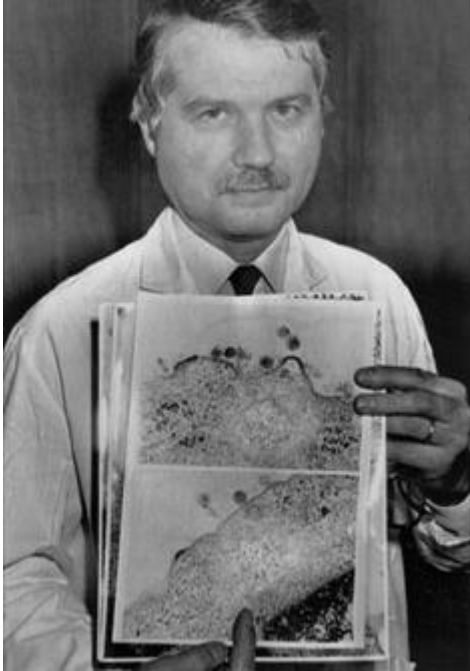
- **ORIGINAL ARTICLE**

An Outbreak of Community-Acquired *Pneumocystis carinii* Pneumonia — Initial Manifestation of Cellular Immune Dysfunction

Henry Masur, M.D., Mary Ann Michelis, M.D., Jeffrey B. Greene, M.D., Ida Onorato, M.D., Robert A. Vande Stouwe, M.D., Ph.D., Robert S. Holzman, M.D., Gary Wormser, M.D., Lee Brettman, M.D., Michael Lange, M.D., Henry W. Murray, M.D., and Susanna Cunningham-Rundles, Ph.D.

***N Engl J Med* 1981; 305:1431-1438 December 10, 1981**

HIV-AIDS 1981



Luc Montagnier (1983)

- [Science](#). 1983 May 20;220(4599):868-71.
- **Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS).**
- [Barré-Sinoussi F](#), [Chermann JC](#), [Rey F](#), [Nugeyre MT](#), [Chamaret S](#), [Gruest J](#), [Dauguet C](#), [Axler-Blin C](#), [Vézinet-Brun F](#), [Rouzioux C](#), [Rozenbaum W](#), [Montagnier L](#).
- **Abstract**
- A retrovirus belonging to the family of recently discovered human T-cell leukemia viruses (HTLV), but clearly distinct from each previous isolate, has been isolated from a Caucasian patient with signs and symptoms that often precede the acquired immune deficiency syndrome (AIDS). This virus is a typical type-C RNA tumor virus, buds from the cell membrane, prefers magnesium for reverse transcriptase activity, and has an internal antigen (p25) similar to HTLV p24. Antibodies from serum of this patient react with proteins from viruses of the HTLV-I subgroup, but type-specific antisera to HTLV-I do not precipitate proteins of the new isolate. The virus from this patient has been transmitted into cord blood lymphocytes, and the virus produced by these cells is similar to the original isolate. From these studies it is concluded that this virus as well as the previous HTLV isolates belong to a general family of T-lymphotropic retroviruses that are horizontally transmitted in humans and may be involved in several pathological syndromes, including AIDS.

The Nobel Prize in Physiology or Medicine 2008
Harald zur Hausen, Françoise Barré-Sinoussi, Luc Montagnier

[The Nobel Prize in Physiology or Medicine 2008](#)
[Nobel Prize Award Ceremony](#)
[Harald zur Hausen](#)
[Françoise Barré-Sinoussi](#)
[Luc Montagnier](#)



Photo: U. Montan



Photo: U. Montan



The Nobel Prize in Physiology or Medicine 2008 was divided, one half awarded to Harald zur Hausen "*for his discovery of human papilloma viruses causing cervical cancer*", the other half jointly to Françoise Barré-Sinoussi and Luc Montagnier "***for their discovery of human immunodeficiency virus***"

Science. 2009 Jan 9;323(5911):206-7. doi:
10.1126/science.323.5911.206.

Unsung hero Robert C. Gallo.

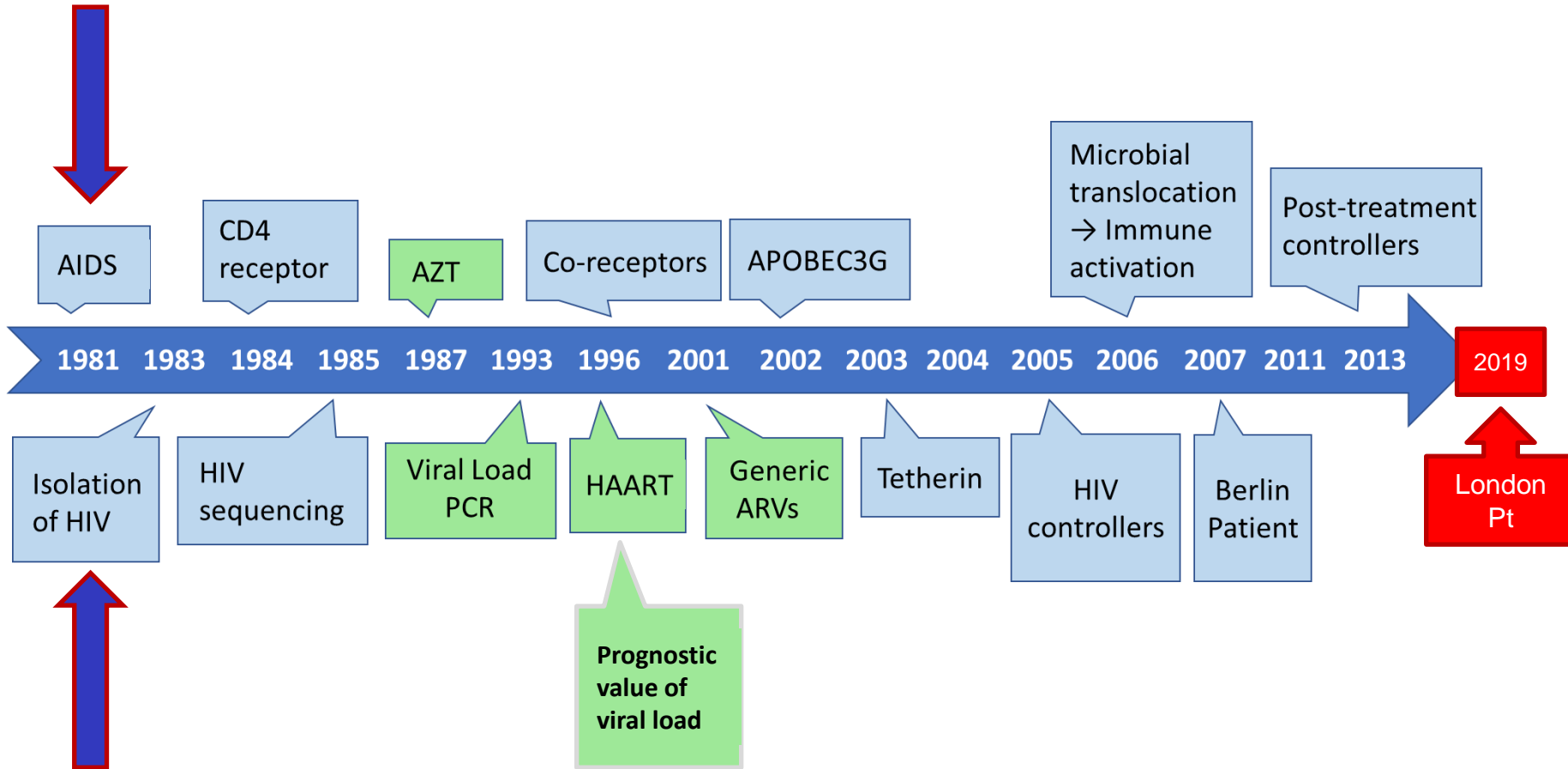
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Data on the size of the HIV/AIDS epidemic in 2017 (source WHO - May 2019)

Country or WHO region	Number of people living with HIV	Number of death/year	Number of new infections/year	Number/1000 uninfected
Europe	2.300.000	37.000	160.000	0,18
Italy	130.000	560	2.700	0,05
Africa	25.700.000	670.000	1.200.000	1,22

MILESTONES IN HIV-AIDS RESEARCH (VIROLOGICAL, DIAGNOSTIC AND PATHOGENETIC ISSUES)



HIV Cure

Timothy Ray Brown and the London patient shared similar medical circumstances.

They were both HIV-1-positive and receiving ART therapy.

They both eventually developed a blood cancer (acute myeloid leukemia and Hodgkin's lymphoma, respectively), which was treated with chemotherapy and various other therapeutics.

Both ultimately required a bone marrow transplant to replenish the blood stem cells that had been destroyed during chemotherapy. In both cases, doctors used bone marrow cells from a donor who was homozygous for a mutation in the gene encoding the HIV co-receptor CCR5 (CCR5 $\Delta 32/\Delta 32$), because this genotype confers resistance to HIV-1 infection. Both patients were cured of their cancer.

Both patients were also cured of their HIV infection, as evidenced by the absence of virus in their blood many months after termination of ART.

Human immunodeficiency virus (HIV)

Taxonomic Classification

Retroviridae

Subfamilia	Genera	Examples
Orthoretrovirinae	Alpharetrovirus	Avian leukosis virus (ALV) Rous sarcoma virus
	Betaretrovirus	Mouse mammary tumor virus (MMTV) Mason-Pfizer monkey virus (M-PMV) Jaagsiekte sheep retrovirus
	Gammaretrovirus	Murine leukemia viruses (MuLV) Feline leukemia virus (FeLV) Gibbon ape leukemia virus (GALV) Reticuloendotheliosis virus (RevT)
	Deltaretrovirus	HTLV-1, -2 Bovine leukemia virus (BLV) STLV-1, -2, -3
	Epsilonretrovirus	Walleye dermal sarcoma virus Walleye epidermal hyperplasia virus 1
	Lentivirus	Human immunodeficiency virus (HIV) type 1 Human immunodeficiency virus type 2 (HIV-2) Simian immunodeficiency virus (SIV) Equine infectious anemia virus (EIAV) Feline immunodeficiency virus (FIV) Caprine arthritis encephalitis virus (CAEV) Visna maedi virus
Spumaretrovirinae	Spumavirus	Human foamy virus

Lentiviruses

Species for viral isolation	Virus	Disease
Non-primate Sheep Goat Horse Cattle Cat	Maedi-visna Caprine Arthritis Encephalitis Equine infectious anemia Bovine immunodeficiency virus Feline immunodeficiency virus	Pneumonia, SNC Arthritis, encephalitis Anemia Feline AIDS
Non-human Primates Chimpanzees Sooty mangabey Macaque African green monkey Sykes monkeys Mandrill Hoest monkey	SIV _{cpz} SIV _{sm} SIV _{mac} SIV _{agm} SIV _{syk} SIV _{mnd} SIV _{hoest}	no development of immunodeficiency in the natural hosts of the virus African primates represent a great reservoir for lentiviruses*
Human	HIV-1 (SIV _{cpz})** HIV-2 (SIV _{sm})***	AIDS

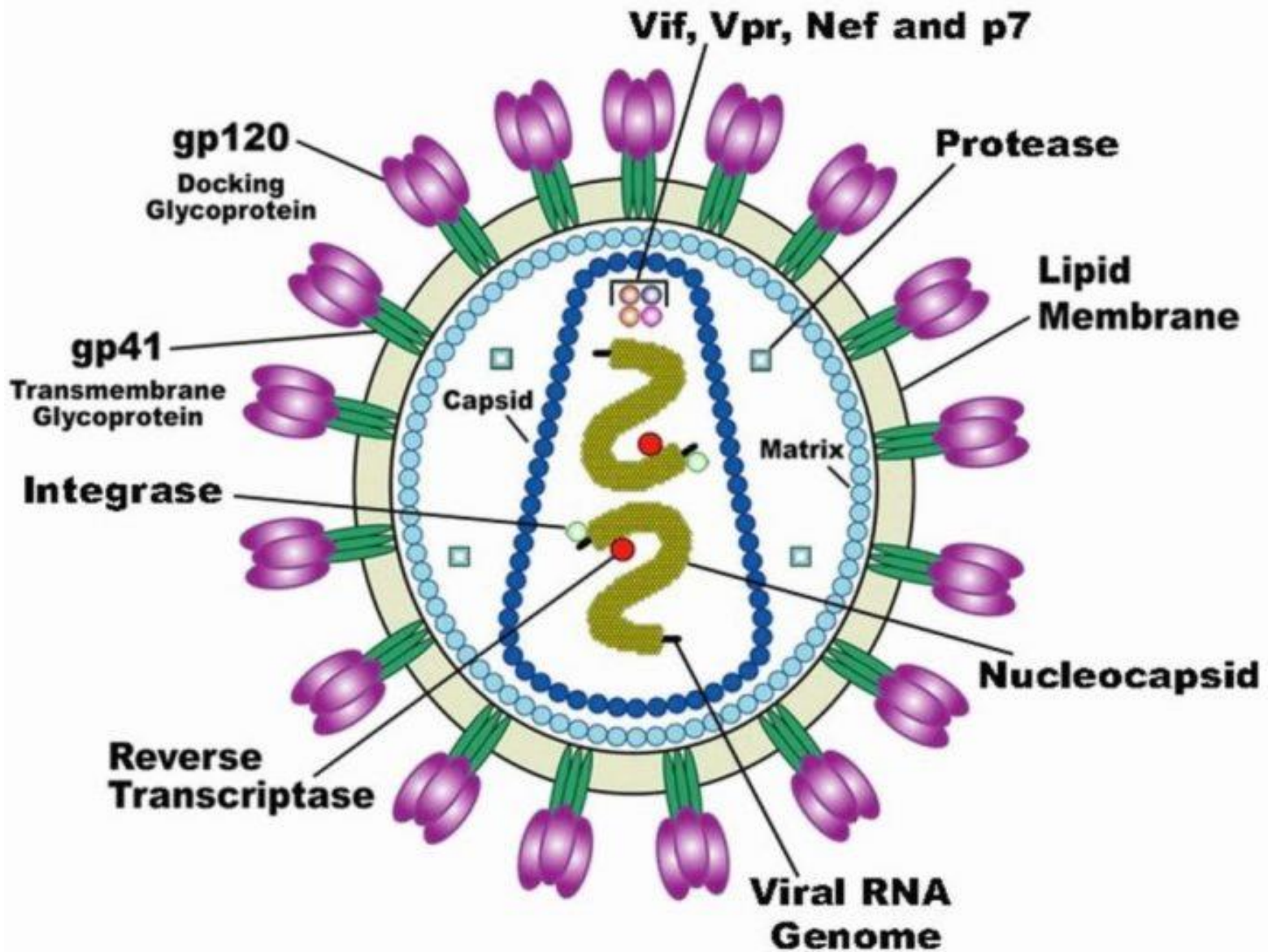
*Accidental infection of primates with viruses whose natural hosts are members of different animal species may occur

**HIV-1 is closely related to SIV_{cpz} isolated from chimpanzee (*Pan troglodytes troglodytes*)

*** HIV-2 is closely related to SIV_{sm} isolated from Sooty mangabey

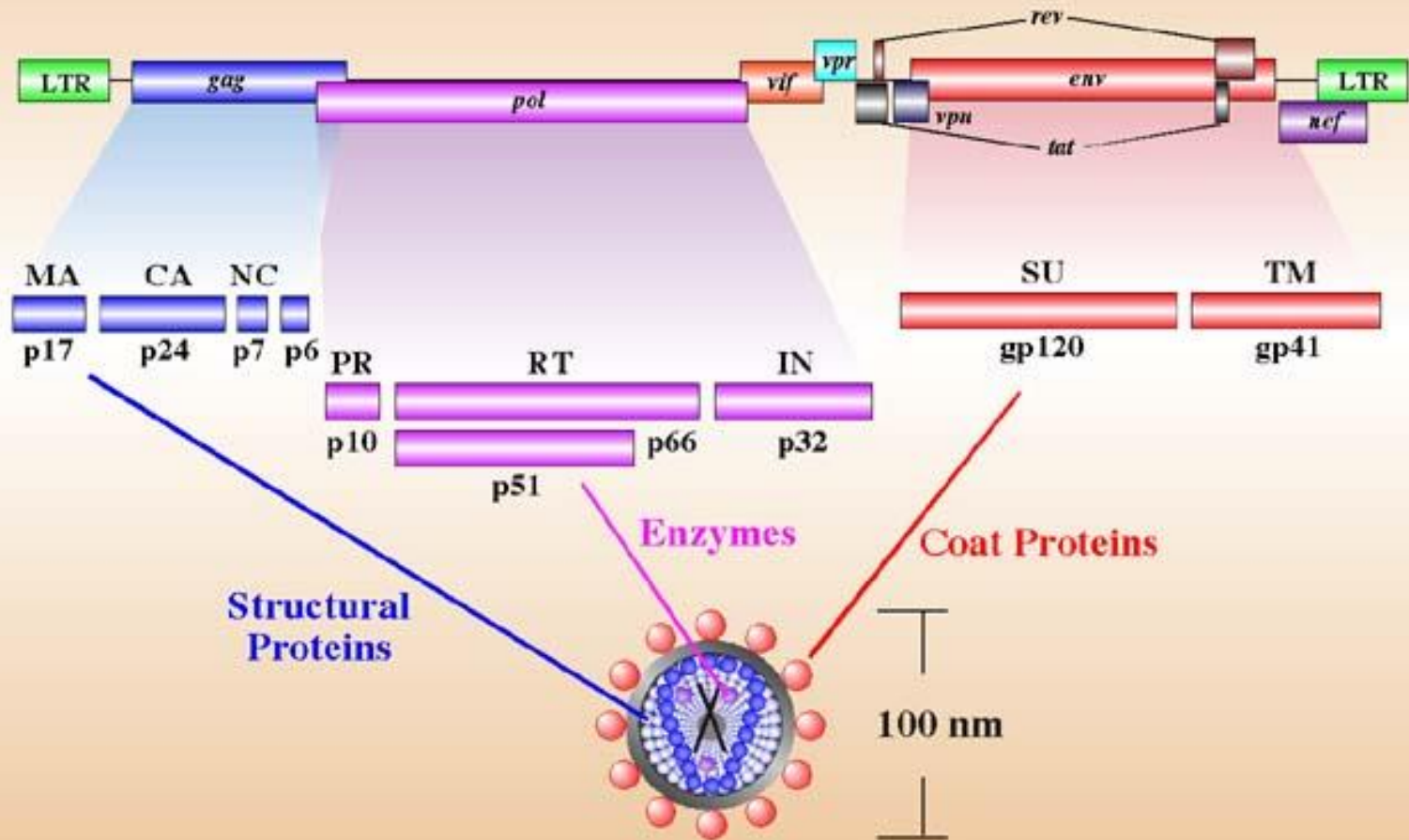
ETIOLOGY

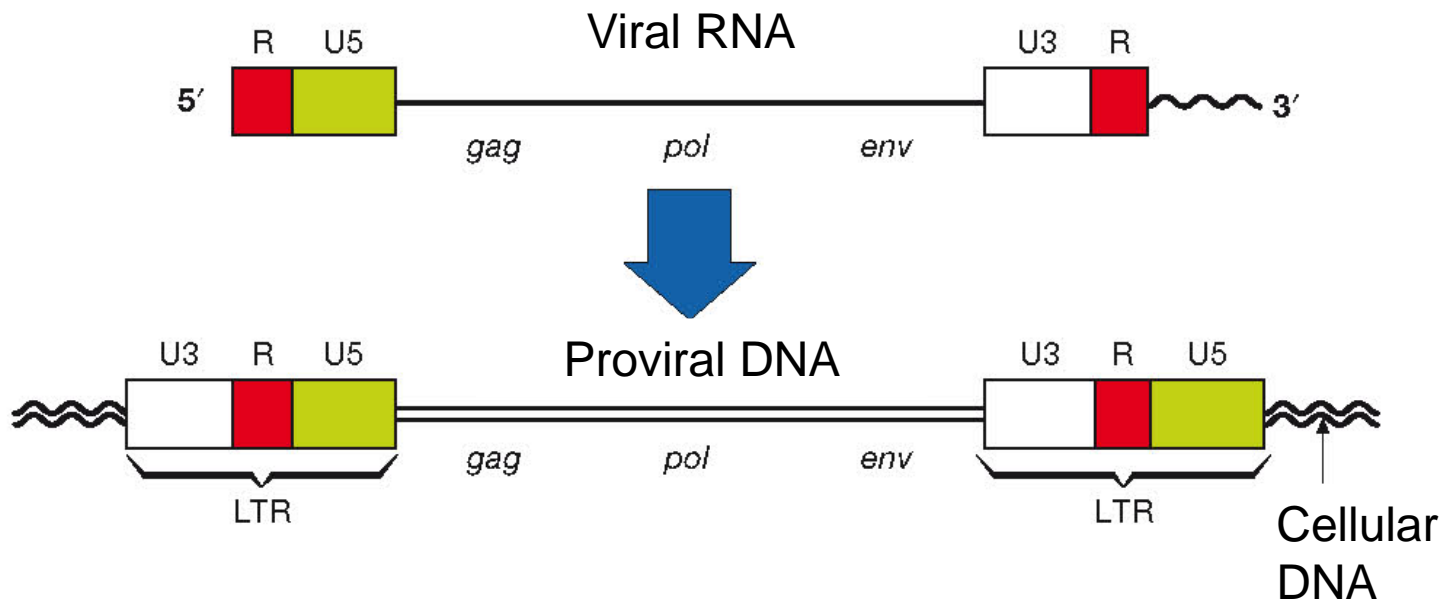
HIV STRUCTURE



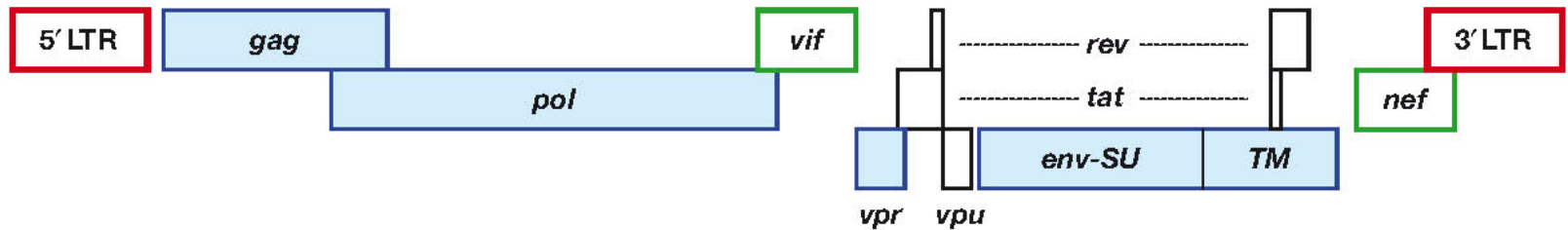


Genomic Organization of HIV-1

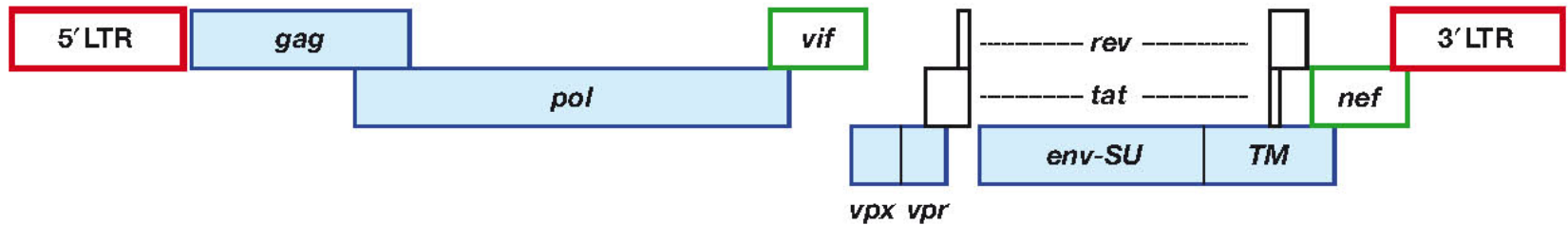




HIV-1



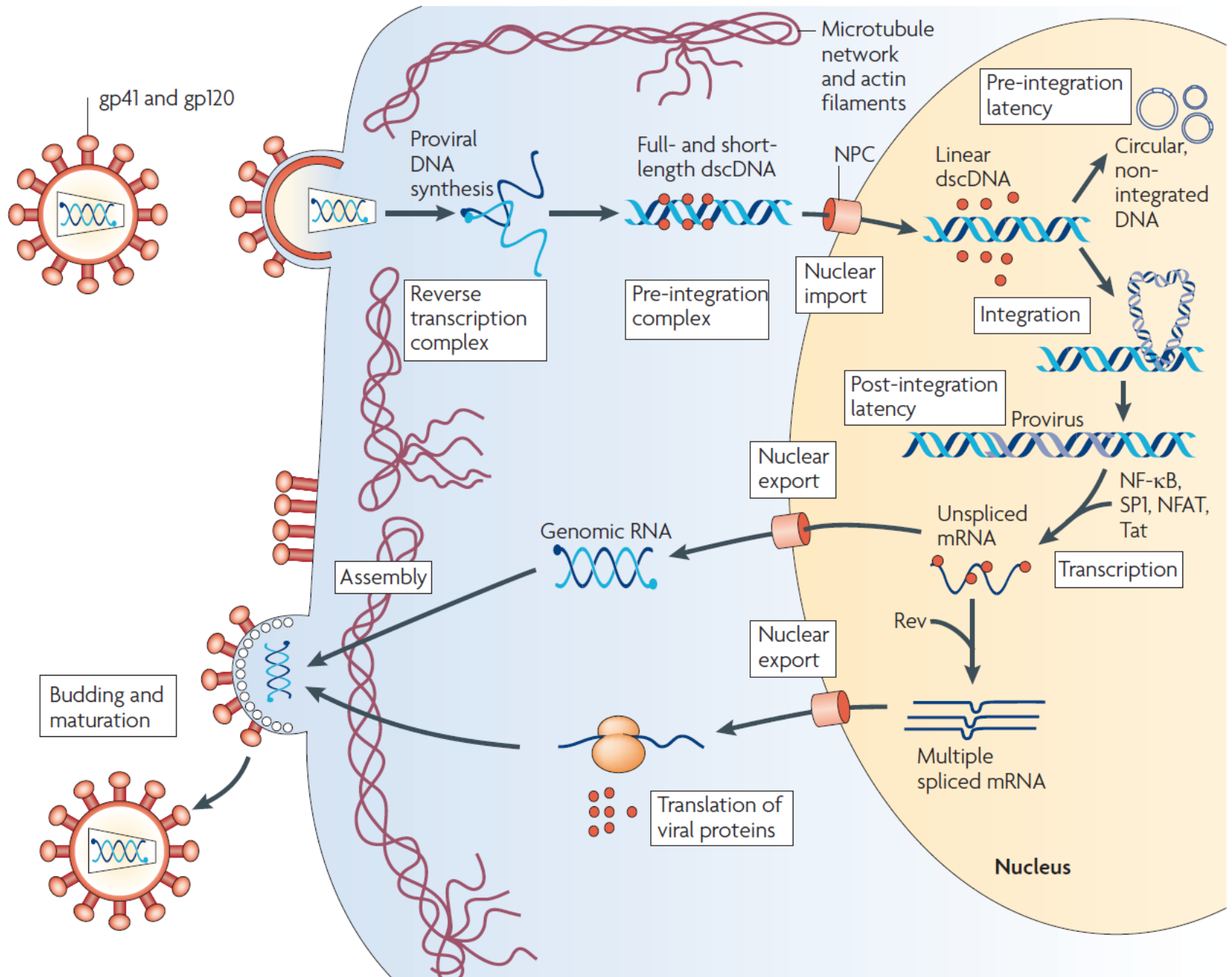
HIV-2 / SIV_{MAC}

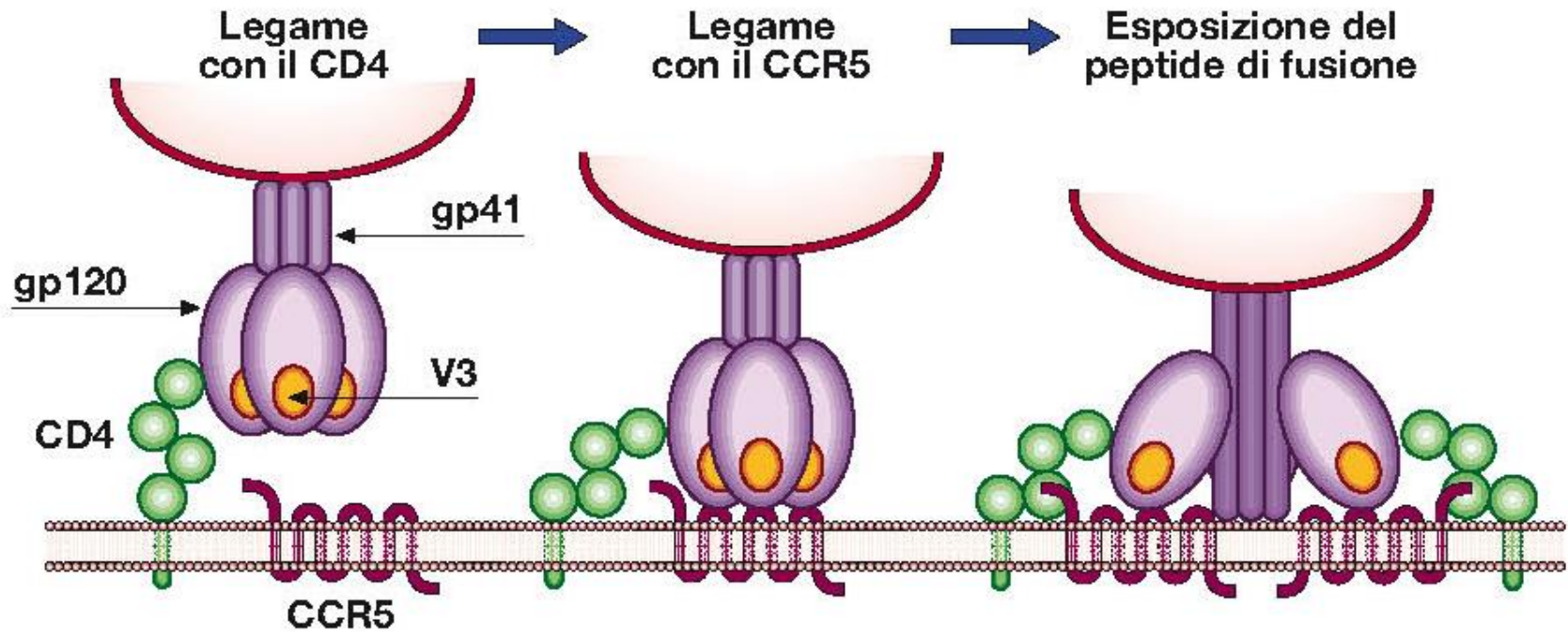


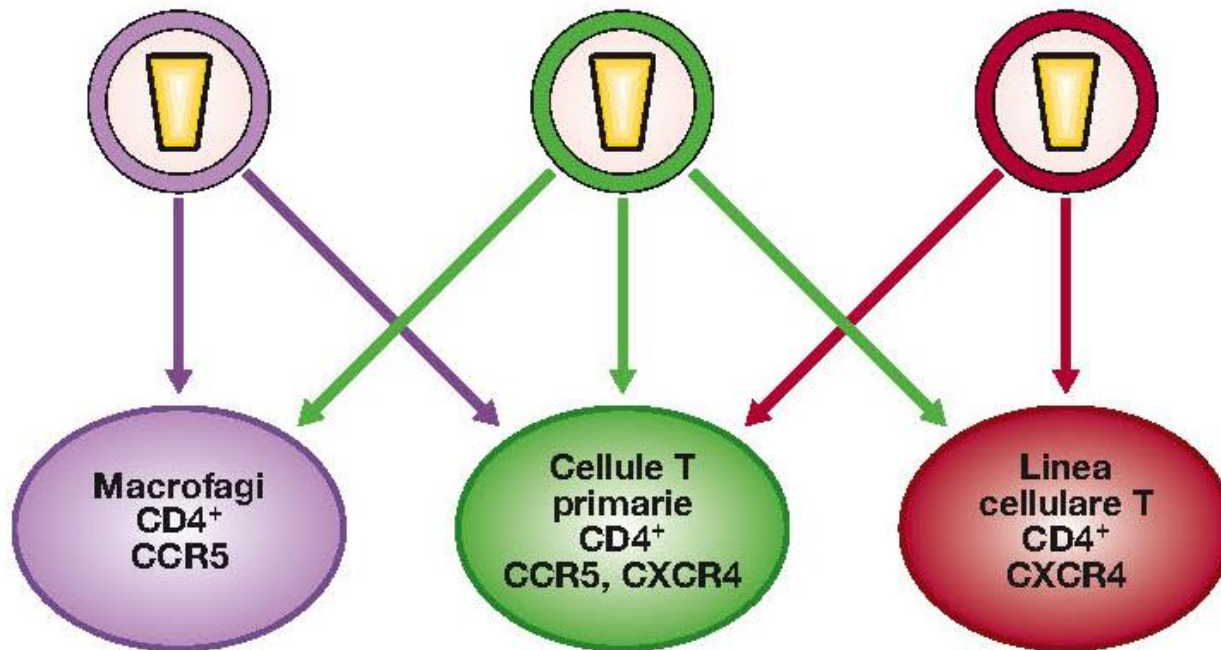
HIV genes and proteins

Genes	Proteins	Functions	Location
Structural			
gag	P55	Polyprotein precursor of the viral core proteins (MA, CA, NC, p7)	Nucleocapsid
pol	P160	Polyprotein precursor of viral enzymes (PR, RT/RNase H, IN)	Virion
env	gp160	Polyprotein precursor of envelope glycoproteins (SU, TM)	Envelope,
Regulators			
tat	p14	Transcriptional transactivation, it binds to TAR and cellular factors	Especially in the cell nucleus
rev	p19	Post-transcriptional transactivation, it binds to RRE and cellular factors, promotes the export of viral RNA from the nucleus	Especially in the cell nucleus
nef	p27	It increases viral infectivity, down-regulates CD4, influence T cells activation	Cell cytoplasm, plasma membrane
vif	p23	Viral infectivity factor	Cell cytoplasm
vpr	P15	Transport of preintegration complex into the nucleus	Virion
vpu	p16	It influence the release of the virus, increases the turnover of CD4	Integral plasma membrane protein

Legend: MA, matrix protein; CA, capsid protein (p24); NC, nucleocapsid protein; PR, protease; RT/RNase H, reverse transcriptase/RNase H; IN, integrase; SU, surface glycoprotein (gp120); TM, transmembrane protein (gp41)







HIV Cure

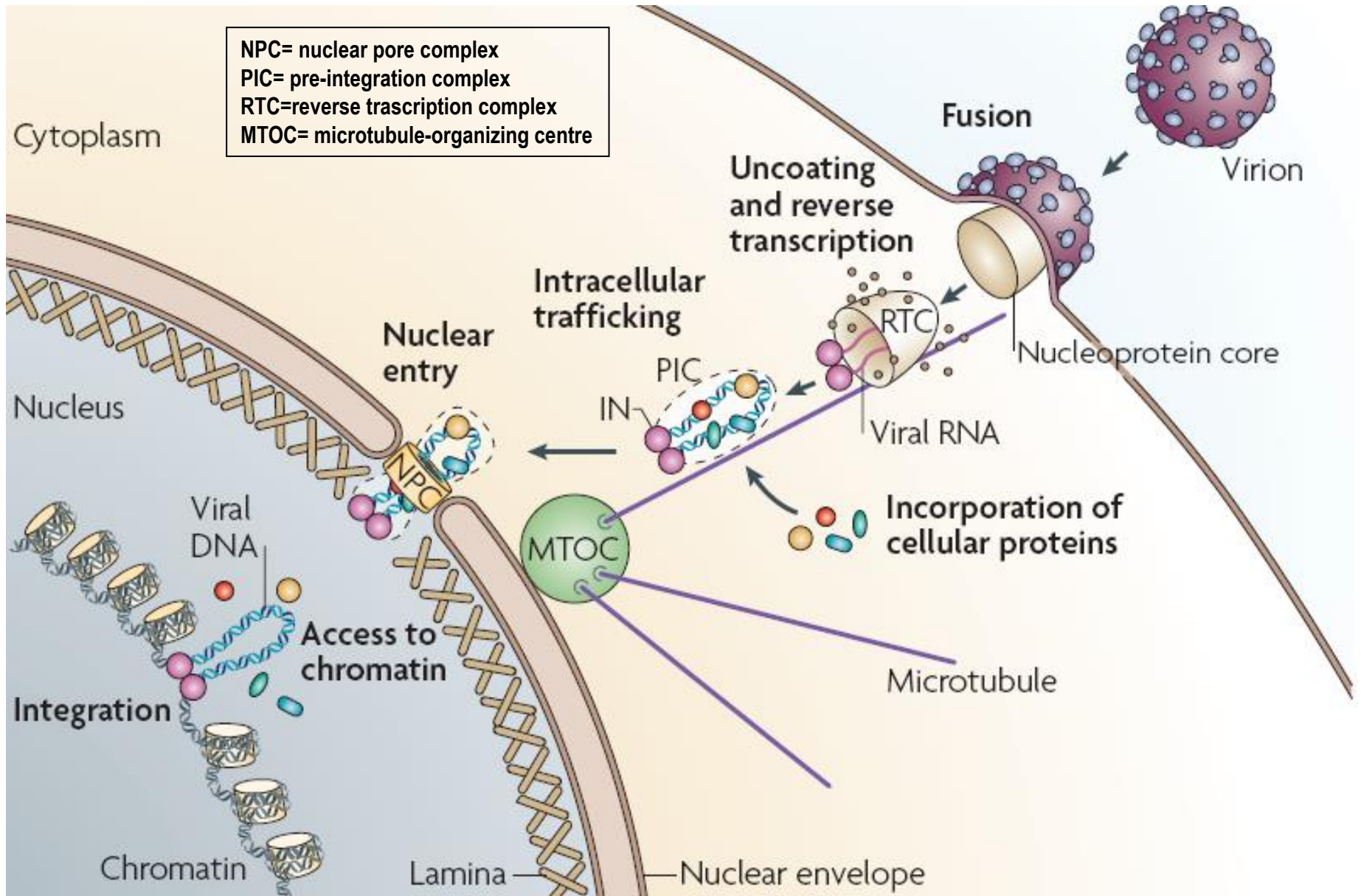
Timothy Ray Brown and the London patient shared similar medical circumstances.

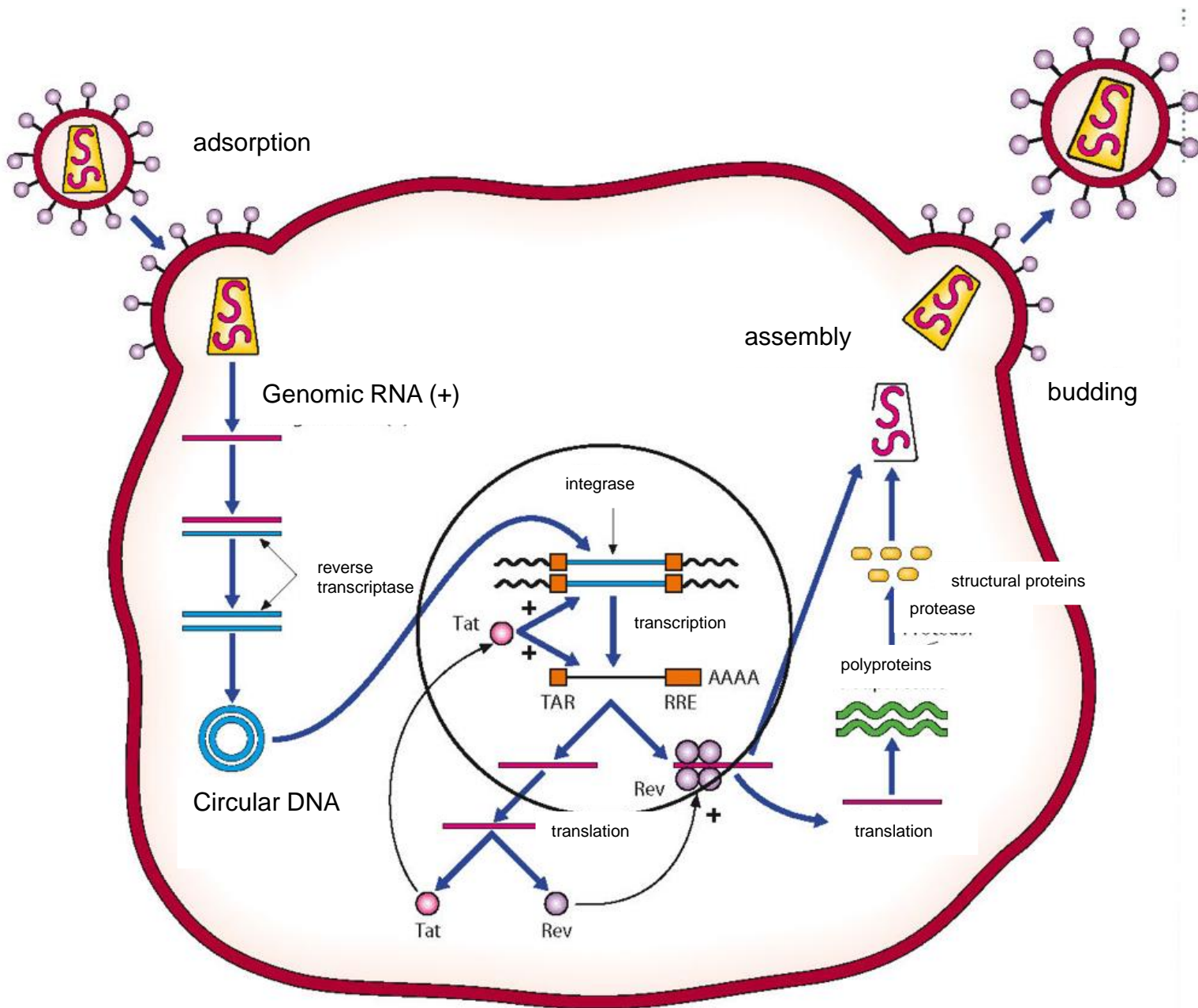
They were both HIV-1-positive and receiving ART therapy.

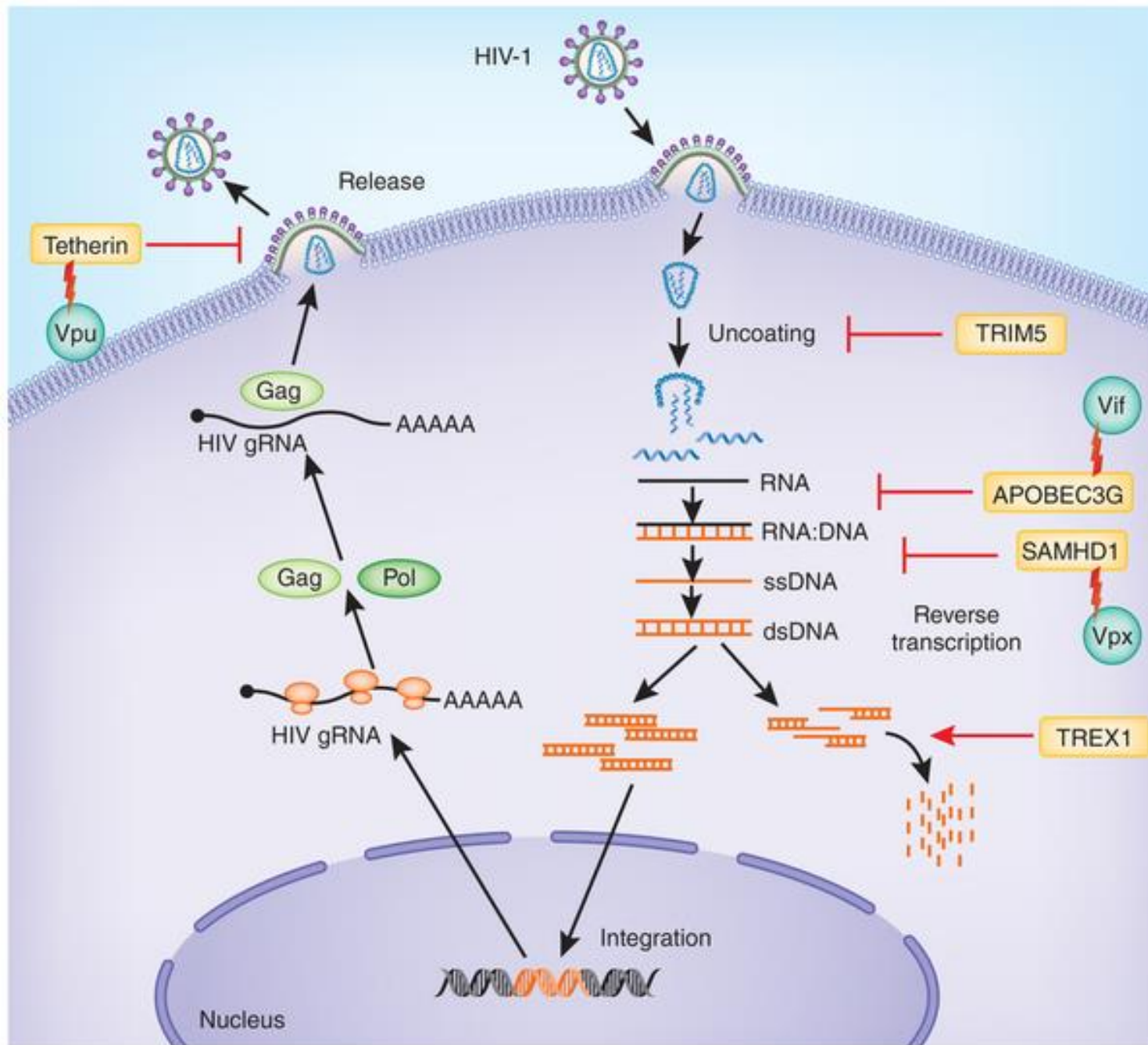
They both eventually developed a blood cancer (acute myeloid leukemia and Hodgkin's lymphoma, respectively), which was treated with chemotherapy and various other therapeutics.

Both ultimately required a bone marrow transplant to replenish the blood stem cells that had been destroyed during chemotherapy. In both cases, doctors used bone marrow cells from a donor who **was homozygous for a mutation in the gene encoding the HIV co-receptor CCR5 (CCR5 $\Delta 32/\Delta 32$)**, because this genotype confers resistance to HIV-1 infection. Both patients were cured of their cancer.

Both patients were also cured of their HIV infection, as evidenced by the absence of virus in their blood many months after termination of ART.







HIV CLASSIFICATION

HIV-1

HIV-2

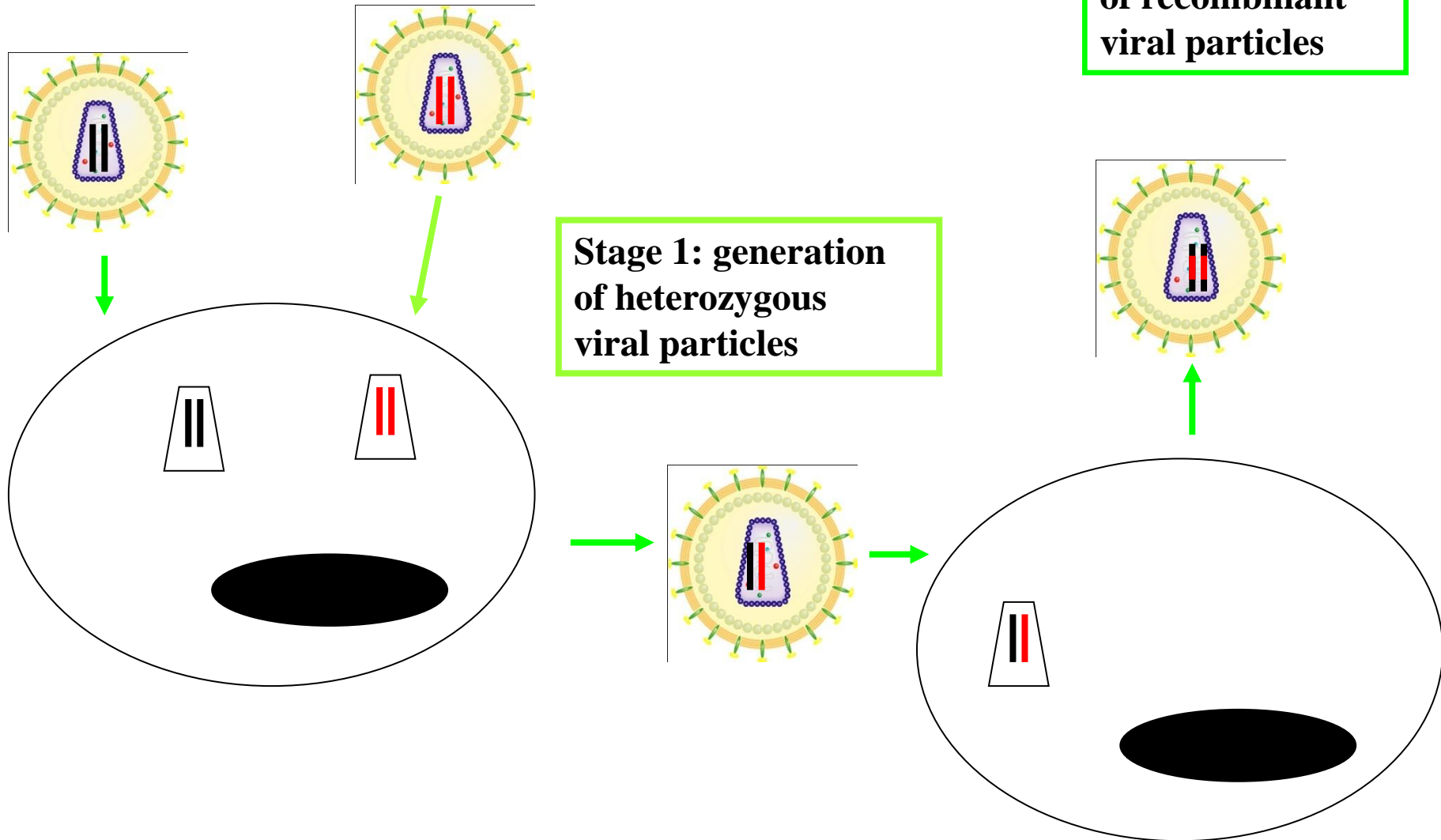
- Group M of HIV-1

- Group M of HIV-2

- Group O of HIV-1

- Group N of HIV-1

POSSIBLE MOLECULAR MECHANISMS ASSOCIATED WITH THE DEVELOPMENT OF RECOMBINANT STRAINS OF HIV (CRF-HIV)



HIV CLASSIFICATION



HIV-1

HIV-2

- **Group M of HIV-1**

9 subtypes: **A, B, C, D, F, G, H, J E and K**
4 sub- subtypes : **A1, A2 and F1, F2**

Circulating recombinant forms (CRF)
Subtype E = CRF

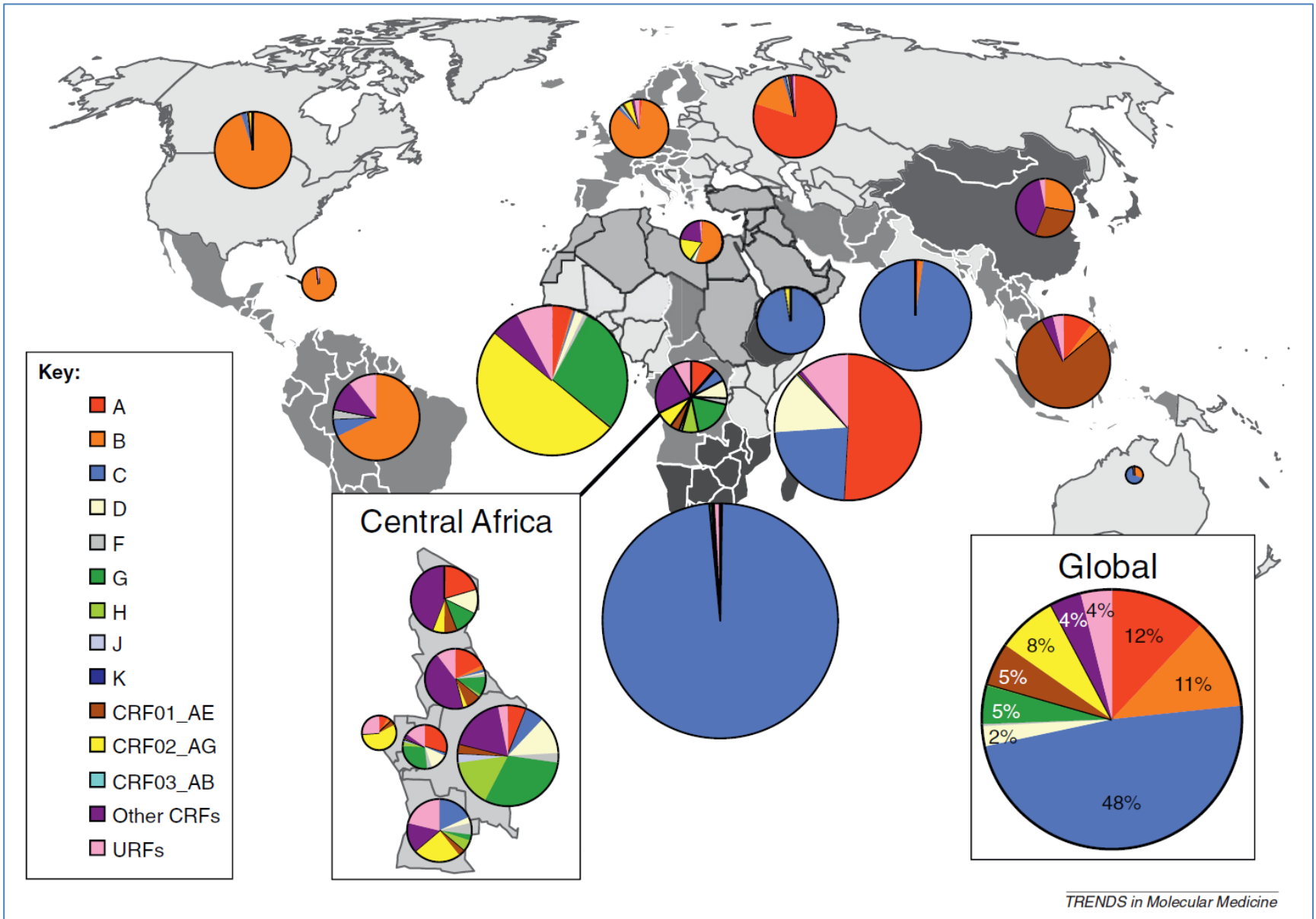
- **Group O of HIV-1**

- **Group N of HIV-1**

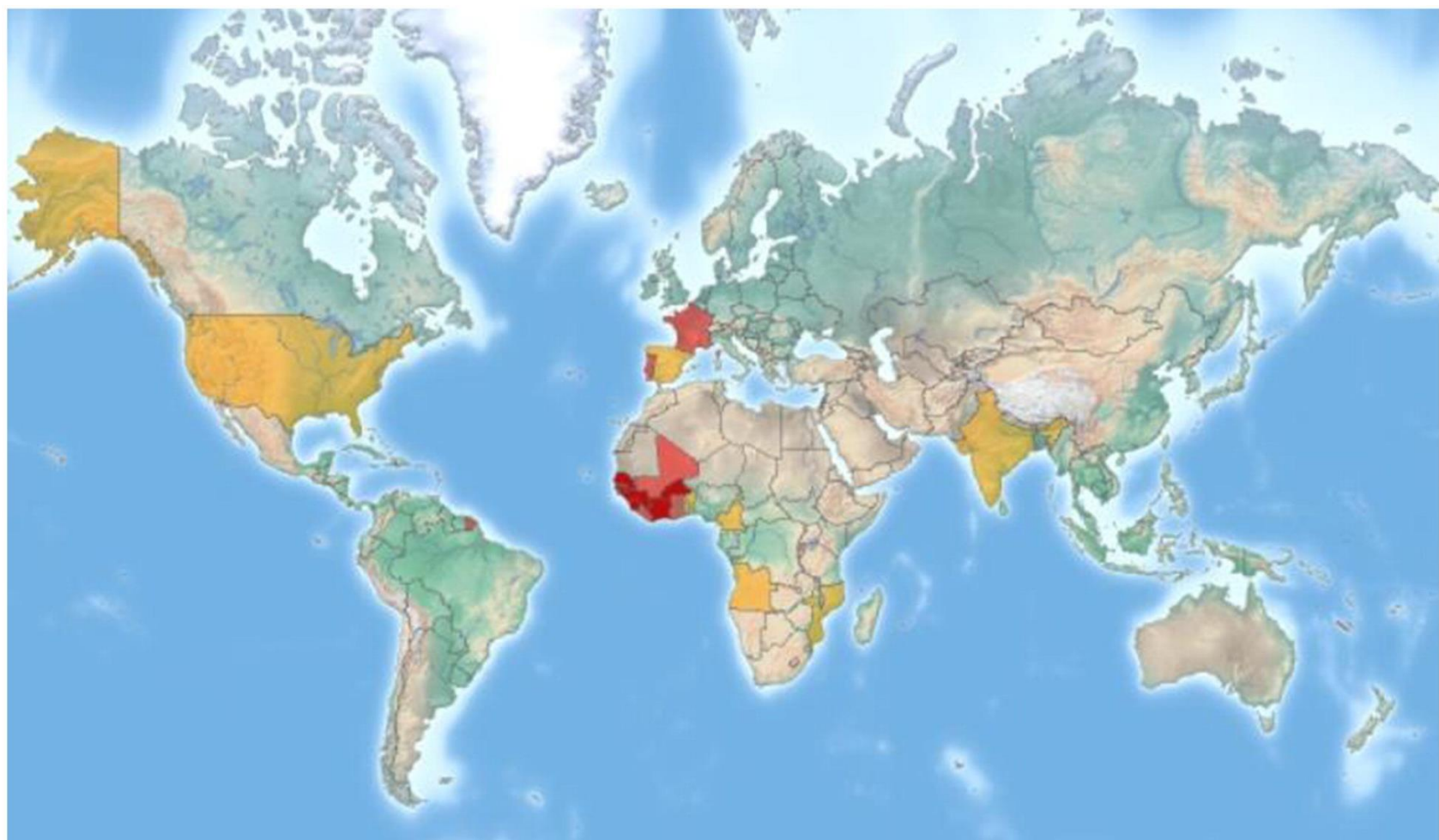
- **Group M of HIV-2**

5 subtypes : **A, B, C, D, E,**

Geographic distribution of HIV-1 groups and subtypes



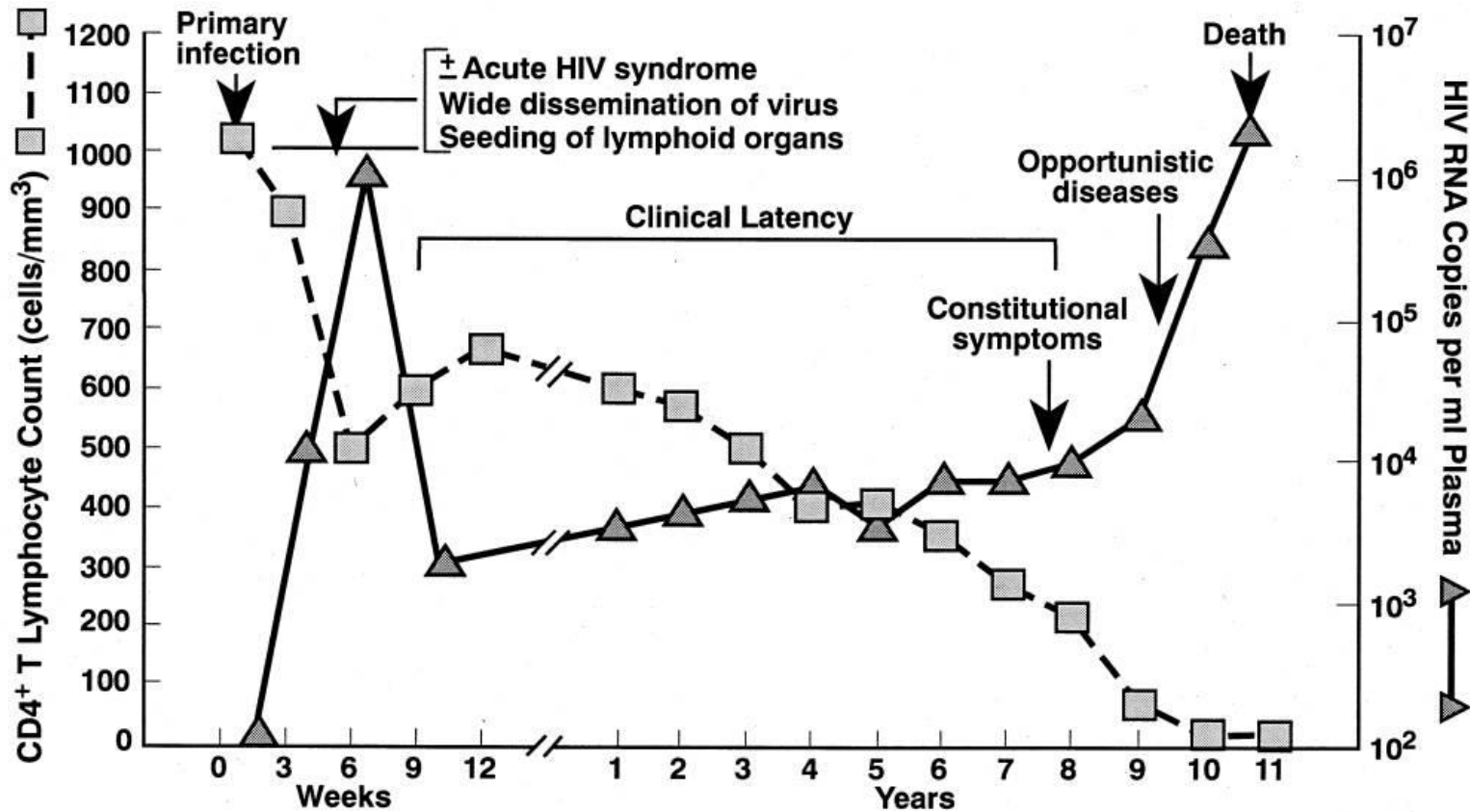
TRENDS in Molecular Medicine



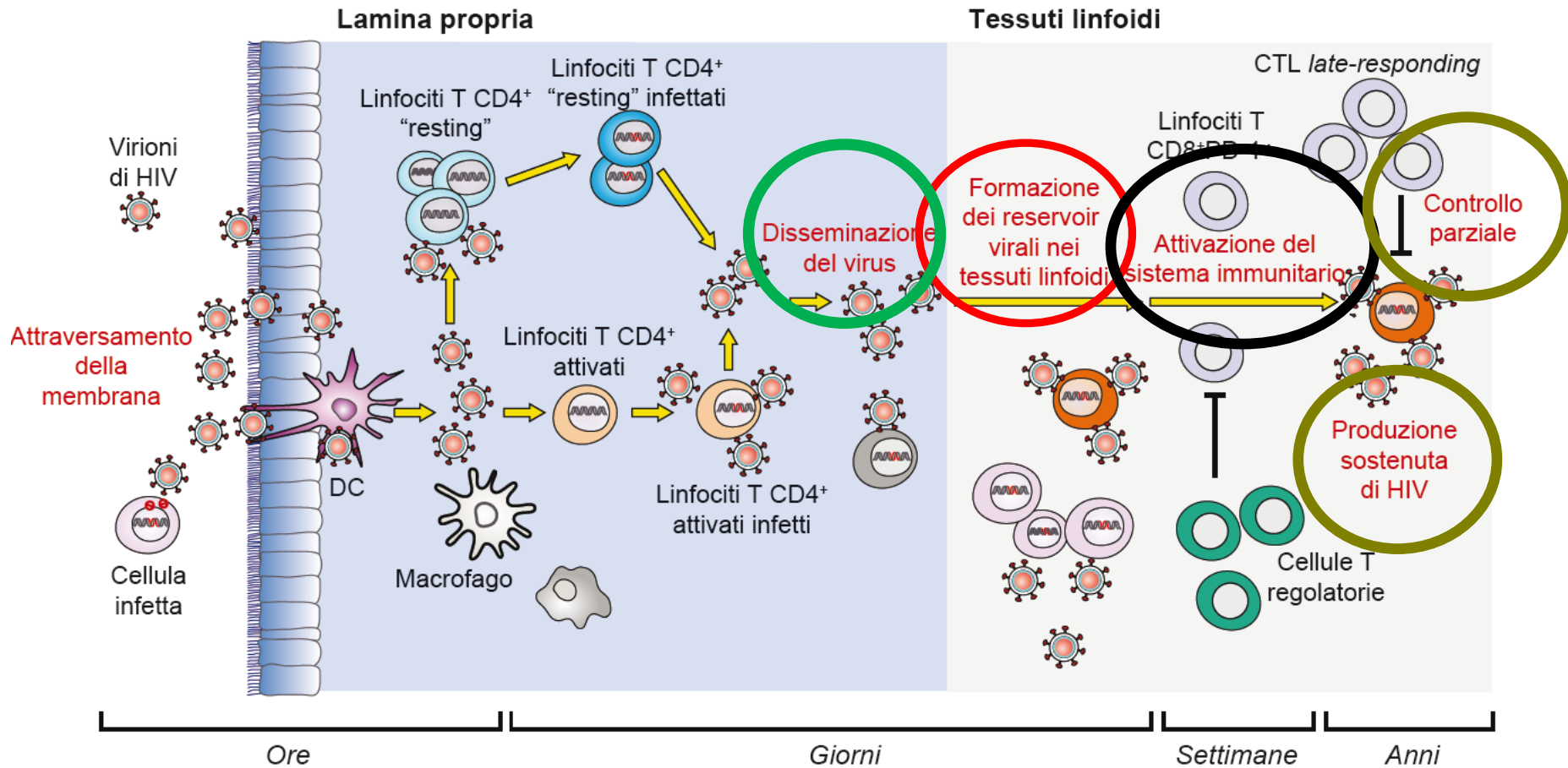
CHARACTERISTICS	HIV-1	HIV-2
<i>Infectivity</i>	High	Low
<i>Virulence</i>	High	Low
<i>Heterosexual Spread</i>	Higher	Lower
<i>Vertical Transmission</i>	20-25%	≤5%
<i>Genetic Diversity</i>	–	Lower
<i>Prevalence</i>	Global	West Africa
<i>Origin</i>	Common Chimpanzee	Sooty Mangabey
<i>Time to Aids</i>	≤10 Years	≥20 Years

Pathogenesis

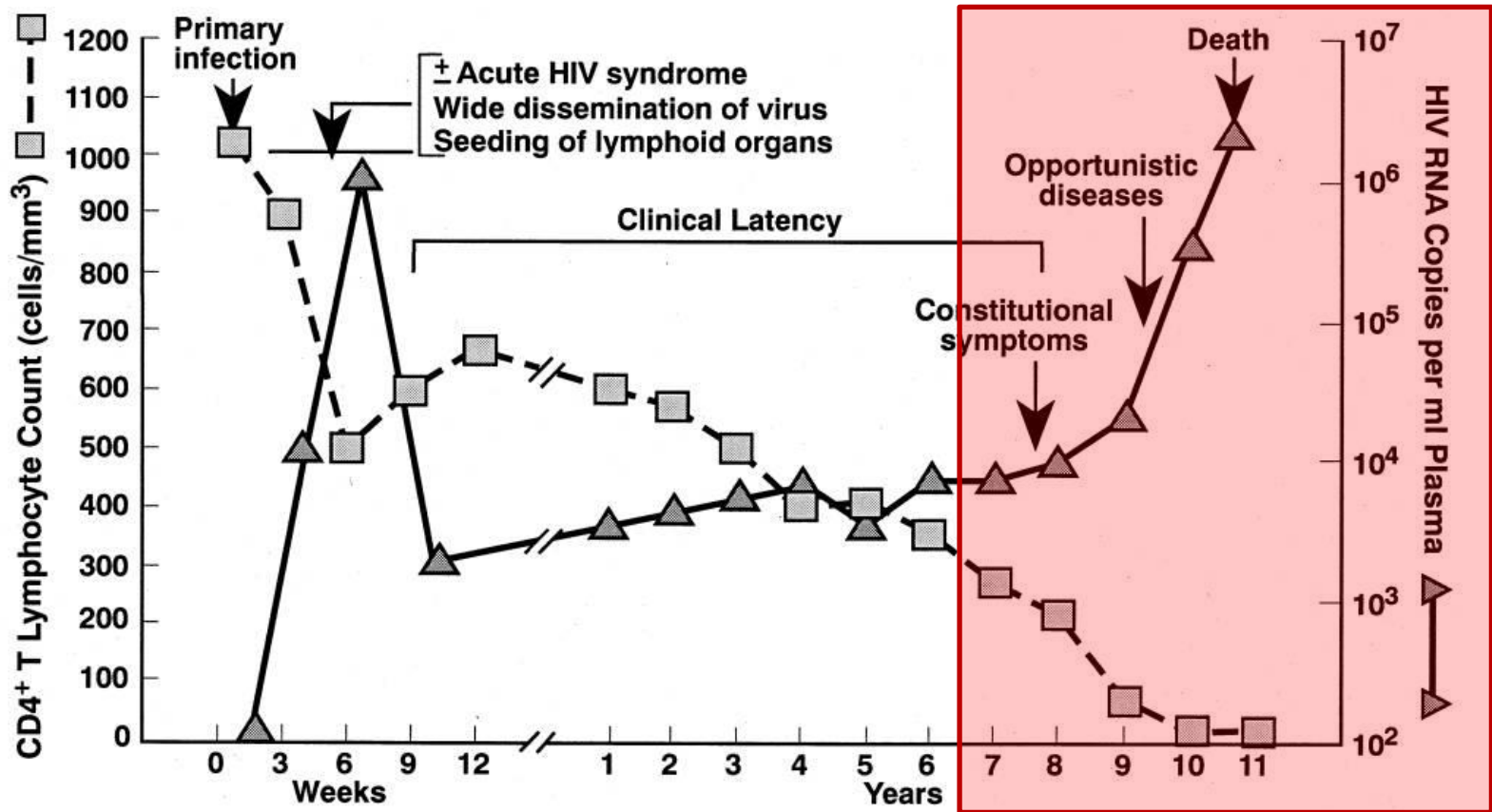
Natural history of HIV infection.



Dinamica dell'infezione da HIV



Natural history of HIV infection.



Opportunistic infections AIDS-related

Viruses	Disseminated CMV (retina, brain, gastrointestinal tract, peripheral nervous system) HSV (liver, gastrointestinal tract, CNS, skin) JCV (brain, progressive multifocal leukoencephalopathy) EBV (hairy leukoplakia, primary brain lymphoma) Parvovirus B19 (infection of the bone marrow, severe anemia)
Bacteria	Mycobacteria (eg. Mycoplasma avium, M. tuberculosis – disseminated, extrapulmonary) Salmonella (recurrent disseminated septicemia) Pyogenic bacteria (eg. Haemophilus, Streptococcus, Pneumococcus – septicemia, pneumonia, meningitis, osteomyelitis, arthritis, abscesses, etc.)
Fungi	Pneumocystis jiroveci (pneumonia) Candida albicans (esophagitis, lung infection) Cryptococcus neoformans (CNS) Histoplasmosis (disseminated, extrapulmonary) Coccidioides (disseminated, extrapulmonary)
Protozoa	Toxoplasma gondii (disseminated, extrapulmonary) Cryptosporidium (chronic diarrhea) Isospora (persistent diarrhea for more than a month)

AIDS-related cancers

Kaposi's sarcoma*
Non-Hodgkin lymphoma
Squamous cell carcinomas of the uterine cervix and anogenital squamous cell carcinomas

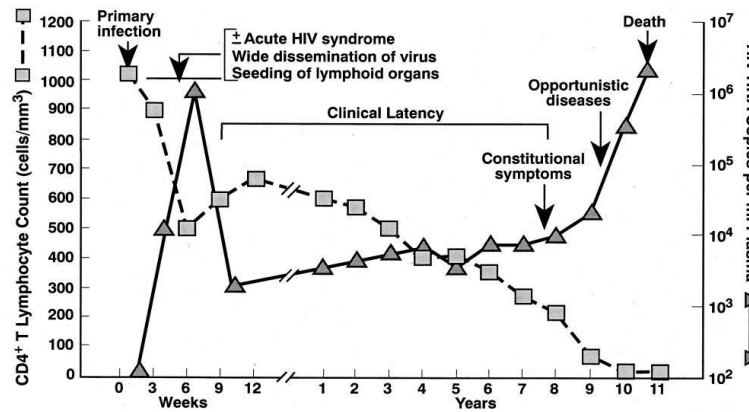
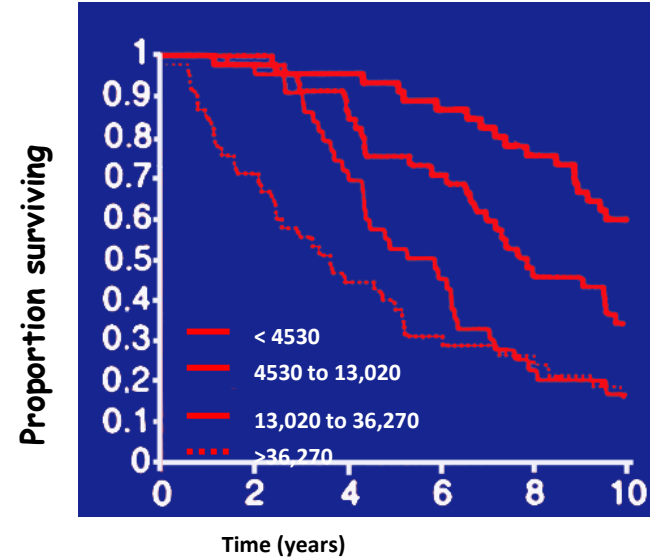
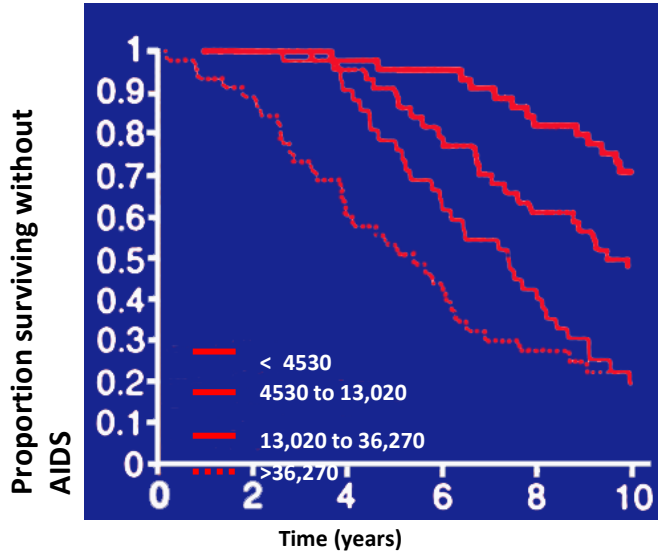
Neurological conditions

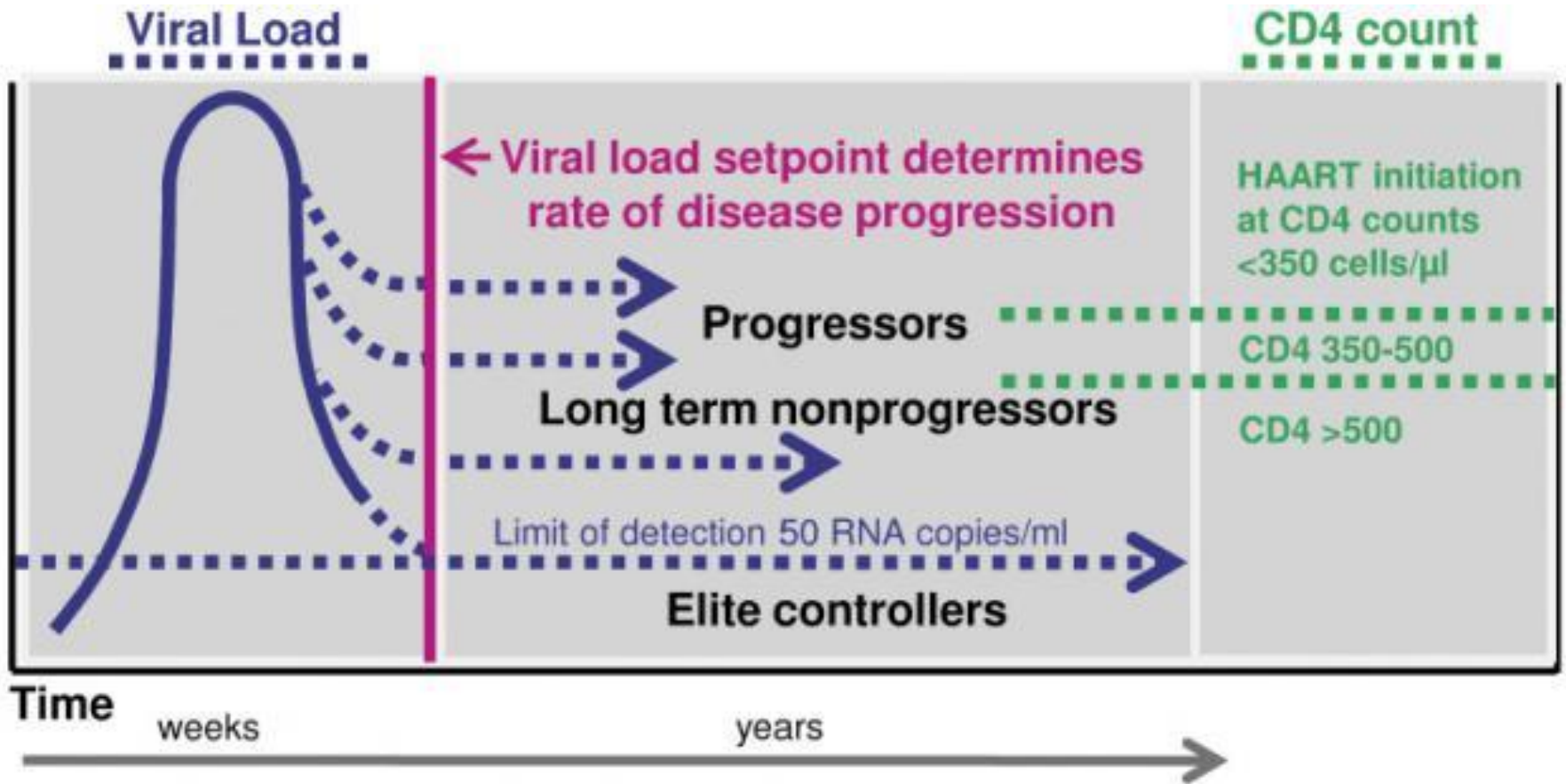
HIV Encephalopathy and AIDS Dementia Complex
Peripheral neuropathy

*Associated to HHV8; 300 times more frequent in the course of AIDS compared to other forms of immunodeficiency

Disease progression: RNA VIRAL LOAD

Mellors JW , Science 1996





LETTERS TO THE EDITOR

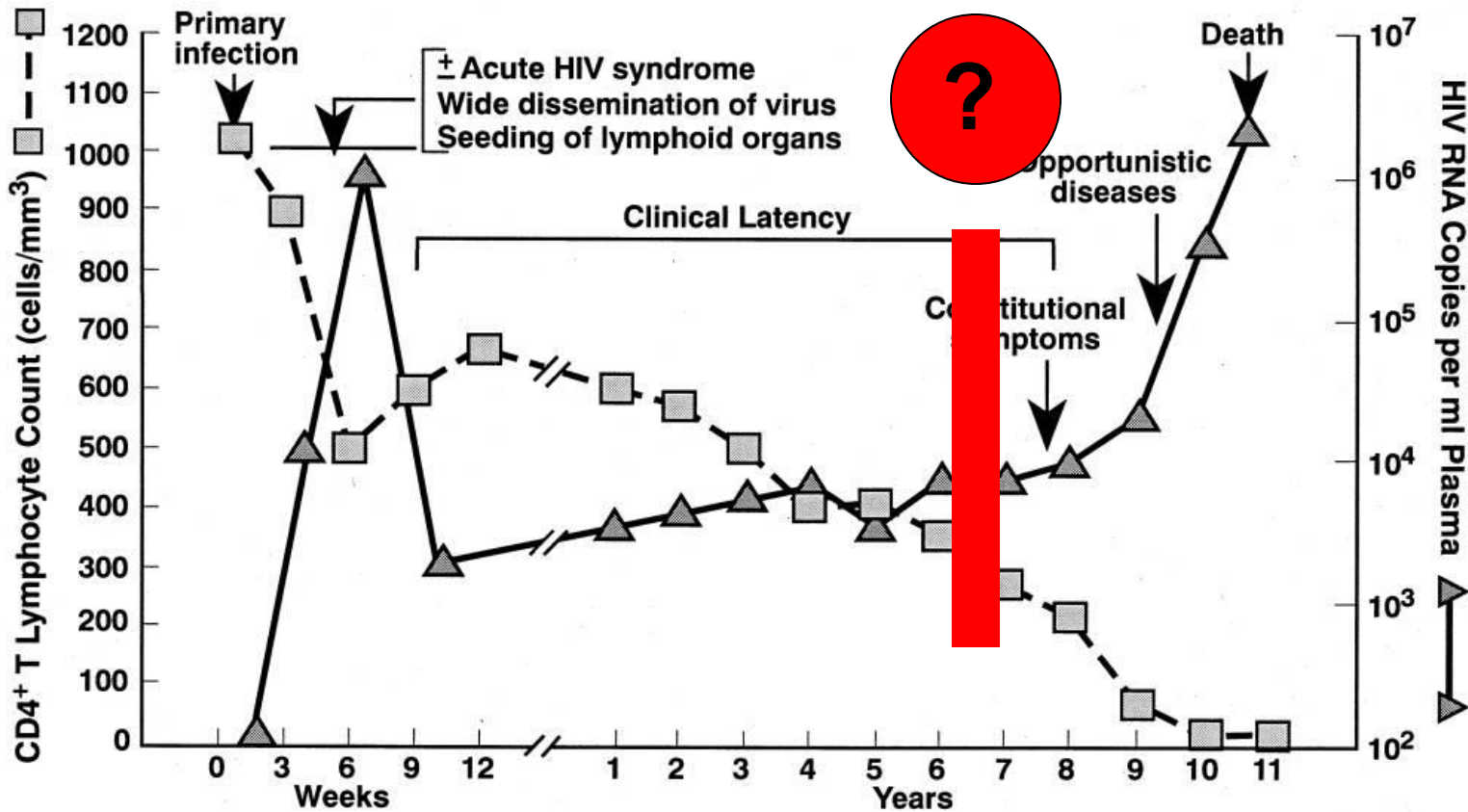
F. DIANZANI¹, G. ANTONELLI²,
E. RIVA¹, S. UCCINI³ & G. VISCO⁴
¹*Institute of Virology*
University "La Sapienza", Rome, Italy

**Correlation between plasma viremia and
number of infected cells in lymph node**

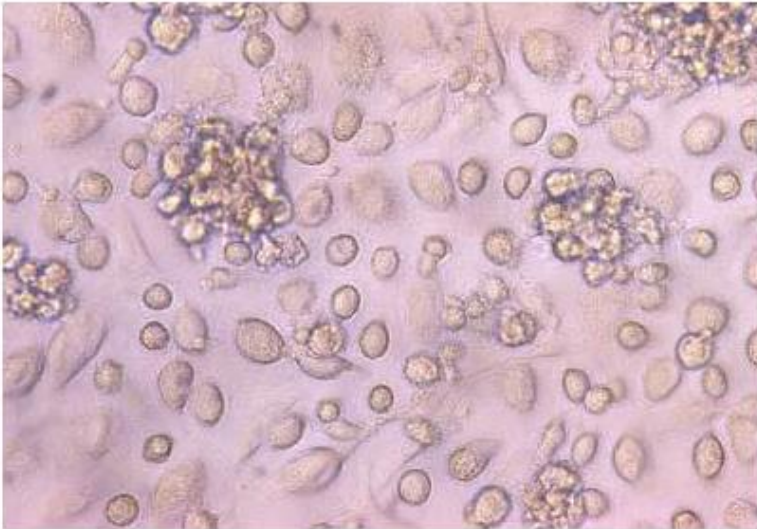
Patient no.	No. infected cells in lymph node/ 10^6 cells	Plasma viremia no. RNA copies/ml
1	15	$<0.01 \times 10^4$
2	128	0.3×10^4
3	512	0.15×10^4
4	512	0.7×10^4
5	512	1.5×10^4
6	512	2.5×10^4
7	2049	3.9×10^4
8	8197	10×10^4

$r = 0.970$. $P < 0.01$.

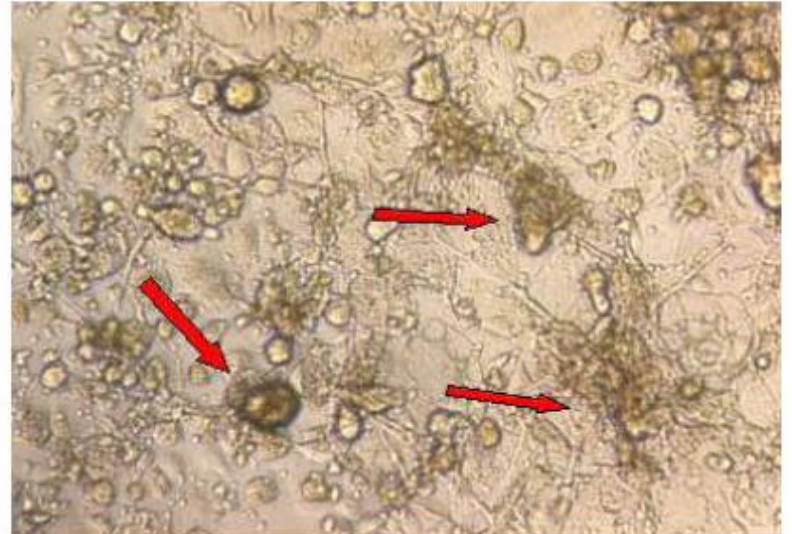
NATURAL HISTORY OF HIV INFECTION

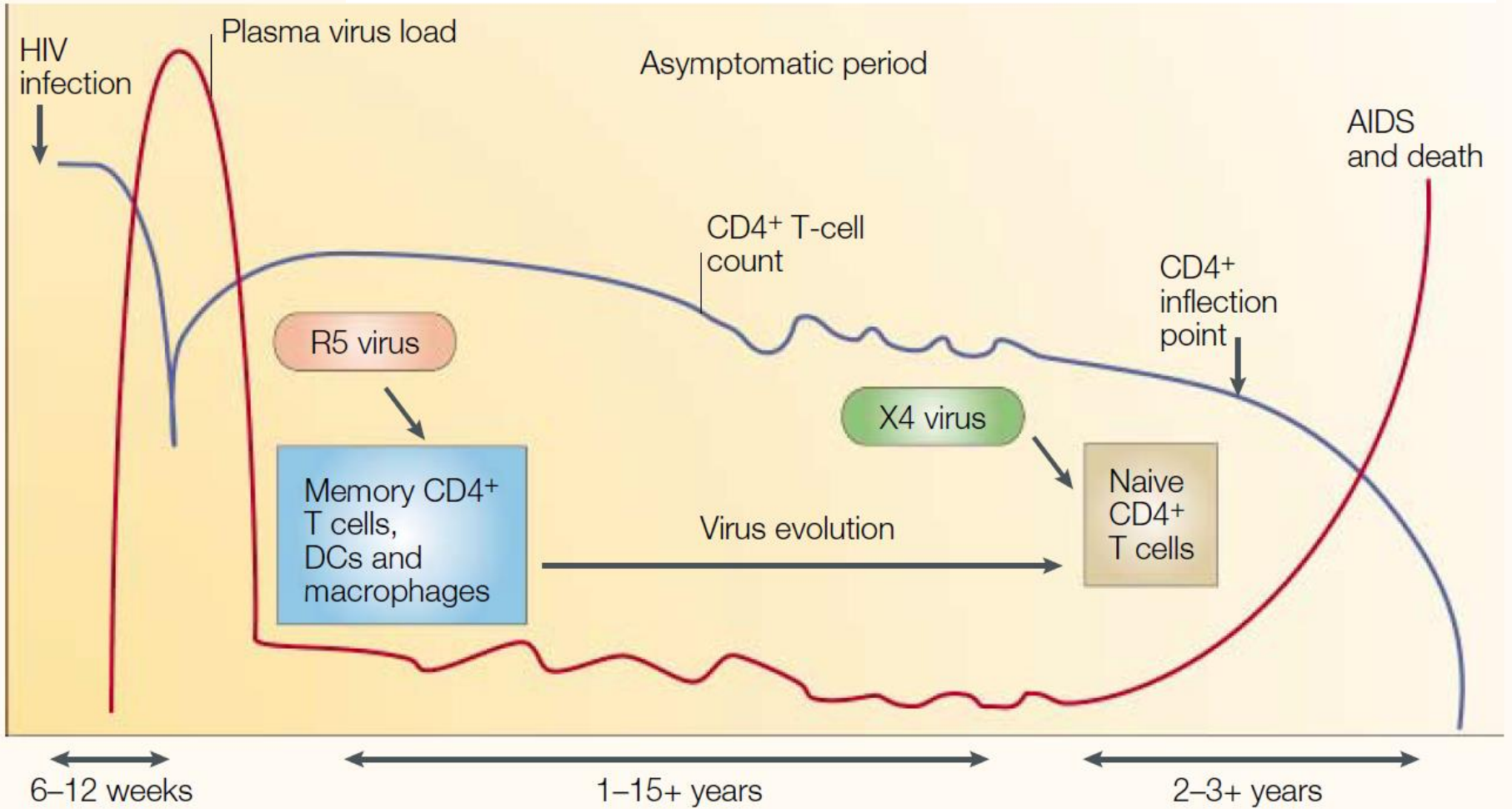


A



B





PATHOGENESIS OF HIV INFECTION

Viral pathogenesis- direct cytopathic effects of infected CD4+ cells due to HIV-1;

HIV-induced immunopathogenesis- indirect cytopathic effects of uninfected cells due to the persistent activation of the host immune system:

- high and continuous virus production
- production of apoptotic ligands and pro-inflammatory cytokines
- viral proteins (gp120, tat, nef)

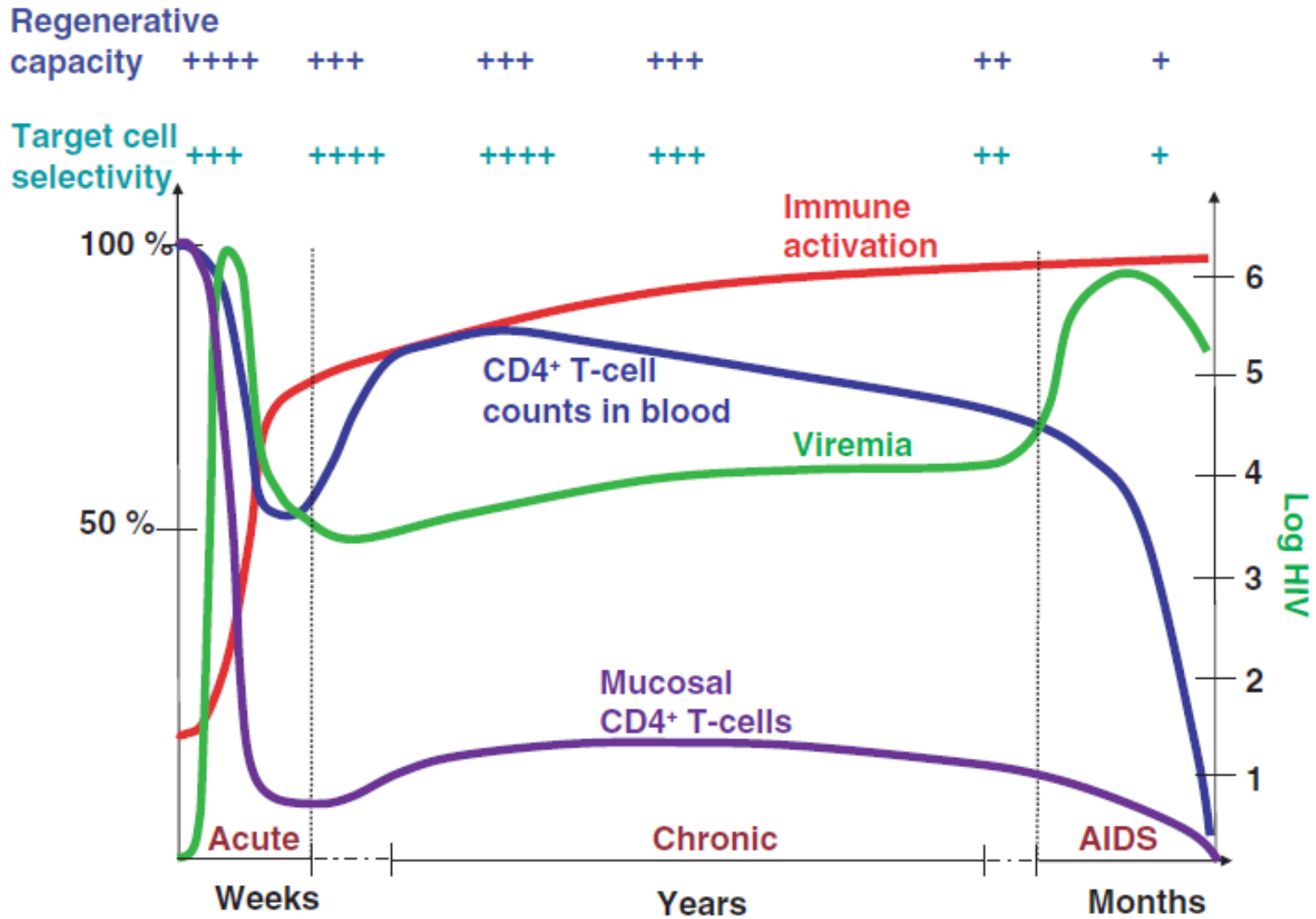
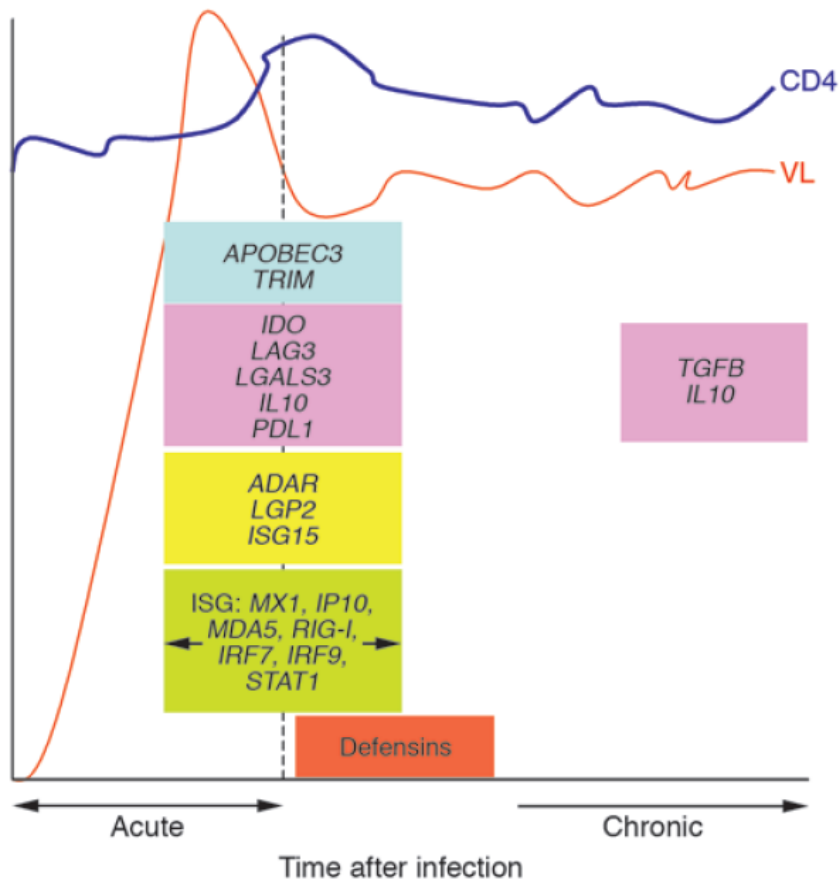
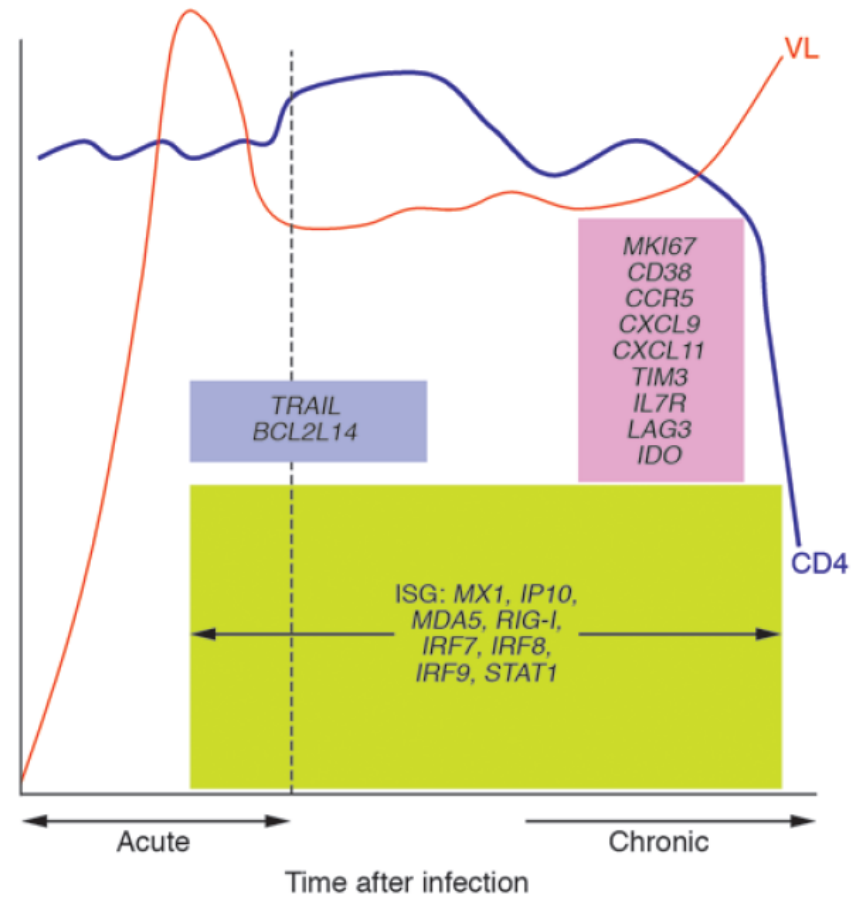


Figure 3 Quantitative and qualitative measures of HIV disease progression.

A Nonpathogenic SIV infection of African green monkeys and sooty mangabeys



B Pathogenic SIV infection of rhesus macaques



Conditions associated with persistent immune activation and inflammation in patients with HIV infection

Accelerated aging syndrome

Bone fragility

Tumors

Cardiovascular diseases

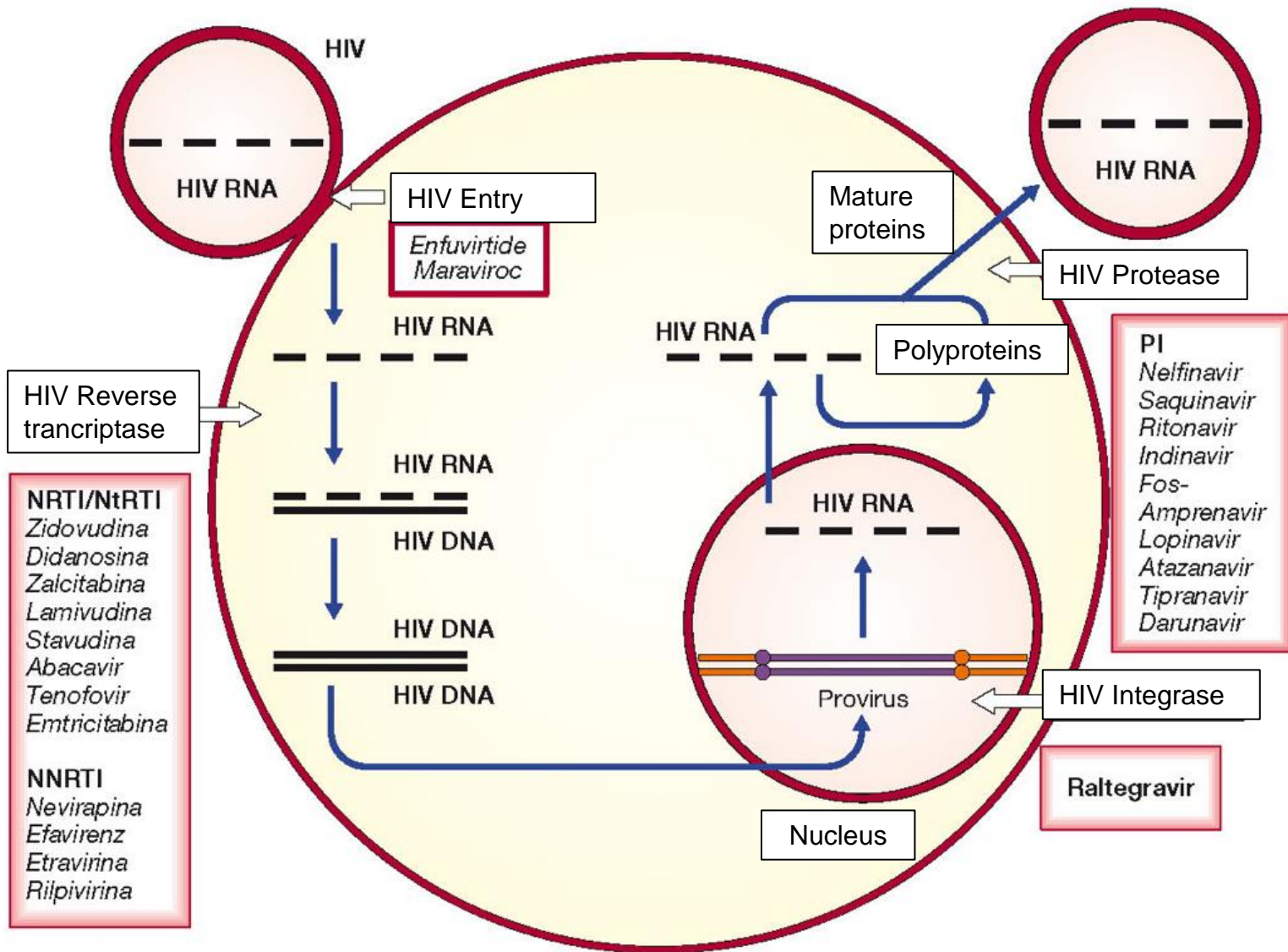
Diabetes

Kidney diseases

Liver diseases

Neurocognitive dysfunctions

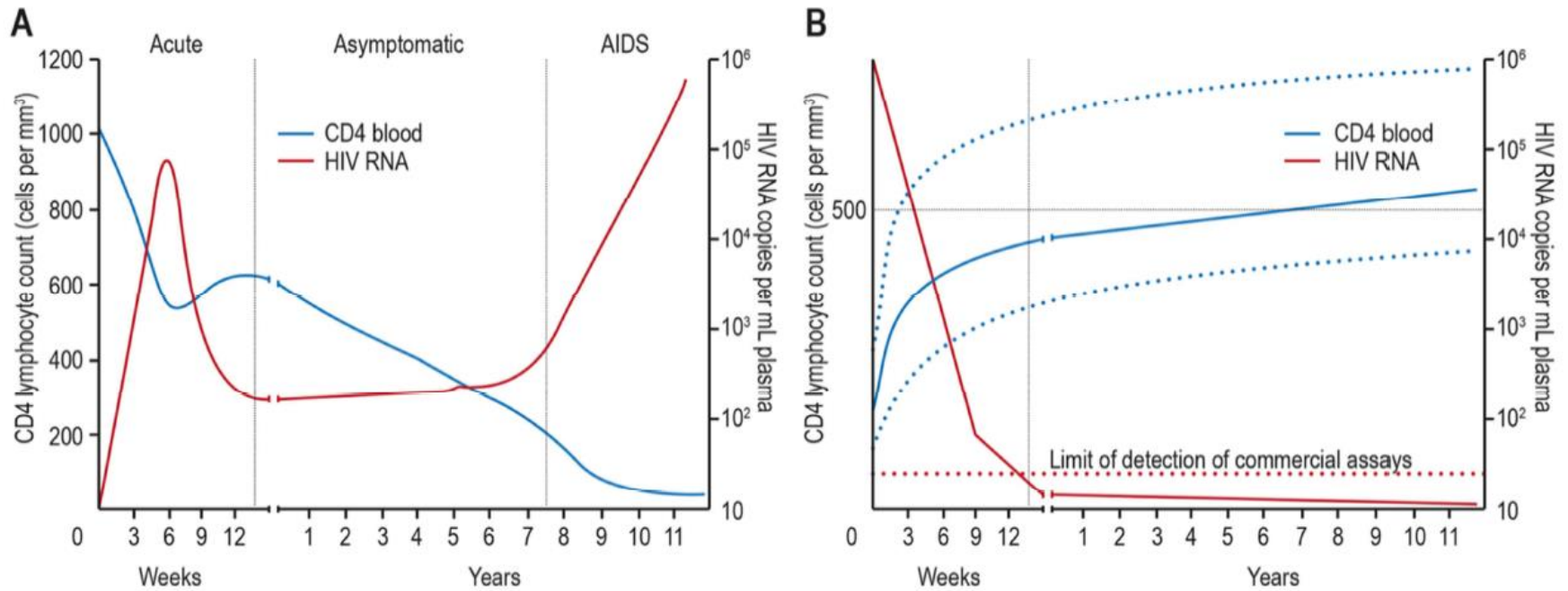
Antiviral drugs



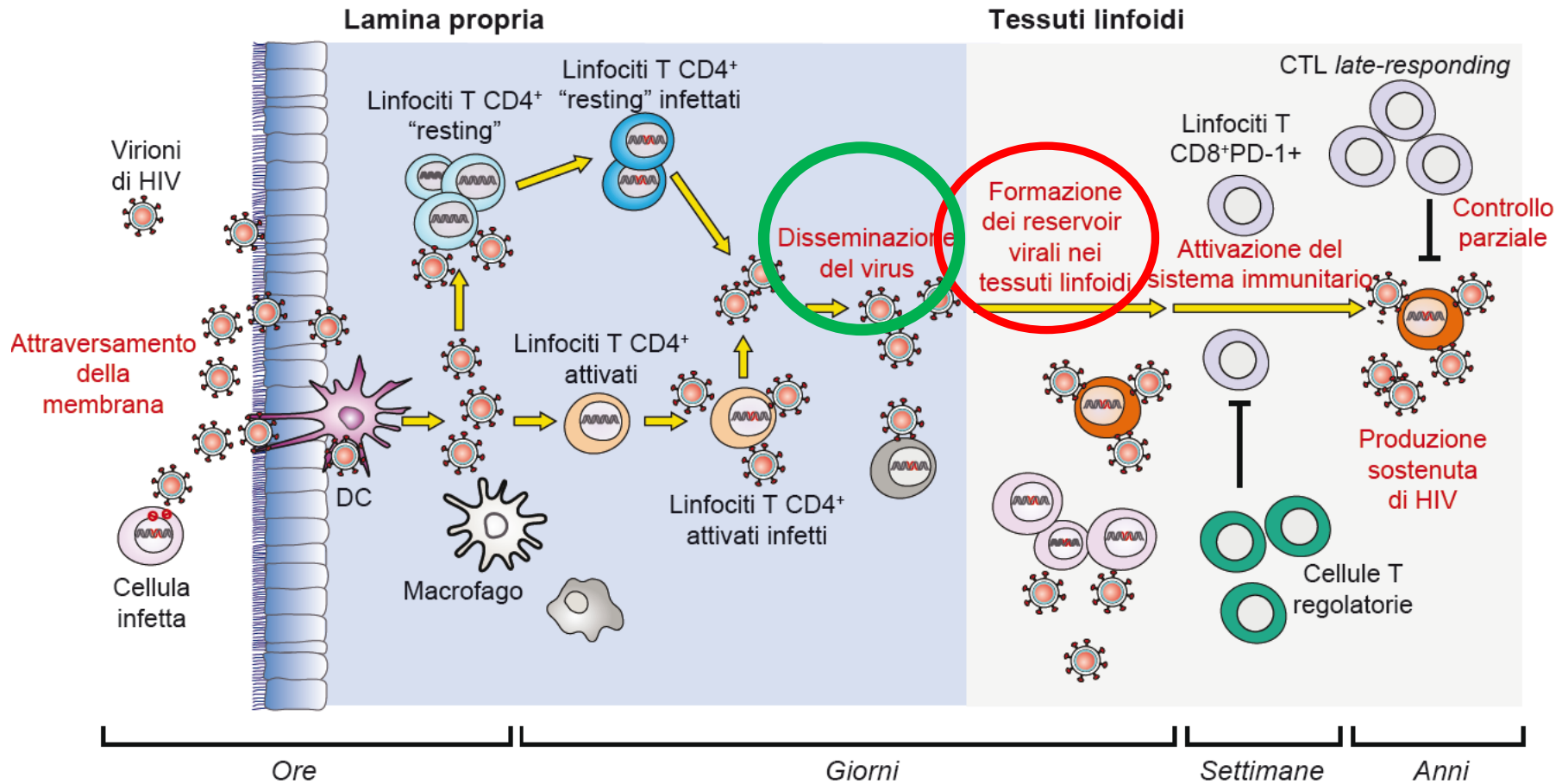
HAART

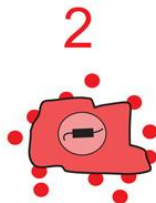
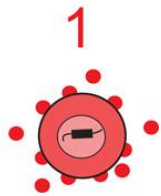
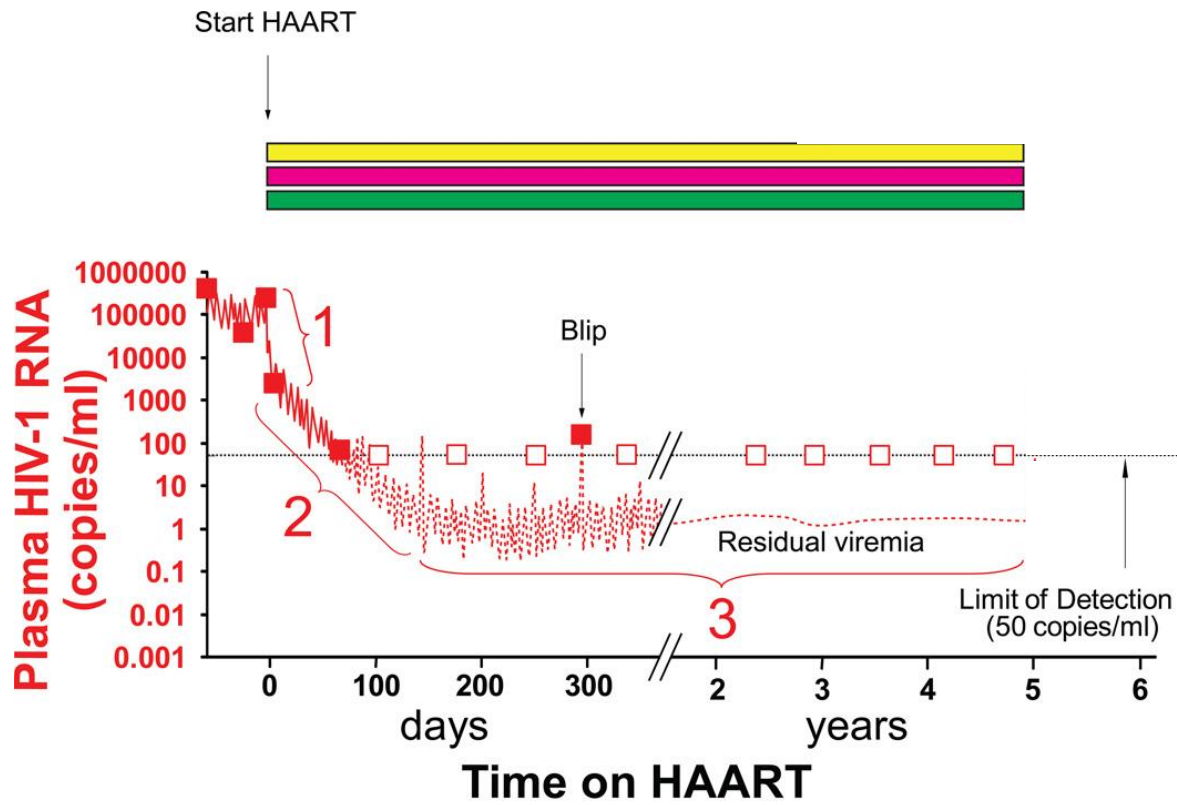
Highly active antiretroviral therapy

J.C. Becerra *et al.* (2016)



Dinamica dell'infezione da HIV

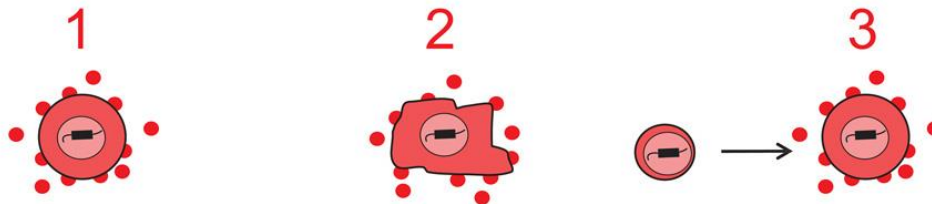
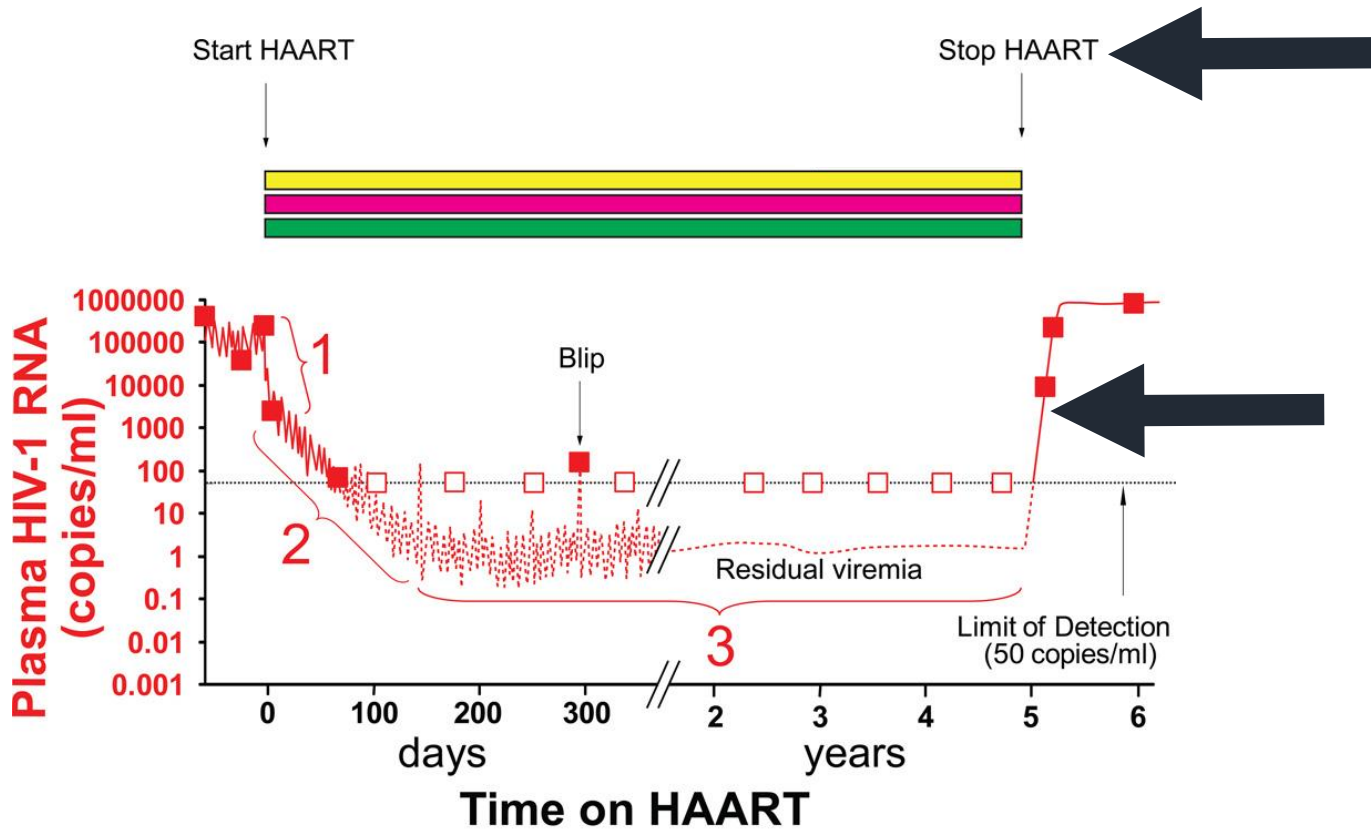




Developing strategies for HIV-1 eradication

Christine M. Durand¹, Joel N. Blankson¹, and Robert F. Siliciano^{1,2}

Trends Immunol. 2012 November ; 33(11): 554-562.

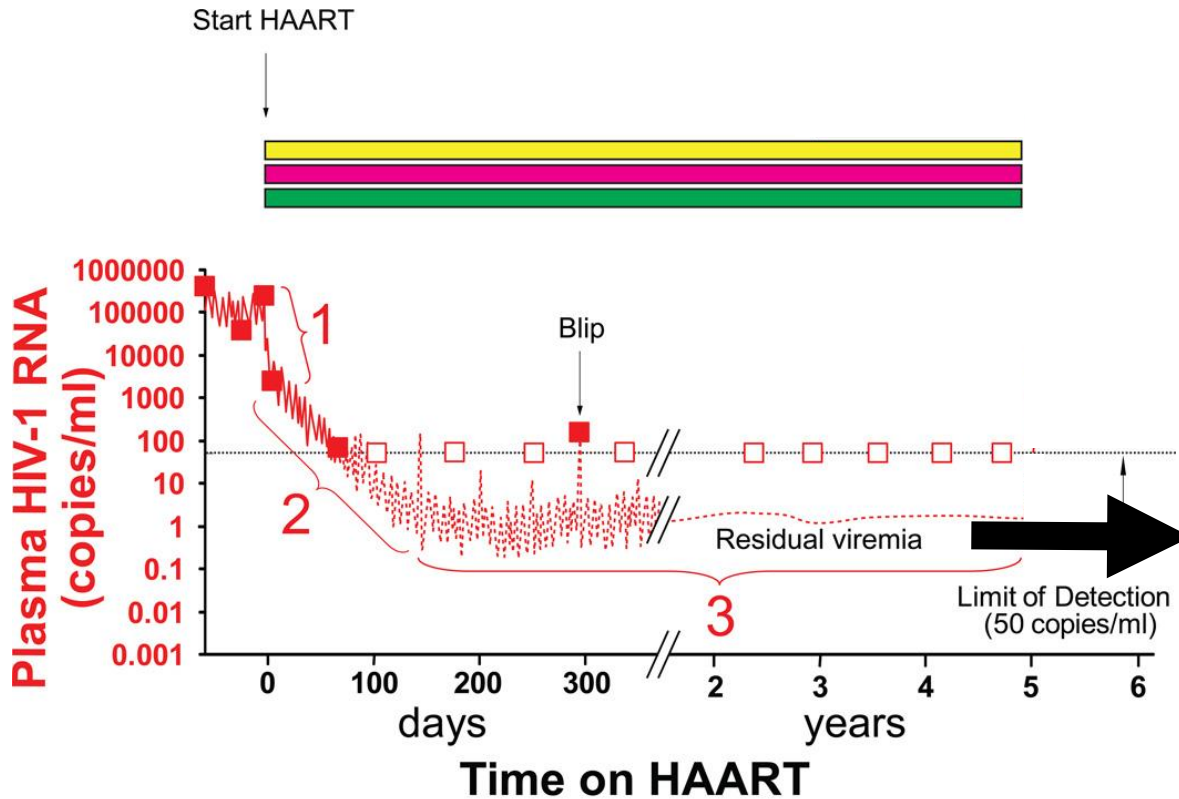


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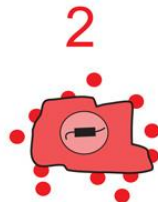
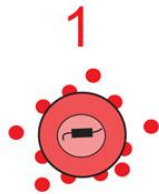
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The persistence of residual Viremia could represent a continuous pro-inflammatory stimulus for the immune system, which underlies to a chronic immune activation and inflammation.



Developing strategies for HIV-1 eradication

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Diagnosis and monitoring of HIV infection

DIAGNOSIS

SEROLOGY

Screening
Confirmation

VIRAL GENOME DETECTION

Qualitative
Quantitative

VIRUS ISOLATION

SCREENING TESTS

Immunoassays : ELISA (INDIRECT, SANDWICH, COMPETITIVE)

Other assays: immunoradiometric assay, neutralization test, complement fixation test, haemagglutination assay

➤ HIGH SENSITIVITY

- Generally, if **sensitivity** of test **increases** the **specificity decreases** and vice versa
- Screening-test-**negative** (i.e., nonreactive) samples require **NO further testing**
- **Reactivity** of samples on initial screening **MUST** be confirmed by **further testing**

CONFIRMATORY TESTS

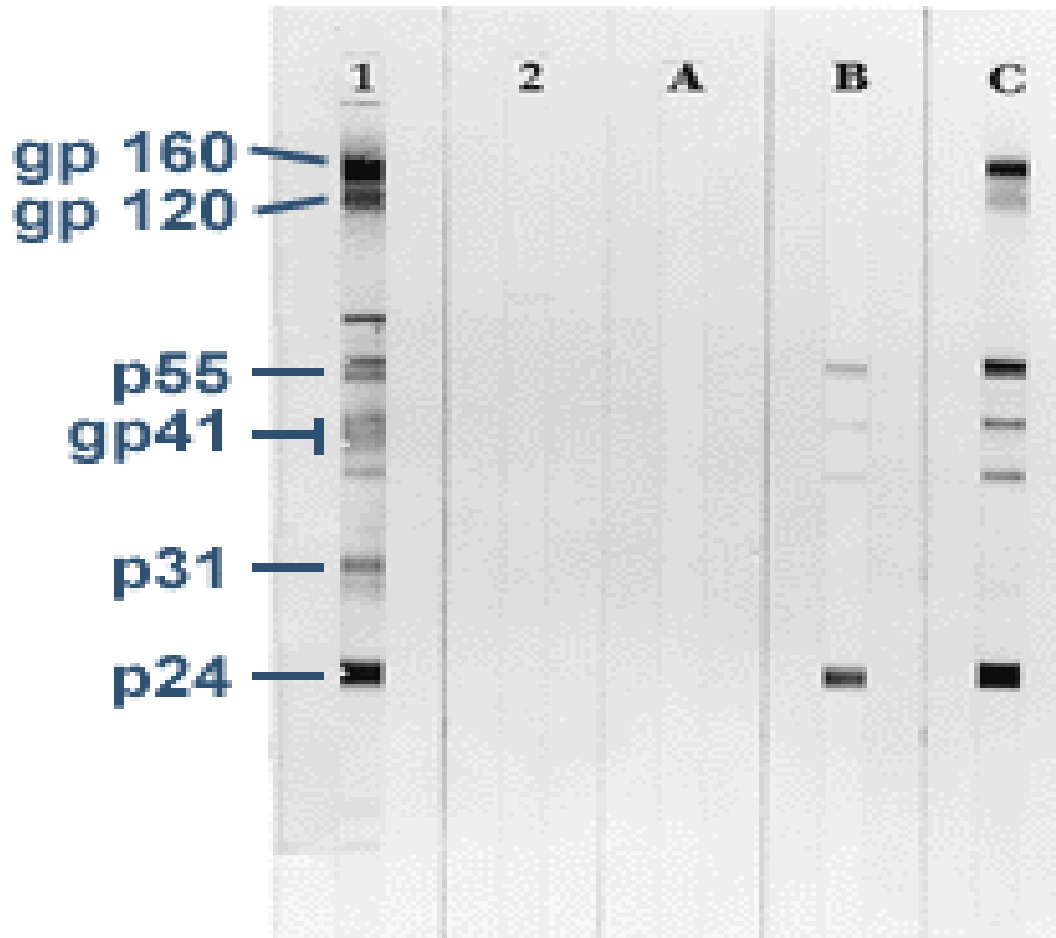
- Confirmatory tests are used to confirm a reactive screening result
- HIGH SPECIFICITY

WESTERN BLOT

Proteins derived from viral lysates, separated on polyacrylamide gel and transferred to nitrocellulose strips

Western blotting is used to determine whether the patient has antibodies that react with one or more viral proteins.

HIV WESTERN BLOT TEST



Lane 1, HIV+ serum (control)

Lane 2, HIV- serum (control)

Lane A, Patient A

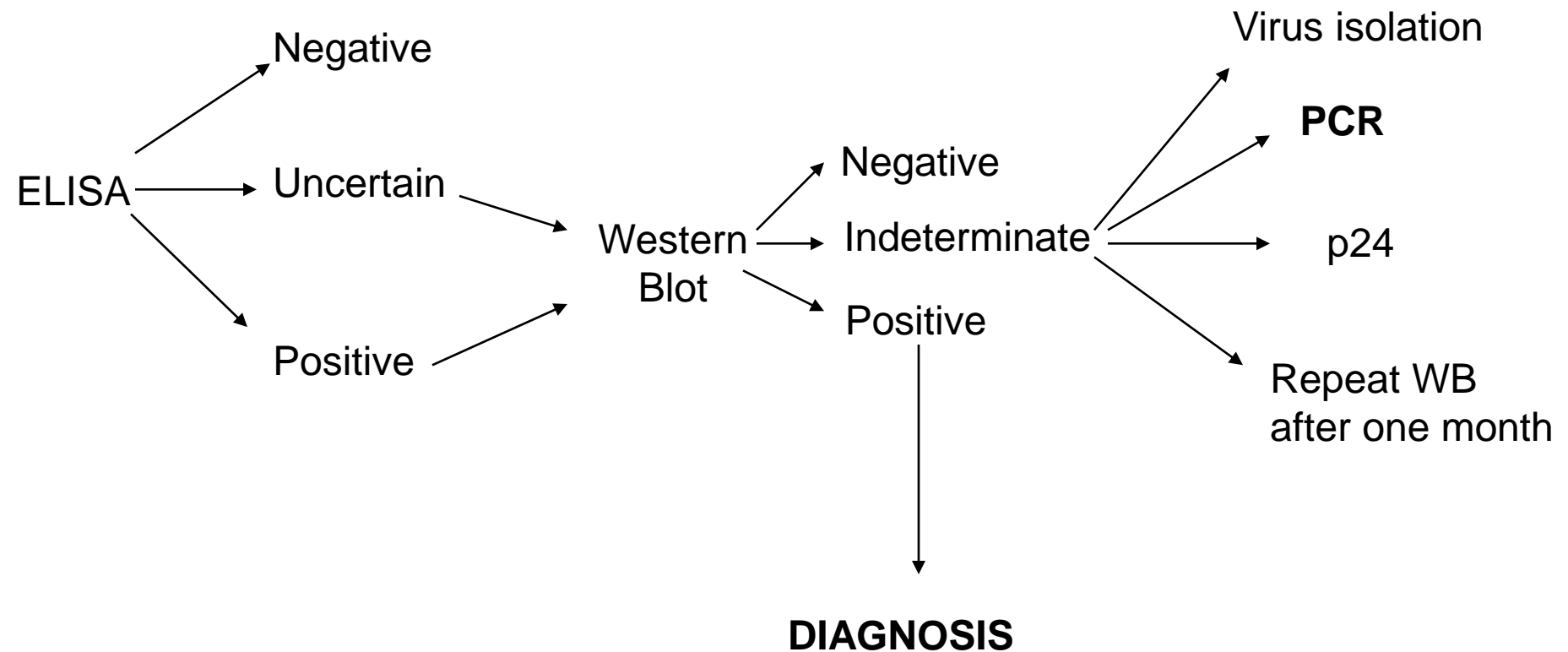
Lane B, Patient B

Lane C, Patient C

Criteria used to define a positive HIV Western blot

Competent authority	Criteria for interpreting results
Centers for Disease Control (CDC)	At least 1 ENV and p24
American Food and Drug Administration (FDA)	P24 and p31 and gp41 or gp120/gp160
World Health Organization (WHO)	two ENV bands with or without GAG or POL
Centre National de Transfusion Sanguigne (France)	two ENV bands with GAG or POL

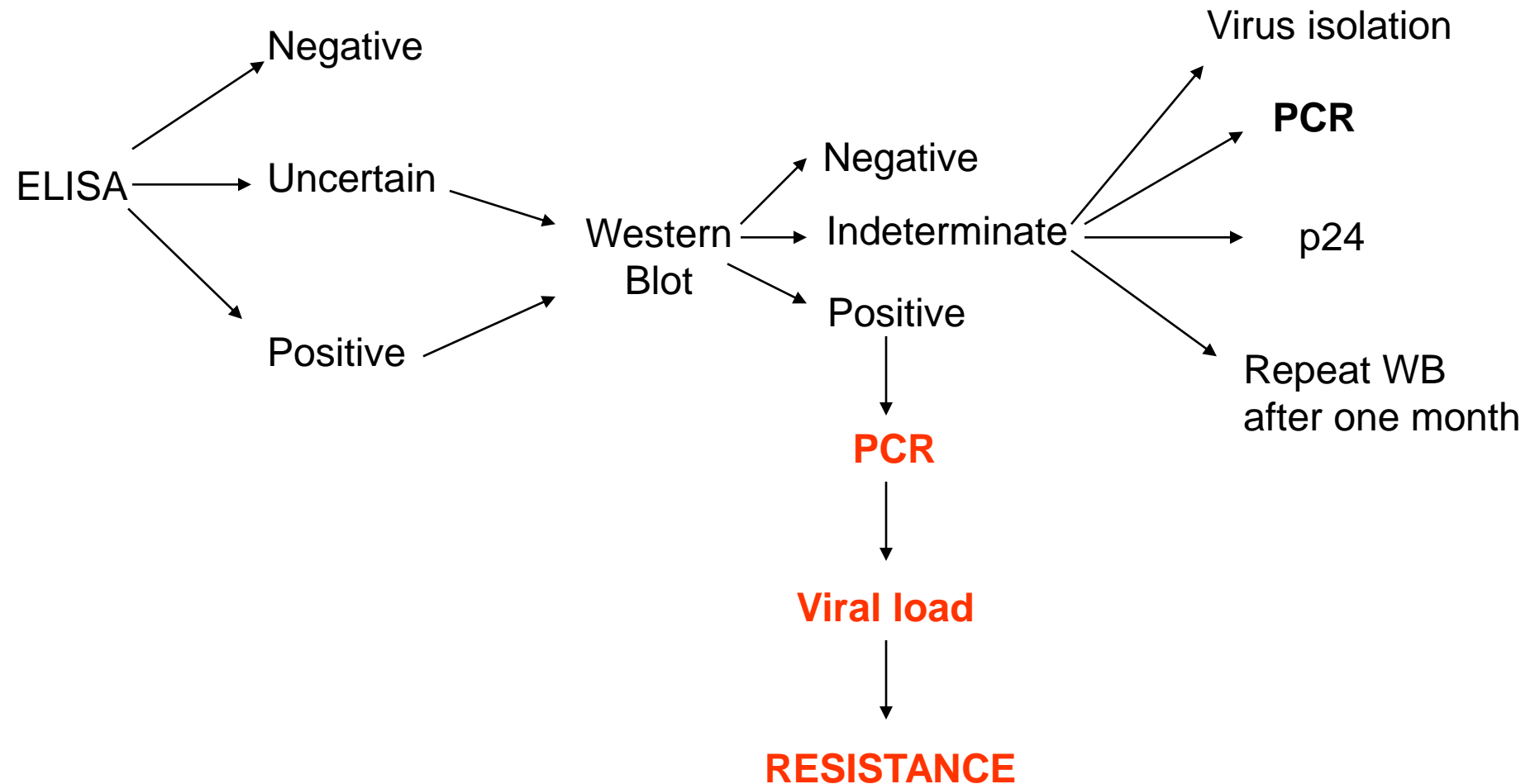
Diagnostic Algorithm for HIV Diagnosis in adults



Direct virological diagnosis

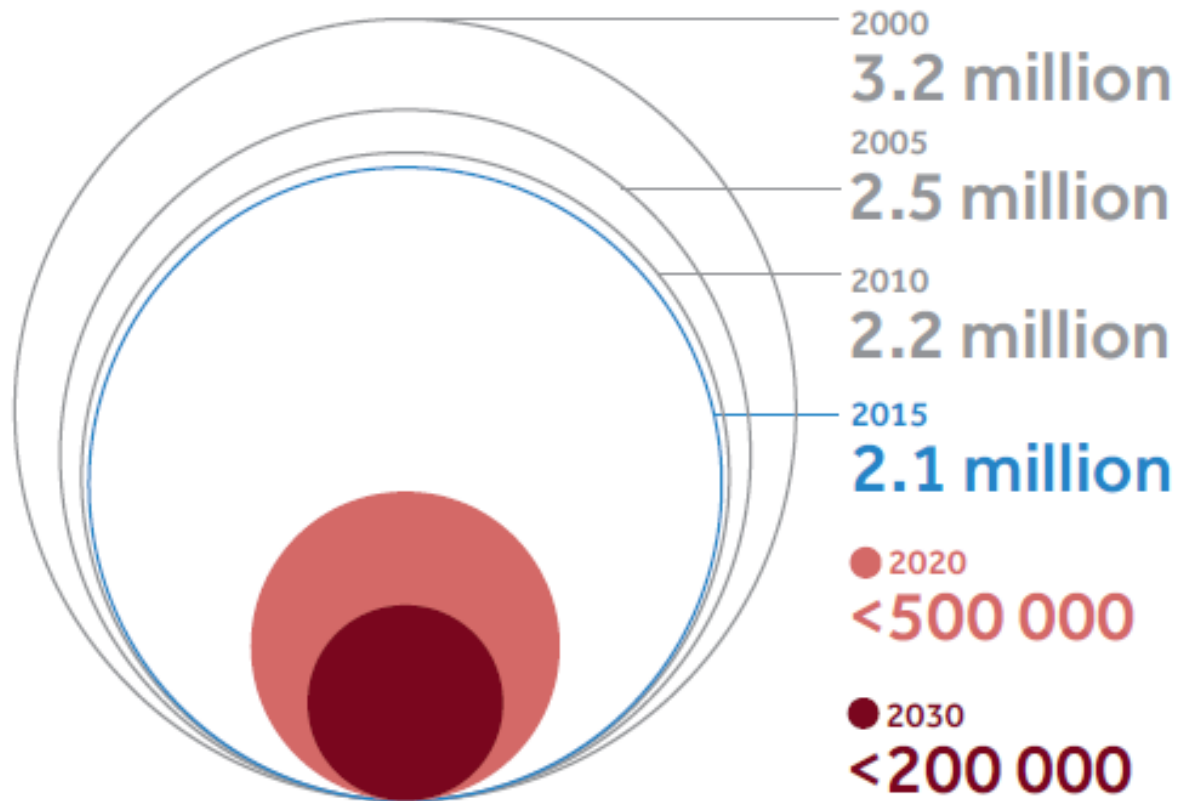
- Virus isolation
- Antigen Detection
- Nucleic Acid Detection
- Electron Microscopy
- Demonstration of the presence of viruses in biological samples

Diagnostic Algorithm for HIV Diagnosis in adults



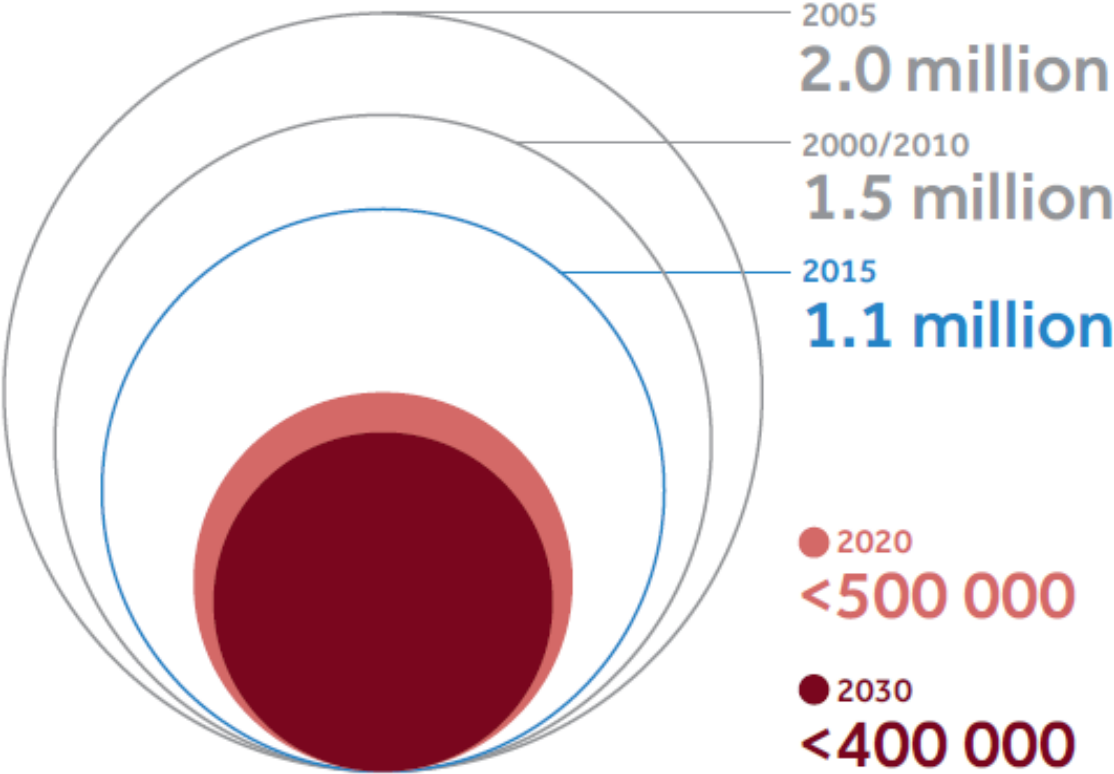
Epidemiology

Number of people newly infected with HIV



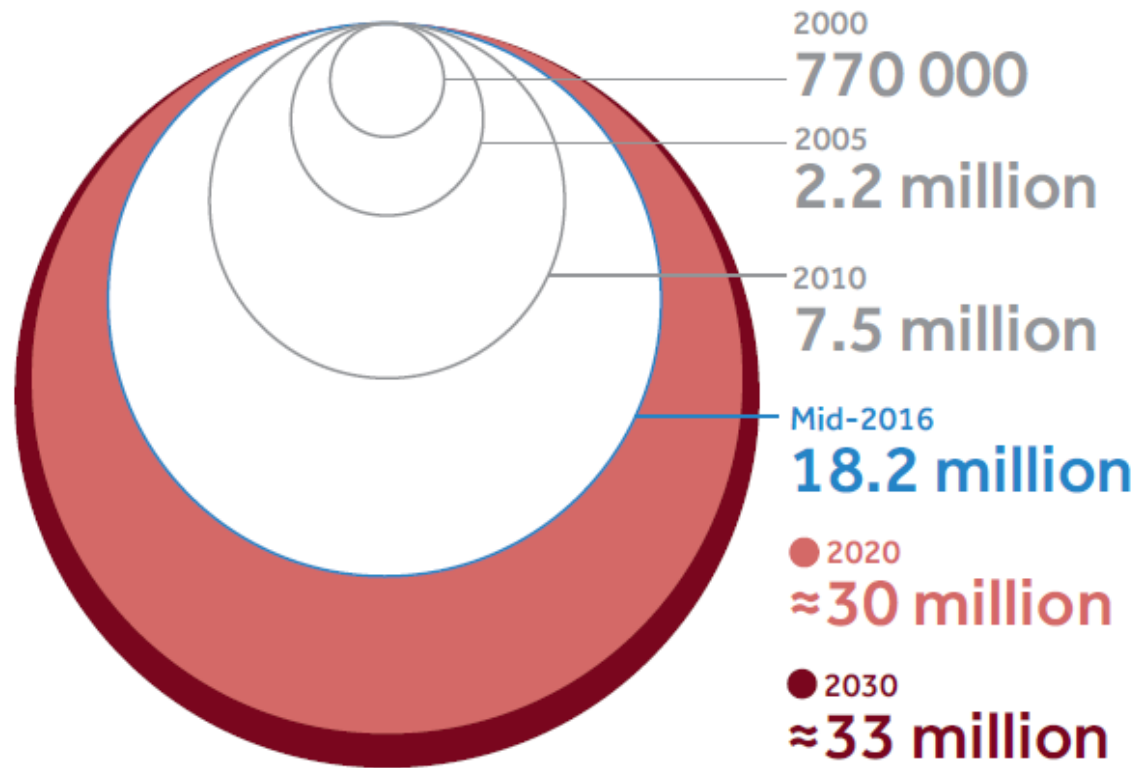
Source: UNAIDS/WHO estimates.
The red shading shows future targets.

Number of people dying from HIV



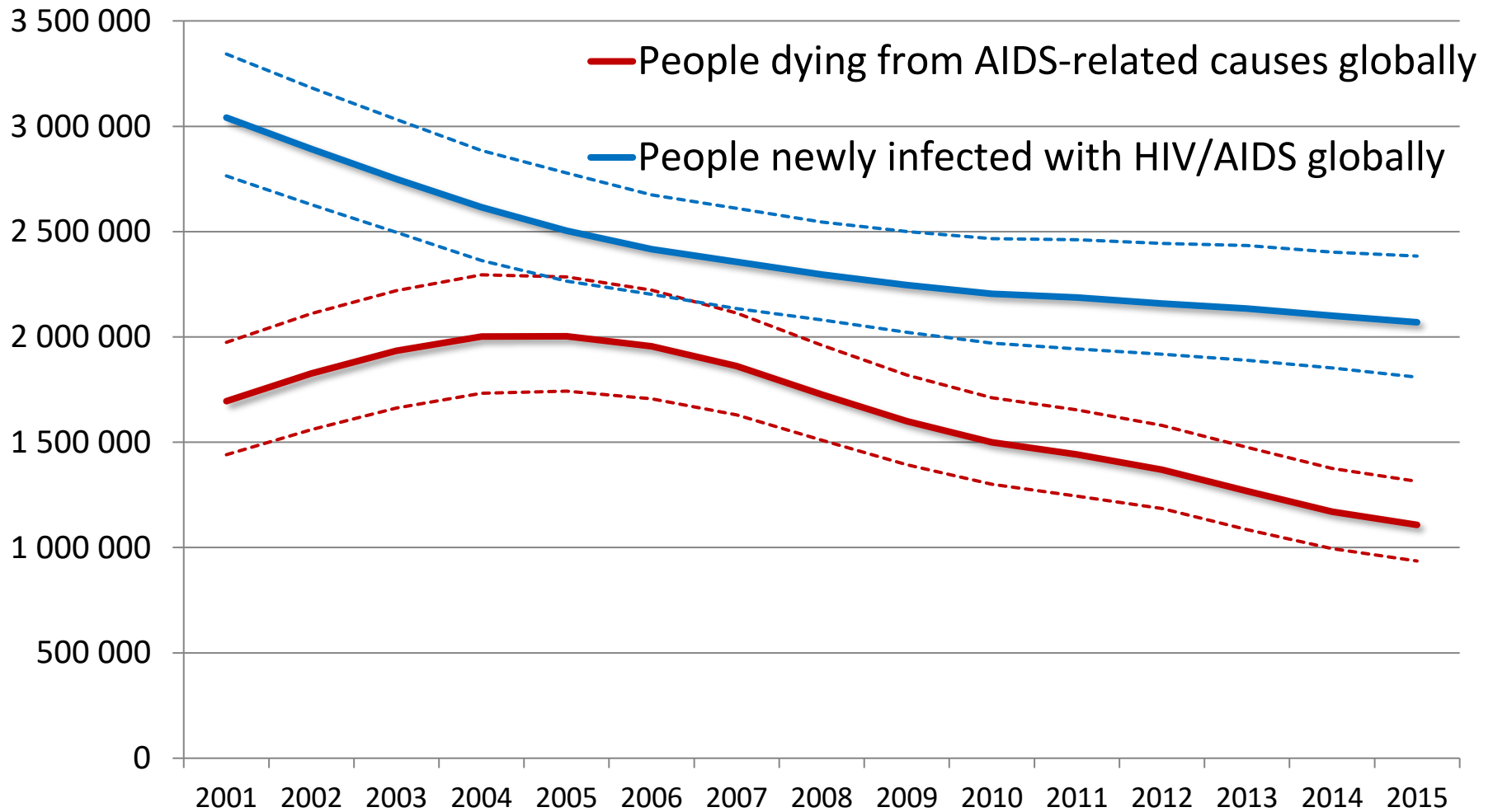
Source: UNAIDS/WHO estimates.
The red shading shows future targets.

Number of people receiving antiretroviral treatment



Source: UNAIDS/WHO estimates.
The red shading shows future targets.

Decline in HIV incidence and mortality over time



Source: UNAIDS/WHO estimates.

Some of the still open questions on HIV

- *Is eradication feasible?*
- *How do we elicit protective immunity to HIV?*
- *How can we make HAART more accessible and sustainable?*
- *Therapy as prevention?*