M1 D²HP Development of Drugs and Health Products

Human Immunodeficiency Virus (HIV) infection

Dorine Bonte (dorine.bonte@universite-paris-saclay.fr)

March 10th 2025

Content

I- Generalities

1- Little history

Discovery of HIV

- 1981: First AIDS cases in California and New York
  - Acquired Immune Deficiency Syndrome (AIDS)
    - High-risk subpopulations
- 1983: Human "Retrovirus"
  - L. Montagnier, F. Barré-Sinoussi *[Barré-Sinoussi, Science, 1983]*
    - LAV = Lymphadenopathy-associated virus

Little history

- **1984:** - HTLV-3 (Human T Lymphotropic Virus) *[Gallo et al., Science, 1984]*
  - ARV = AIDS-Associated Retrovirus *[Levy et al., Science, 1984]*
  - CD4 molecule = virus receptor *[Dalgleish et al., Nature, 1984 ; Klatzmann et al., Nature, 1984]*
  - Antibody screening *[Brun-Vezinet et al., Lancet, 1984]*
  - Nucleotide sequence of the viral genome *[Alizon et al., Nature, 1984 ; Hahn et al., Nature, 1984]*
- **1985:** - HIV nomenclature = Human Immunodeficiency Virus
- **1986:** - Isolation of HIV-2 in subjects from West Africa
  - Availability of the first antiretroviral treatment: zidovudine or AZT
- **1989 - 1994: Different antiretroviral molecules**
  - ↳ didanosine, stavudine, lamivudine, protease inhibitors
- **1997:** Recommendation for HAART = first triple-drug therapy

I- Generalities

2- A virus from the monkey

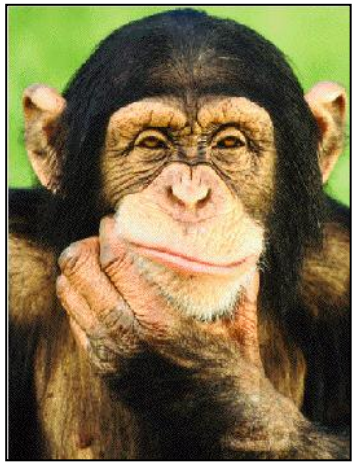
From SIV to HIV

- **Mutation of a virus of simian origin: SIV**

- **Genetic works**

  - **Existence of a genetic link between**

    - HIV-1, groups M and N, and the simian retrovirus SIVcpz hosted by the chimpanzee *[Keele et al., Science, 2006]*



1st serum 1959
Reportedly transmitted to humans in 1908

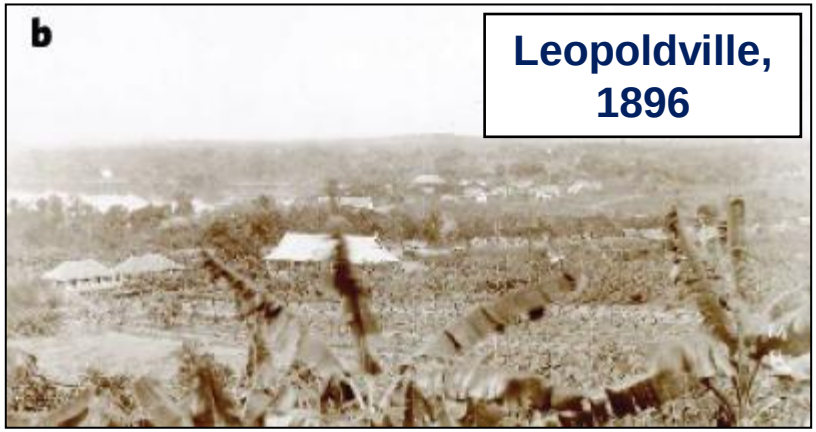
- HIV-1, Group O, and SIVgor retrovirus hosted by the gorilla *[Van Heuverswyn et al., Nature, 2006]*

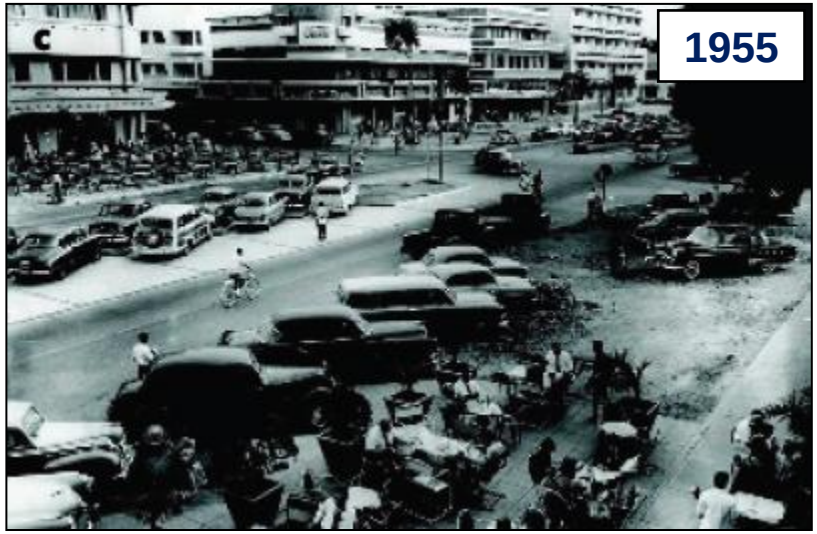
  - **HIV-2 related to mangabey SIV (West Africa)**

1st serum 1963
Reportedly transmitted to humans in 1930-1940

Prehistory of HIV-1

☞ **Epidemia born in Central Africa at the beginning of the 20th century**



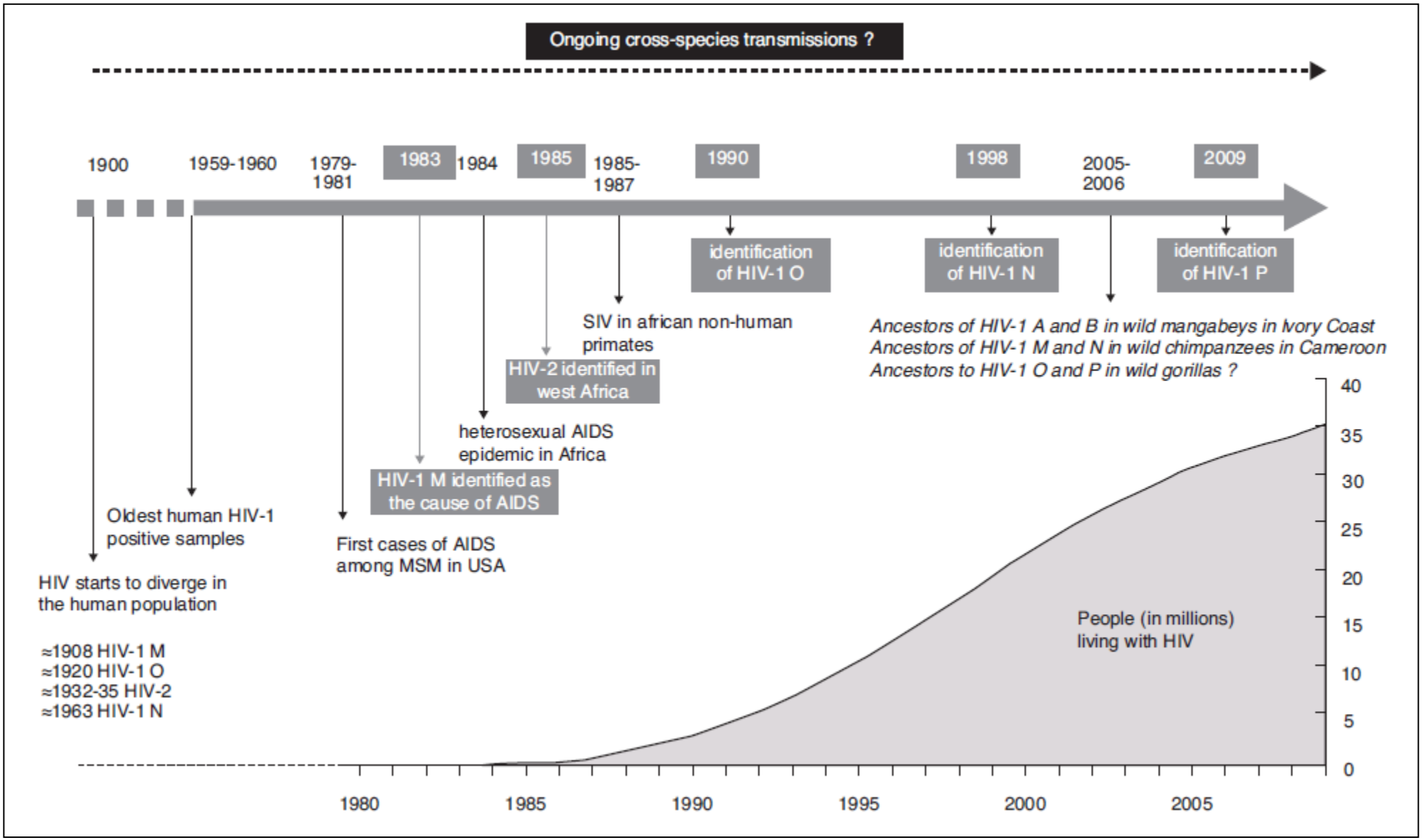


[Sharp and Hahn, Nature, 2008]

Sources of human infection

- Exposure to blood and other secretions from infected animals
  - hunting, monkey meat at markets
- Domesticated or wild monkeys
  - bites, wounds (claws)

History of the HIV pandemic



[Locatelli and Peeters, AIDS, 2012]

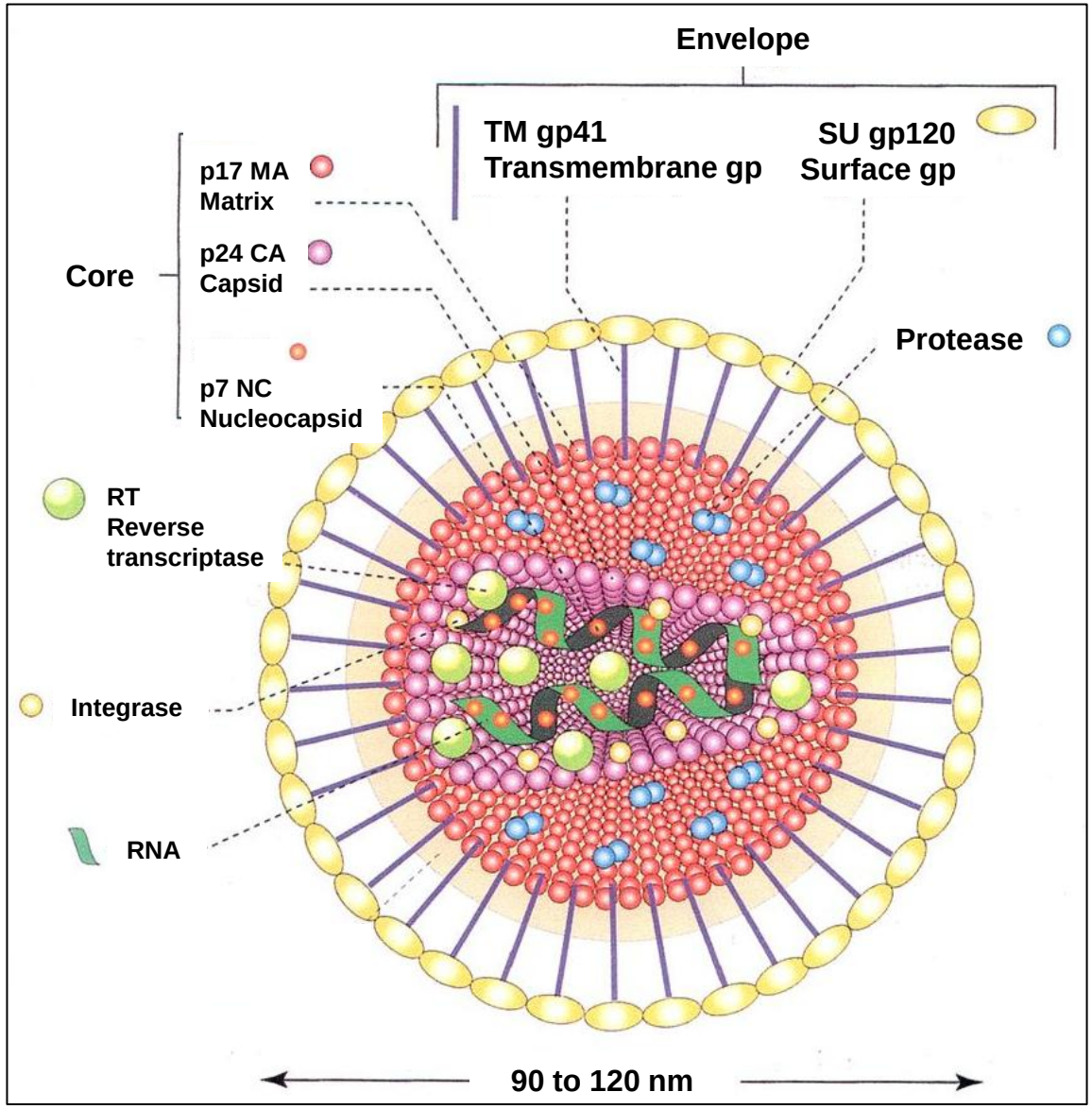
II- Etiology

1- Human Immunodeficiency Virus (HIV)

Classification

- **Family**
  - ***Retroviridae***
- **Subfamily**
  - ***Orthoretrovirinae***
- **Genus**
  - ***Alpha-*, *Beta-*, *Epsilon-* et *Gammaretrovirus***
    - ↳ **tumours and leukemia in animals**
  - ***Deltaretrovirus***
    - **HTLV-1 and HTLV-2**
      - ↳ **leukemia in humans**
  - ***Lentivirus***
    - **HIV-1 and HIV-2**
    - **SIV**
    - **FIV**

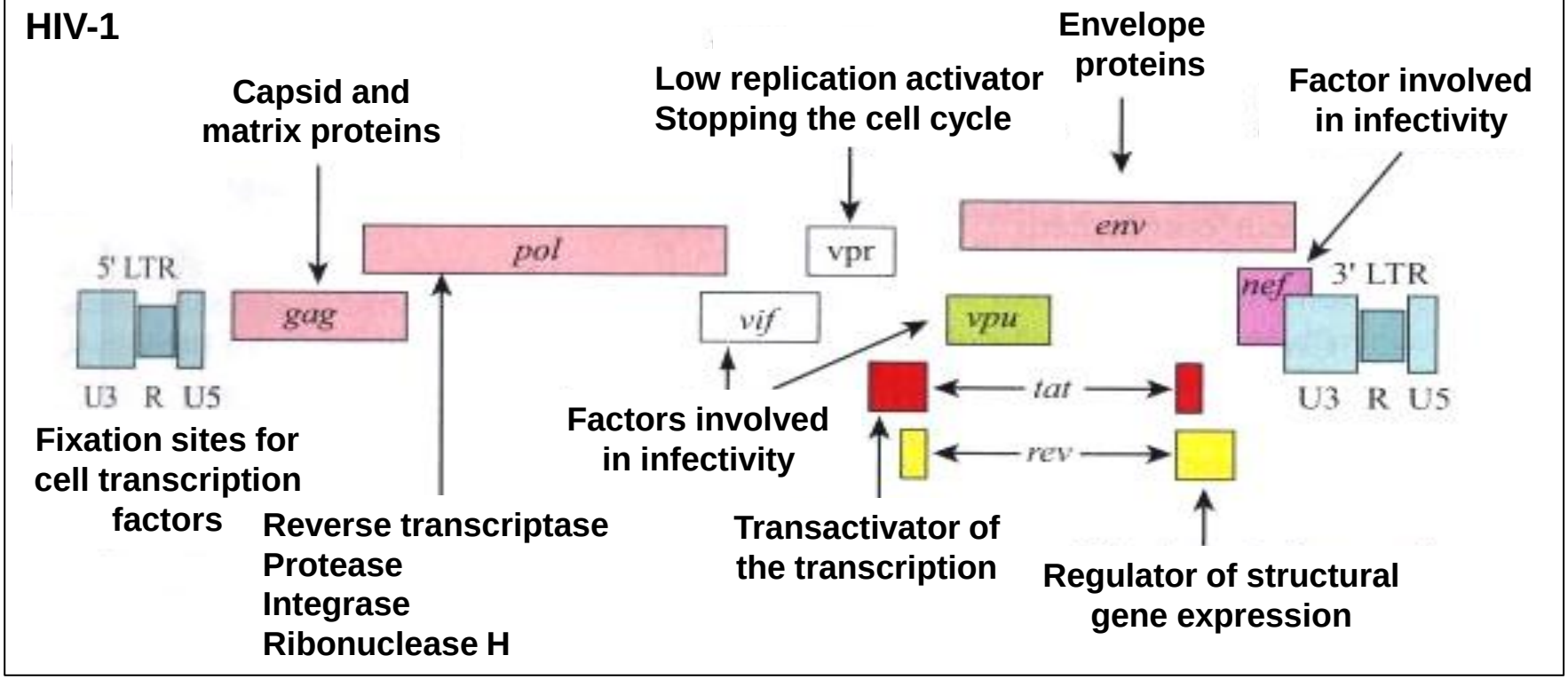
Virus structure



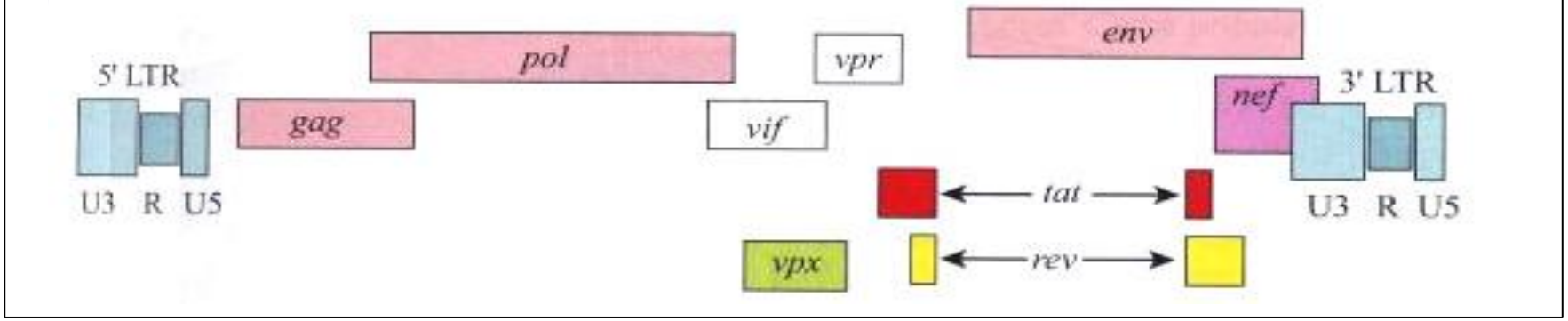
[Huraux, Traité de Virologie Médicale, 2003]

Genome

HIV-1



HIV-2

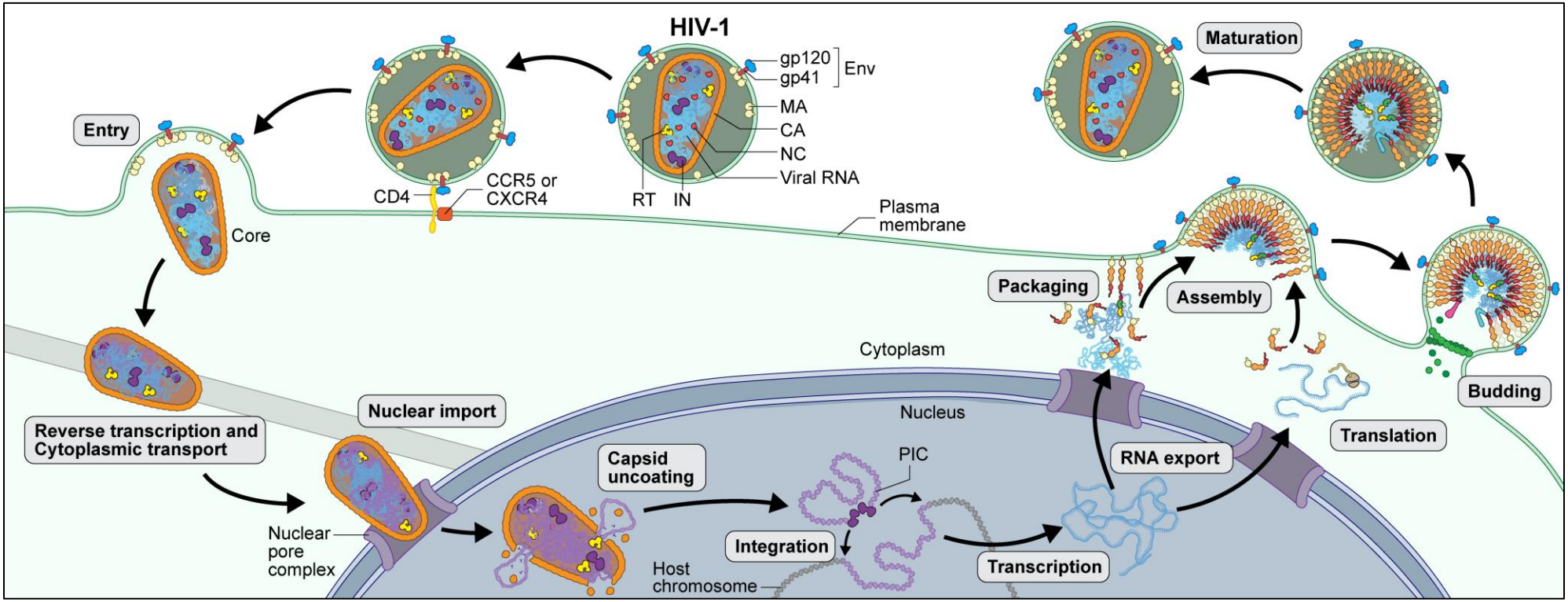


[Huraux, 2003, Traité de Virologie Médicale]

Function of HIV-1 proteins

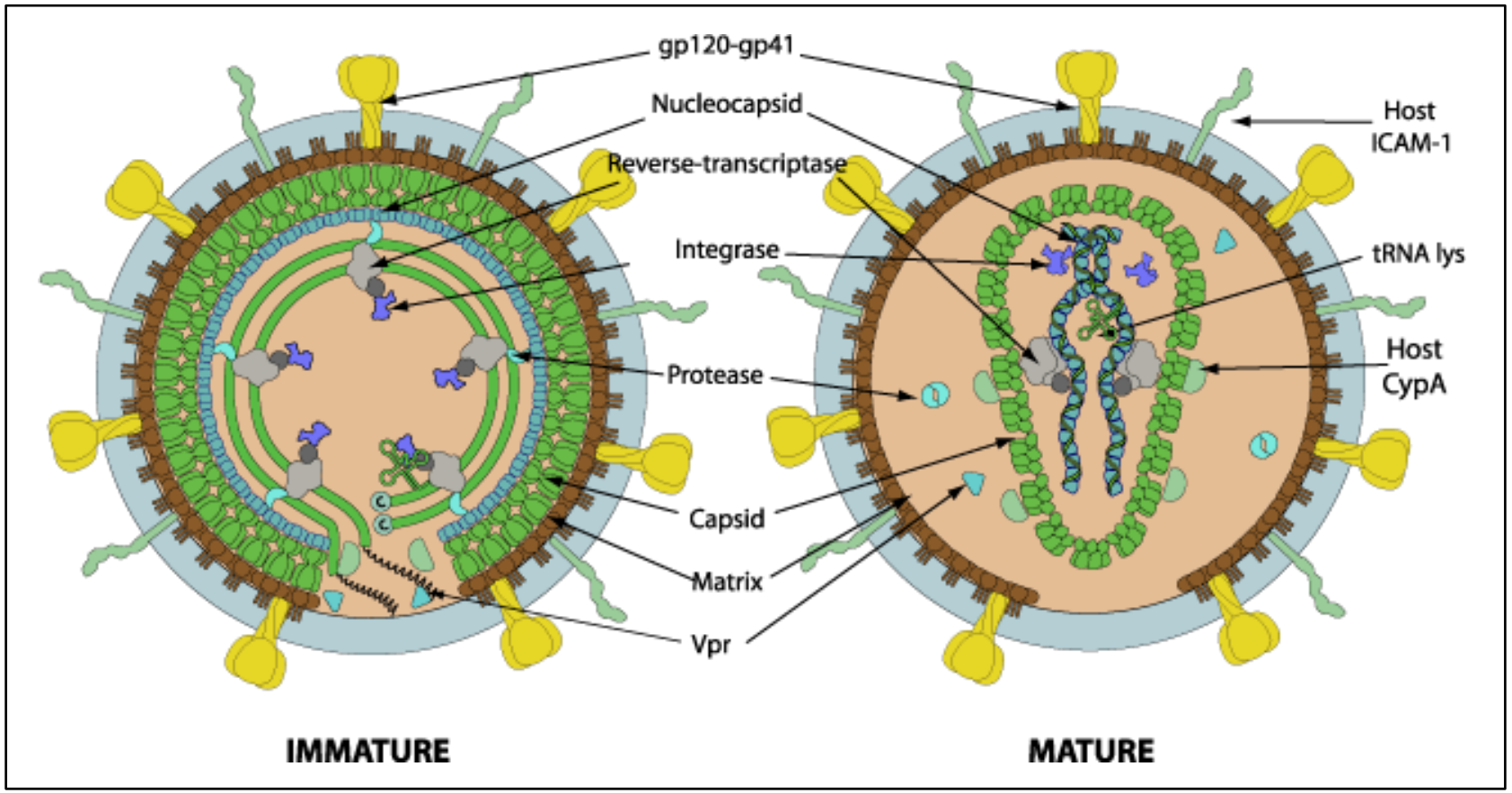
Genes		Proteins and functions
env	envelope	gp120 binds the CD4 receptor and the co-receptor gp41 fuses the membranes
gag	group specific antigen	Structural proteins: p17, p24 and p7
pol	polymerase	Enzymes: reverse transcriptase, protease and integrase
tat	transactivator	Increases transcriptional activity
vif	viral infectivity factor	Binds the APOBEC3G protein preventing DNA deamination
vpr	viral protein R	Transports viral DNA to the nucleus, increases viral production and regulates the cell cycle
vpu	viral protein U	Decreases the expression of CD4
nef	negative regulation factor	Increases viral regulation and decreases the expression of CD4, MHC I and II
rev	regulator of viral expression	Allows the export of unspliced transcripts out of the nucleus

Cycle of multiplication



[scienceofhiv.org]

Maturation of the virus in the extracellular medium



[ViralZone, 2021]

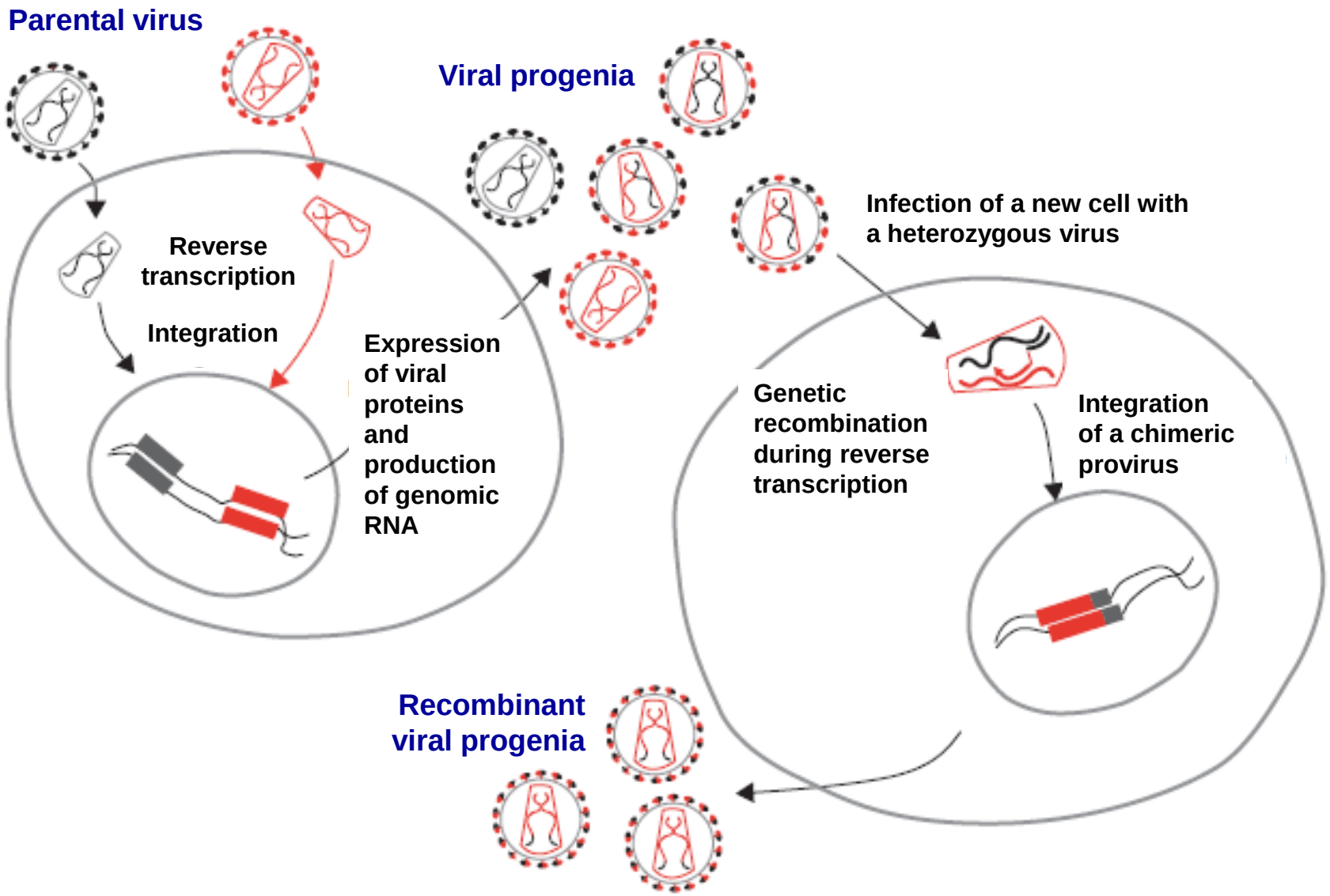
II- Etiology

2- Variability and diversity

HIV variability

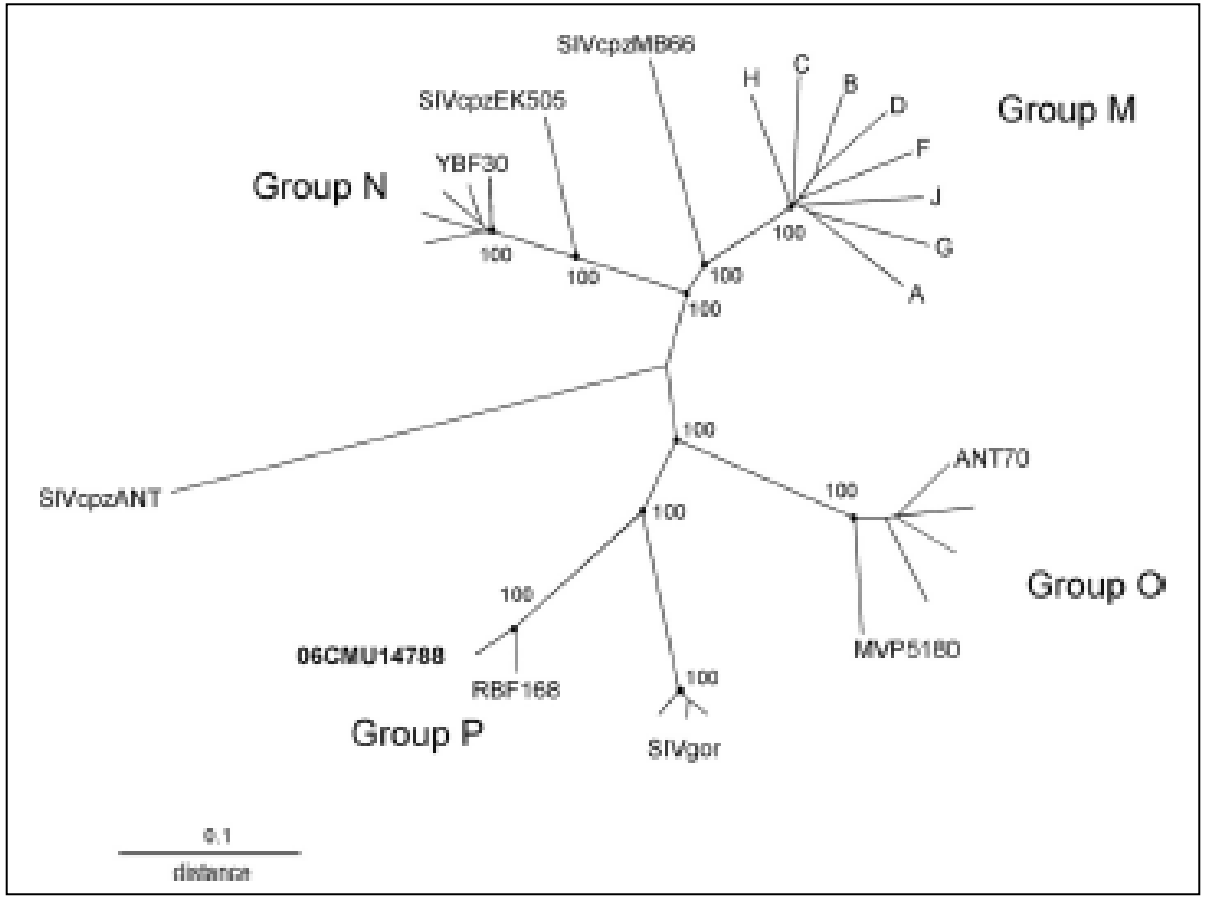
- Many factors
  - * Important dynamics of viral replication
    - ↳ 10 billion viruses produced per day
  - * Low fidelity of reverse transcriptase
    - ⇨ no proofreading activity
      - ↳ one error per 10,000 bases per cycle
    - ⇨ these errors occur in a variable manner
      - 1% of the genome per year for *env*
      - 0.5% for the *gag* gene
      - more conserved *pol* gene
  - * Recombination
    - ⇨ possible during reverse transcription
      - ↳ appearance of mosaic viruses

Recombination



[Simon-Lorière et al., Virologie, 2006]

Diversity of HIV-1 (1)



[Plantier et al., Nat. Medicine, 2009 ; Vallari et al., J. Virol., 2011]

Diversity of HIV-1 (2)

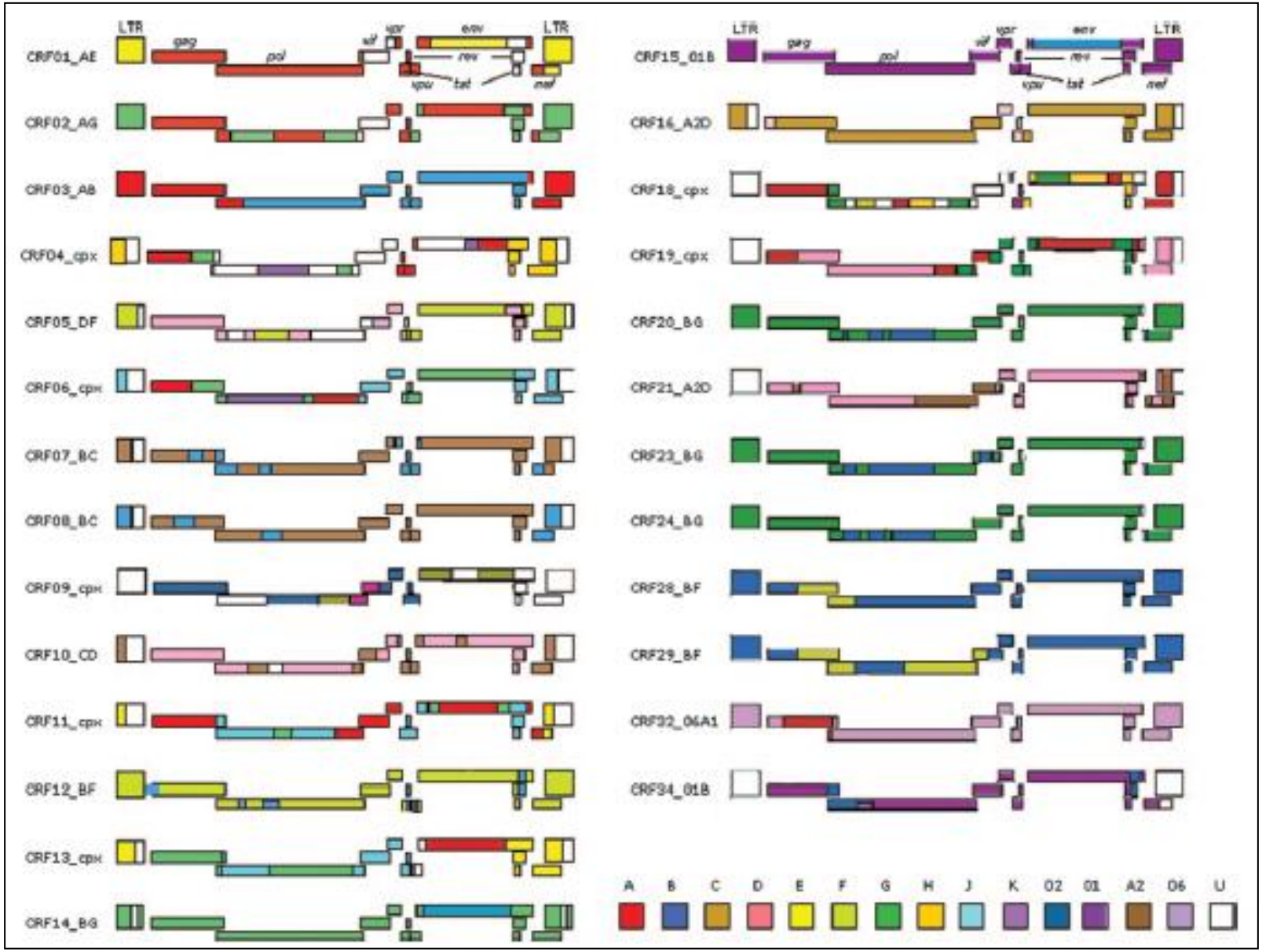
- Group M (Major)
  - subtype B (Europe, America, Australia)
  - subtypes non-B
    - A, C, D, F, G, H, J, K and L
  - > 130 circulating recombinant forms = CRF
    - inter-subtype recombinants or between recombinant forms themselves
  - Unique Recombinant Forms = URF
- Group O (Outlier)

  Africa
- Group N (non-M, non-O)

  Gabon, Cameroon
- Group P

  Cameroon

Mosaic structure of CRF



[Buonaguro et al., J. Virol., 2007]

Diversity of HIV-2

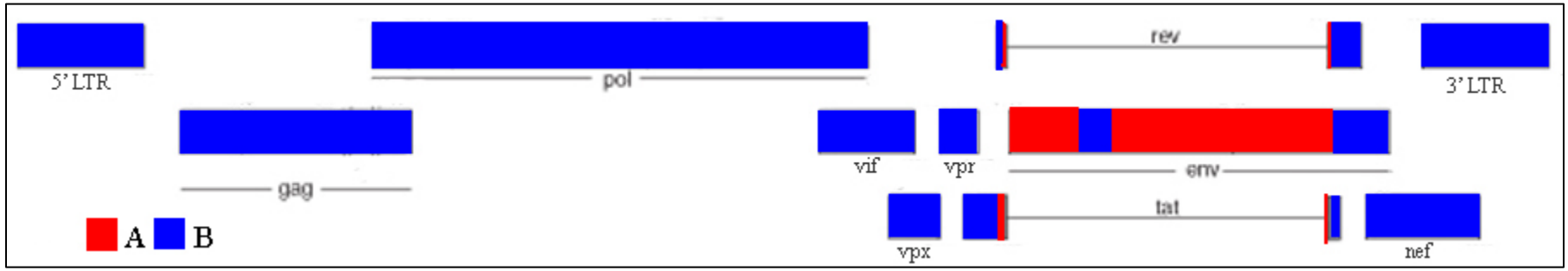
☞ **9 groups**

A (sub-groups A1 and A2), B, C, D, E, F, G, H, and I

- A, endemic in West Africa (Cape Verde, Guinea, Senegal)

- B, especially in Ivory Coast, Mali, Burkina Faso

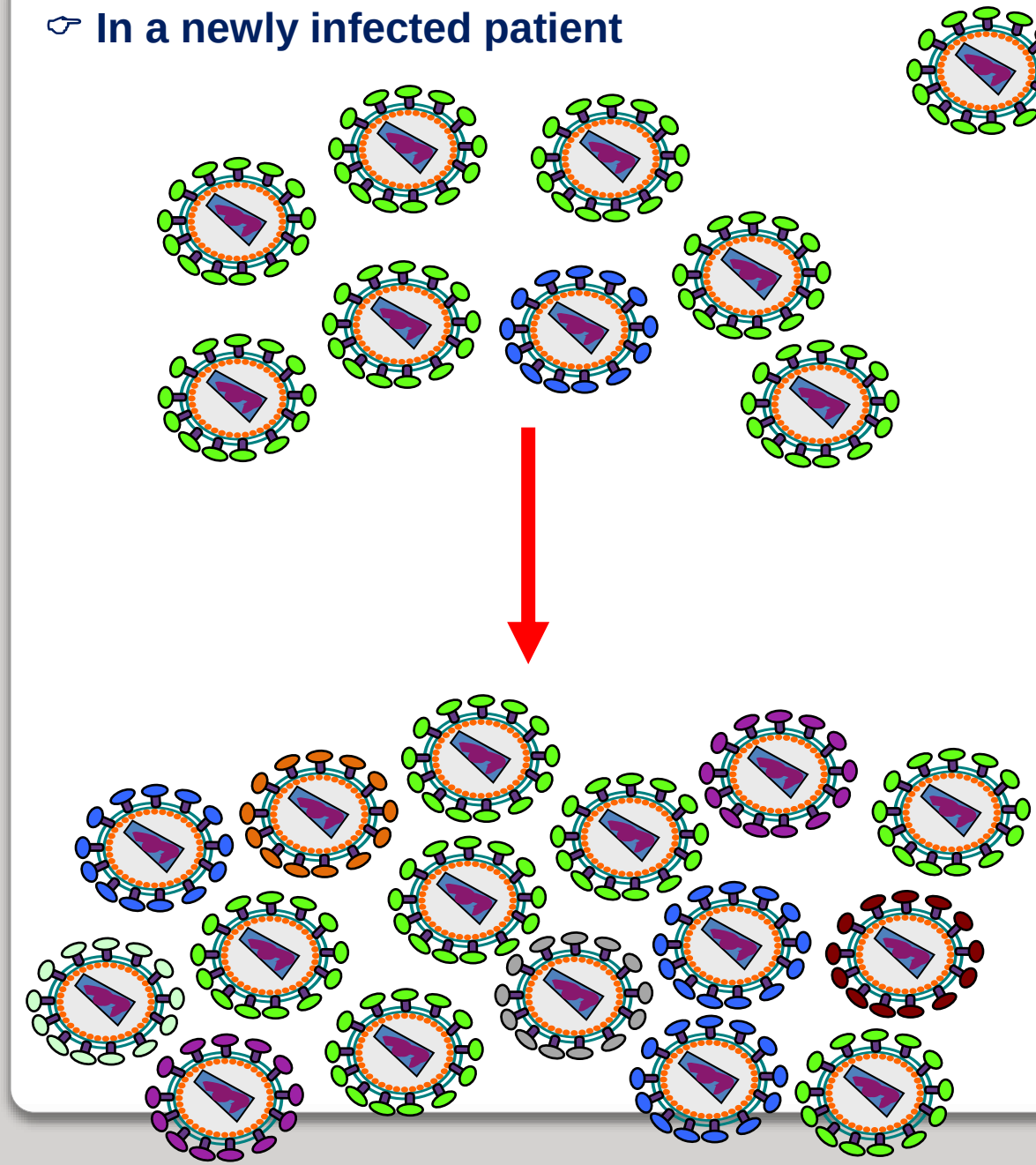
- 1 described CRF HIV2_CRF01_AB (groups A and B) ***[Ibe et al., J. Acquir. Immune Defic. Syndr., 2010]***



↳ **No recombinant HIV-1 and HIV-2 isolated to date**

Viral quasispecies

☞ In a newly infected patient



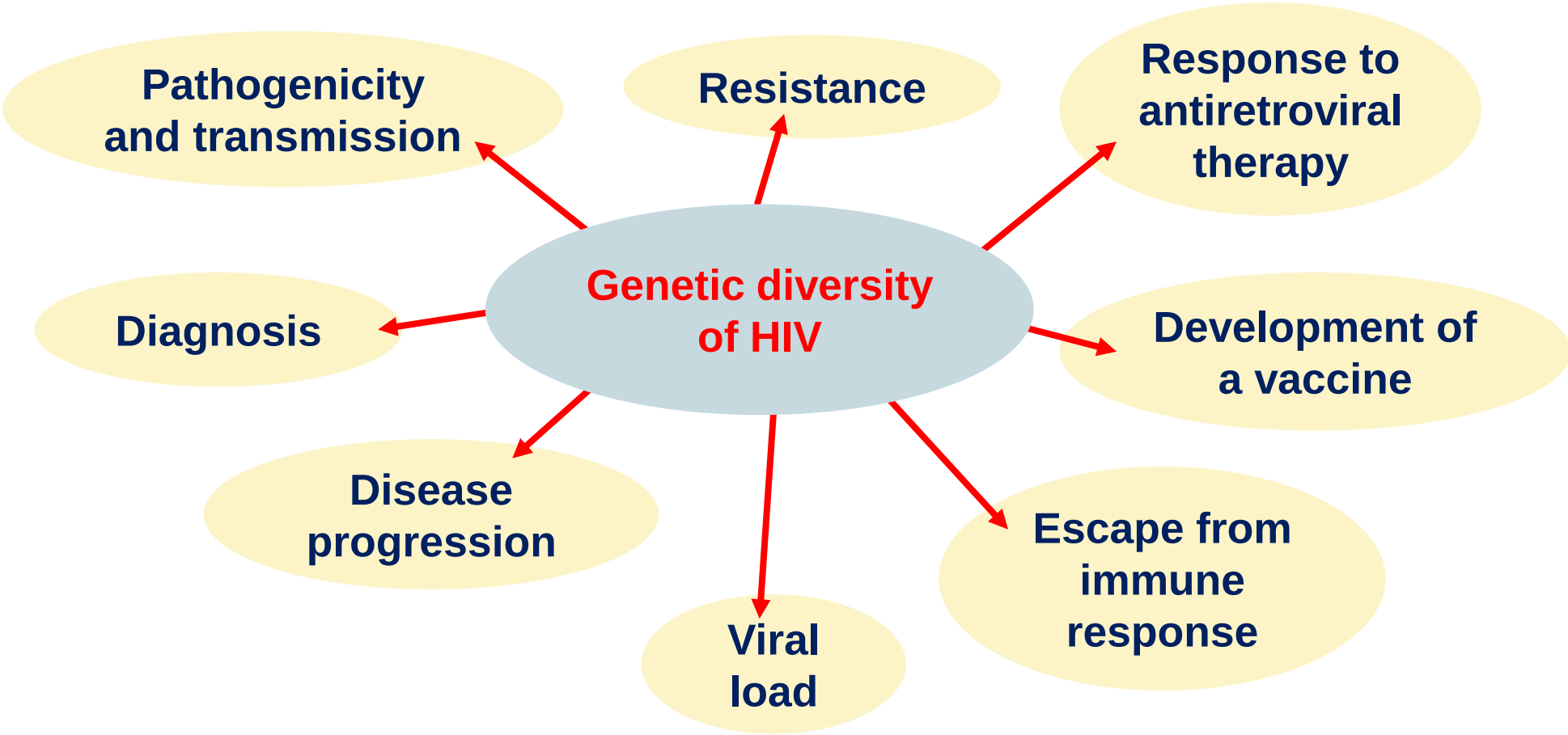
One virus causing the infection

Initial virus population relatively homogeneous

Viral population with a multitude of variants = quasispecies, in just a few weeks

Genetic diversity and consequences

☞ Direct impacts on multiple aspects of patient management



[Hemelar et al., Journal of Infection, 2013]

II- Etiology

3- HIV-1 and HIV-2

Comparison of HIV-1 and HIV-2

- **Sequence homologies**
  - 50% for *gag* and *pol*
  - 40% for *env*
- **Envelope glycoproteins**
  - gp120 and gp41 for HIV-1
  - gp105 and gp36 for HIV-2
- **Infection**
  - slower progression of HIV-2 infection (without treatment)
  - lower risk of HIV-2 transmission
- **Treatment**
  - HIV-2 naturally resistant to
    - * the non-nucleoside reverse transcriptase inhibitors
    - * the fusion inhibitor and attachment inhibitor
    - * and with reduced sensitivity to certain protease inhibitors

III- Pathophysiology

1- Transmission of HIV

Modes of transmission

- Sexual route
  - 80% of new infections worldwide
  - more than 90% in Africa

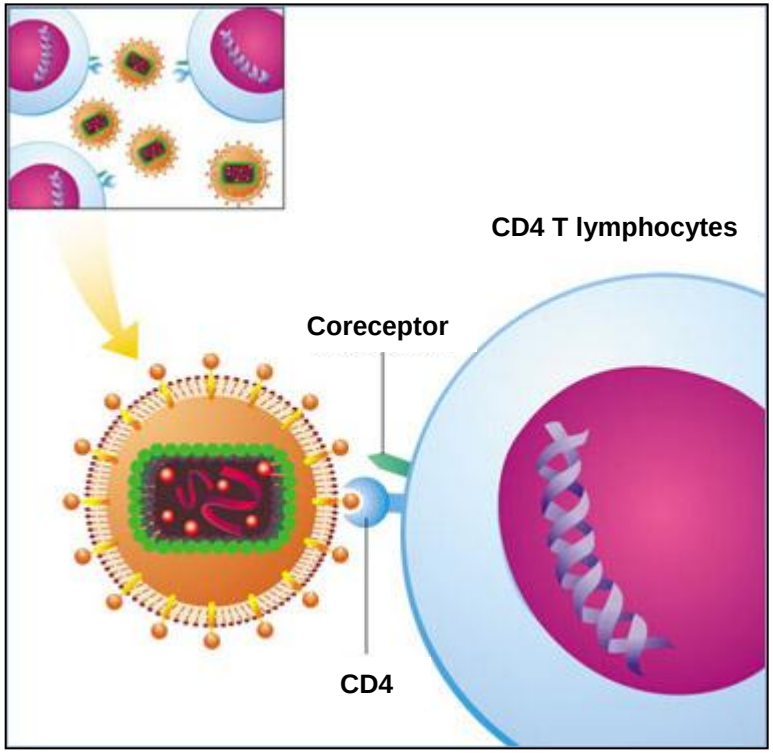
- By blood

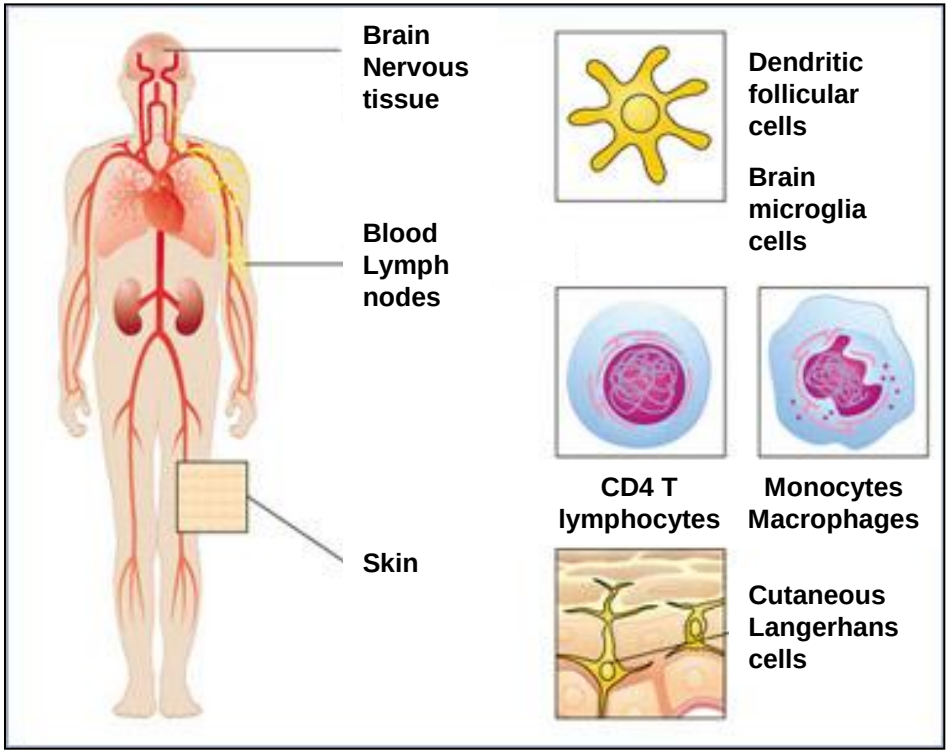
- Transmission from mother to child
  - pregnancy
  - childbirth +++
  - breastfeeding

III- Pathophysiology

2- Target cells and viral tropism

HIV target cells





CD4 T lymphocytes = primary HIV targets

HIV-1 and HIV-2 receptor and coreceptors

- **HIV-1 and HIV-2 receptor**

  CD4 = high affinity receptor

- **HIV-1 coreceptors**

  - CCR5

  Receptor for chemokines β

  Receptor for viruses with "macrophagic" or "M" tropism

  ↳ Viral strains "R5"

  - CXCR4

  Receptor for chemokines α

  Receptor for viruses with "lymphocytic" or "T" tropism

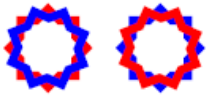
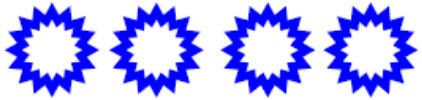
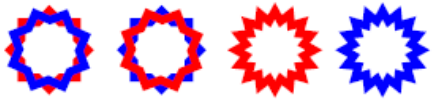
  ↳ Viral strains "X4"

- **HIV-2 coreceptors**

  - CCR5 and CXCR4 (like HIV-1)

  - Alternative coreceptors: CXCR6, GPR15 (G Protein-coupled Receptor 15), etc.

HIV-1 tropism

Coreceptor	CCR5	CCR5, CXCR4	CXCR4
Trofile	R5	D/M	X4
Clone			
Isolate			
Tropism			
CD4⁺ T cell	memory	naïve and memory	naïve and memory
Thymocytes	-	++	+++
Precursors	-	++	+++
Macrophages	+++	+	+/-
Dendritic cells	+++	+	+/-
T cell lines	-	++	+++

[Schuitemaker et al., J. Translational Medicine, 2010]

Polymorphism of CXCR4 and CCR5 coreceptors

☞ **CXCR4**

Little genetic polymorphism

☞ **CCR5**

Level of expression varies from one individual to another

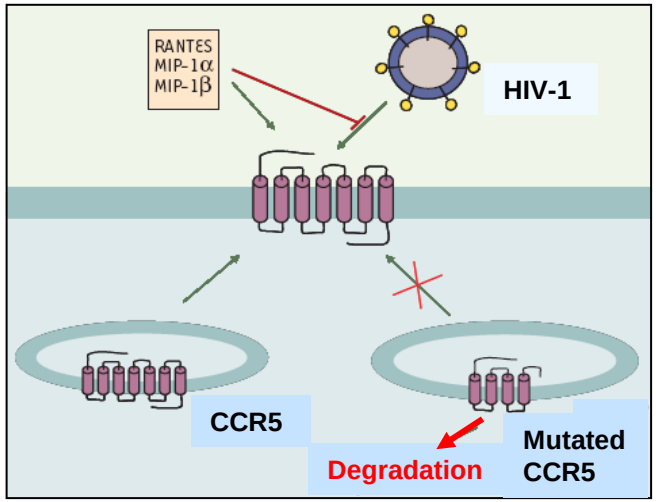
Different polymorphisms of CCR5 in the human population

There is a 32bp deletion: *CCR5Δ32*

↳ **Homozygous form of this mutation ⇨ 1% of the population**

*** protection of subjects from infection by R5 viruses**

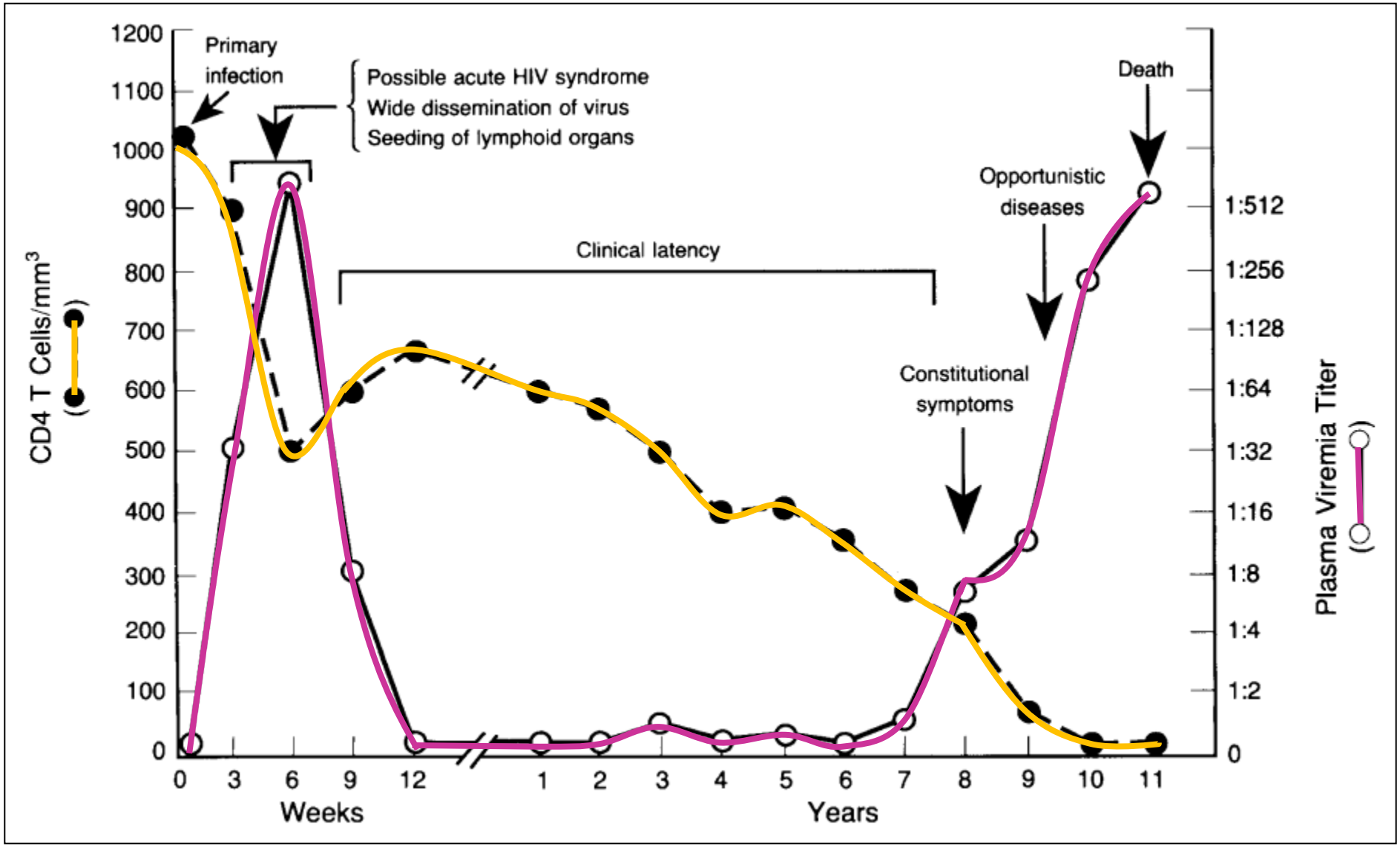
*** BUT possible infection with X4 or R5/X4 viruses**



III- Pathophysiology

3- Natural history

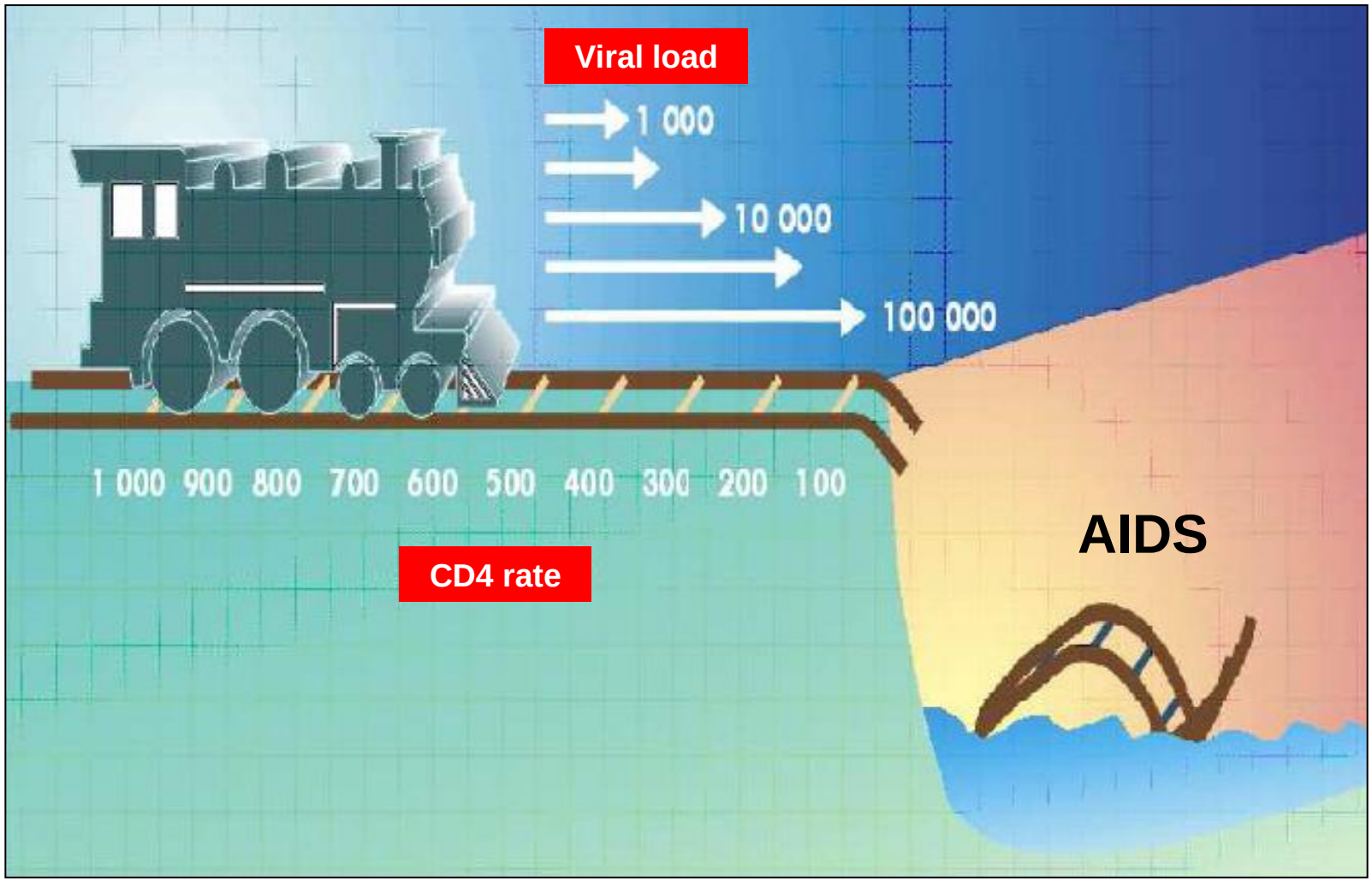
The different phases



[Pantaleo et al., New Eng. J. Med., 1993]

Viral load and CD4 T-cell count

↳ 2 biological markers of the evolution of HIV infection



[D'après La lettre de l'Infectiologue, Coffin, 1996]

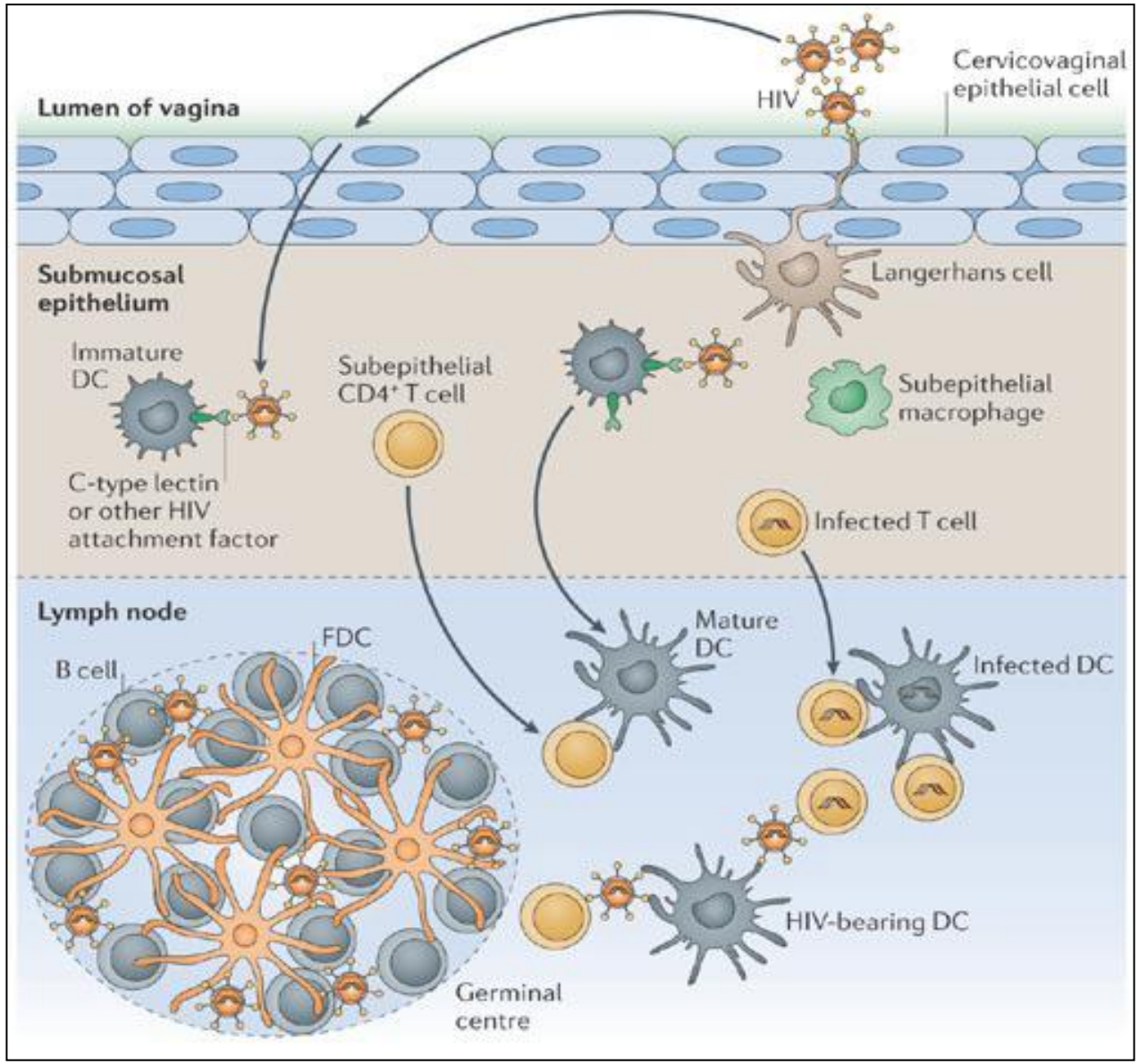
III- Pathophysiology

4- HIV infection

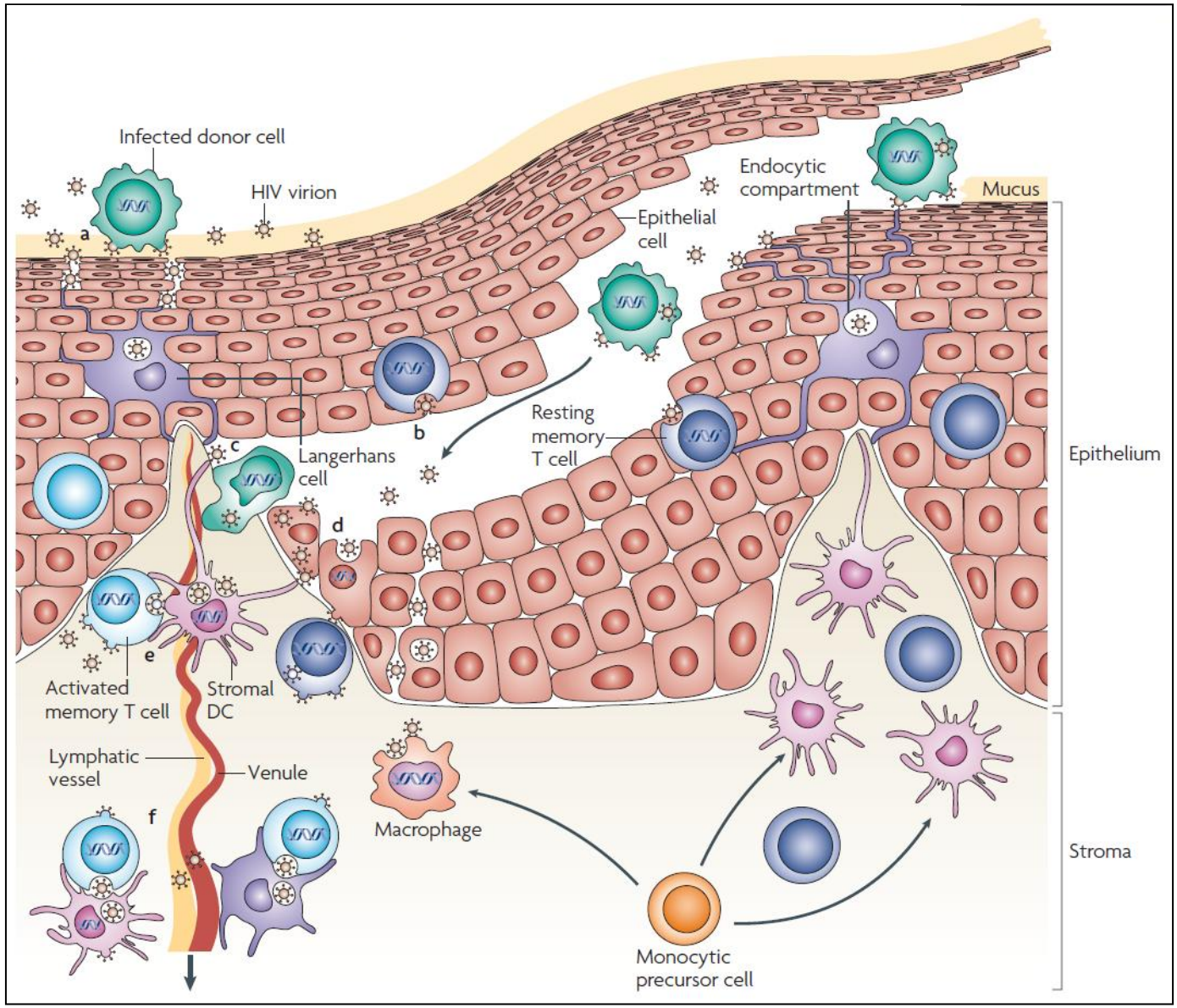
Establishment of the infection (1)

- When a person is infected with HIV
  - the virus spreads rapidly in the body
    - it initially interacts with dendritic cells
    - it reaches the blood (CD4 T lymphocytes) in 4 to 6 hours
    - it reaches the lymph nodes in 48 hours
    - it is detectable in the blood in 4 to 11 days
    - HIV antibodies can be detected after 1 month

Establishment of the infection (2)

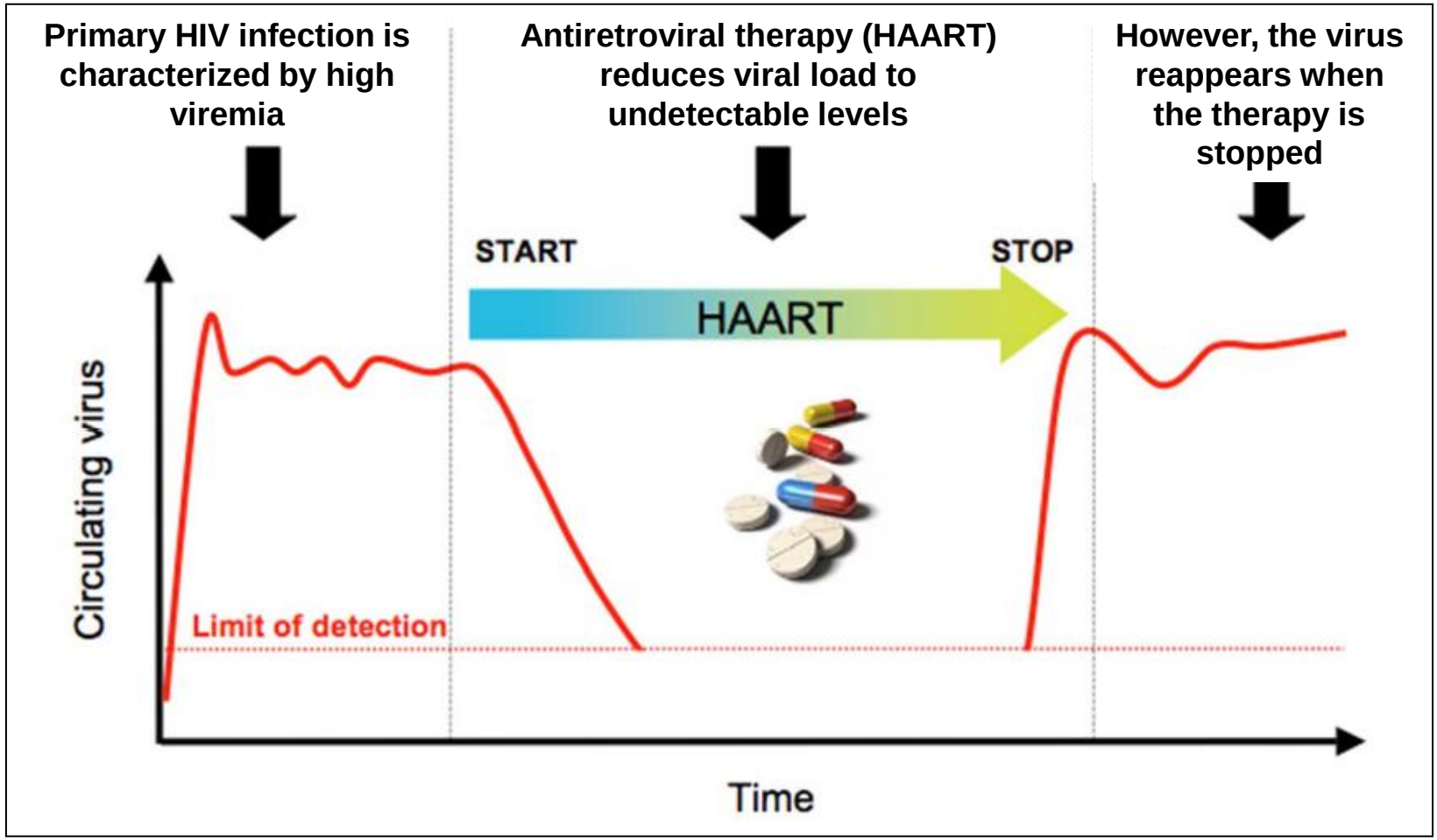


Establishment of the infection (3)



[Hladik and McElrath, Nat. Rev. Immunol., 2008]

Evidence of a HIV reservoir



Place of HIV persistence

☞ **Anatomically: potential HIV reservoirs**

- central nervous system
- lymph nodes
- lymphoid tissue associated with digestive tissue
- bone marrow
- genital tract
- blood
- spleen
- fatty tissue
- lungs

⇨ **lymphoid tissue associated with digestive tissue + lymph nodes = main reservoirs**

☞ **At the cellular level**

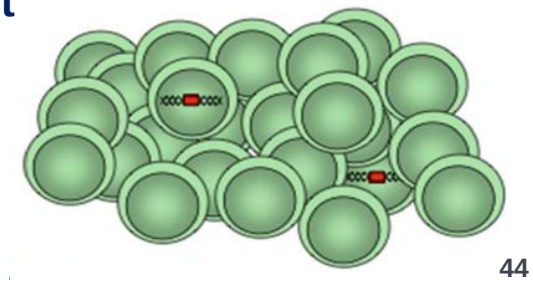
⇨ a small number of cells carry the HIV DNA integrated in their genome

↳ very low frequency = 1 cell in 1 million of quiescent T CD4 lymphocytes

⇨ HIV can persist in this latent state as long as the cell carrying it

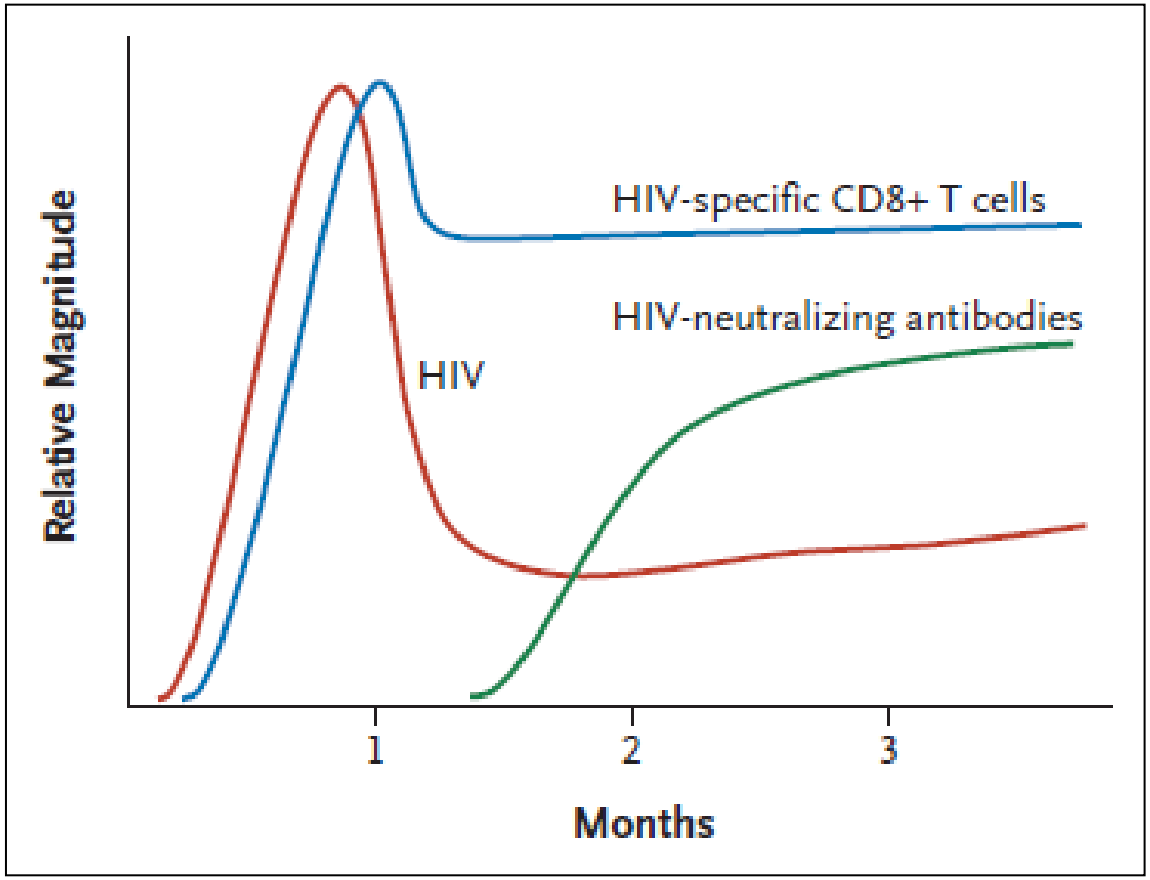
↳ persistence for decades on antiretroviral treatment

⇨ **HIV reservoir half-life estimated at 44 months**



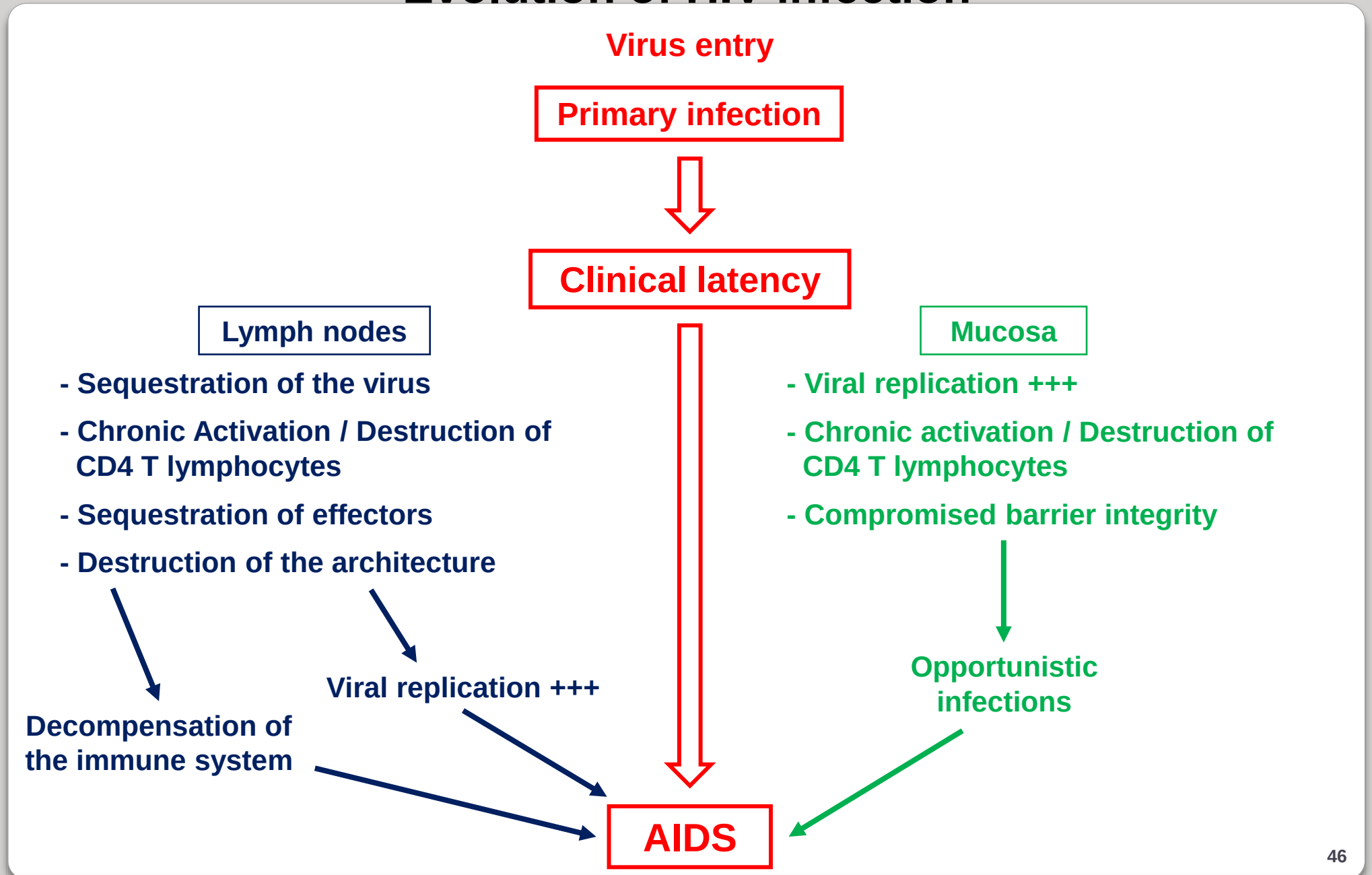
Immune system response

- **Cellular Response / Humoral Response**
  - **CD8 T lymphocytes**
  - **neutralizing antibodies**

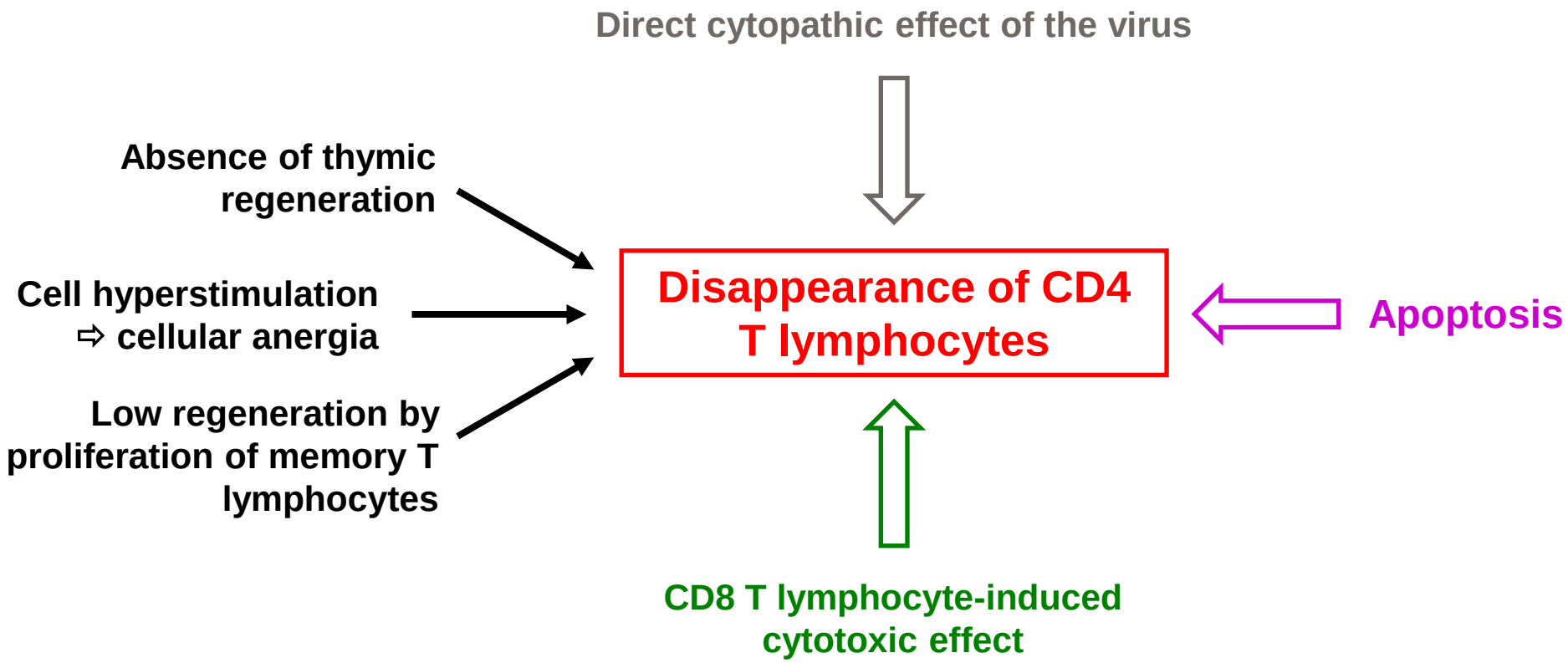


[Johnston and Fauci, N. Engl. J. Med., 2007]

Evolution of HIV infection



Progressive destruction of CD4 T lymphocytes



III- Pathophysiology

5- Clinical signs

HIV primary infection

- **50% of patients are symptomatic**

  if clinical signs, appearance within 15 days after contamination

- **Clinical signs**

  - acute viral syndrome (fever +++, headache +++, malaise, asthenia)

  - polyadenopathy +++

  - cutaneous-mucous manifestations (angina or pharyngitis, rash)

  - digestive disorders (diarrhea)

  - neurological symptoms +++ (cognitive impairment, motor deficit, neuropathy, lymphocytic meningitis, encephalitis)

- **Biology abnormalities**

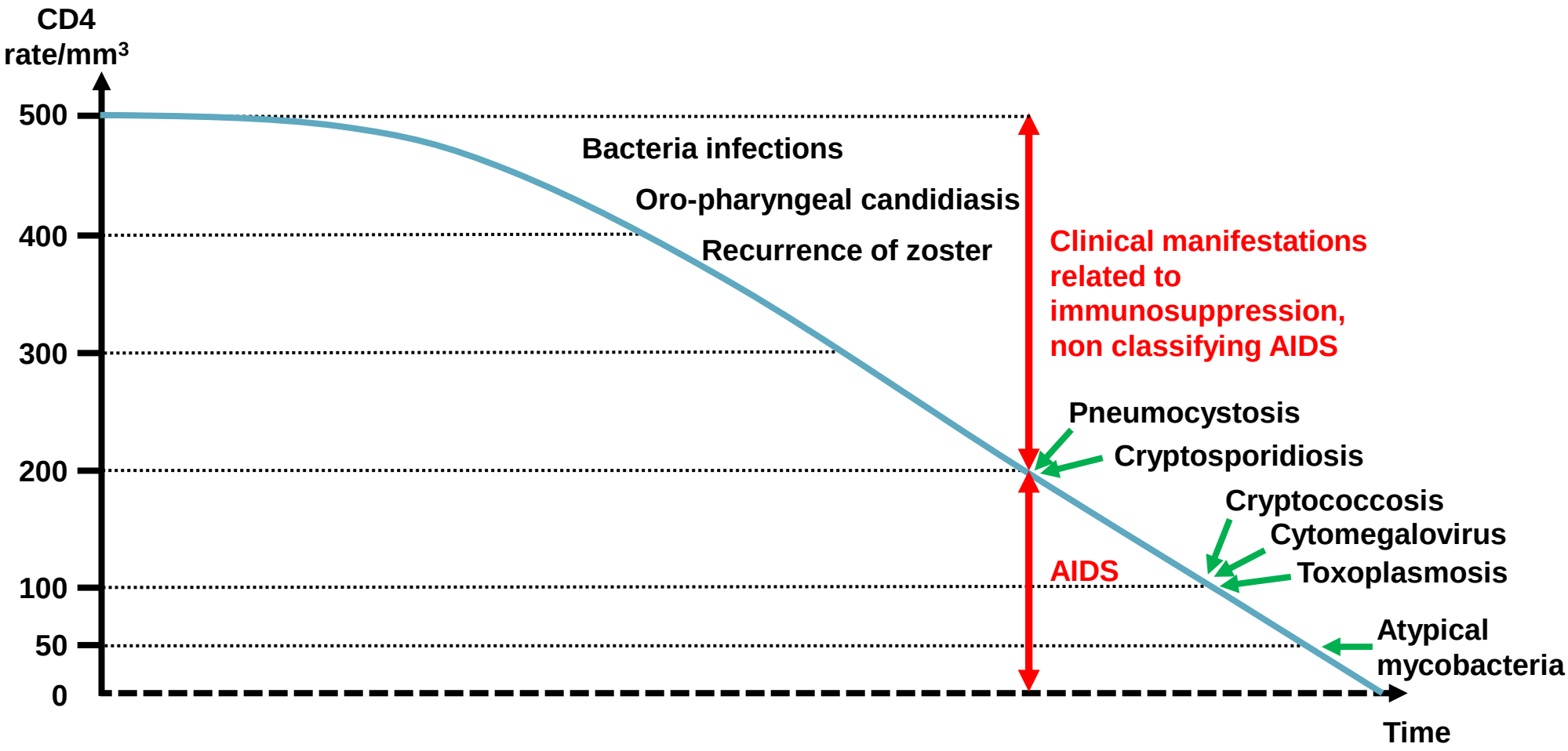
  - hematological (thrombocytopenia, neutropenia, hyperlymphocytosis as part of a mononucleosis syndrome or early lymphopenia)

  - hepatic cytolysis

Then these signs disappear…

Occurrence of infections by CD4 T lymphocyte rate

A few months to a few years after contamination, after a long phase with no apparent signs, symptoms (re)appear



Possible progression to patient death

[D'après SIDA, Girard, 1996]

Classification from the Centers for Disease Control (CDC) (1)

Category A

One or more criteria listed below in an HIV-infected adult or adolescent, if none of the criteria in categories B and C exist:

- Asymptomatic HIV infection
- Generalized persistent lymphadenopathy
- Symptomatic primary infection

Category B

Clinical manifestations in an HIV-infected adult or adolescent which are not in category C and meet at least one of the following conditions:

- Bacillary angiomatosis
- Oro-pharyngeal candidiasis, persistent, frequent or poorly responding vulvovaginal candidiasis
- Cervical dysplasia (moderate or severe), *in situ* carcinoma
- Constitutional syndrome: fever (≥ 38.5°C) or diarrhea for more than a month
- Oral leukoplakia of the tongue
- Recurrent zoster or invasive zoster (more than one dermatome)
- Idiopathic thrombocytopenic purpura
- Salpingitis
- Listeriosis
- Peripheral neuropathy

Classification from the CDC (2)

☞ Category C = Major opportunistic infections

- Bronchial, tracheal or pulmonary candidiasis
- Esophageal candidiasis
- Invasive cervical cancer
- Disseminated or extrapulmonary coccidioidomycosis
- Extrapulmonary cryptococcosis
- Intestinal cryptosporidiosis that has been evolving for more than a month
- Cytomegalovirus infection (other than liver, spleen or lymph nodes)
- HIV-related encephalopathy
- Herpetic infection: chronic ulcers lasting > 1 month or bronchial, pulmonary, esophageal infection
- Disseminated or extrapulmonary histoplasmosis
- Chronic intestinal isosporidiosis > 1 month
- Kaposi sarcoma
- Immunoblastic lymphoma
- Primary brain lymphoma
- Burkitt lymphoma
- *Mycobacterium avium* or *kansaii* infection disseminated or extrapulmonary
- *Mycobacterium tuberculosis* infection regardless of location (pulmonary or extrapulmonary)

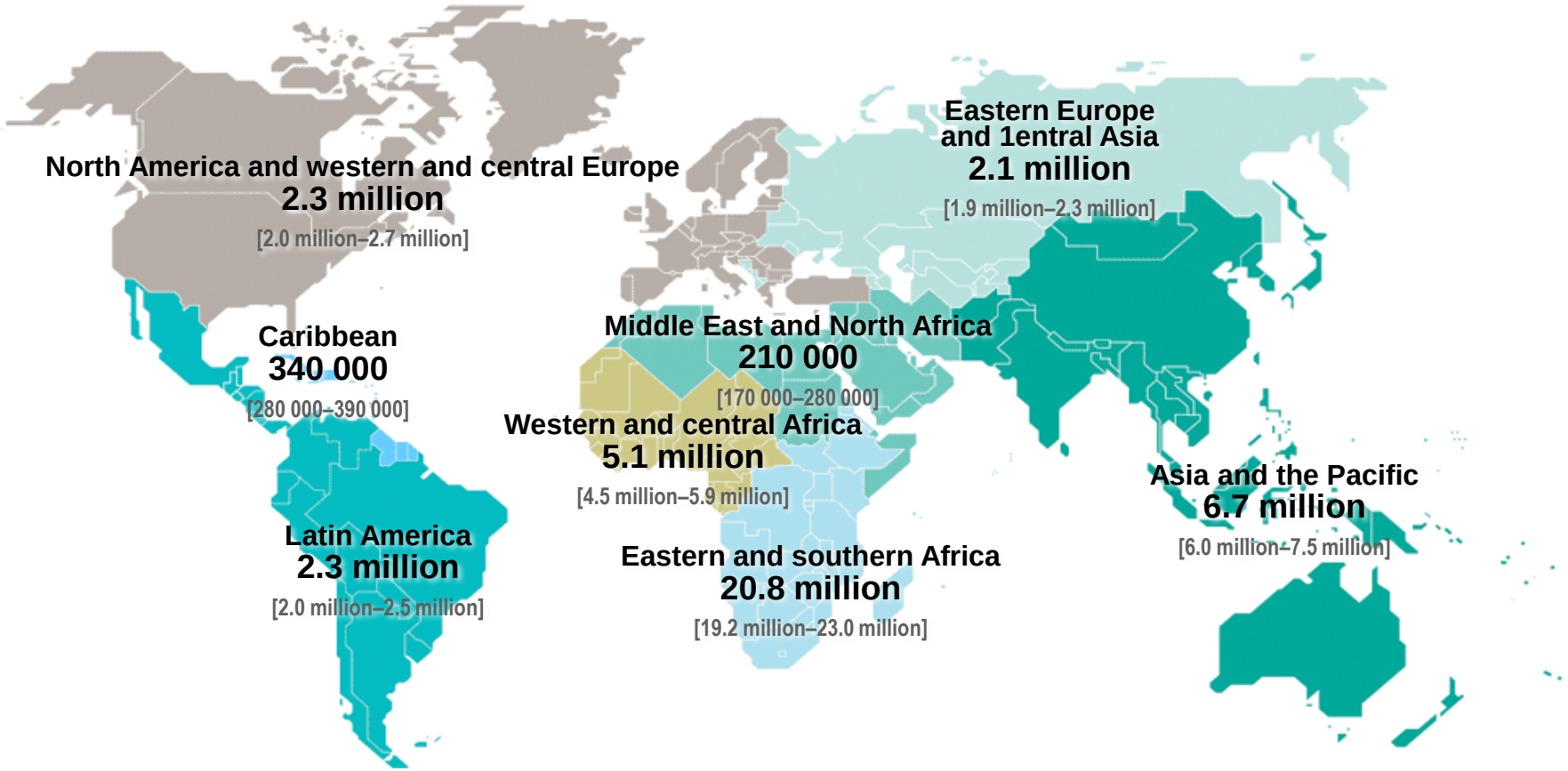
Classification from the CDC (3)

☞ Category C (continued)

- Mycobacteria infection other or unidentified, disseminated or extra-pulmonary
- Pneumocystosis with *Pneumocystis jiroveci*
- Recurrent lung disease
- Progressive multifocal leukoencephalopathy (PML)
- Recurrent Salmonella non *typhi* sepsis
- Cerebral toxoplasmosis
- Cachectic syndrome due to HIV

IV- Epidemiology

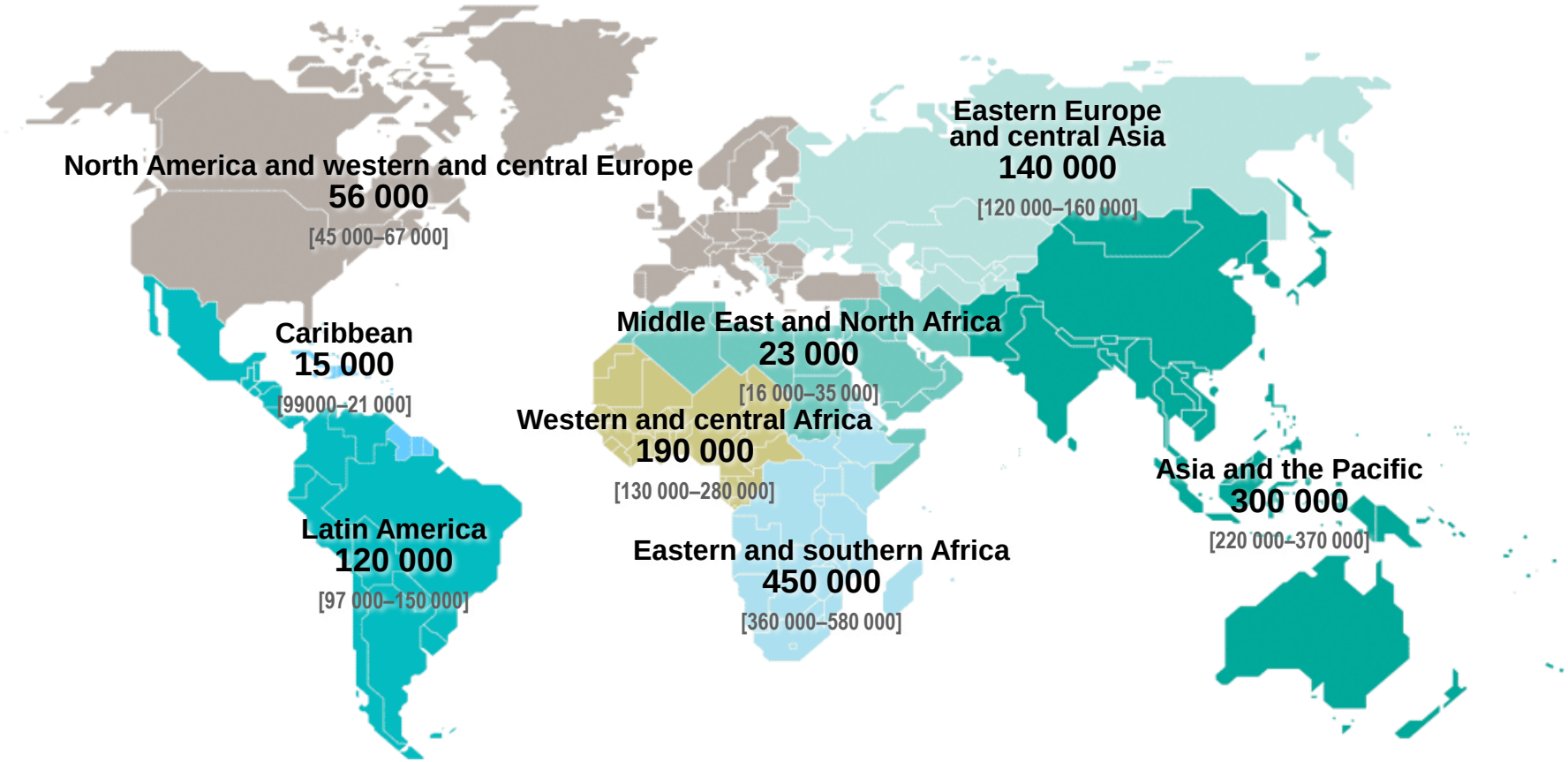
Estimated number of adults and children living with HIV worldwide, 2023



Total: 39.9 million [36.1 million - 44.6 million]

[UNAIDS, 2024]

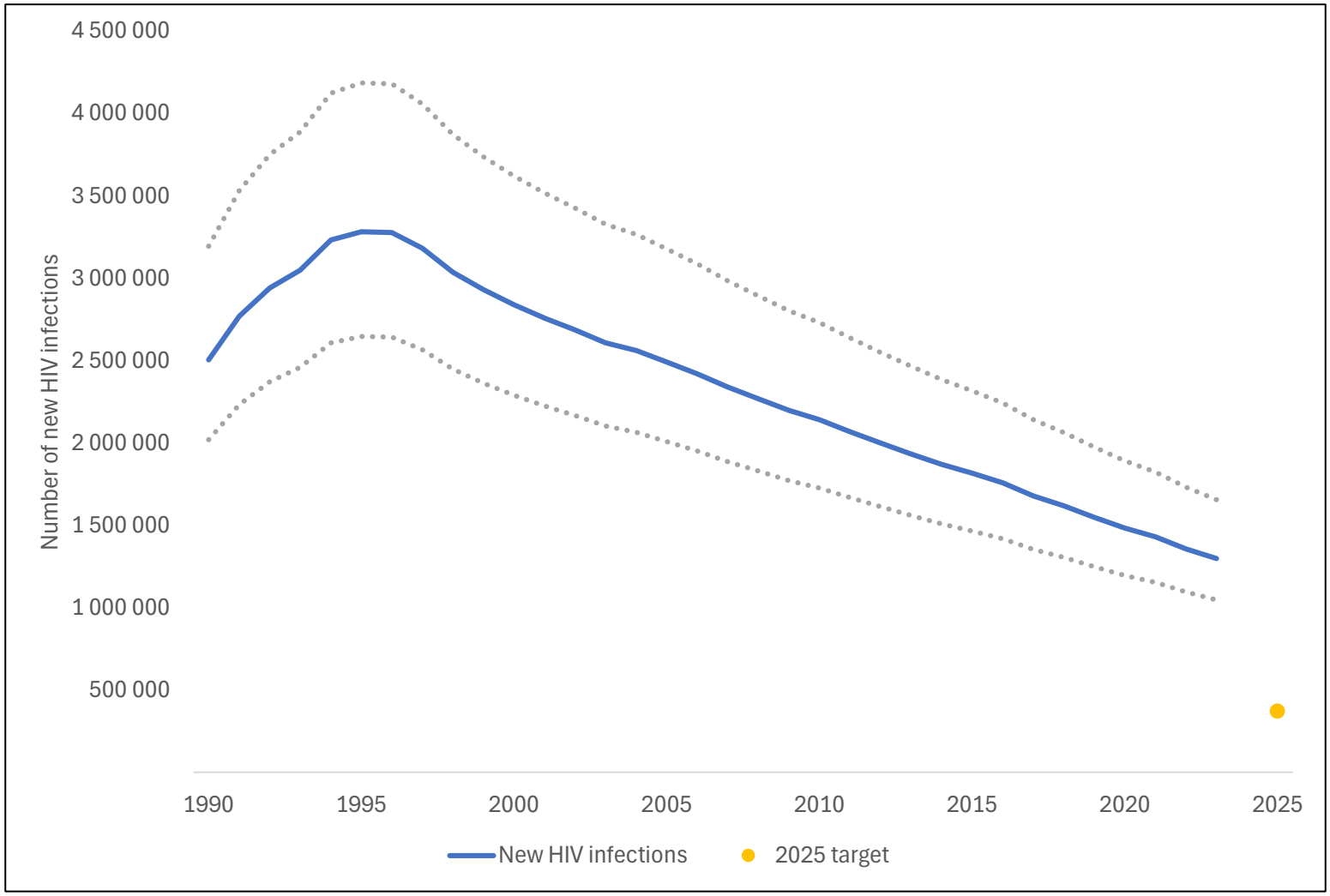
Estimated number of adults and children newly infected with HIV worldwide, 2023



Total : 1.3 million [1.0 million - 1.7 million]

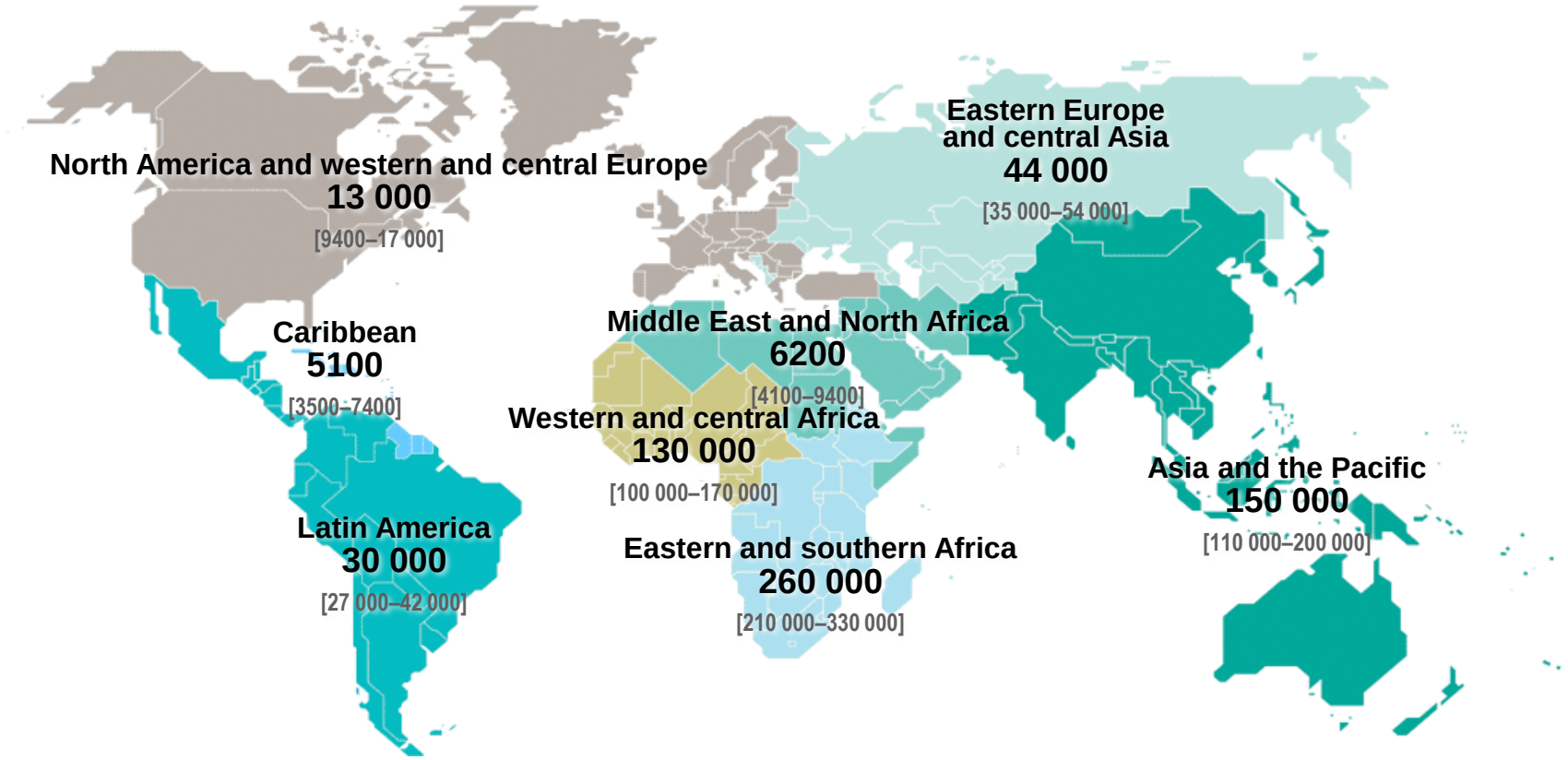
[UNAIDS, 2024]

Estimated number of new HIV infections worldwide, 1990 - 2023 and objective 2025



[UNAIDS, 2024]

Estimated number of adult and child deaths due to AIDS worldwide, 2023



Total : 630,000 [500,000 - 820,000]

[UNAIDS, 2024]

Evolution of the pandemic

- **Currently,**
  - **if prevention options have slowed the pandemic**
    - **thousands of people continue to be infected every day**

- **About 3,600 new HIV infections per day in 2023**
  - **about 50% in Sub-Saharan Africa**
  - **about 320 children under 15**
  - **approximately 3,280 adults aged 15 years and older, including**
    - **about 44% of women**
    - **about 30% of young adults aged between 15 and 24 years**

[UNAIDS, 2024]