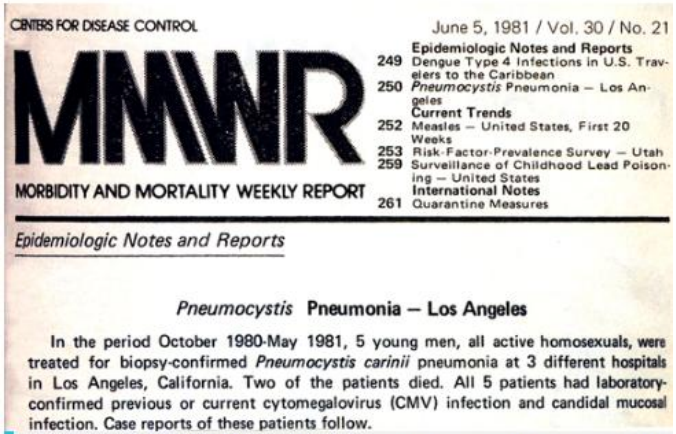
INITIAL REPORTS of AIDS

1981



CENTERS FOR DISEASE CONTROL

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

June 5, 1981 / Vol. 30 / No. 21

Epidemiologic Notes and Reports

Pneumocystis **Pneumonia — Los Angeles**

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Banner from CDC's 1981 MMWR publication on the cases that became known as AIDS.
Credit: CDC

In June of 1981, a team of clinicians led in Los Angeles reported an unusual occurrence of opportunistic infections in the Morbidity and Mortality Weekly Report, a publication led by the US Centers for Disease Control and Prevention (CDC).
Five apparently healthy individuals in Los Angeles had contracted Pneumocystis pneumonia (PCP), a serious infection that is normally limited to individuals who are severely immunosuppressed.
At the time of the report, two of the patients had died.

These were the first published incidences of an unrecognized deadly illness,

- **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

By Lawrence K. Altman

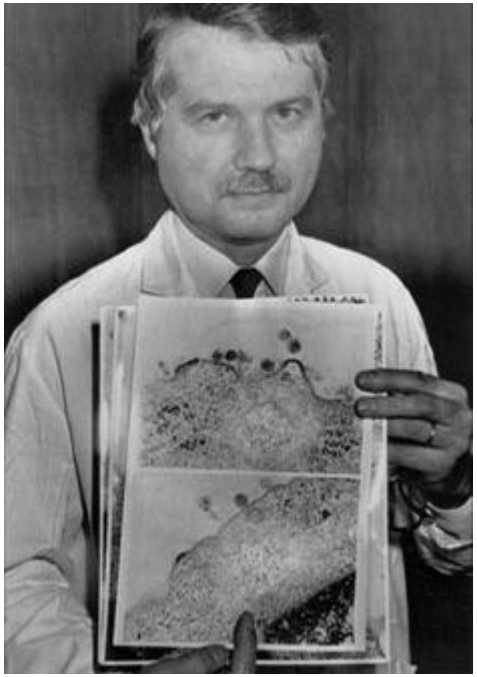
The New York Times

July 3, 1981

RARE CANCER SEEN IN 41 HOMOSEXUALS

Doctors in New York and California have diagnosed among homosexual men 41 cases of a rare and often rapidly fatal form of cancer. Eight of the victims died less than 24 months after the diagnosis was made.

The cause of the outbreak is unknown, and there is as yet no evidence of contagion. But the doctors who have made the diagnoses, mostly in New York City and the San Francisco Bay area, are alerting other physicians who treat large numbers of homosexual men to the problem in an effort to help identify more cases and to reduce the delay in offering chemotherapy treatment.



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.

Abbadessa G, Accolla R, Aiuti F, Albini A, Aldovini A, Alfano M, Antonelli G, Bartholomew C, Bentwich Z, Bertazzoni U, Berzofsky JA, Biberfeld P, Boeri E, Buonaguro L, Buonaguro FM, Bukrinsky M, Burny A, Caruso A, Cassol S, Chandra P, Ceccherini-Nelli L, Chieco-Bianchi L, Clerici M, Colombini-Hatch S, de Giuli Morghen C, de Maria A, de Rossi A, Dierich M, Della-Favera R, Dolei A, Douek D, Erfle V, Felber B, Fiorentini S, Franchini G, Gershoni JM, Gotch F, Green P, Greene WC, Hall W, Haseltine W, Jacobson S, Kallings LO, Kalyanaraman VS, Katinger H,Khalili K, Klein G, Klein E, Klotman M, Klotman P, Kotler M, Kurth R, Lafeuillade A, La Placa M, Lewis J, Lillo F, Lisziewicz J, Lomonico A,Lopalco L, Lori F, Lusso P, Macchi B, Malim M, Margolis L, Markham PD, McClure M, Miller N, Mingari MC, Moretta L, Noonan D, O'Brien S,Okamoto T, Pal R, Palese P, Panet A, Pantaleo G, Pavlakis G, Pistello M, Plotkin S, Poli G, Pomerantz R, Radaelli A, Robertguroff M,Roederer M, Sarngadharan MG, Schols D, Secchiero P, Shearer G, Siccardi A, Stevenson M, Svoboda J, Tartaglia J, Torelli G, Tornesello ML, Tschachler E, Vaccarezza M, Vallbracht A, van Lunzen J, Varnier O, Vicenzi E, von Melchner H, Witz I, Zagury D, Zagury JF, Zauli G,Zipeto D.

World Health Organization

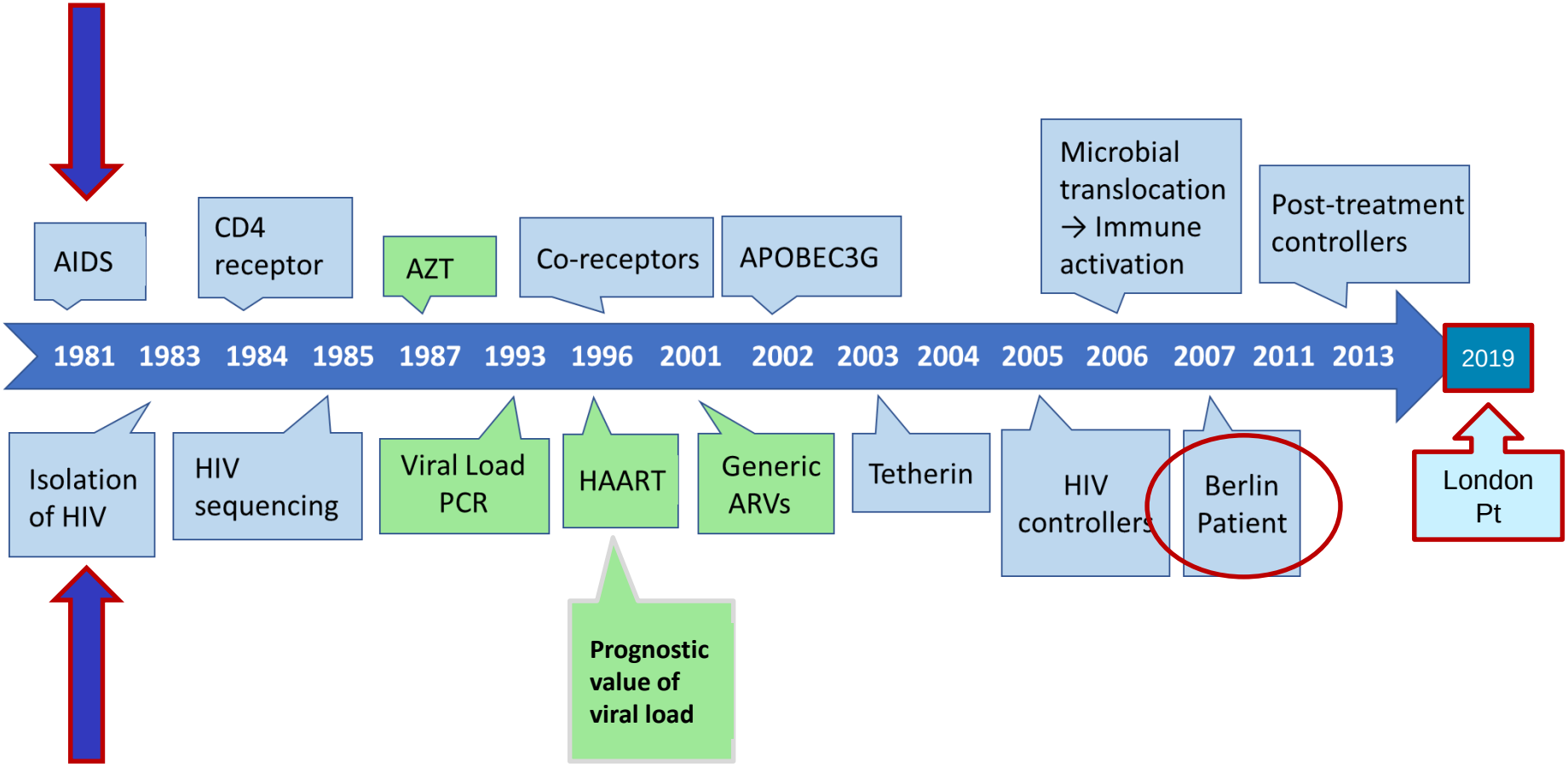
HIV/AIDS

22 July 2024

Key facts

- HIV remains a major global public health issue, having claimed an estimated 42.3 million lives to date. Transmission is ongoing in all countries globally.
- There were an estimated 39.9 million people living with HIV at the end of 2023, 65% of whom are in the WHO African Region.
- In 2023, an estimated 630 000 people died from HIV-related causes and an estimated 1.3 million people acquired HIV.
- There is no cure for HIV infection. However, with access to effective HIV prevention, diagnosis, treatment and care, including for opportunistic infections, HIV infection has become a manageable chronic health condition, enabling people living with HIV to lead long and healthy lives.
- WHO, the Global Fund and UNAIDS all have global HIV strategies that are aligned with the SDG target 3.3 of ending the HIV epidemic by 2030.
- By 2025, 95% of all people living with HIV should have a diagnosis, 95% of whom should be taking lifesaving antiretroviral treatment, and 95% of people living with HIV on treatment should achieve a suppressed viral load for the benefit of the person's health and for reducing onward HIV transmission. In 2023, these percentages were 86%, 89%, and 93% respectively.
- In 2023, of all people living with HIV, 86% knew their status, 77% were receiving antiretroviral therapy and 72% had suppressed viral loads.

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



HIV Cure 2007 ; 2020

Timothy Ray Brown (Berlin patient) and Adam Castillejo (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.

Credit: Bloomberg/Rob Waters via Getty Images

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 Δ32/Δ32), 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.

Brief Communication | Open Access | Published: 20 February 2023

In-depth virological and immunological characterization of HIV-1 cure after CCR5Δ32/Δ32 allogeneic hematopoietic stem cell transplantation

Björn-Erik Ole Jensen, Elena Knops, Leon Cords, Nadine Lübke, Maria Salgado, Kathleen Busman-Sahay, Jacob D. Estes, Laura E. P. Huyveneers, Federico Perdomo-Celis, Melanie Wittner, Cristina Gálvez, Christiane Mummert, Caroline Passaes, Johanna M. Eberhard, Carsten Münk, Ilona Hauber, Joachim Hauber, Eva Heger, Jozefien De Clercq, Linos Vandekerckhove, Silke Bergmann, Gábor A. Dunay, Florian Klein, Dieter Häussinger, ... Guido Kobbe + Show authors

Nature Medicine (2023) | Cite this article

Third person free of HIV after transplant

A 53-year-old man in Germany has become at least the third person with HIV to be declared cleared of the virus after undergoing a procedure that replaced his bone marrow cells with HIV-resistant stem cells from a donor. The man, who is being referred to as the 'Düsseldorf patient', received the treatment after being diagnosed with acute myeloid leukaemia. Stem-cell transplants are not suitable for people who don't need them to treat blood cancer because they are risky and difficult: the man called his treatment a "very rocky road".

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

HIV-1 Remission after Allogeneic Hematopoietic-Cell Transplantation

N ENGL J MED 390;7 NEJM.ORG FEBRUARY 15, 2024

…….We report the results of the 60-month follow-up of a **63-year-old man who was found to be free of human immunodeficiency virus type 1 (HIV-1) infection after undergoing hematopoietic-cell transplantation (HCT) for the treatment of acute myelogenous leukemia (AML).** The transplant was obtained from a donor with a Δ32 mutation, which causes a CCR5 deletion (CCR5-Δ32/Δ32) that has been associated with resistance to HIV-1 infection……

Human immunodeficiency virus (HIV)

RETROVIRIDAE

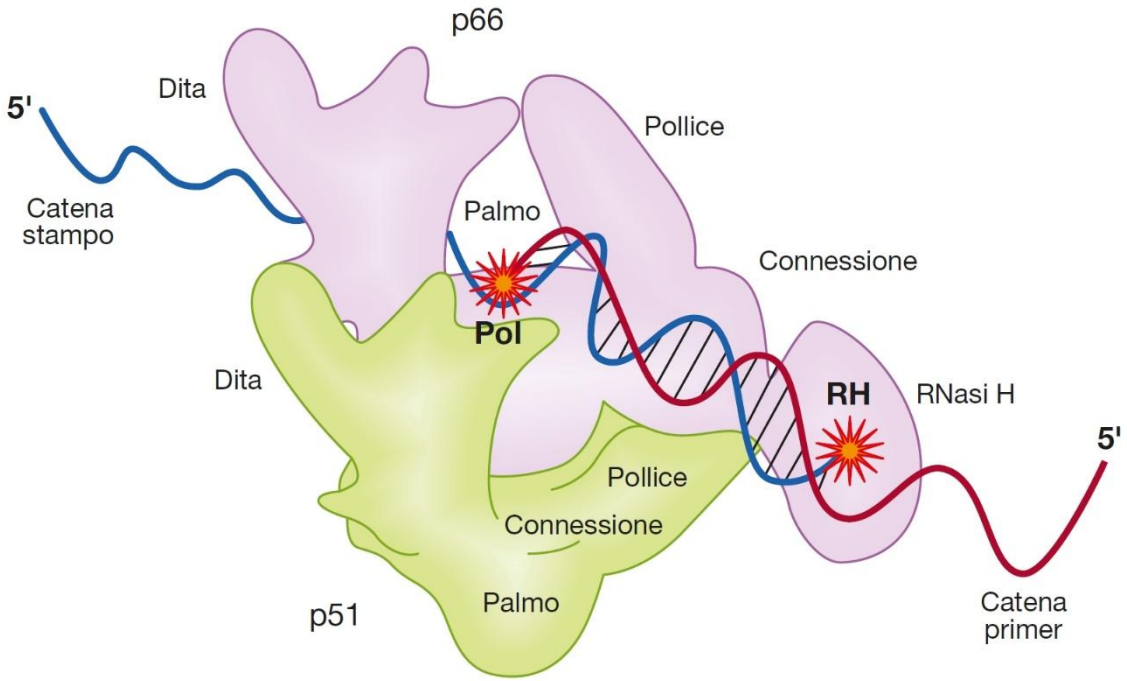


Figura 63.3 Struttura della trascrittasi inversa. La trascrittasi inversa è un eterodimero composto dai due polipeptidi p51 e p66 che interagiscono formando una struttura asimmetrica che ricorda una mano destra. Il sito catalitico si trova in una fenditura del palmo ed è rappresentato da una sequenza costante nei diversi retrovirus.

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	Maedi-visna	Pneumonia, SNC
Goat	Caprine Arthritis Encephalitis	Arthritis, encephalitis
Horse	Equine infectious anemia	Anemia
Cattle	Bovine immunodeficiency virus	
Cat	Feline immunodeficiency virus	Feline AIDS
Non-human Primates		
Chimpanzees	SIV_{cpz}	no development of immunodeficiency in the natural hosts of the virus African primates represent a great reservoir for lentiviruses*
Sooty mangabey	SIV_{sm}	
Macaque	SIV_{mac}	
African green monkey	SIV_{agm}	
Sykes monkeys	SIV_{syk}	
Mandrill	SIV_{mnd}	
Hoest monkey	$SIV_{hoes}t$	
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

G. Antonelli, M. Clementi, G. Pozzi, G.M. Rossolini
Principi di Microbiologia medica, II ed.

Etiologic agent

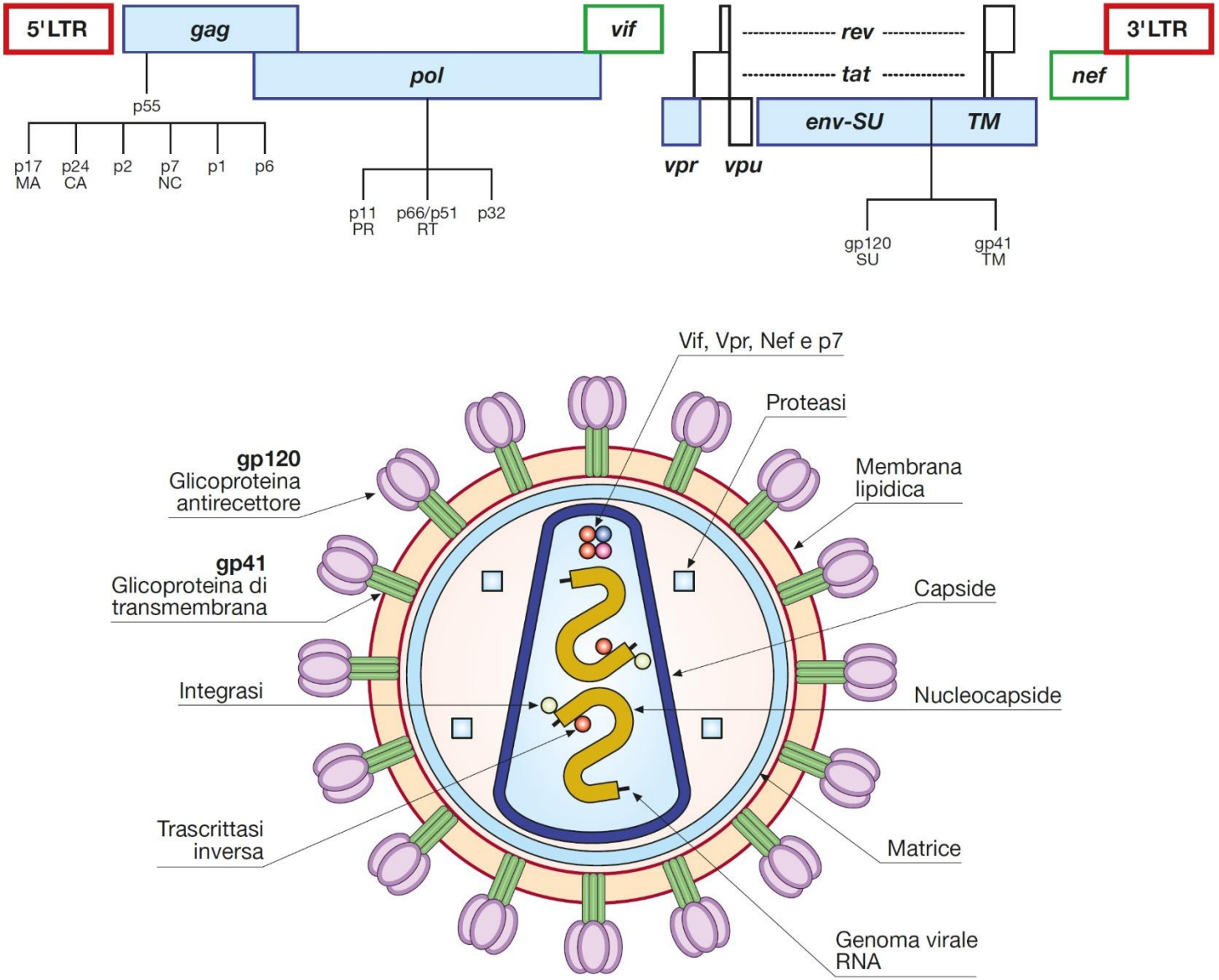
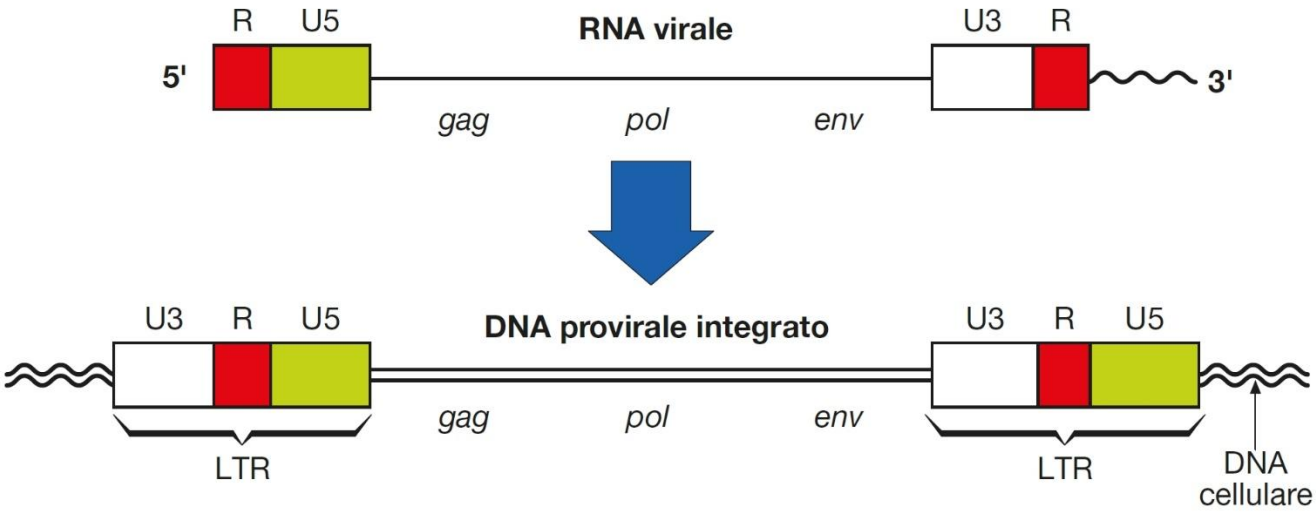


Figura 63.1 Struttura del virione. La parte superiore della figura mostra il genoma di HIV-1 e le proteine corrispondenti ai geni *gag*, *pol* ed *env*. La parte inferiore rappresenta la struttura schematica del virus.

Figura 63.2 **Organizzazione dell'RNA di HIV-1 e del DNA provirale integrato nel genoma della cellula ospite.**



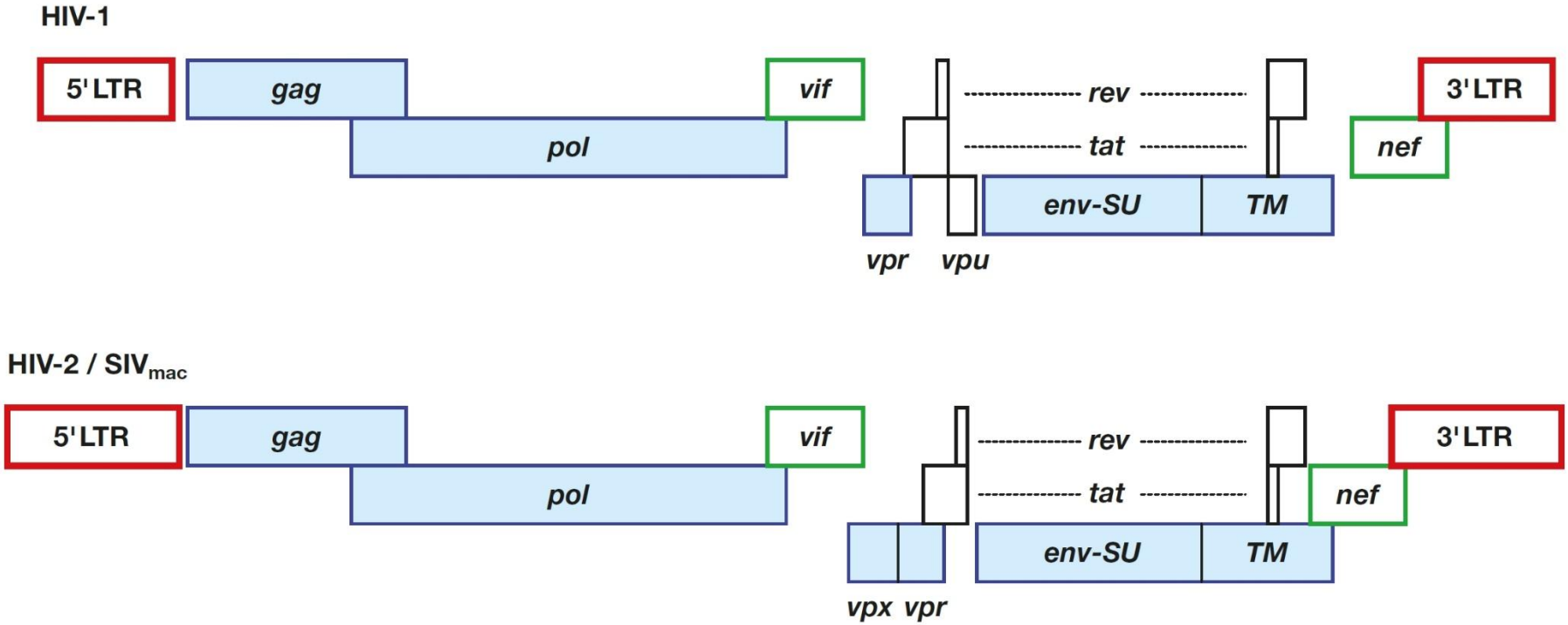
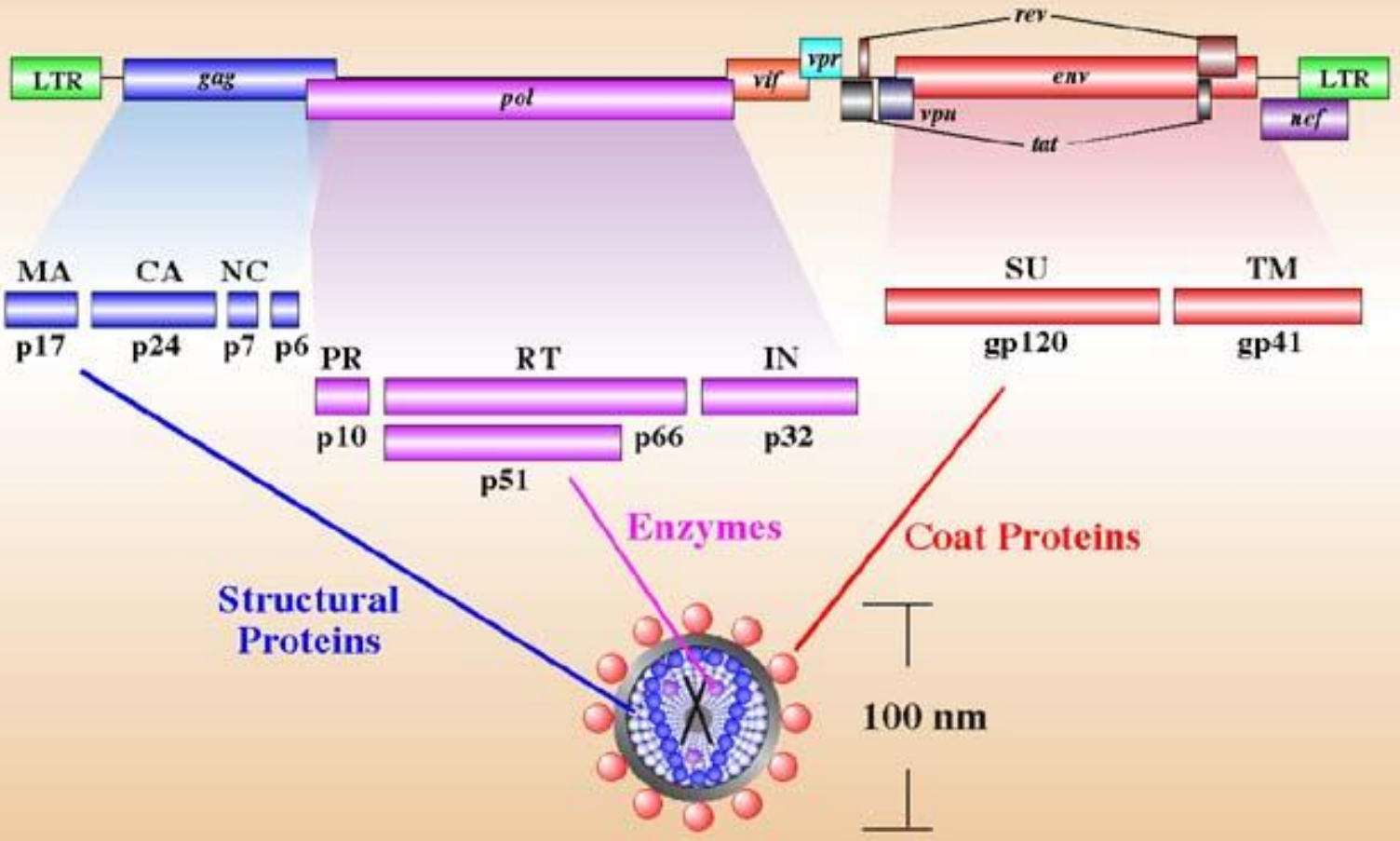


Figura 63.4 Organizzazione del genoma dei lentivirus dei primati: HIV-1 e HIV-2.

Genomic Organization of HIV-1

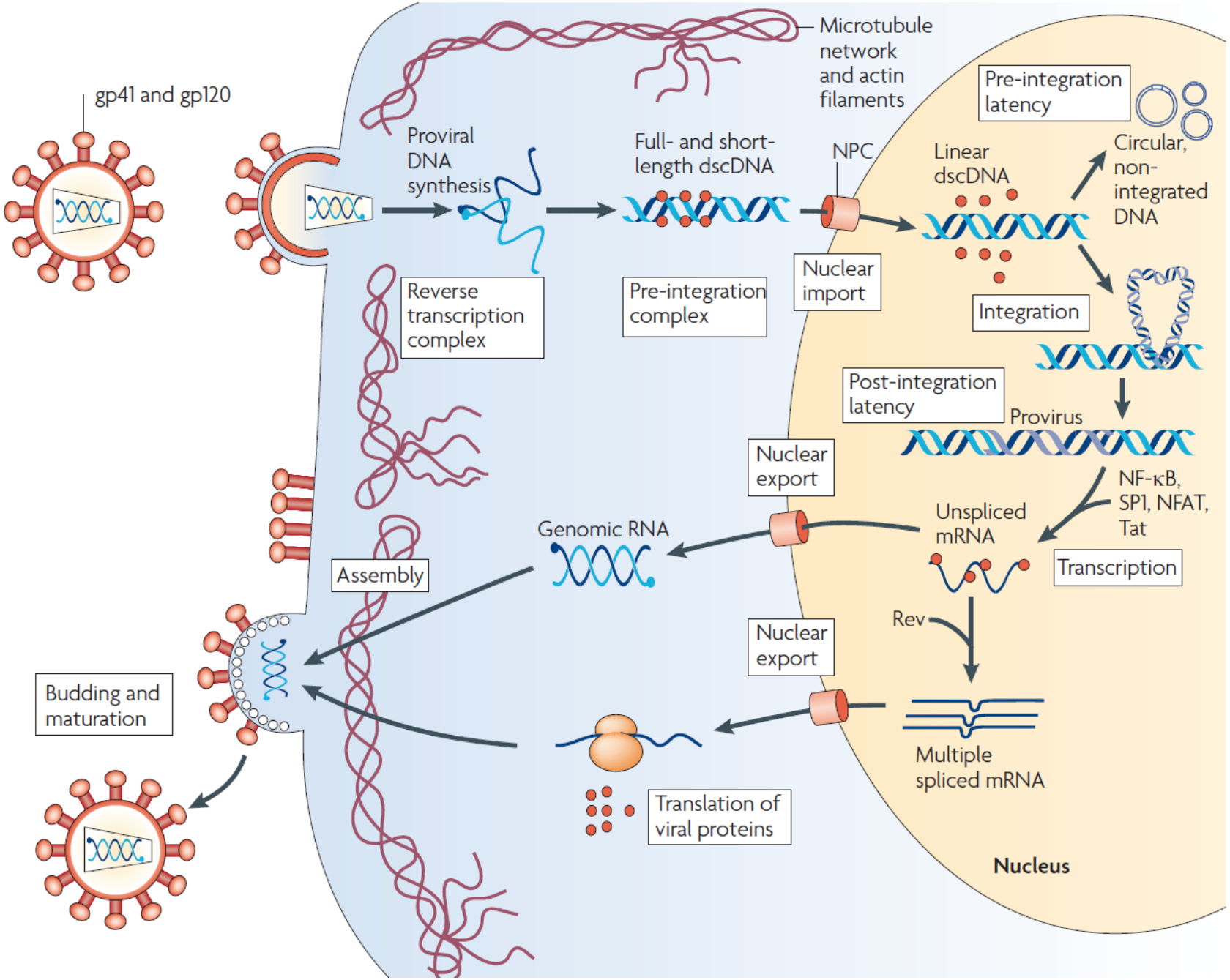


MWCHO

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)


gp41 and gp120
Microtubule network and actin filaments
Proviral DNA synthesis
Full- and short-length dscDNA
NPC
Pre-integration latency
Linear dscDNA
Circular, non-integrated DNA
Reverse transcription complex
Pre-integration complex
Nuclear import
Integration
Post-integration latency
Provirus
Nuclear export
NF-κB, SP1, NFAT, Tat
Genomic RNA
Unspliced mRNA
Transcription
Assembly
Rev
Nuclear export
Budding and maturation
Multiple spliced mRNA
Translation of viral proteins
Nucleus

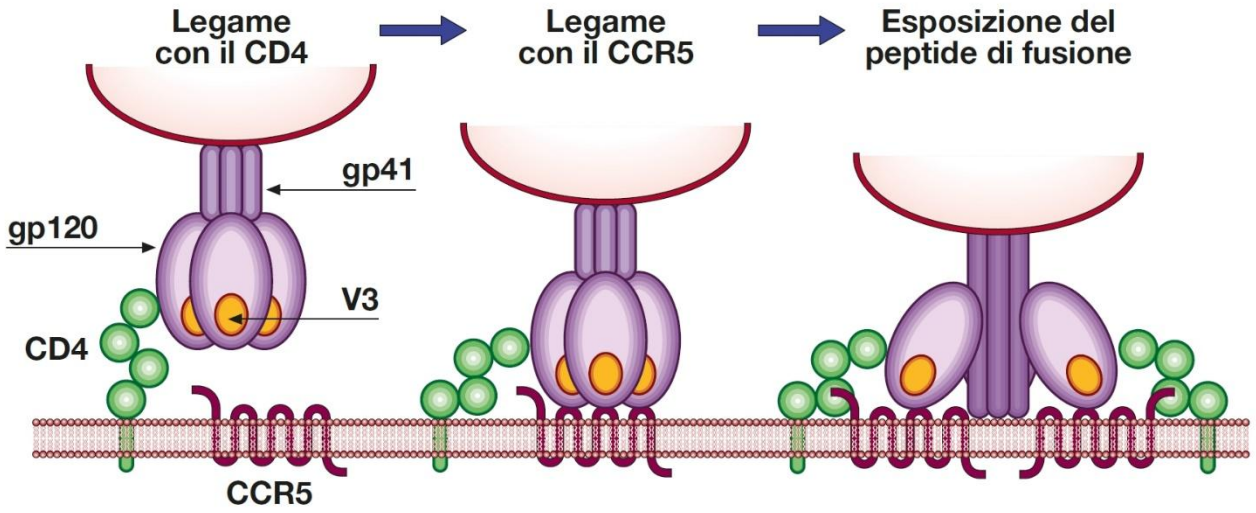


Figura 63.7 Rappresentazione dell'entrata di HIV-1 nelle cellule target. Il virus attraverso la proteina gp120 lega due recettori in sequenza, CD4 e CCR5. Il completamento del legame porta all'esposizione del peptide di fusione presente all'estremità amminoterminale della gp41. Tali eventi guidano la fusione dell'envelope virale con la membrana citoplasmatica della cellula che sarà infettata.

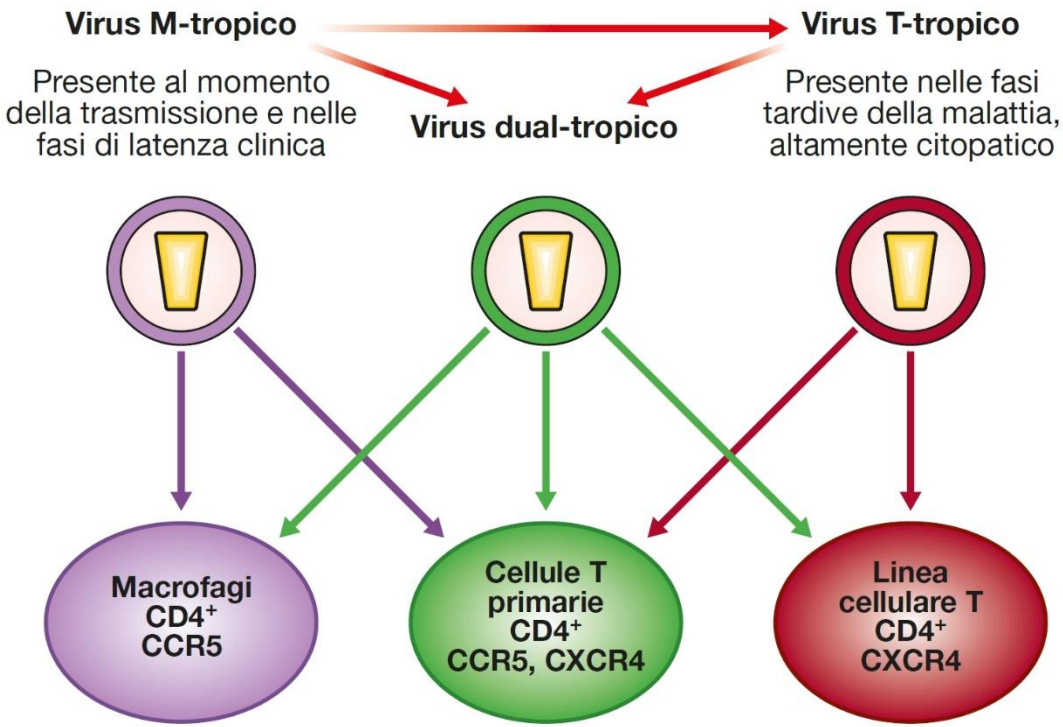


Figura 63.5 **Tropismo cellulare: uso del corecettore da parte di HIV-1.**

Biological properties of R5, X4 and R5X4 viruses

	Co-receptor usage		Infected cells		Syncytia induction		Replication rate in PBMC	
	CCR5	CXCR4	Naive Tcells	Memory T cells	NO (NSI)*	YES (SI)*	S/L	R/H
R5	+	-	-	+	+	-	+	-
X4	-	+	+	+	-	+	-	+
R5X4	+	+	+	+	-	+	-	+

Legend: NSI, Non Syncytium Inducing; SI, Syncytium Inducing; S/L, Slow/Low; R/H, Rapid/High; PBMC, Peripheral Blood Mononuclear Cells.

HIV Cure

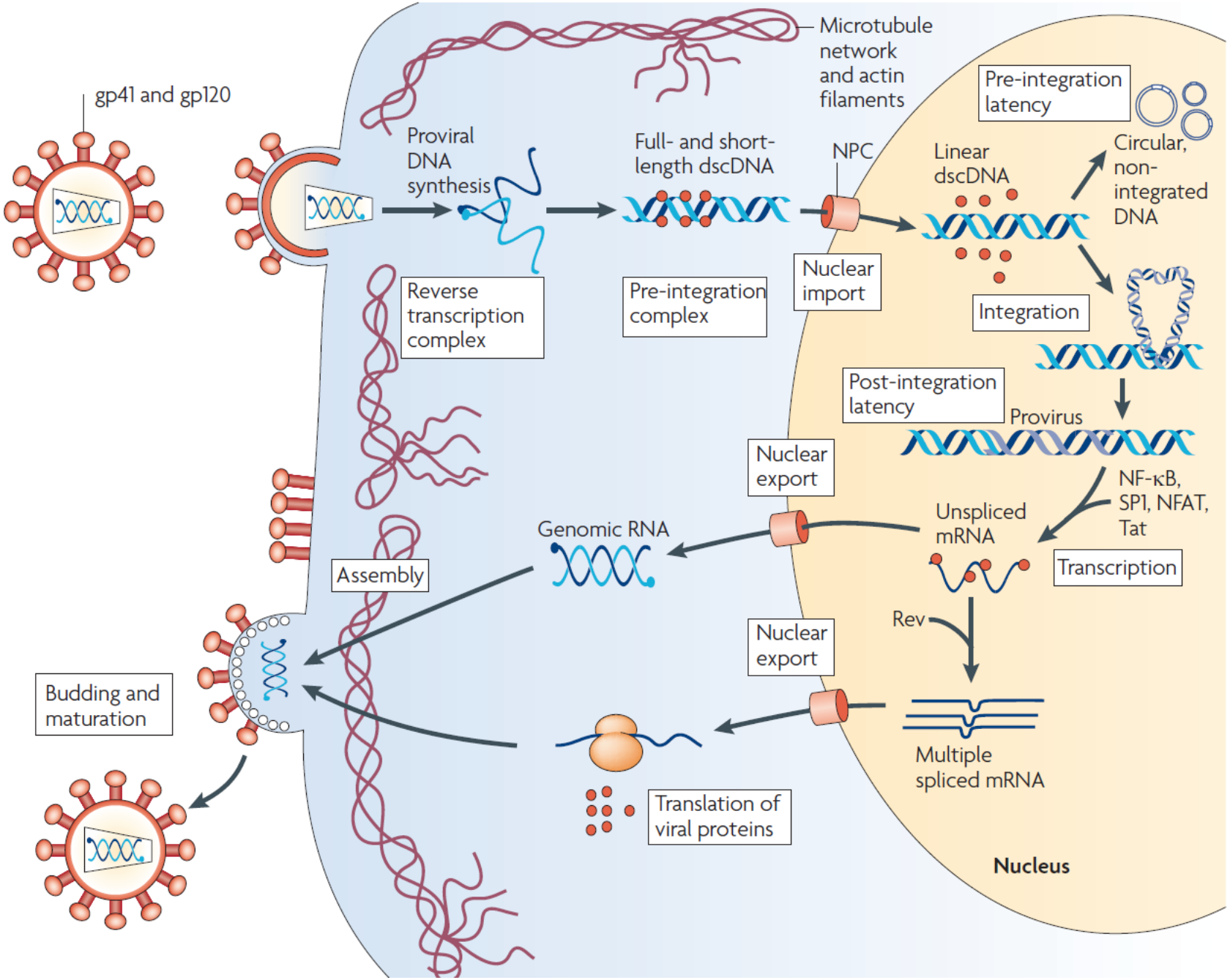
Timothy **Ray Brown (Berlin patient) and the London patient** shared similar medical circumstances.

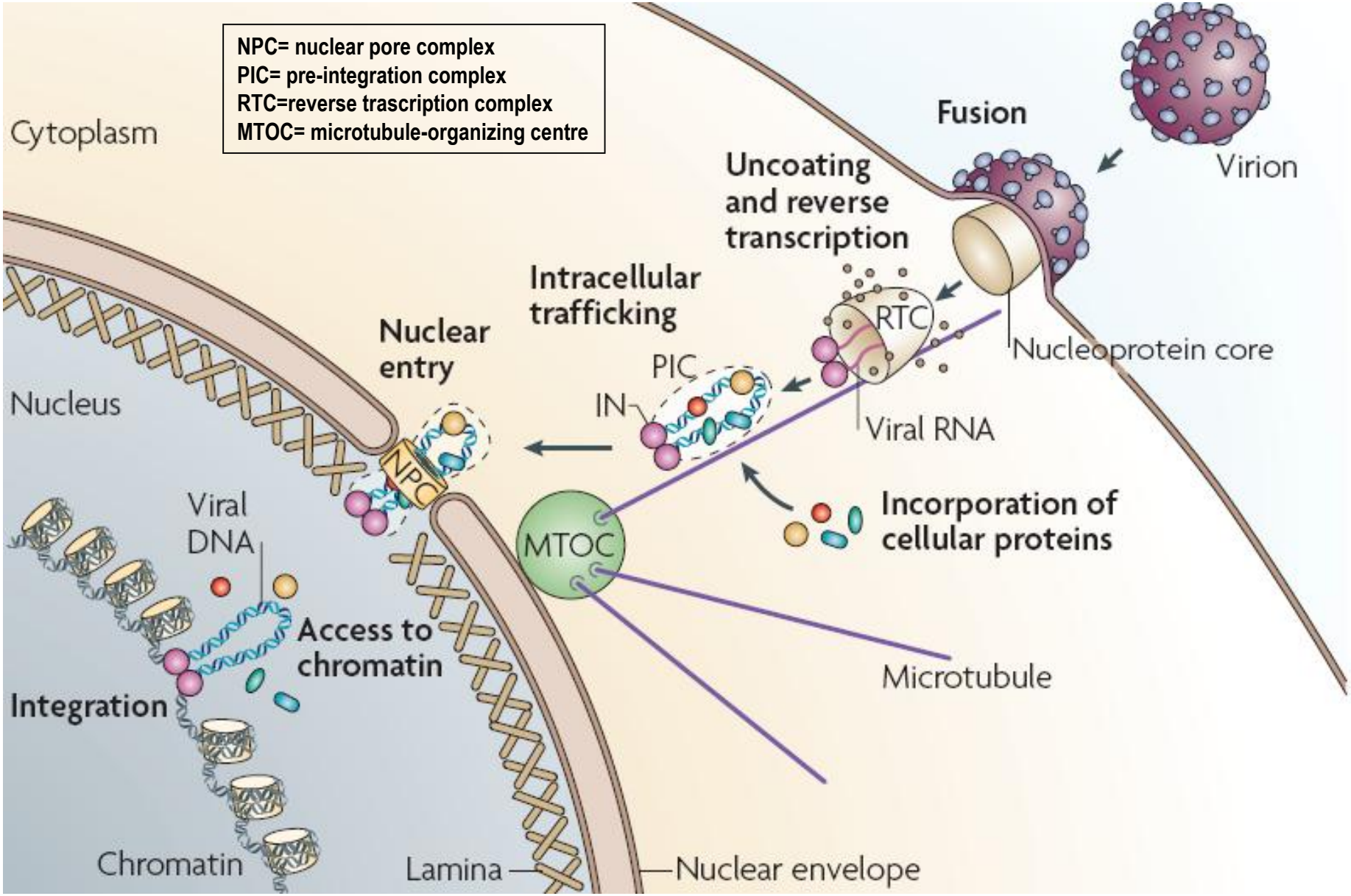
They were both HIV-1-positive and receiving ART therapy.
They both eventually developed a blood cancer (acute myeloid leukemia and Hodgkin's lymphoma, respectively), which was treated with chemotherapy and various other therapeutics.

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 Δ32/Δ32),** 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.


gp41 and gp120
Microtubule network and actin filaments
Proviral DNA synthesis
Full- and short-length dscDNA
NPC
Pre-integration latency
Linear dscDNA
Circular, non-integrated DNA
Reverse transcription complex
Pre-integration complex
Nuclear import
Integration
Post-integration latency
Provirus
Nuclear export
NF-κB, SP1, NFAT, Tat
Genomic RNA
Unspliced mRNA
Transcription
Assembly
Rev
Nuclear export
Budding and maturation
Multiple spliced mRNA
Translation of viral proteins
Nucleus


NPC= nuclear pore complex
PIC= pre-integration complex
RTC=reverse trascription complex
MTOC= microtubule-organizing centre
Cytoplasm
Fusion
Virion
Uncoating and reverse transcription
Intracellular trafficking
Nuclear entry
RTC
Nucleoprotein core
PIC
IN
Viral RNA
Nucleus
NPC
Viral DNA
MTOC
Incorporation of cellular proteins
Access to chromatin
Microtubule
Integration
Chromatin
Lamina
Nuclear envelope

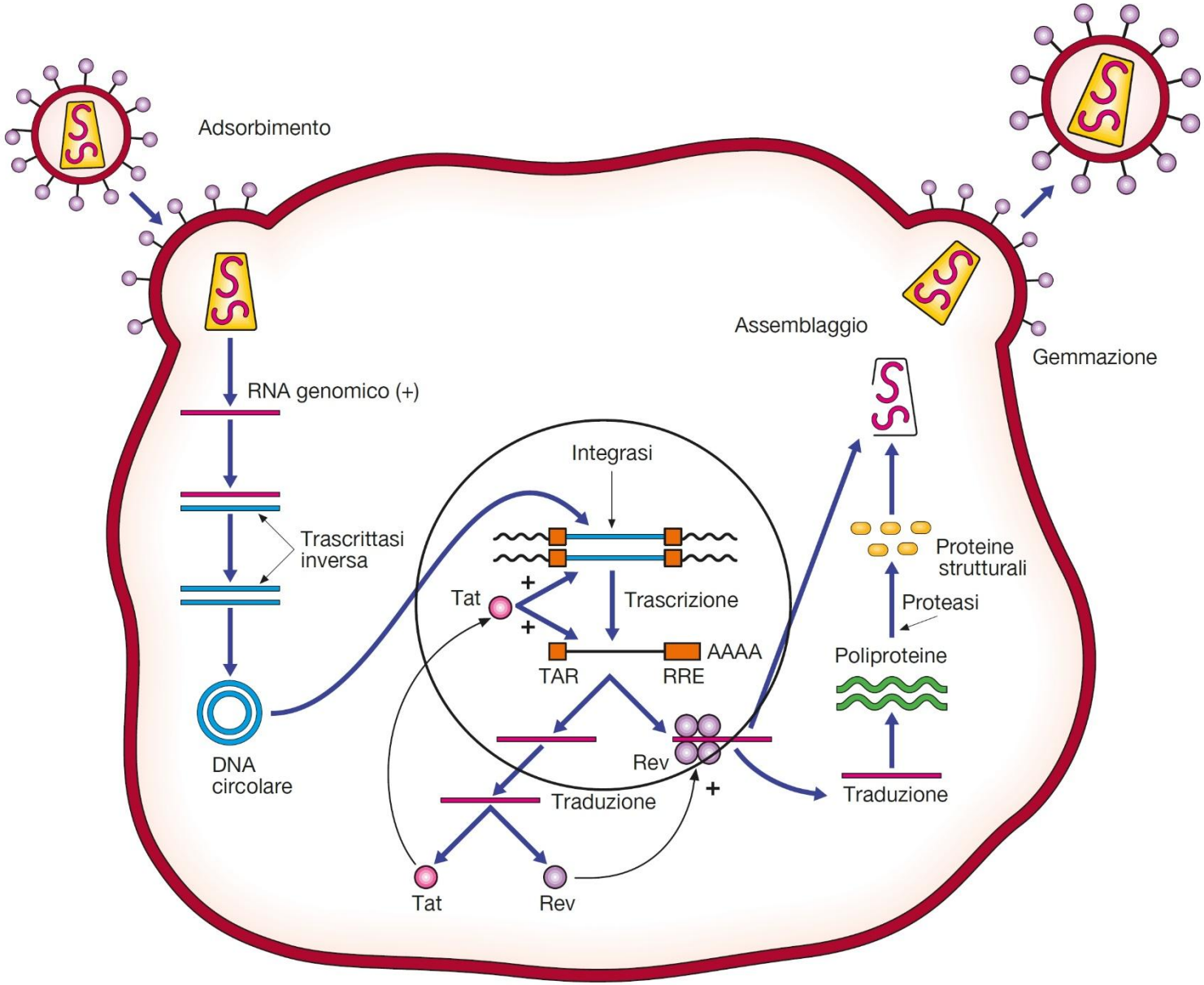
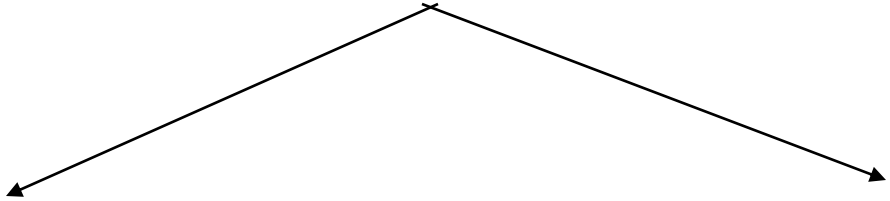


Figura 63.6 **Rappresentazione schematica del ciclo replicativo di HIV-1.**

HIV CLASSIFICATION



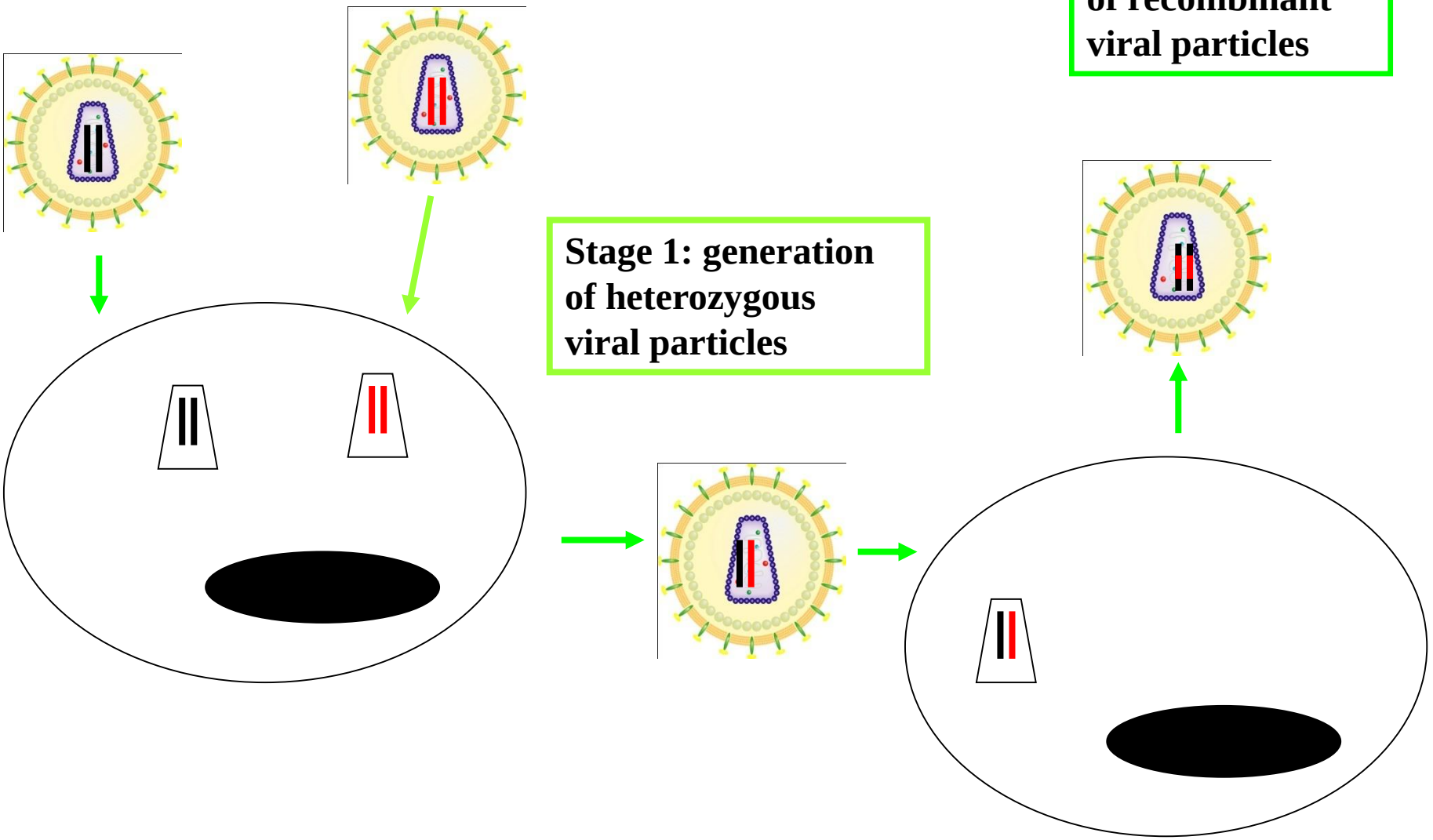
HIV-1

- **Group M of HIV-1**
- **Group O of HIV-1**
- **Group N of HIV-1**

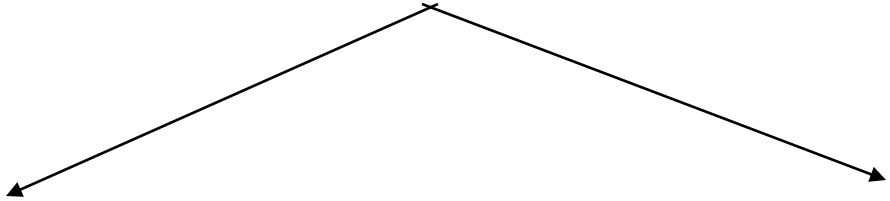
HIV-2

- **Group M of HIV-2**

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



HIV CLASSIFICATION



HIV-1

- **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

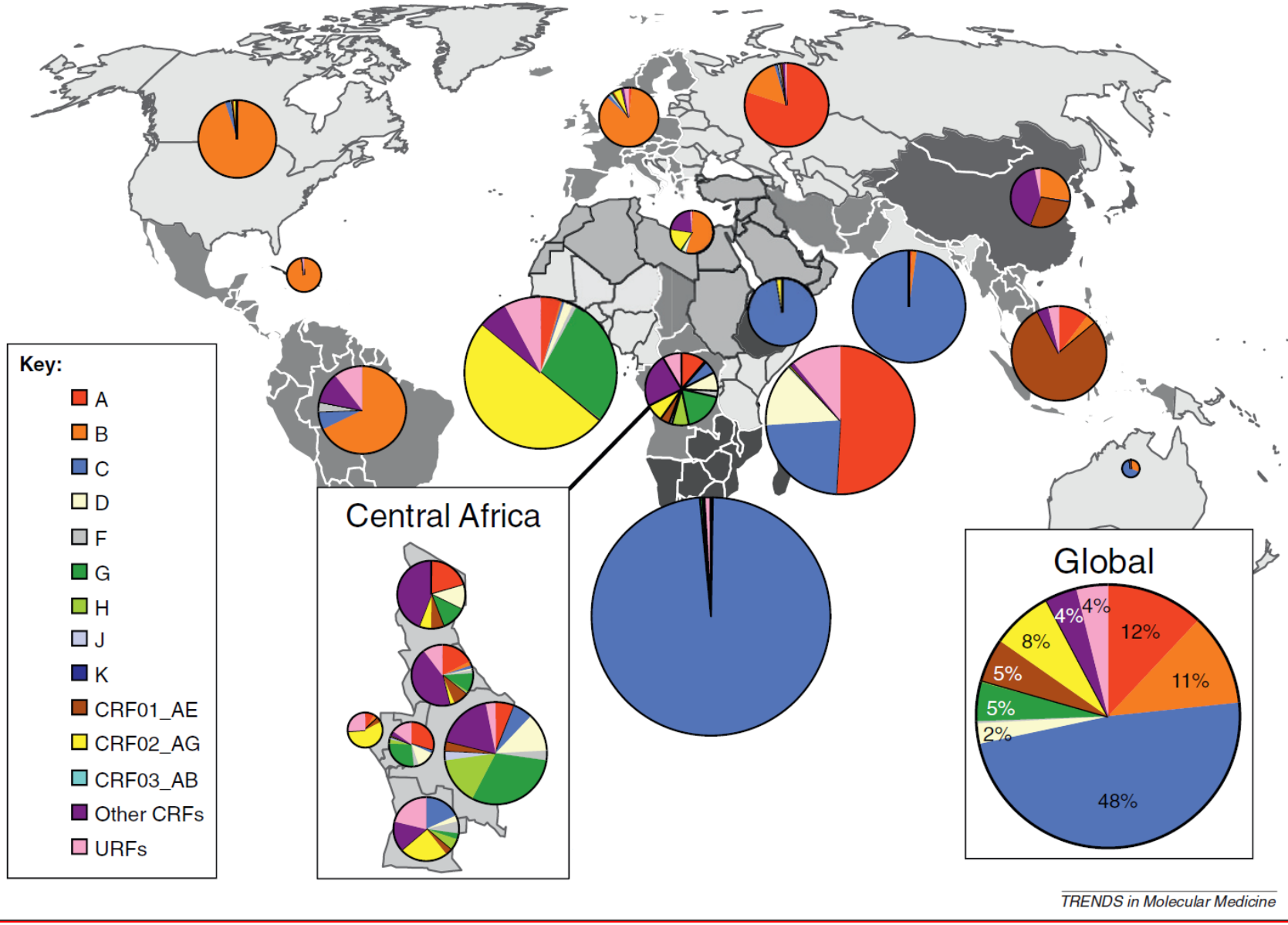
- **Group O of HIV-1**
- **Group N of HIV-1**

HIV-2

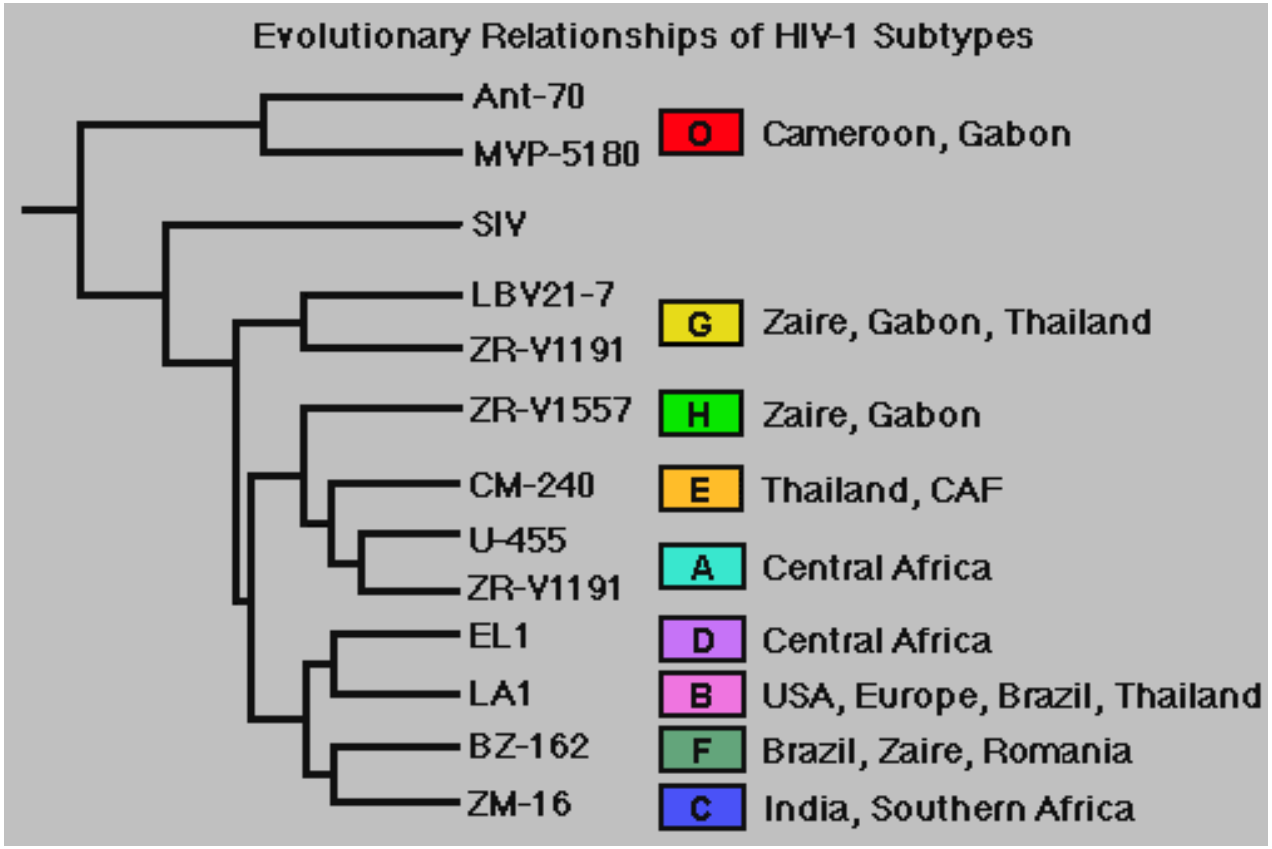
- **Group M of HIV-2**

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

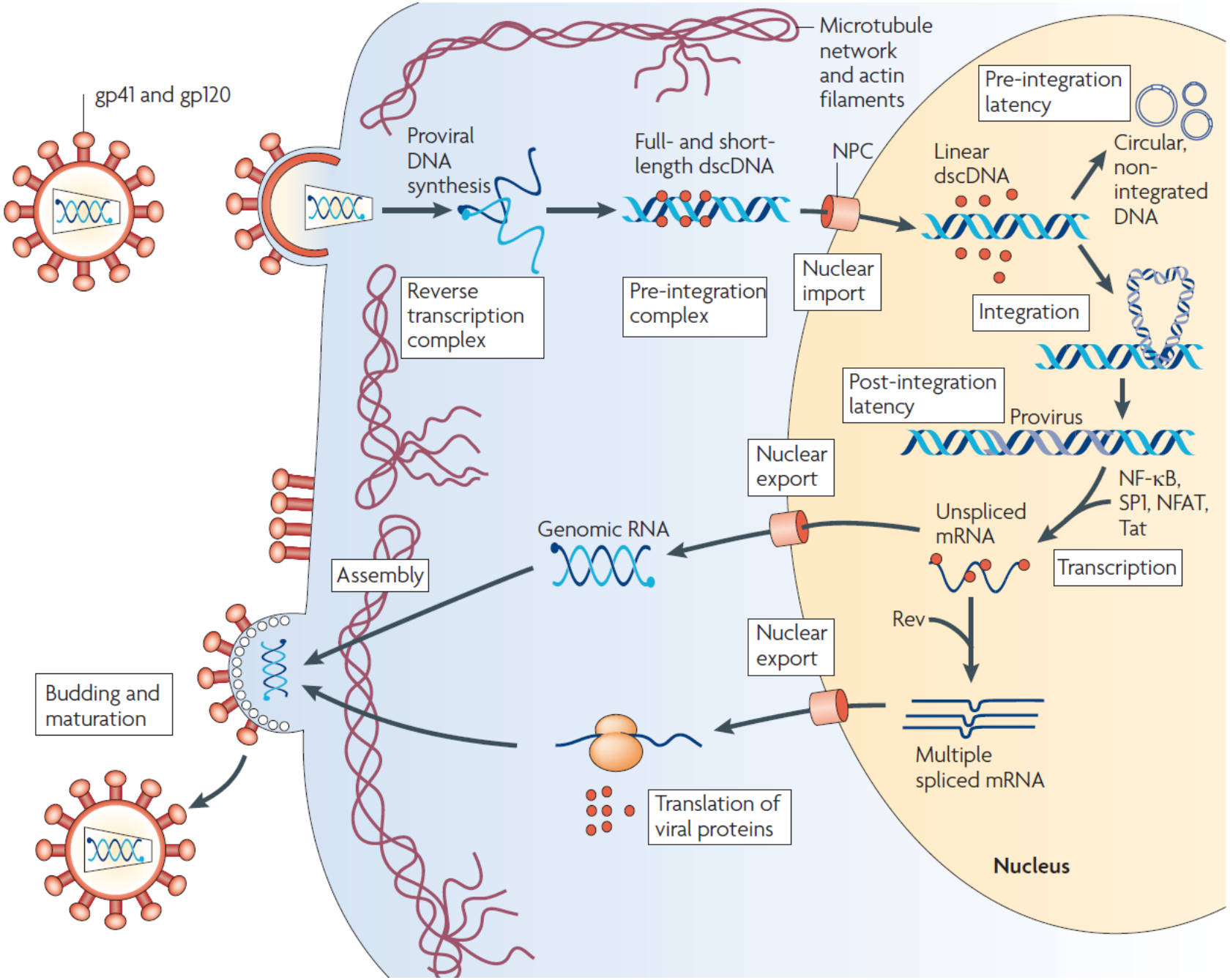
Geographic distribution of HIV-1 groups and subtypes



HIV GENOTYPES



Pathogenesis


gp41 and gp120
Microtubule network and actin filaments
Proviral DNA synthesis
Full- and short-length dscDNA
NPC
Pre-integration latency
Linear dscDNA
Circular, non-integrated DNA
Reverse transcription complex
Pre-integration complex
Nuclear import
Integration
Post-integration latency
Provirus
Nuclear export
NF-κB, SP1, NFAT, Tat
Genomic RNA
Unspliced mRNA
Transcription
Assembly
Rev
Nuclear export
Budding and maturation
Multiple spliced mRNA
Translation of viral proteins
Nucleus

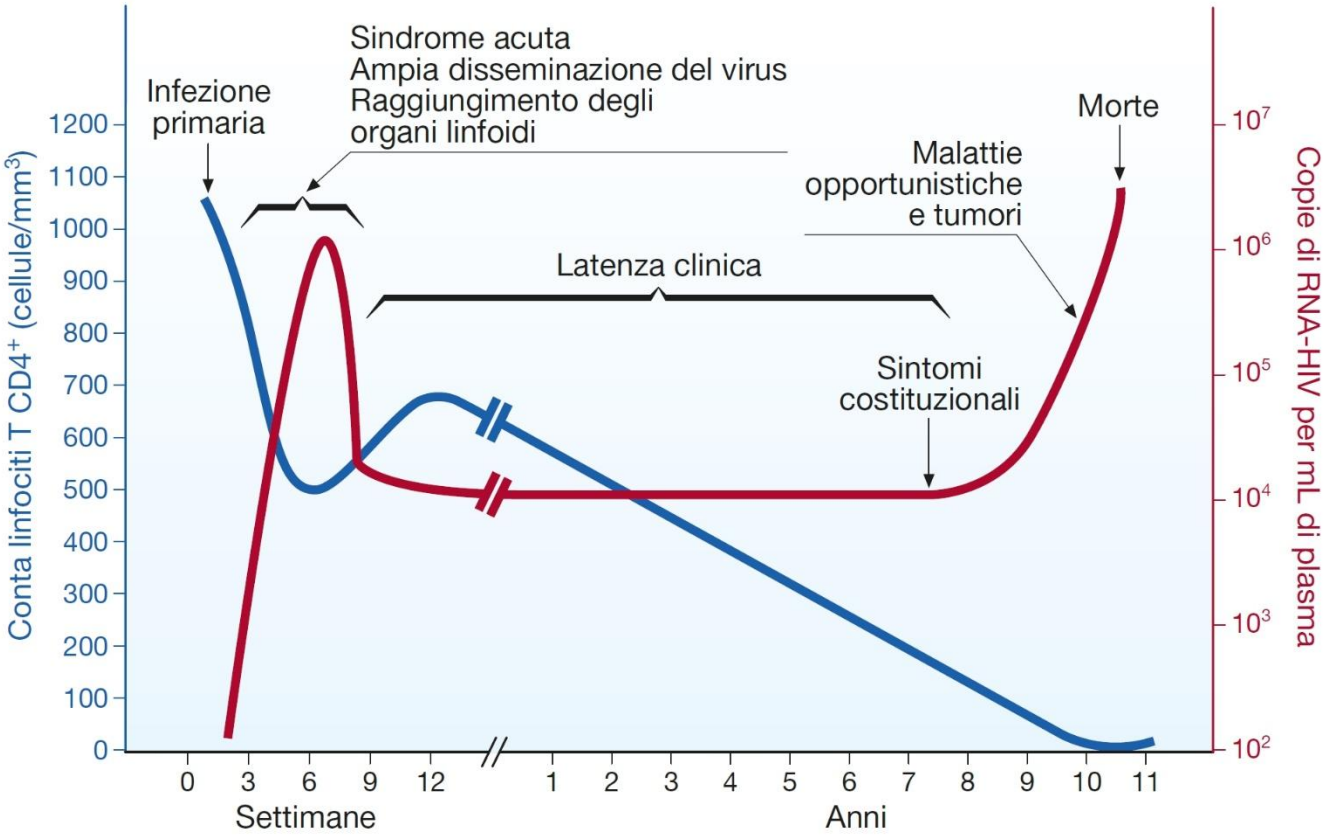


Figura 63.8 Andamento della carica virale e dei linfociti CD4 durante il corso dell'infezione da HIV-1.

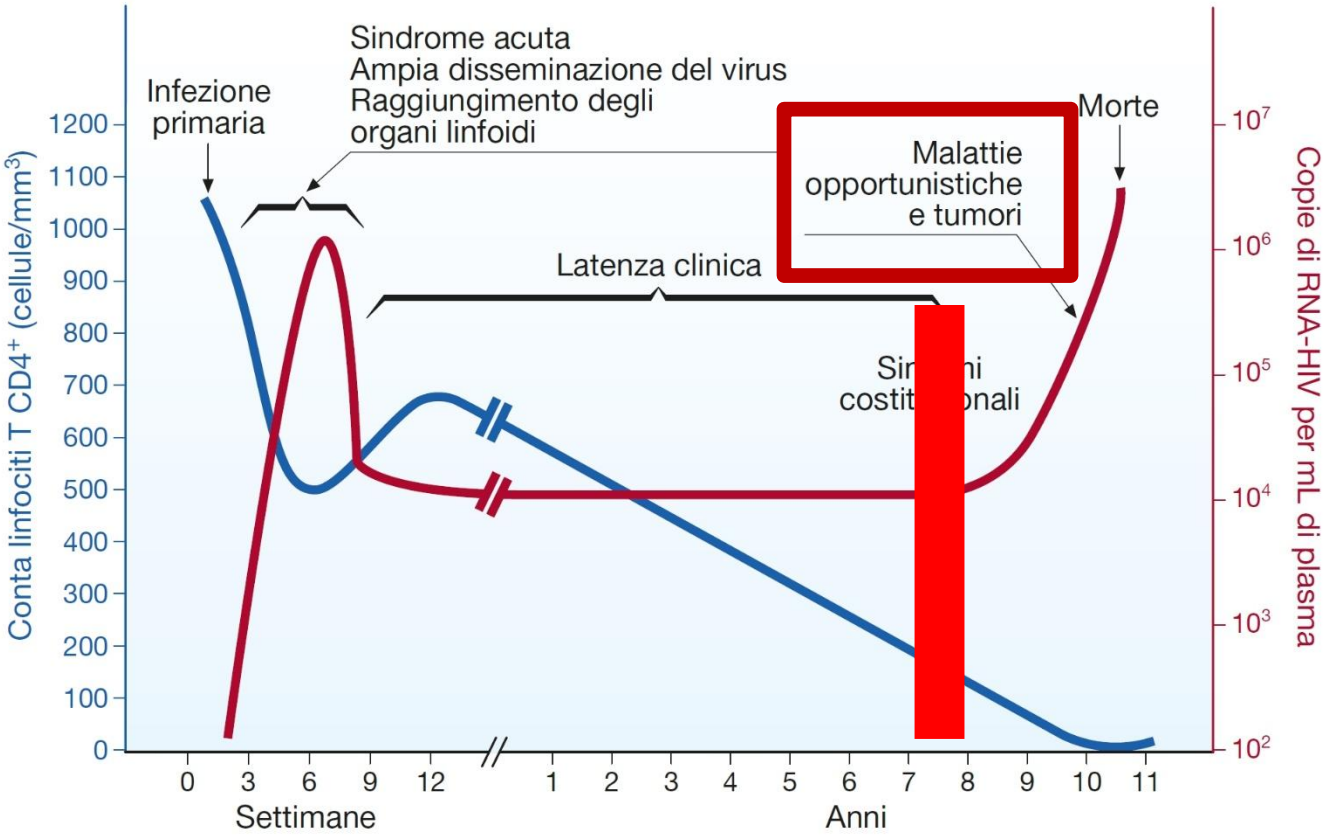


Figura 63.8 Andamento della carica virale e dei linfociti CD4 durante il corso dell'infezione da HIV-1.

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

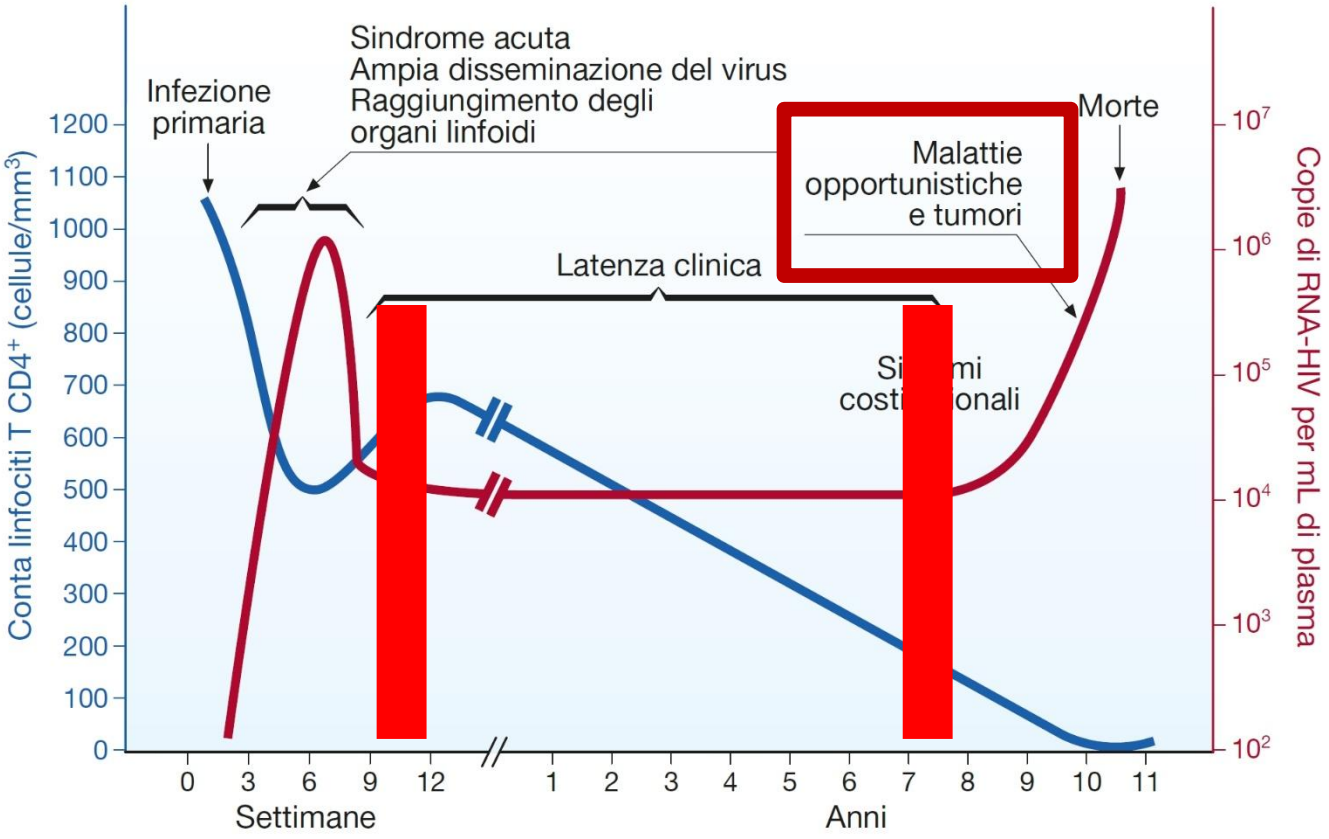
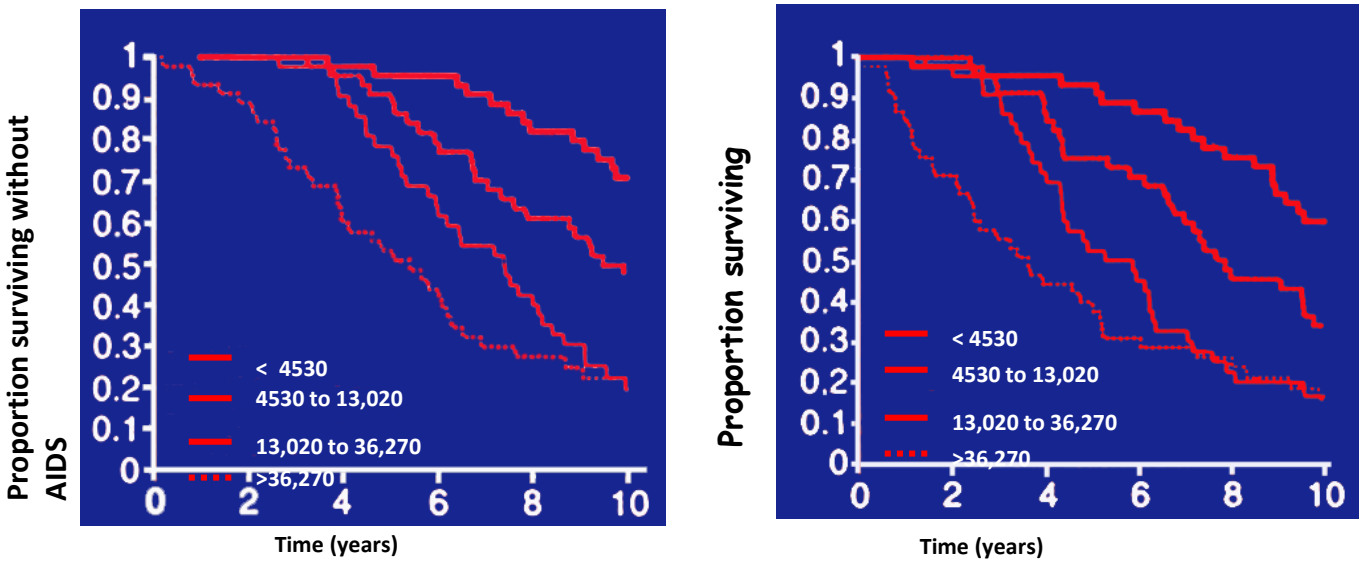


Figura 63.8 Andamento della carica virale e dei linfociti CD4 durante il corso dell'infezione da HIV-1.

Disease progression: RNA VIRAL LOAD

Mellors JW , Science 1996



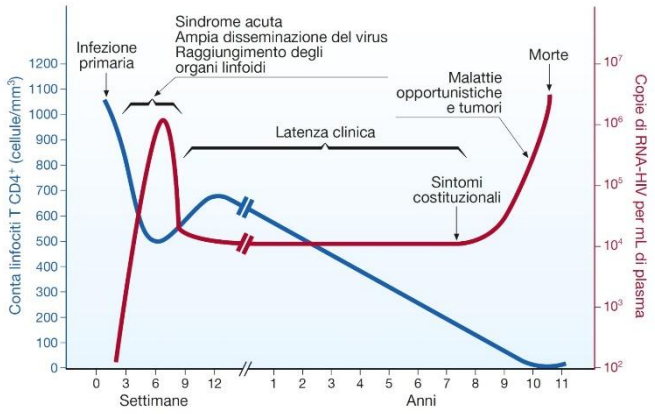


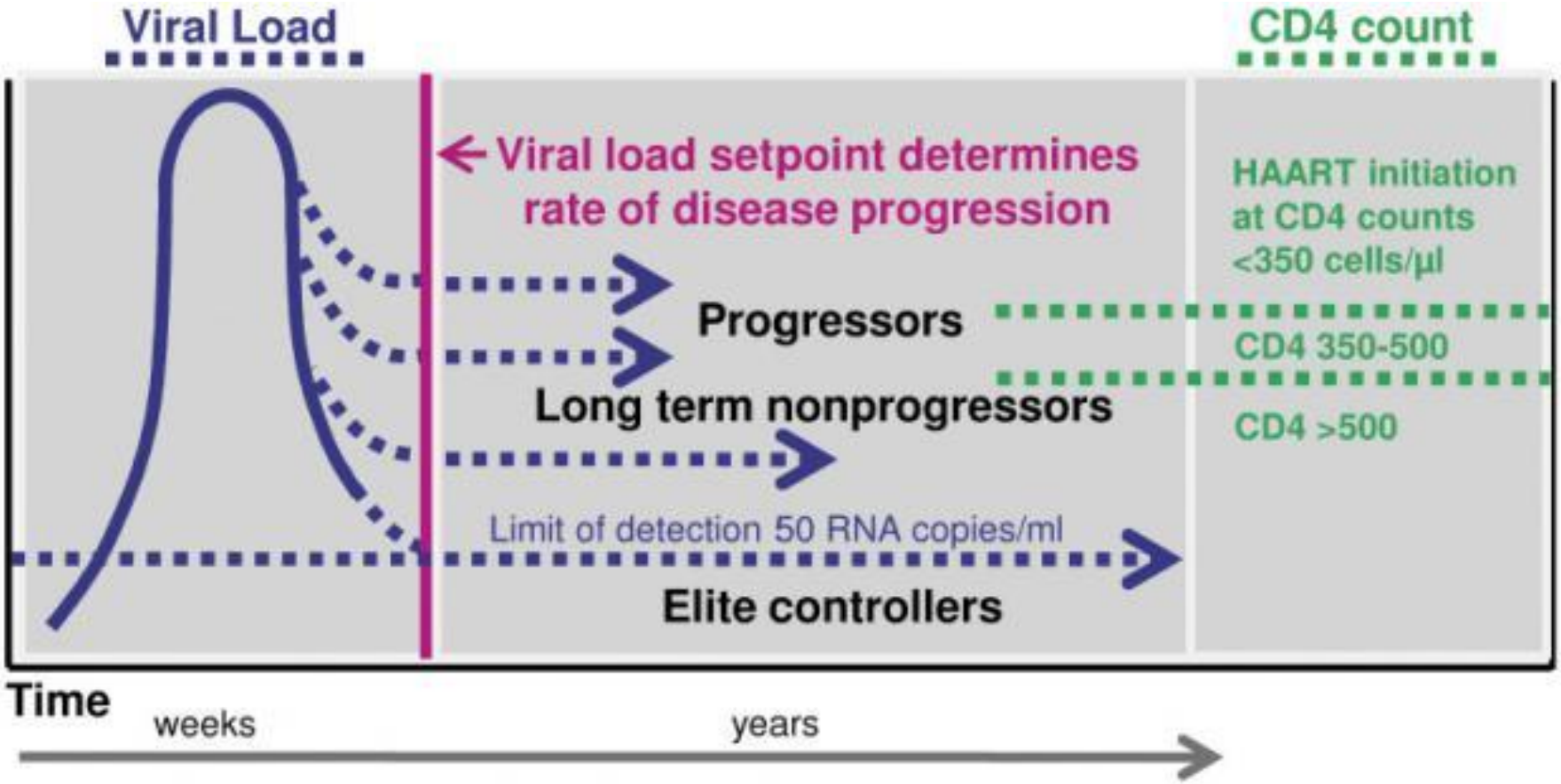
Figura 63.8 **Andamento della carica virale e dei linfociti CD4 durante il corso dell'infezione da HIV-1.**

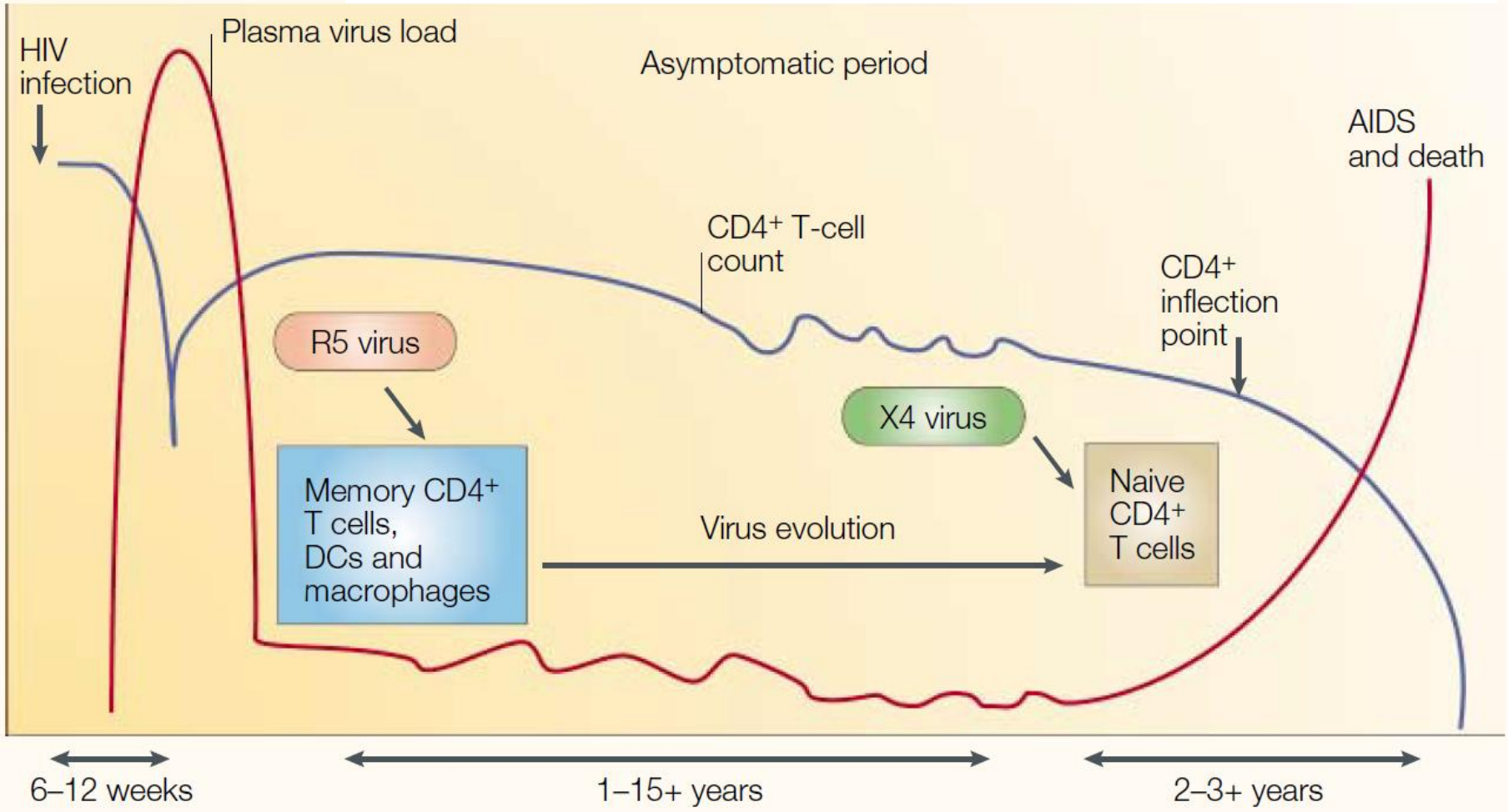
F. Dianzani[1], G. Antonelli[2], E. Riva[1], S. Uccini[3] & G. Visco[4]
[1]*Institute of Virology*
University "La Sapienza", Rome, Italy

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

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


Viral Load
CD4 count
Viral load setpoint determines rate of disease progression
HAART initiation at CD4 counts <350 cells/µl
Progressors
CD4 350-500
Long term nonprogressors
CD4 >500
Limit of detection 50 RNA copies/ml
Elite controllers
Time
weeks
years


HIV infection
Plasma virus load
Asymptomatic period
AIDS and death
CD4+ T-cell count
CD4+ inflection point
R5 virus
X4 virus
Memory CD4+ T cells, DCs and macrophages
Virus evolution
Naive CD4+ T cells
6–12 weeks
1–15+ years
2–3+ years

PATHOGENESIS OF HIV INFECTION

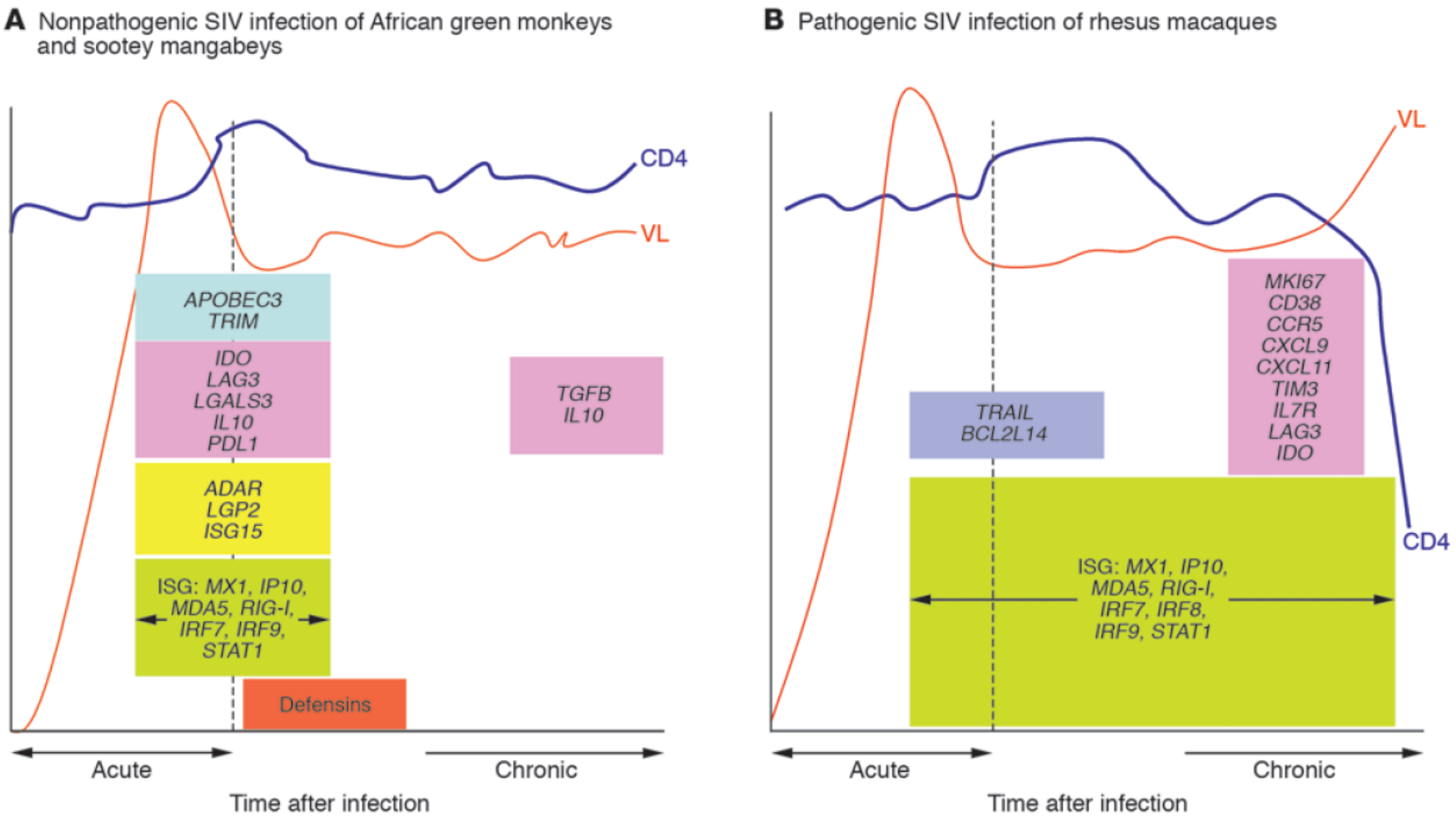
Viral pathogenesis- direct cytopatic effects of infected CD4+ cells due to HIV-1;

HIV-induced immunopathogenesis- indirect cithopatic 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)


A Nonpathogenic SIV infection of African green monkeys and sootey mangabeys
CD4
VL
APOBEC3
TRIM
IDO
LAG3
LGALS3
IL10
PDL1
TGFB
IL10
ADAR
LGP2
ISG15
ISG: MX1, IP10, MDA5, RIG-I, IRF7, IRF9, STAT1
Defensins
Acute
Chronic
Time after infection
B Pathogenic SIV infection of rhesus macaques
VL
MKI67
CD38
CCR5
CXCL9
CXCL11
TIM3
IL7R
LAG3
IDO
TRAIL
BCL2L14
CD4
ISG: MX1, IP10, MDA5, RIG-I, IRF7, IRF8, IRF9, STAT1
Acute
Chronic
Time after infection

Grossman z, Nature Medicine 2006

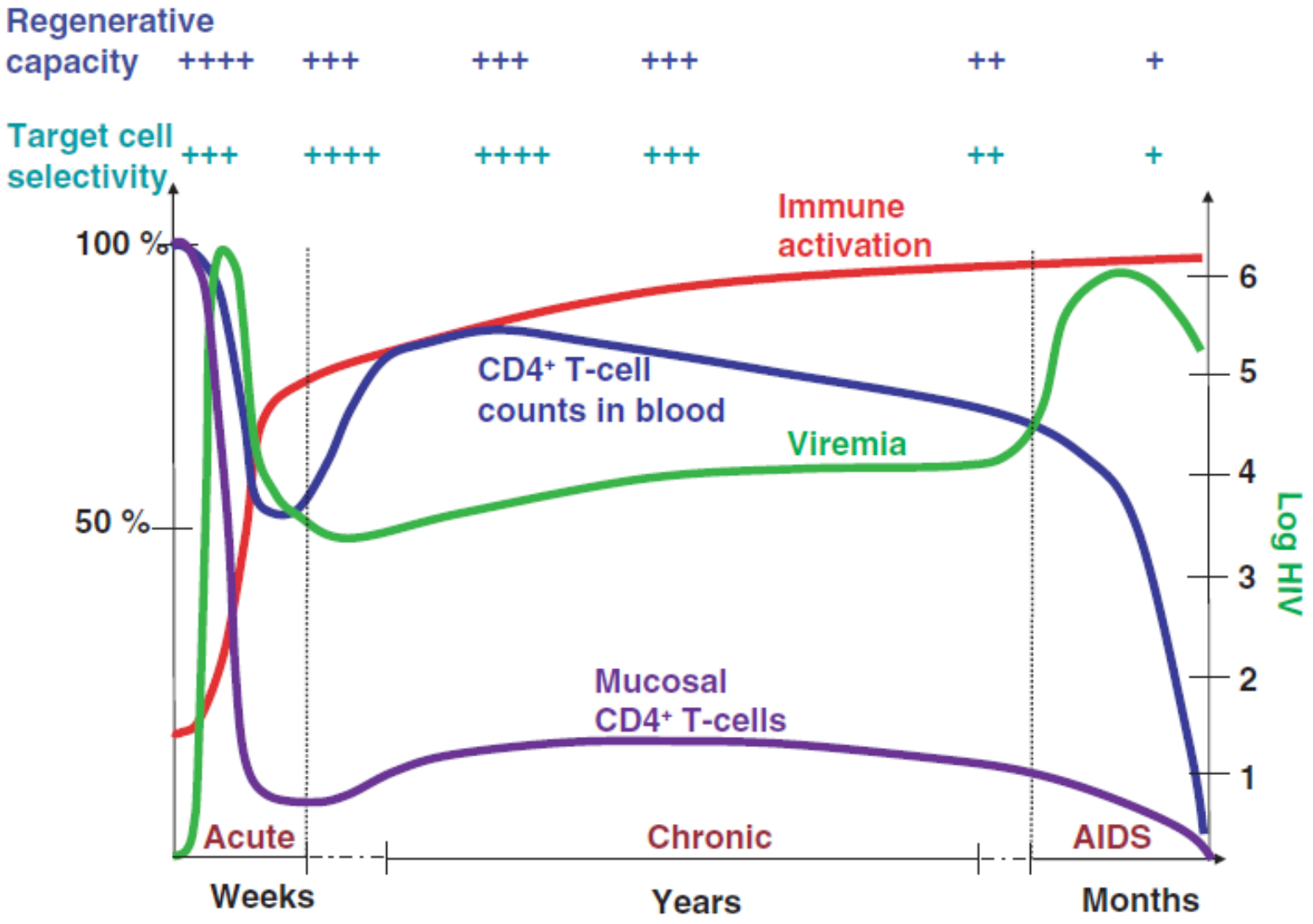
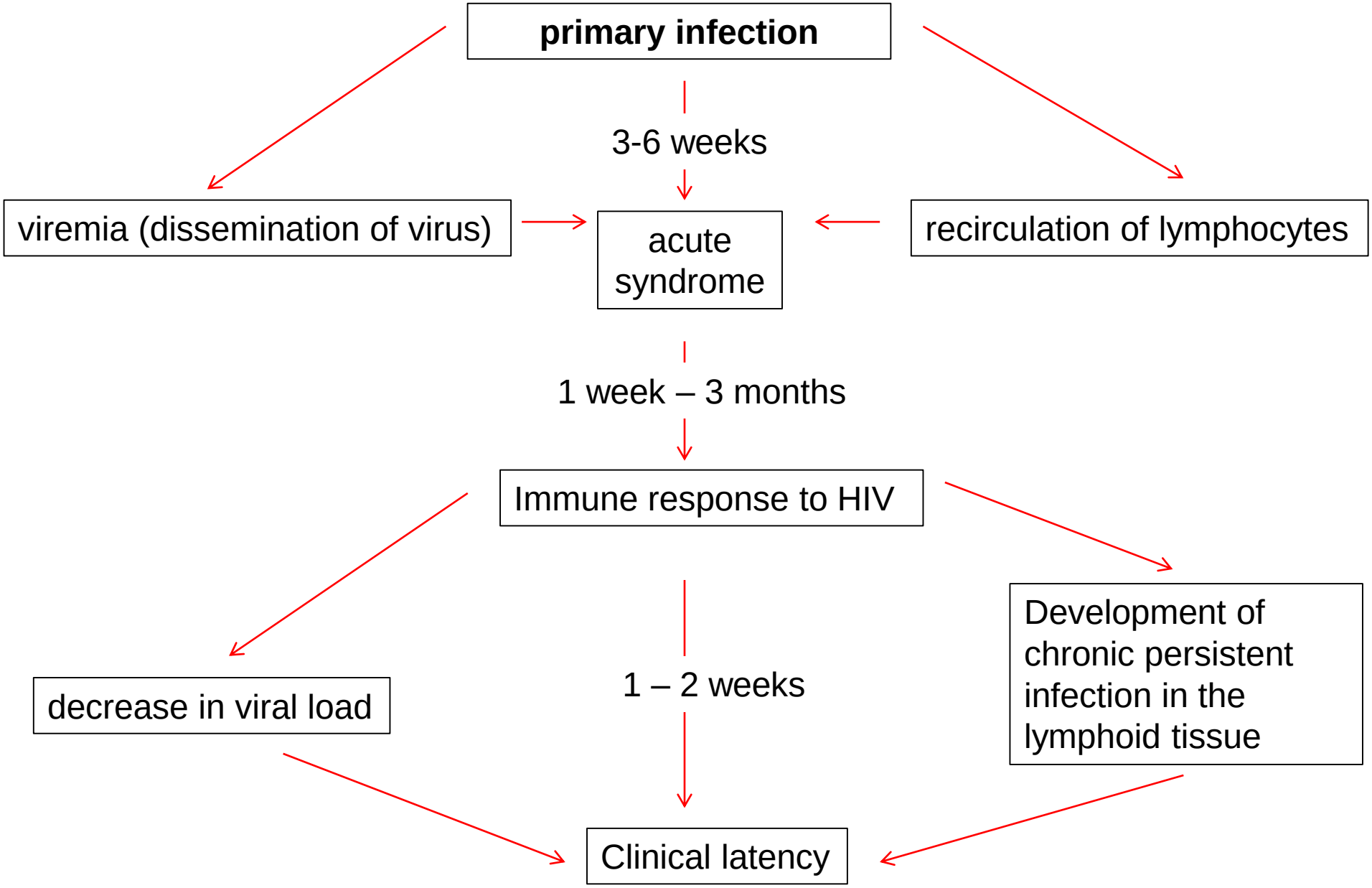


Figure 3 Quantitative and qualitative measures of HIV disease progression.

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


primary infection
3-6 weeks
viremia (dissemination of virus)
acute syndrome
recirculation of lymphocytes
1 week – 3 months
Immune response to HIV
decrease in viral load
1 – 2 weeks
Development of chronic persistent infection in the lymphoid tissue
Clinical latency

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

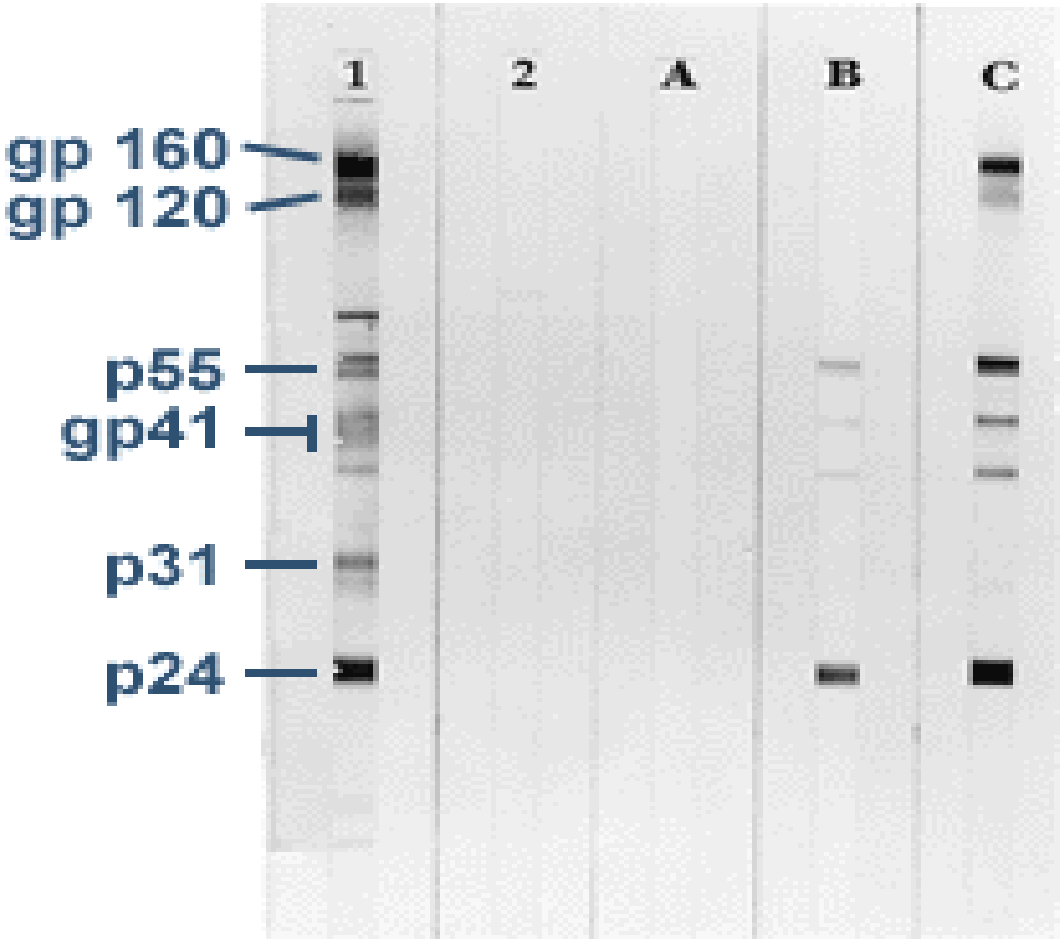
- **Confirmatory tests are used to confirm a reactive screening result**
- **HIGH SPECIFICITY**

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

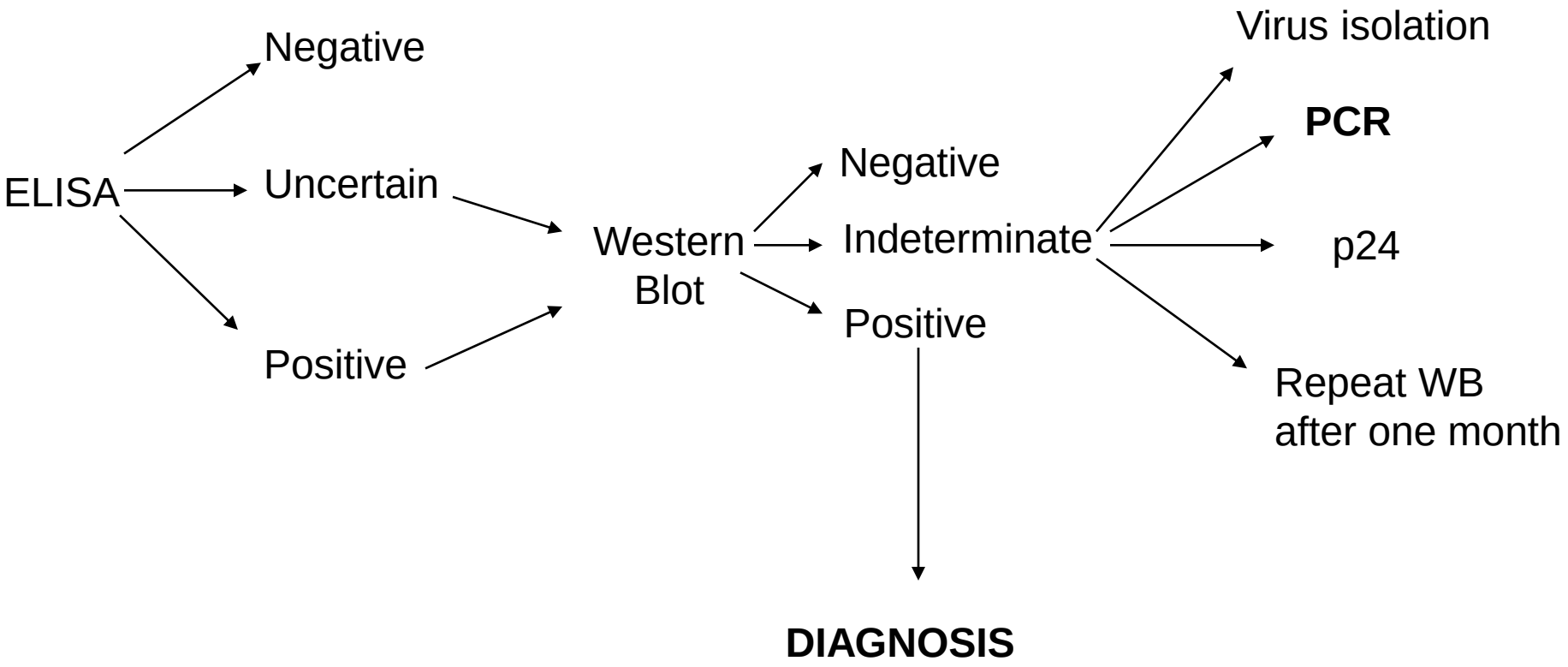


Lane 1, HIV+ serum (control)
Lane 2, HIV- serum (control)
Lane A, Patient A
Lane B, Patient B
Lane C, Patient C

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

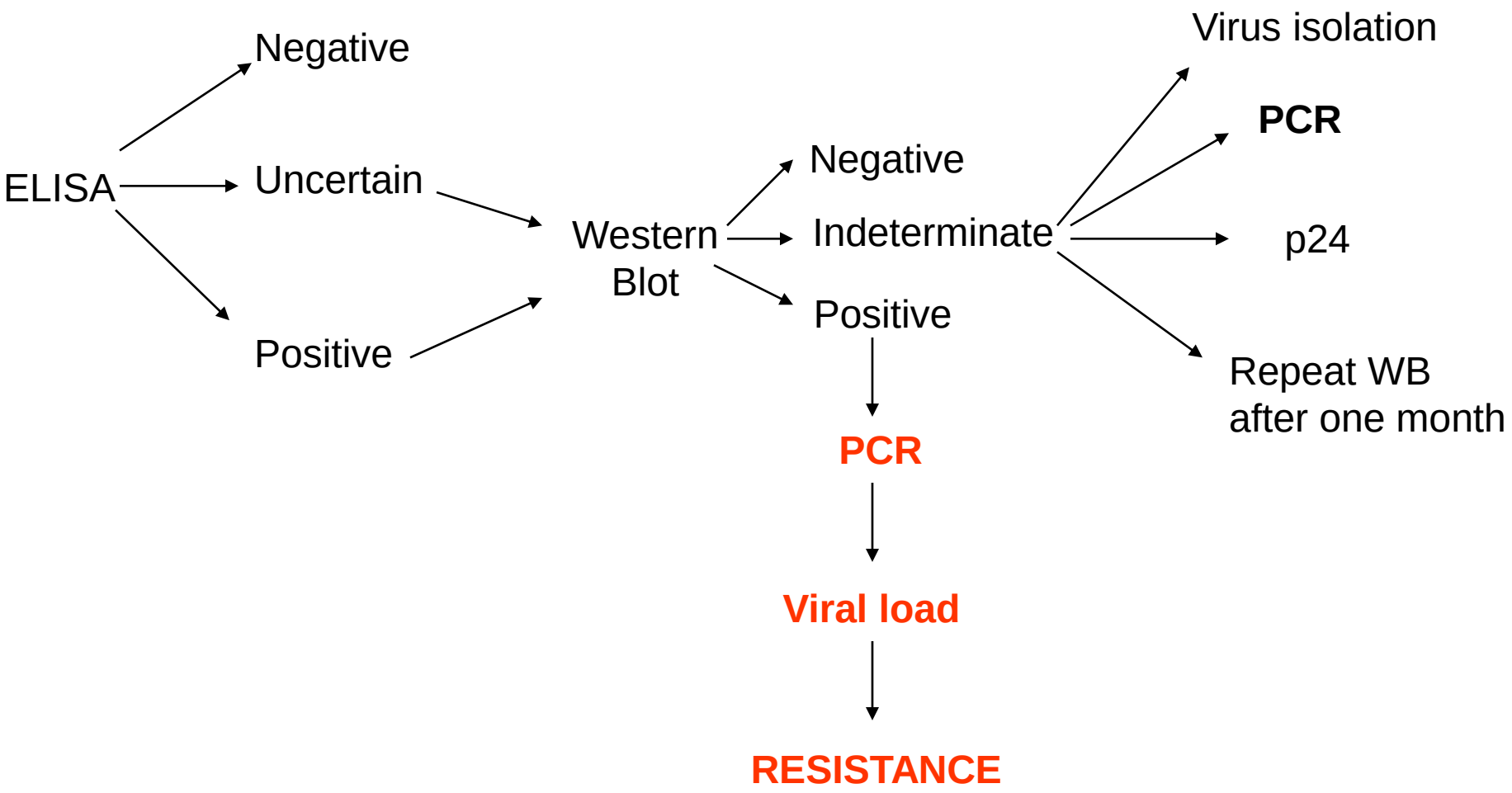
Diagnostic Algorithm for HIV Diagnosis in adults



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



Antiviral drugs

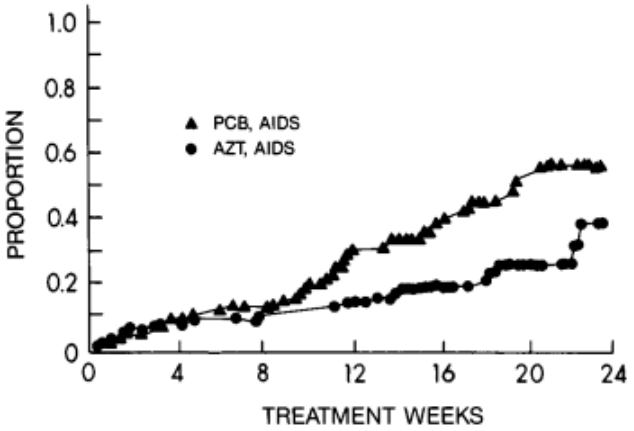
1987

Introduction of antiviral therapy – AZT

ORIGINAL ARTICLE FREE PREVIEW ARCHIVE

The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex

Margaret A. Fischl, M.D., Douglas D. Richman, M.D., Michael H. Grieco, M.D., J.D., Michael S. Gottlieb, M.D., Paul A. Volberding, M.D., Oscar L. Laskin, M.D., John M. Leedom, M.D., Jerome E. Groopman, M.D., Donna Mildvan, M.D., Robert T. Schooley, M.D., George G. Jackson, M.D., David T. Durack, M.B., D.Phil., et al.



AZT was approved by the FDA on March 19, 1987.
It was approved in record time with only one trial on humans instead of the standard three.
That trial was stopped after 19 weeks because the patients on the placebo were dying faster and the need for a treatment outweighed the need for full testing

Introduction of HAART

1996-1998

The New England
Journal of Medicine

VOLUME 338 MARCH 26, 1998 NUMBER 13

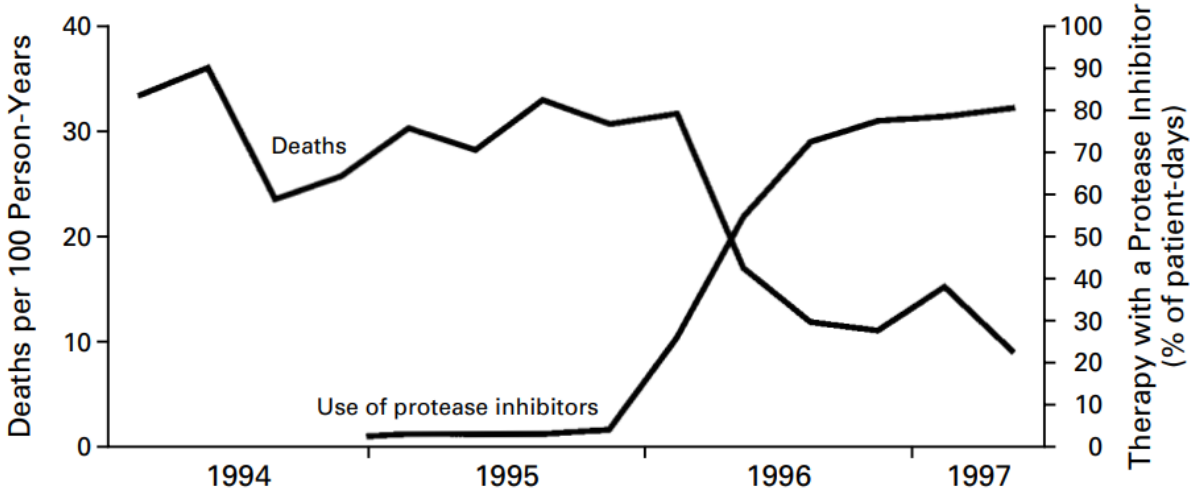
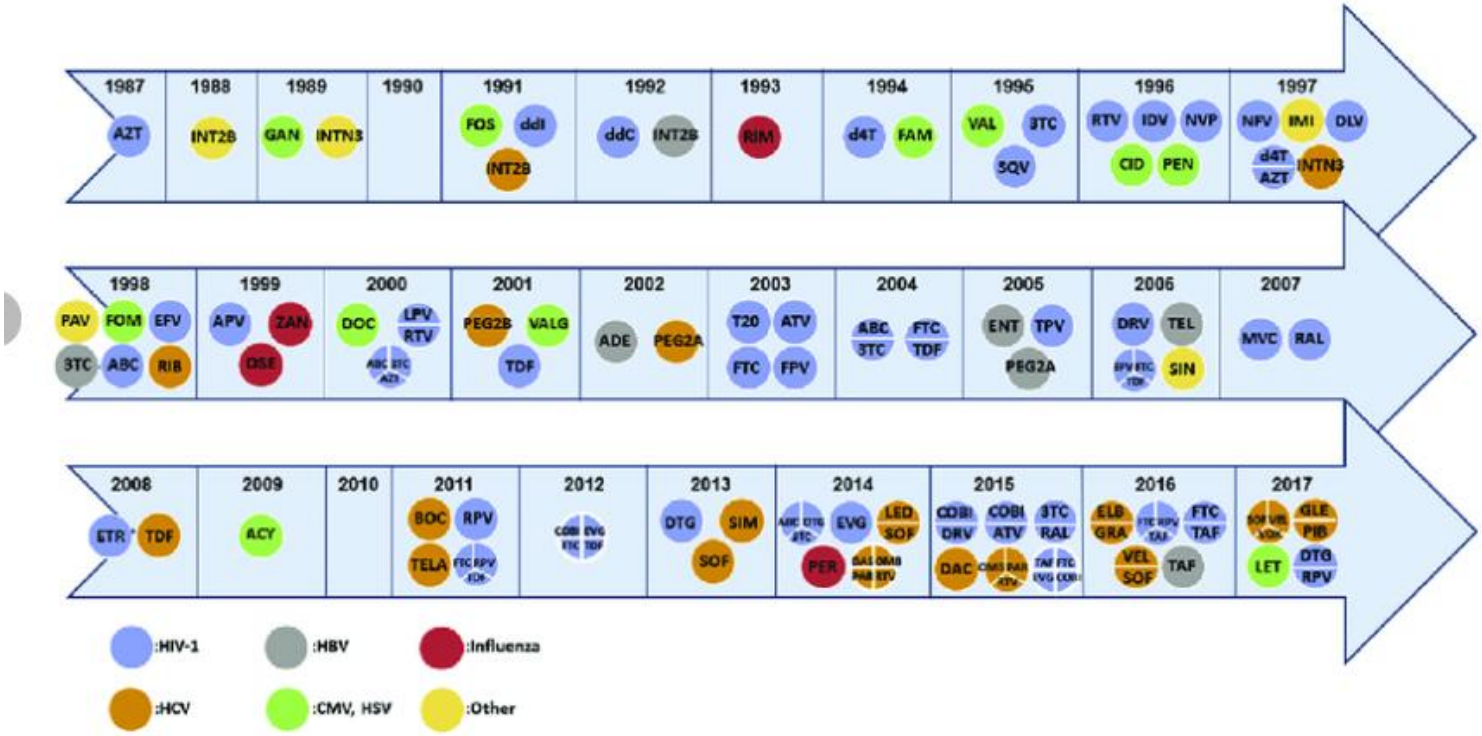


Figure 1. Mortality and Frequency of Use of Combination Antiretroviral Therapy Including a Protease Inhibitor among HIV-Infected Patients with Fewer Than 100 CD4+ Cells per Cubic Millimeter, According to Calendar Quarter, from January 1994 through June 1997.

Antiviral Drug Approvals 1987-2017



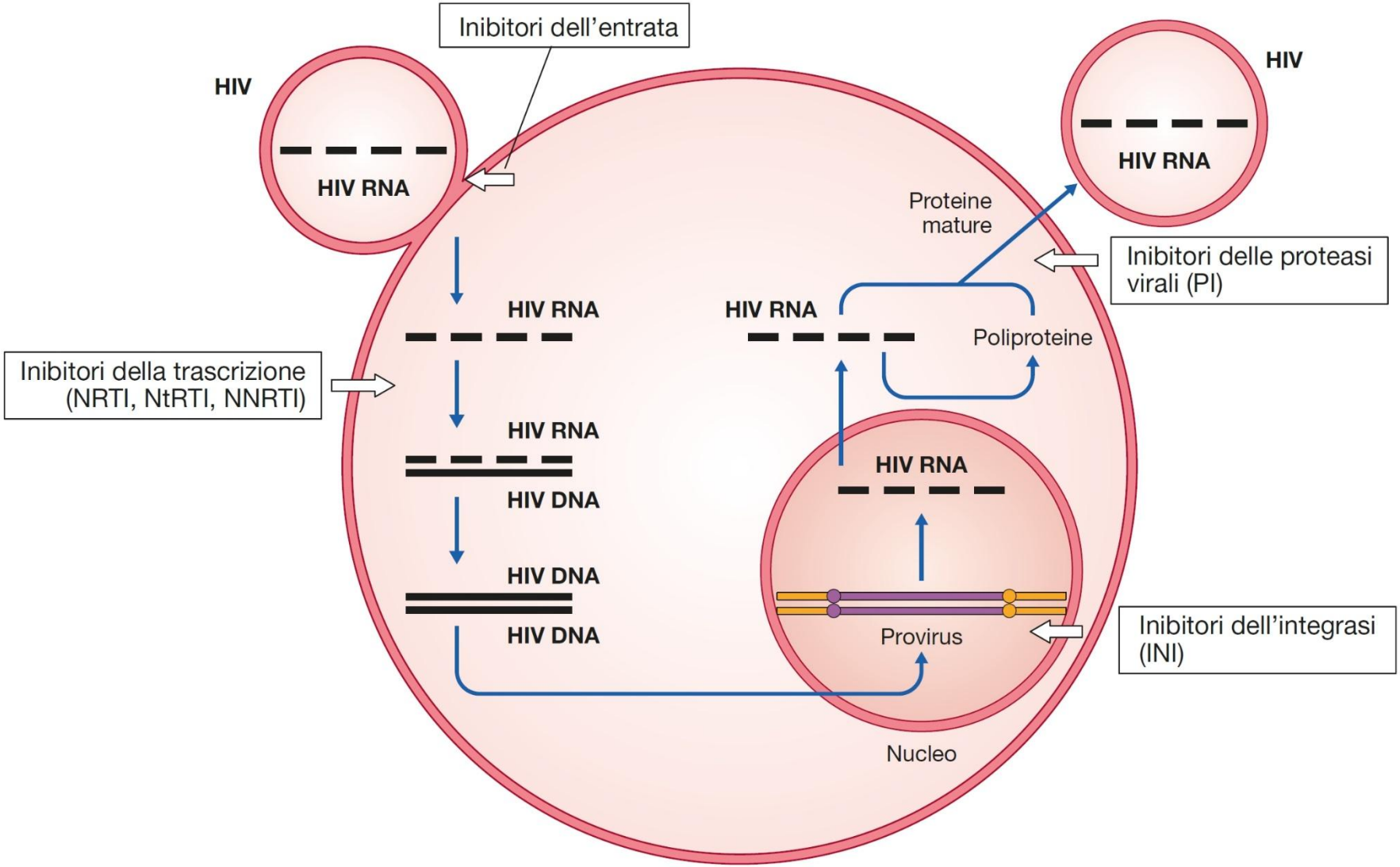
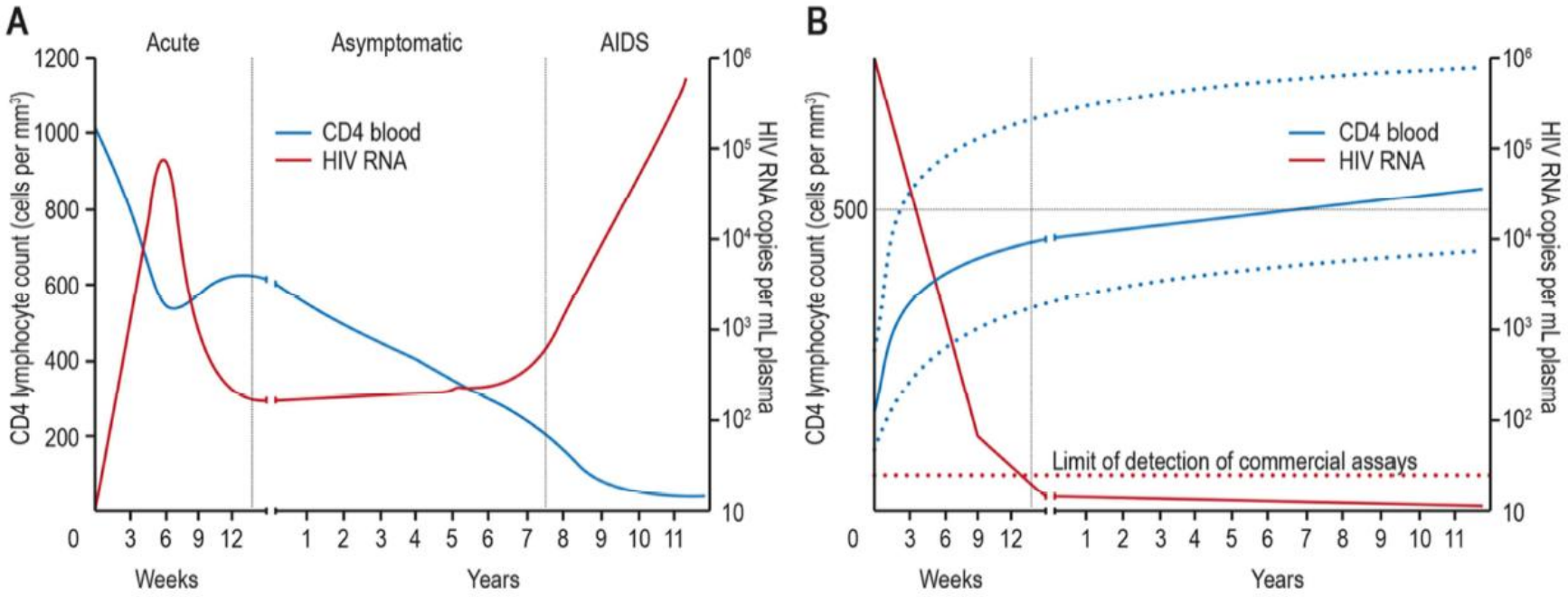


Figura 63.10 Inibitori della replicazione del ciclo di replicazione di HIV-1 (*vedi* anche tabella 63.5)

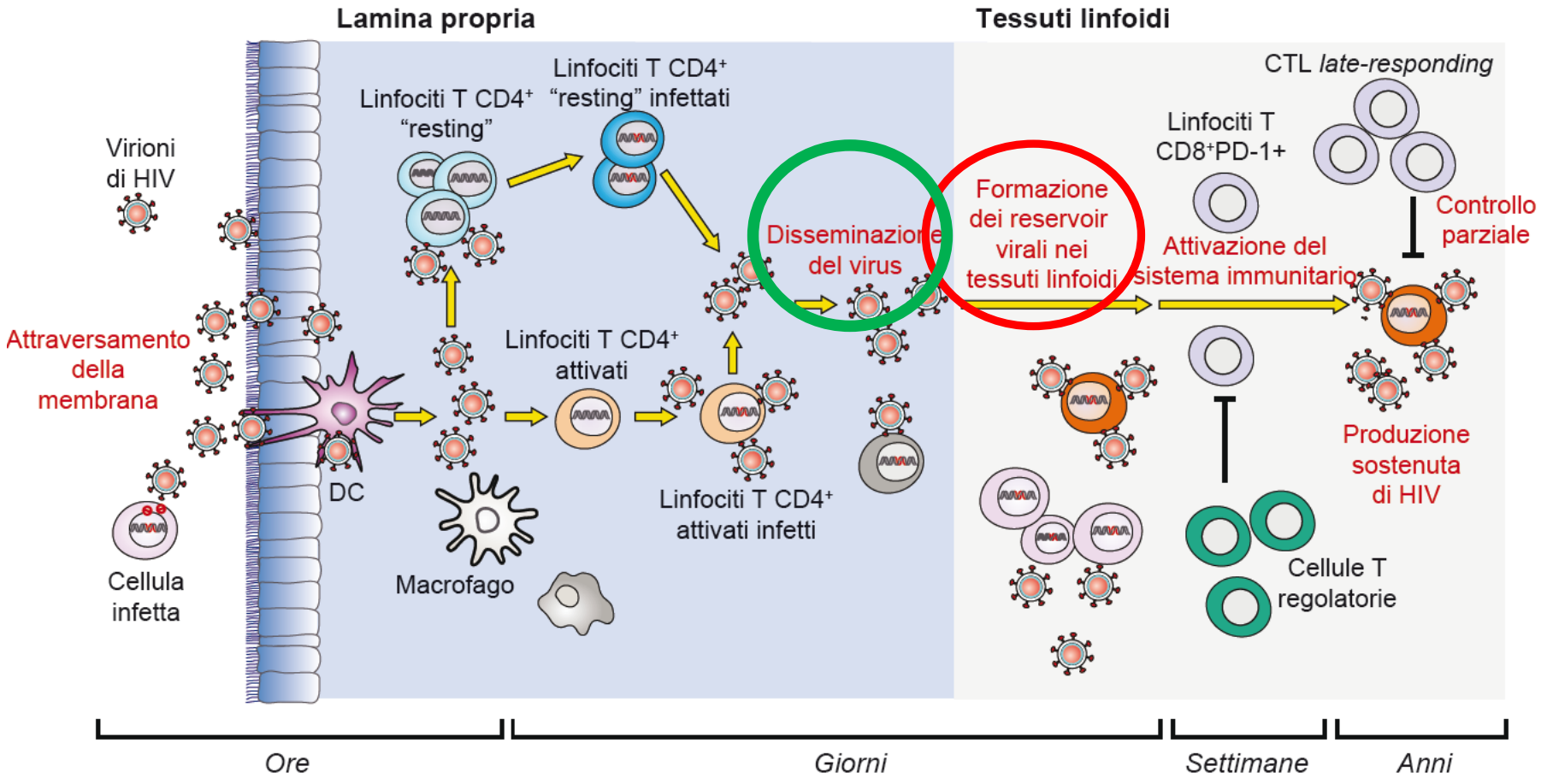
HAART

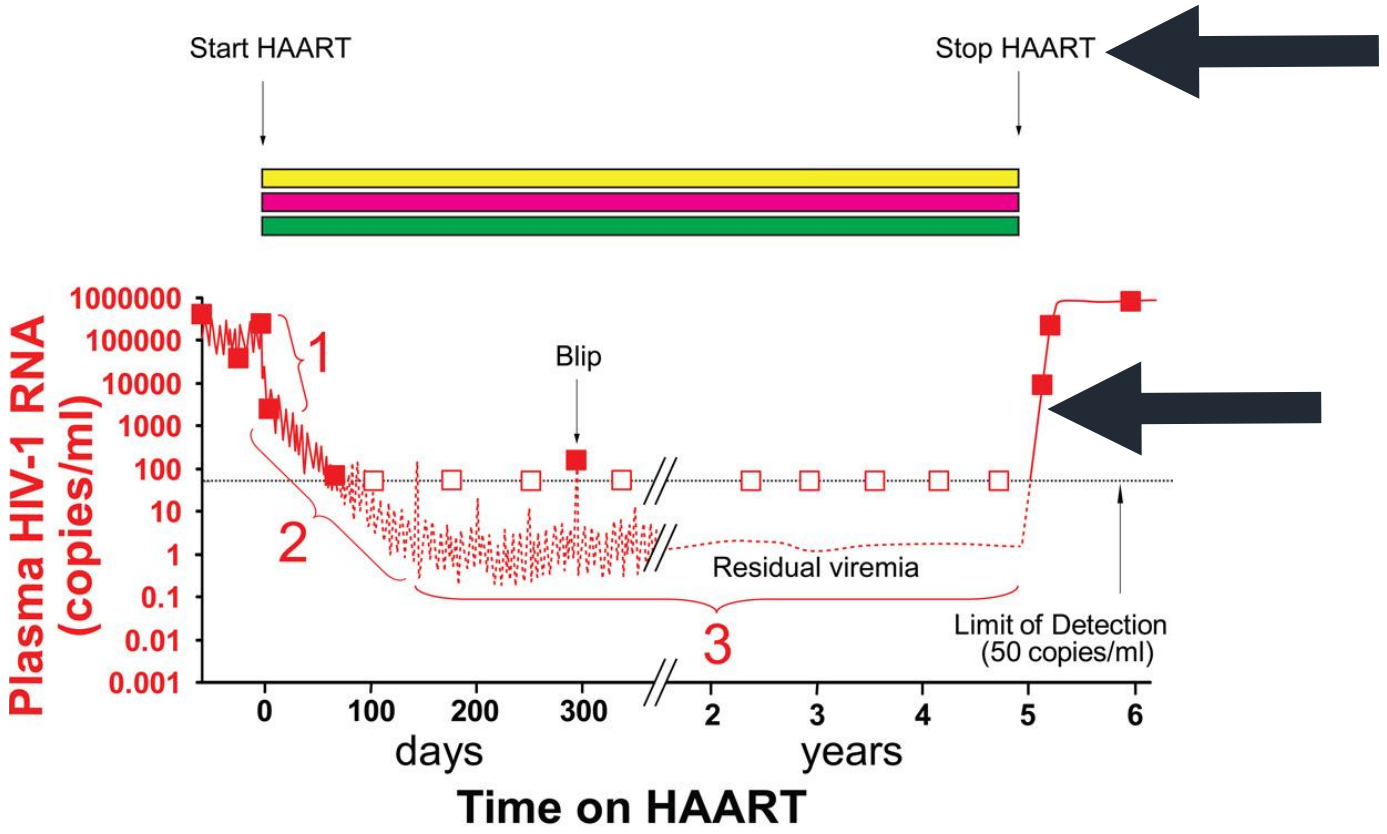
Highly active antiretroviral therapy

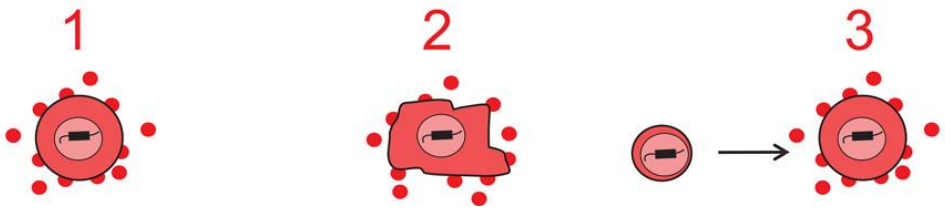
J.C. Becerra *et al*. (2016)



Dinamica dell'infezione da HIV







Modified from

Developing strategies for HIV-1 eradication

Christine M. Durand[1], Joel N. Blankson[1], and Robert F. Siliciano[1,2]

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

Epidemiology

World Health Organization

HIV/AIDS

Key facts

- HIV remains a major global public health issue, having claimed 40.1 million [33.6–48.6 million] lives so far with ongoing transmission in all countries globally; with some countries reporting increasing trends in new infections when previously on the decline.
- There were an estimated 38.4 million [33.9–43.8 million] people living with HIV at the end of 2021, two thirds of whom (25.6 million) are in the WHO African Region.
- In 2021, 650 000 [510 000–860 000] people died from HIV-related causes and 1.5 million [1.1–2.0 million] people acquired HIV.
- There is no cure for HIV infection. However, with access to effective HIV prevention, diagnosis, treatment and care, including for opportunistic infections, HIV infection has become a manageable chronic health condition, enabling people living with HIV to lead long and healthy lives.
- WHO, Global Fund and UNAIDS all have global HIV strategies that are aligned with the SDG targets 3.3 of ending the HIV epidemic by 2030.
- To achieve this, 95 % of all people living with HIV (PLHIV) should have a diagnosis, 95% of those should be taking lifesaving antiretroviral treatment (ART) and 95% of PLHIV on treatment should achieve a suppressed viral load for the benefit of the person's health and for reducing onward HIV transmission.