



DEPARTAMENTO DE
MICroBiologia
UNIVERSIDADE DE SÃO PAULO



Vírus da Imunodeficiência humana: modelo de patogênese

Enrique Boccardo

Depto. Microbiologia – ICB/USP

eboccardo@usp.br

Origem do HIV

Relembrar é viver...

- **1981- AIDS** ou síndrome da imunodeficiência adquirida é descrita em adultos jovens, do sexo masculino e homossexuais, com sarcoma de Kaposi.
- **1983- Françoise Barré-Sinoussi**, do grupo de **Luc Montagnier**, (Instituto Pasteur, França), identificou um vírus associado à linfadenopatia (LAV).
- **1984- Robert Gallo**, nos EUA, descreveu o HTLV-III.
- **1986-** Fica evidente que o LAV e o HTLV-III são, na realidade, o mesmo vírus.

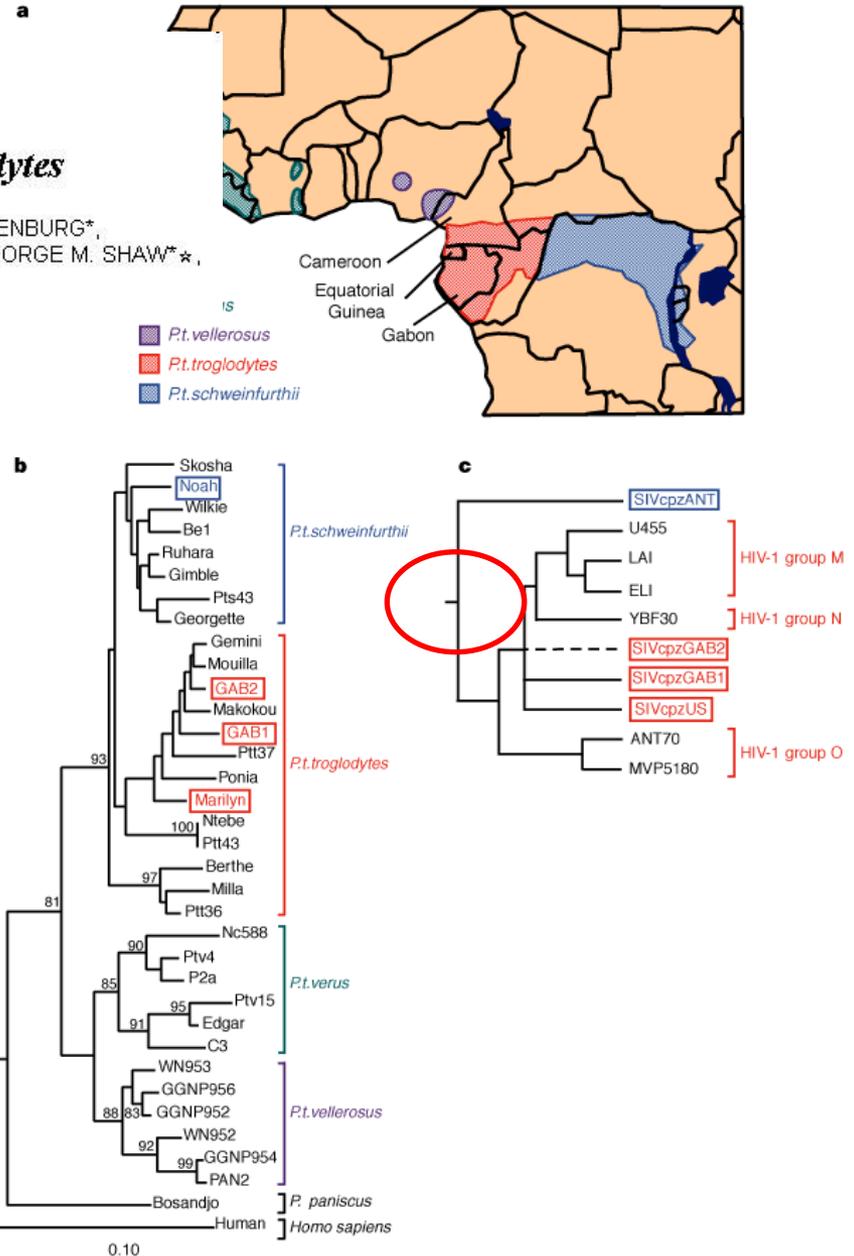
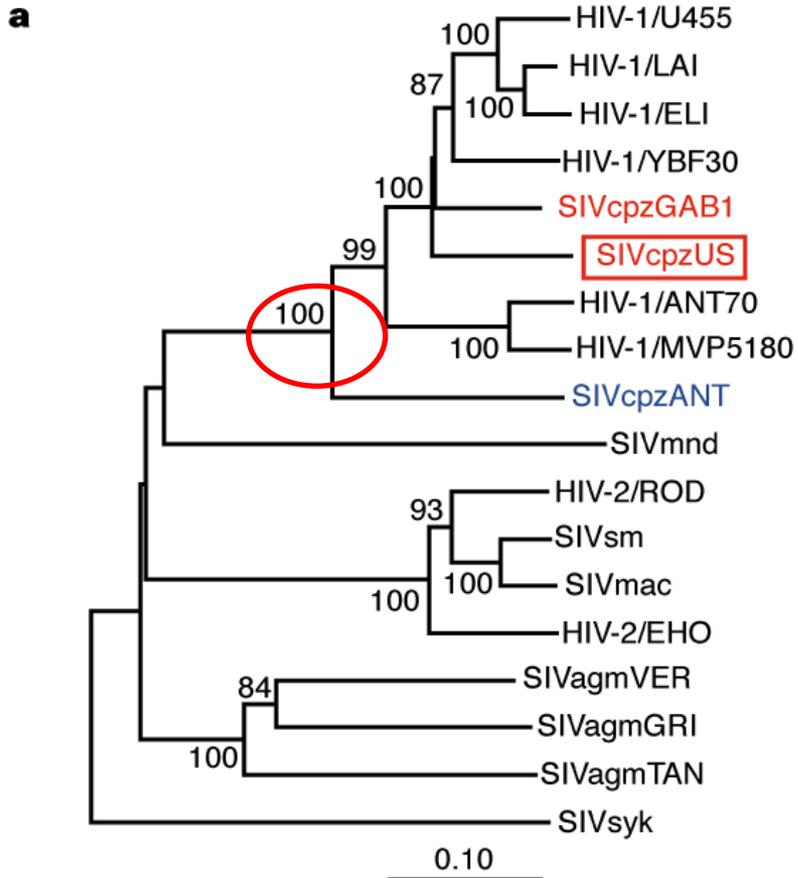
A Origem do HIV

letters to nature

Nature 397, 436 - 441 (1999) © Macmillan Publishers Ltd.

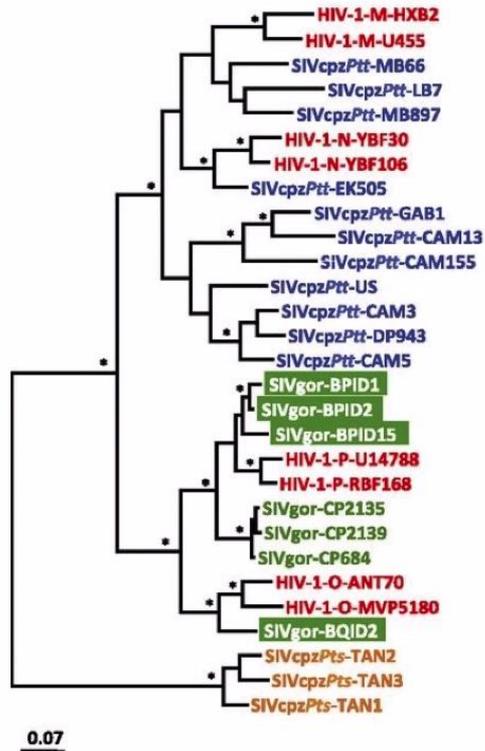
Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*

FENG GAO*, ELIZABETH BAILEST†, DAVID L. ROBERTSON‡, YALU CHEN*, CYNTHIA M. RODENBURG*, SCOTT F. MICHAEL*§, LARRY B. CUMMINS||, LARRY O. ARTHUR¶, MARTINE PEETERS#, GEORGE M. SHAW***, PAUL M. SHARP† & BEATRICE H. HAHN*

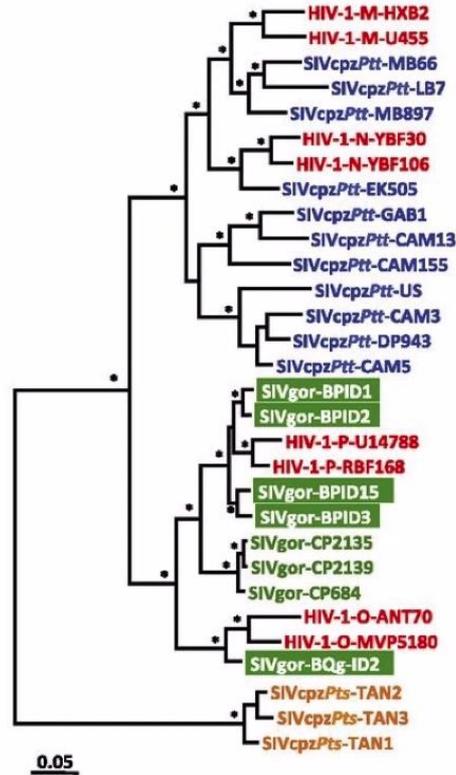


A Origem do HIV

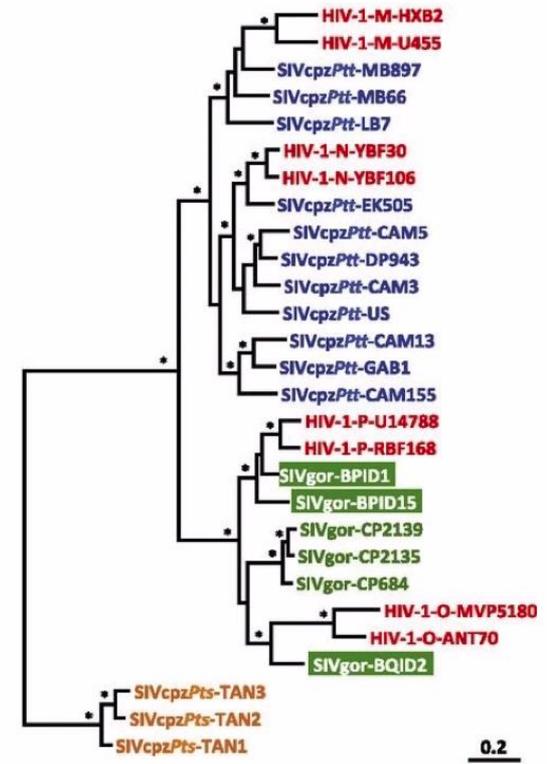
A Gag (488aa)



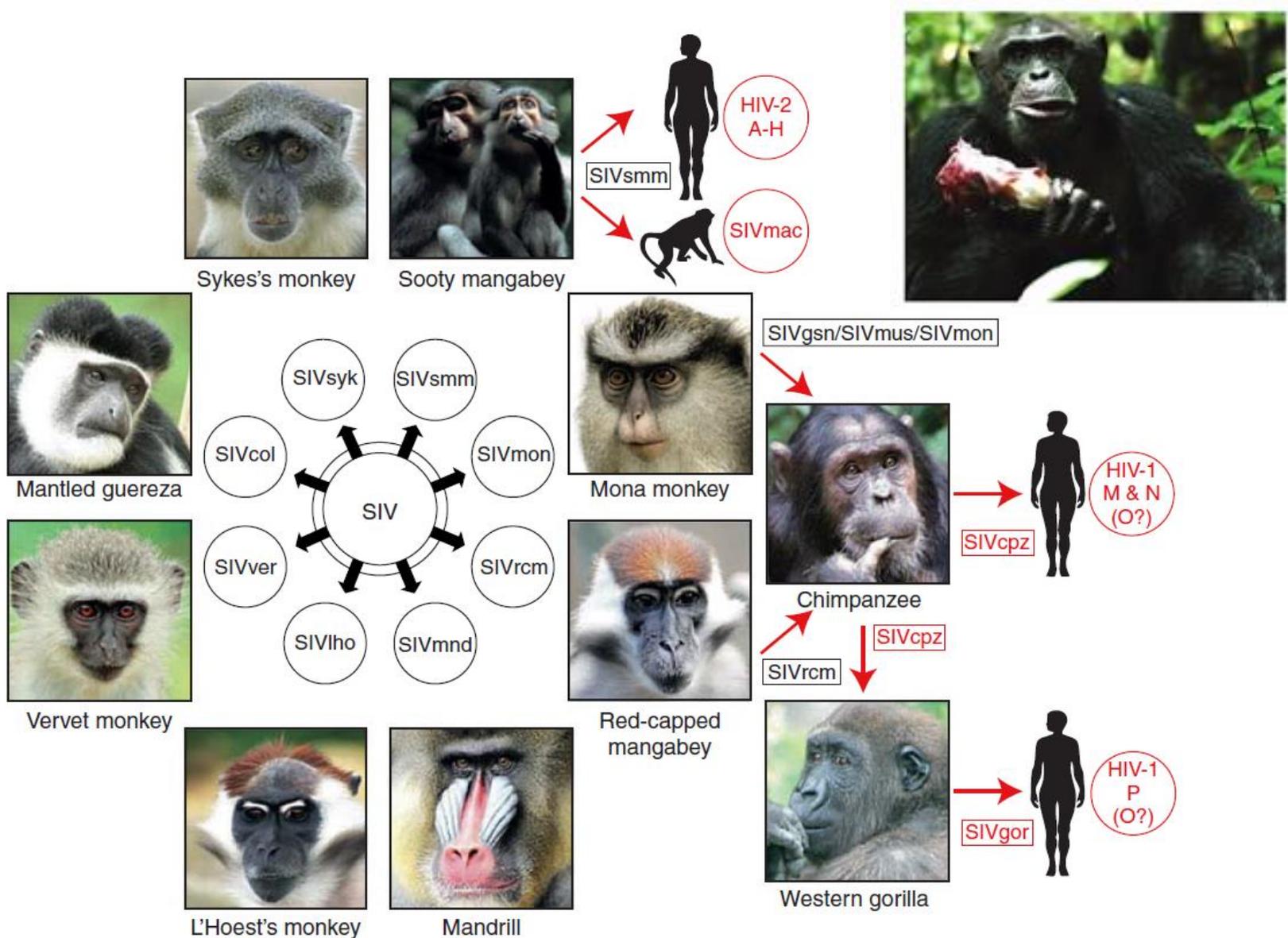
B Pol (927aa)



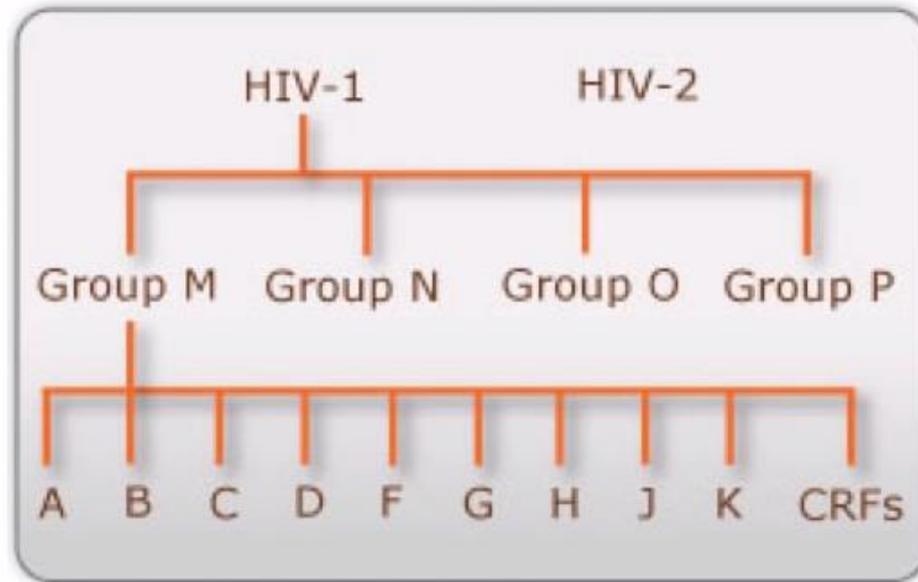
C Env/Nef (854aa)



A Origem do HIV



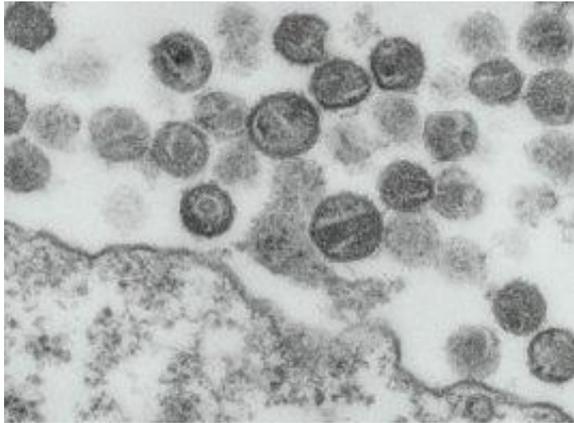
A Origem do HIV e sua diversidade



- O grupo M se divide em 9 subtipos
- Indivíduos de alto risco podem ser reinfetados e gerar recombinantes
- Subtipos vs AIDS, não existe diferença clara (infectados com subtipo D morrem mais rápido)
- Subtipo C é liberado em maior quantidade no trato reprodutor feminino.

O vírus

Vírus da imunodeficiência Humana (HIV)

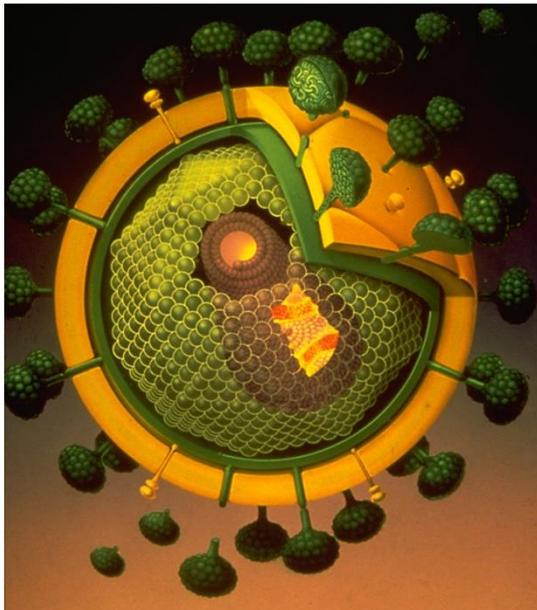


Família : *Retroviridae*
Gênero: Lentivírus

Vírus pequenos de RNA envelopados

RNA linear simples-fita (~9,3 kb)

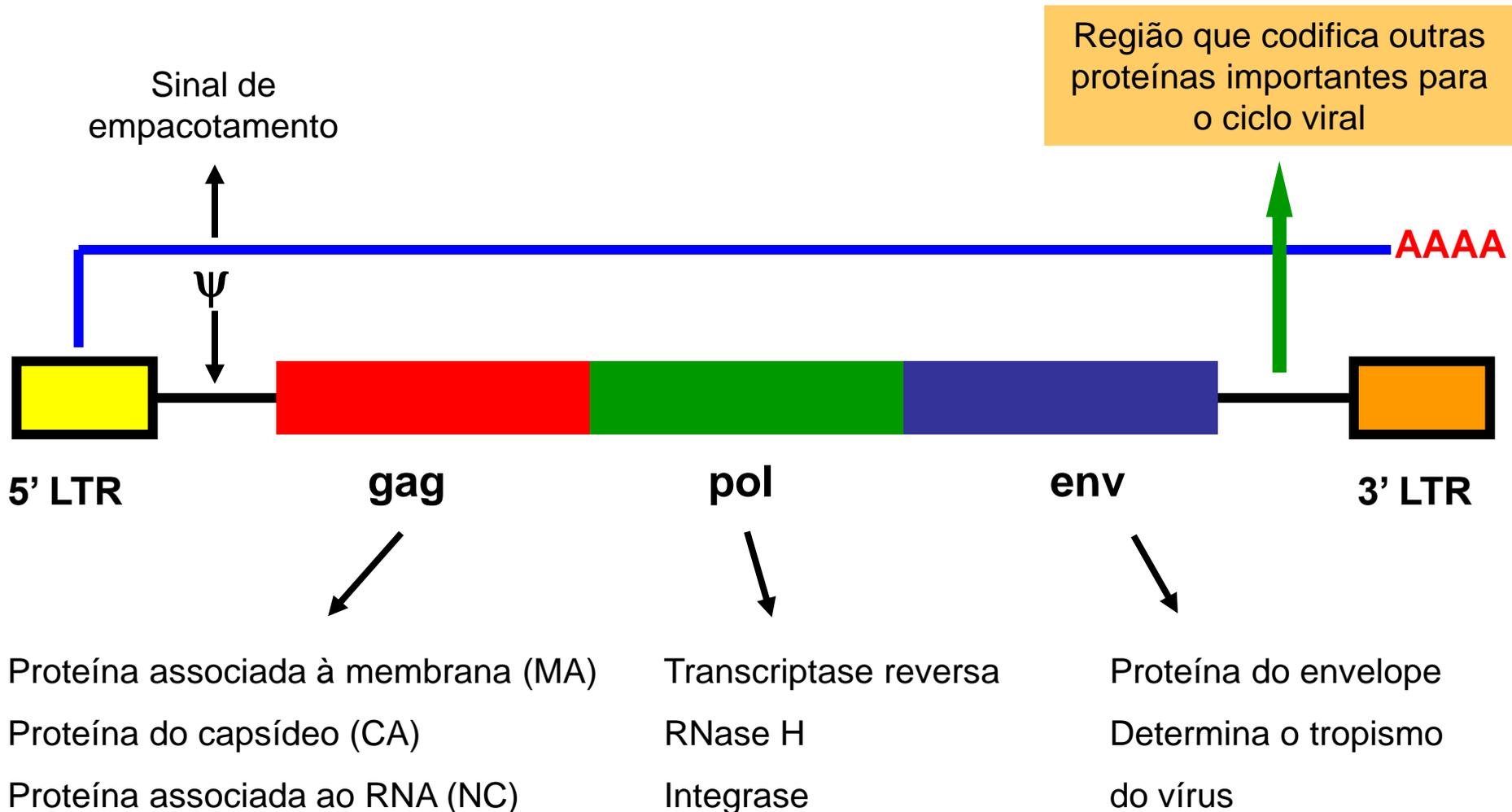
Célula alvo: Linfócitos T CD4⁺



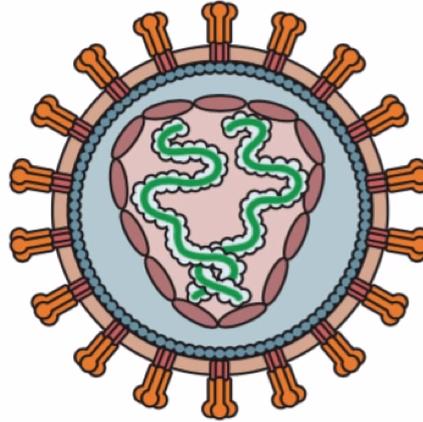
Etiologicamente associado com:

- AIDS
- Linfoma associado à AIDS
- Doença de Hodgkin
- Mieloma múltiplo

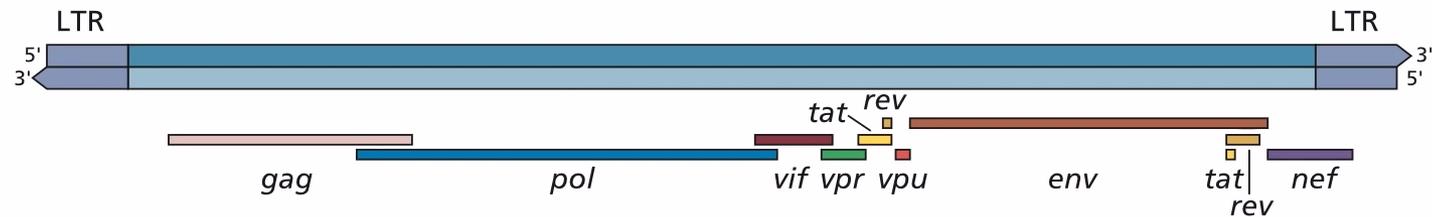
O HIV é um retrovírus complexo



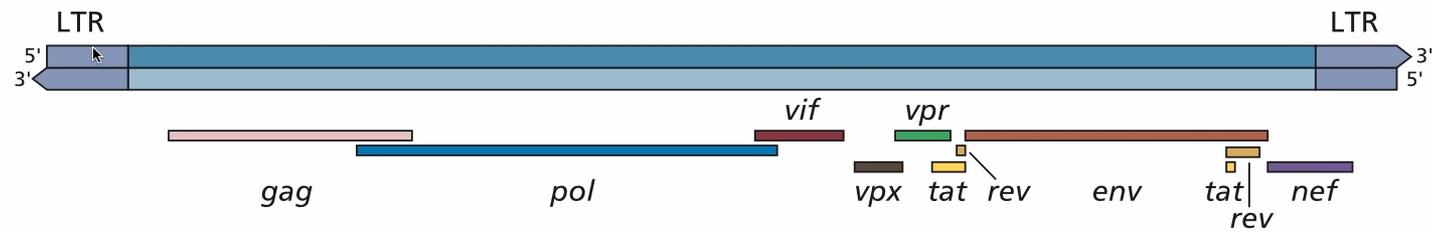
O HIV é um retrovírus complexo



A HIV-1

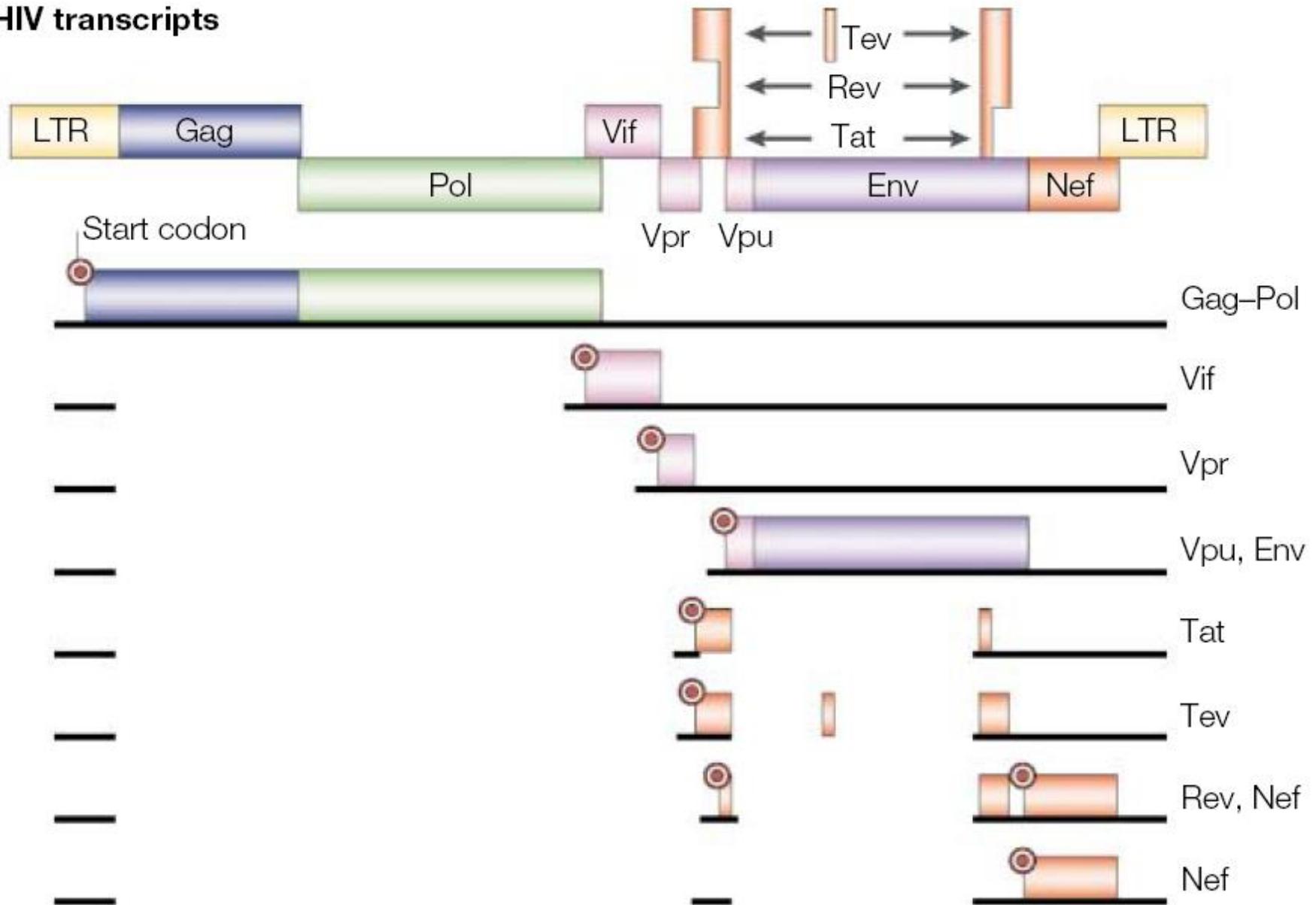


B HIV-2

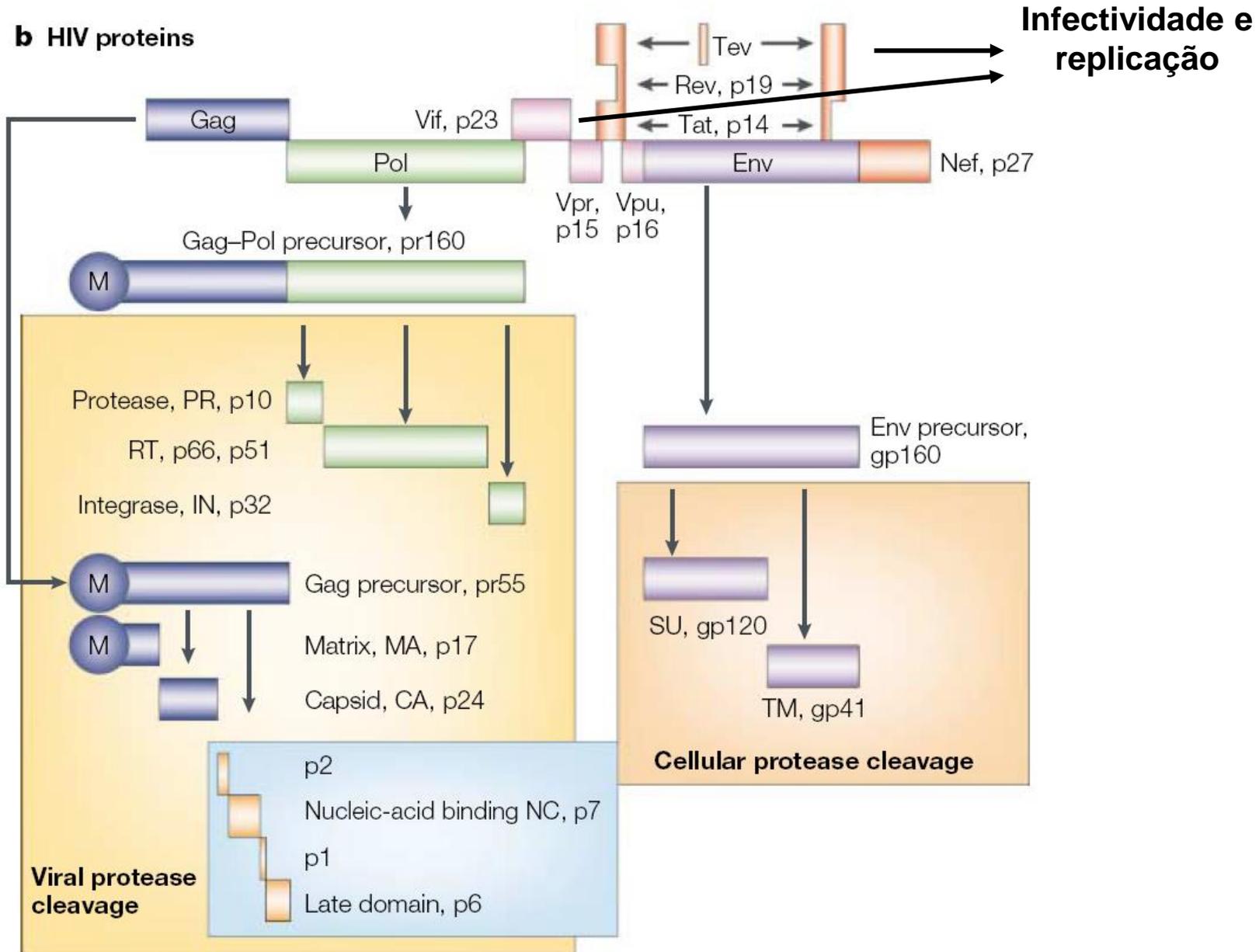


Genoma e transcritos do HIV

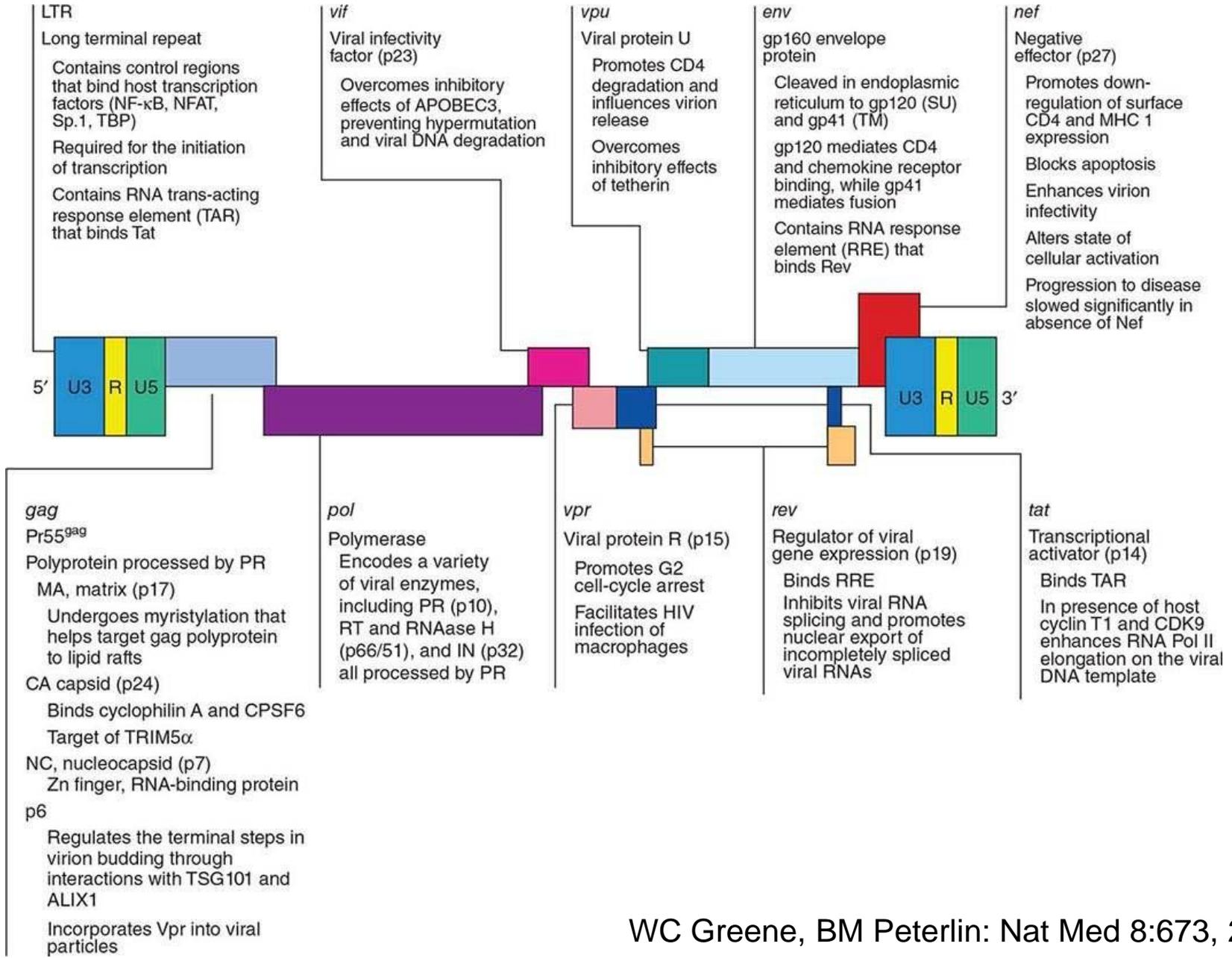
a HIV transcripts



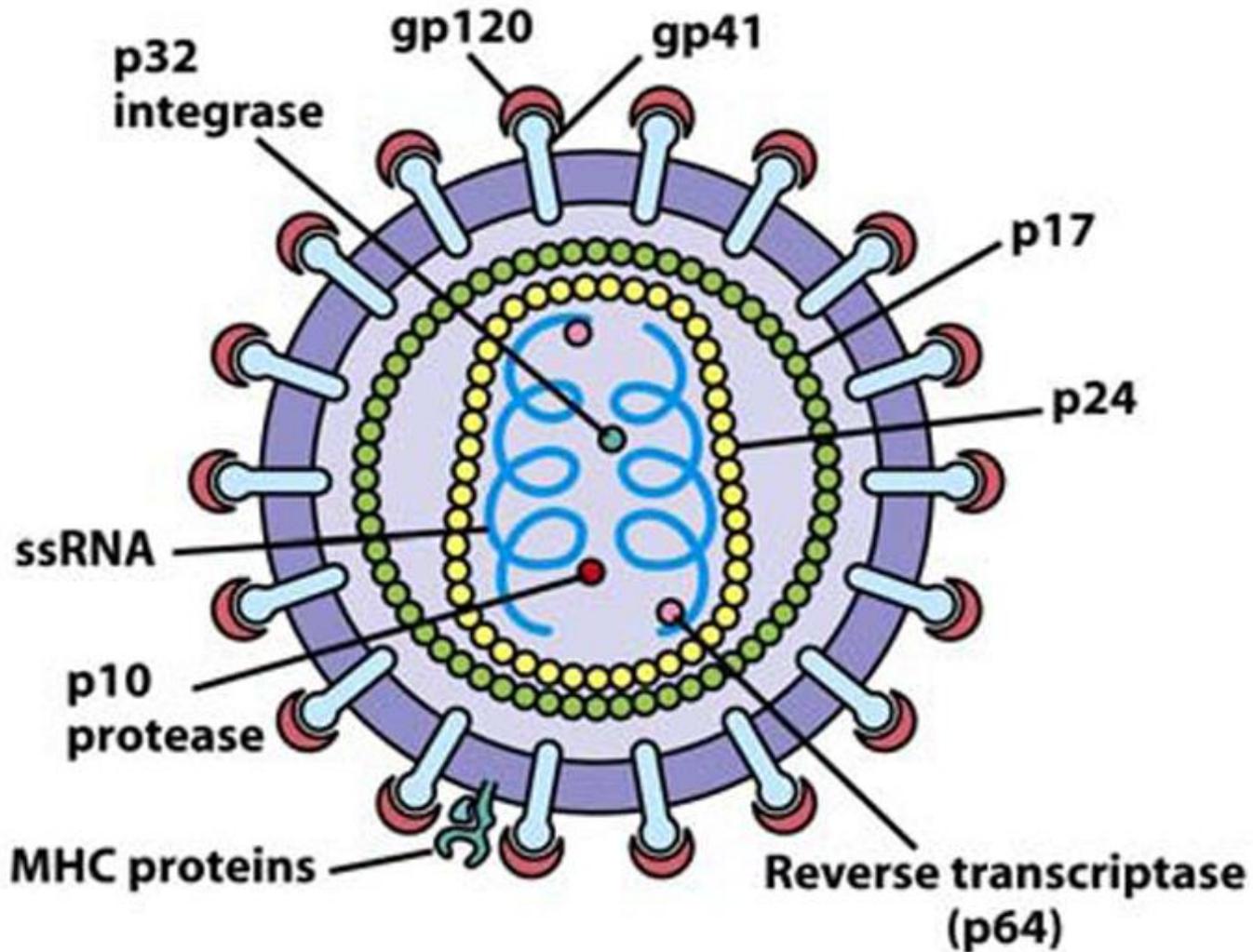
Proteínas do HIV



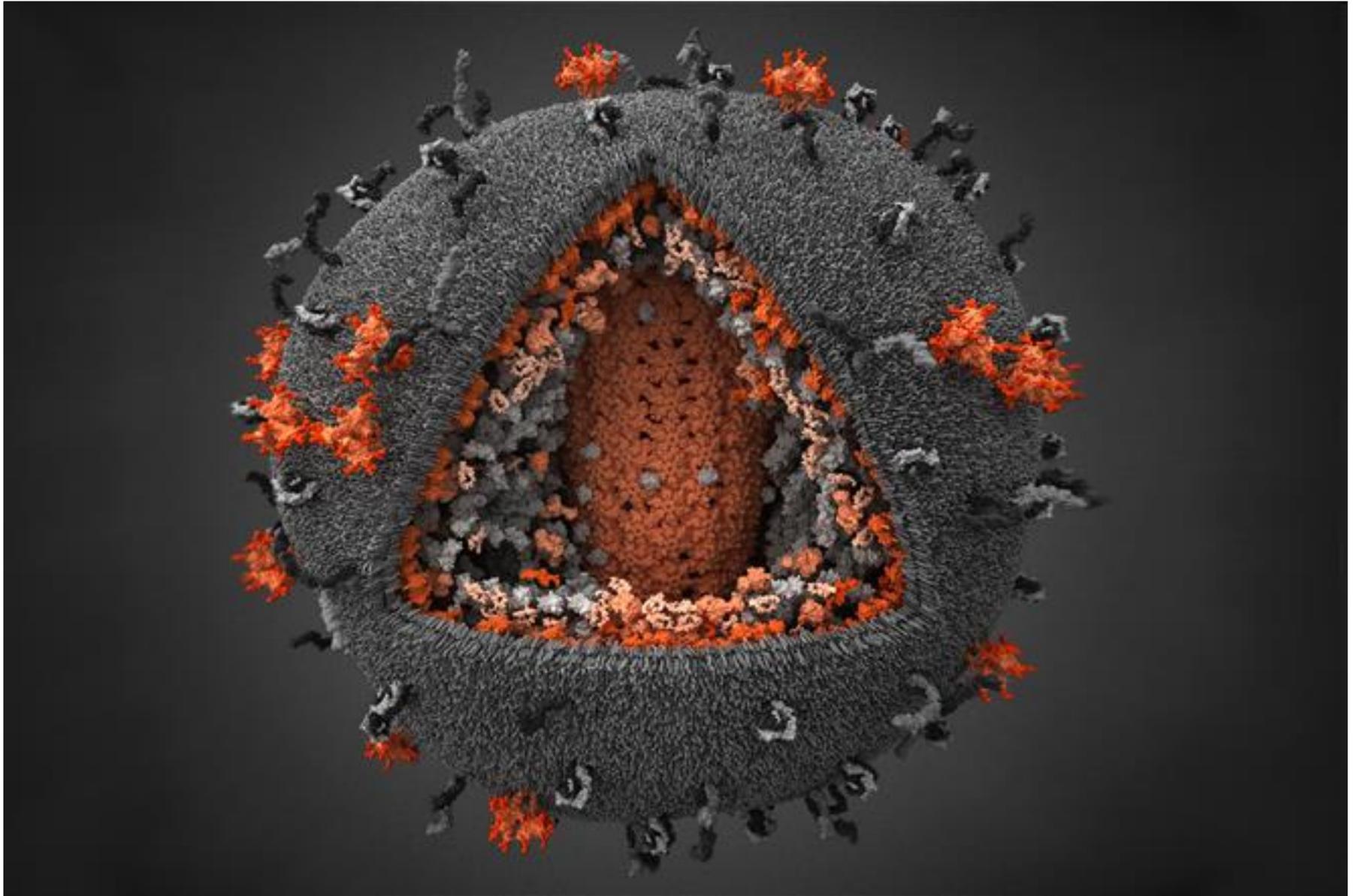
Proteínas do HIV



Estrutura do HIV



Estrutura do HIV



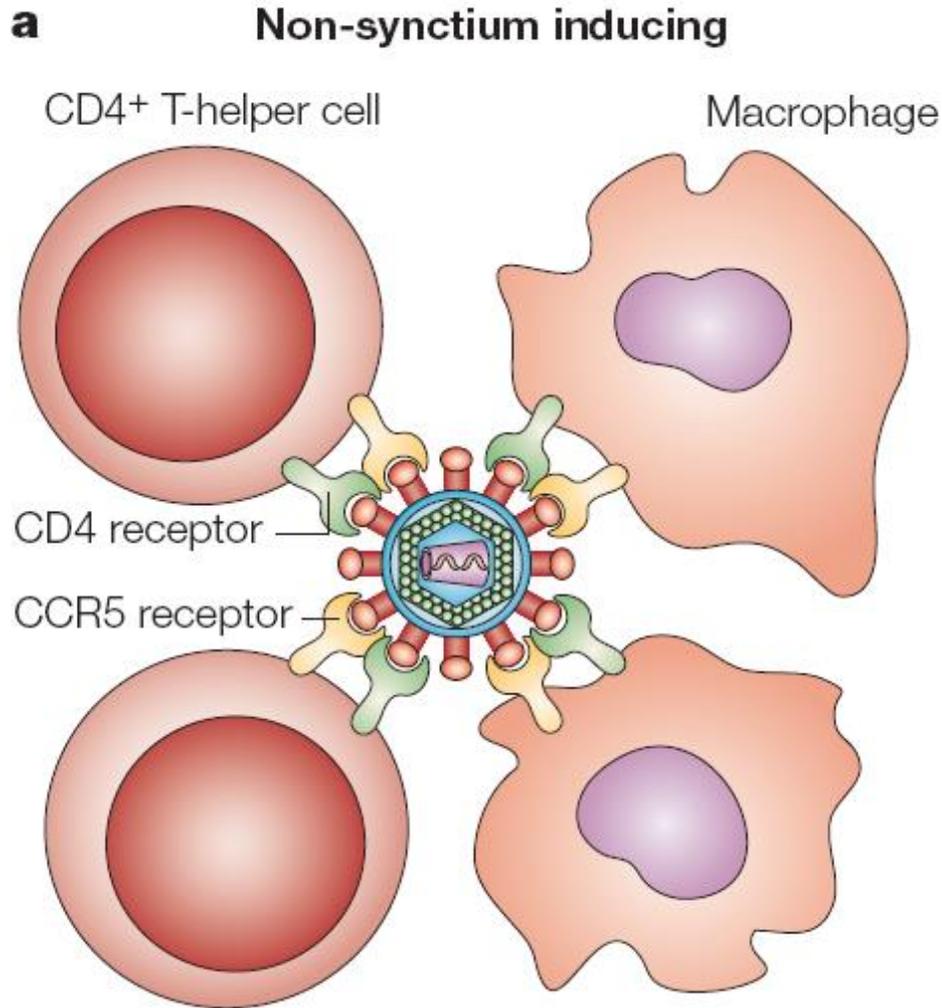
O ciclo viral

Células alvo do HIV

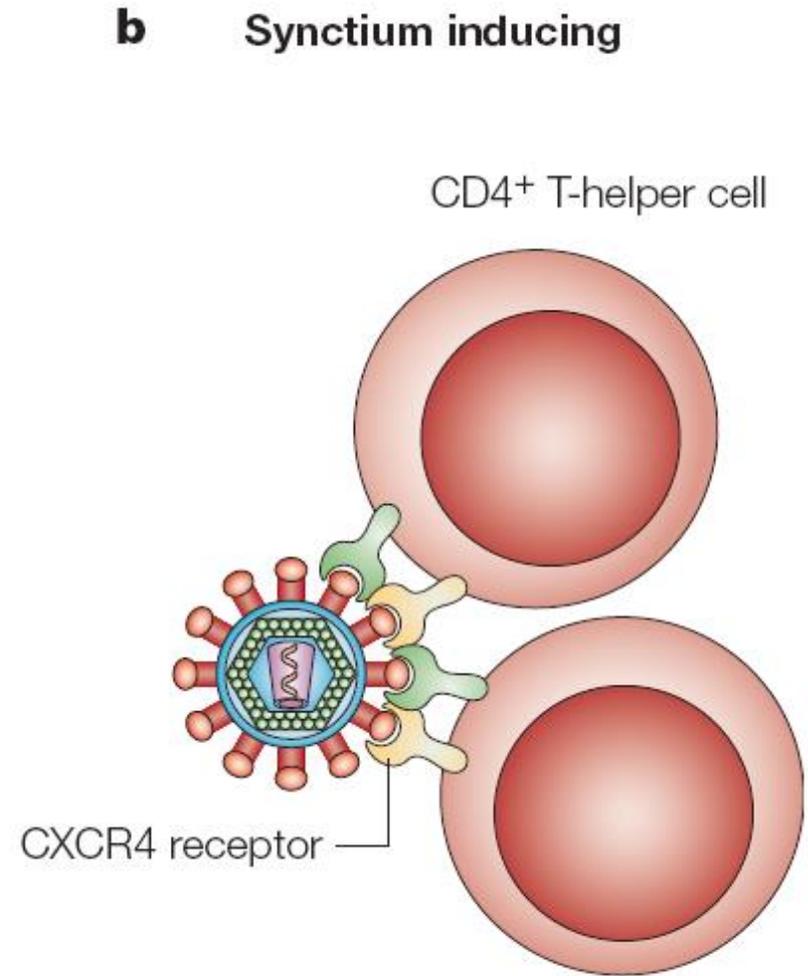
Células que apresentam o Receptor CD4 e os Co-receptores CXCR4 ou CCR5, entre elas:

- Linfócito T Auxiliar CD4+
- Macrófagos
- Células Dendríticas

Receptores do HIV

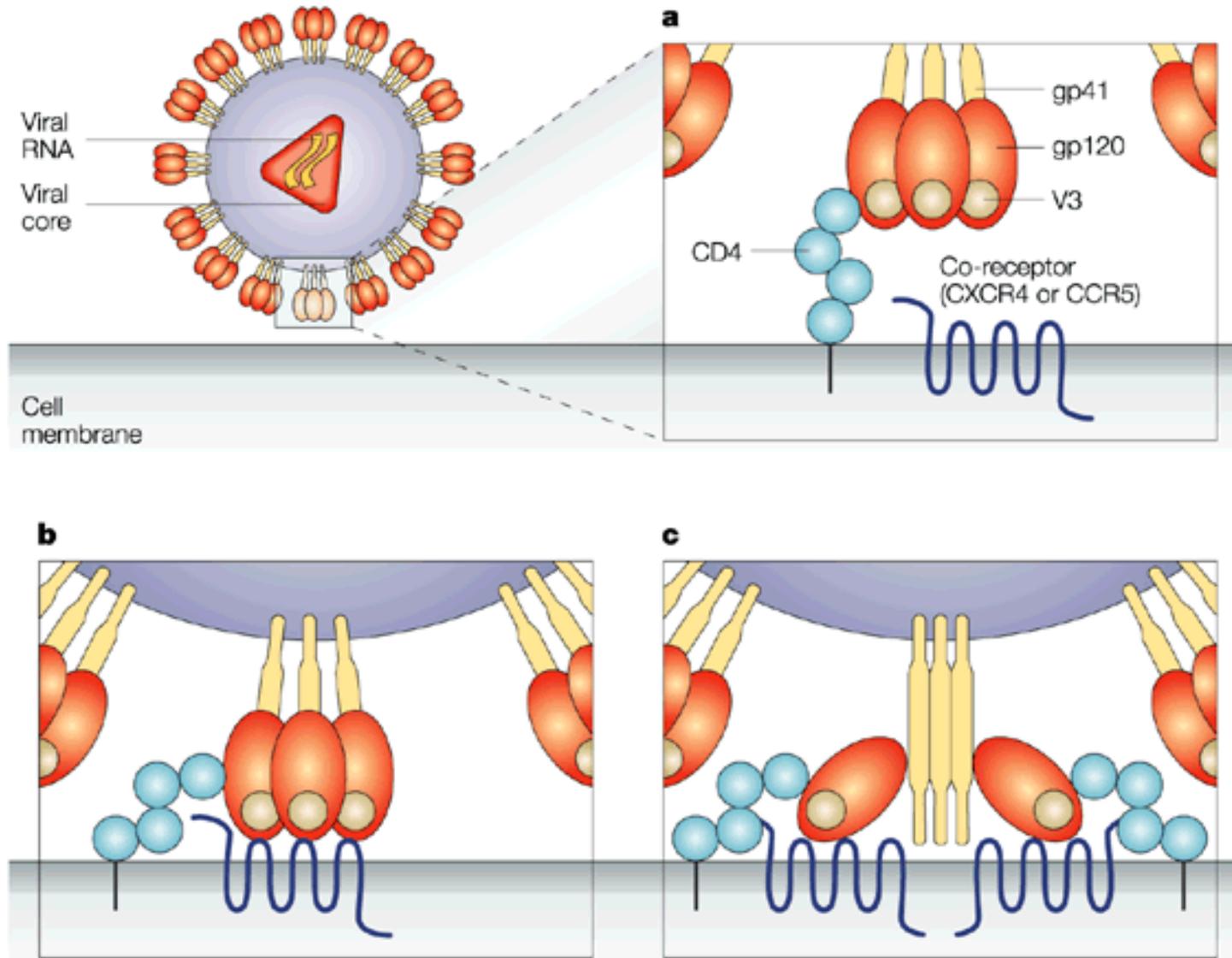


Cepas "R5"

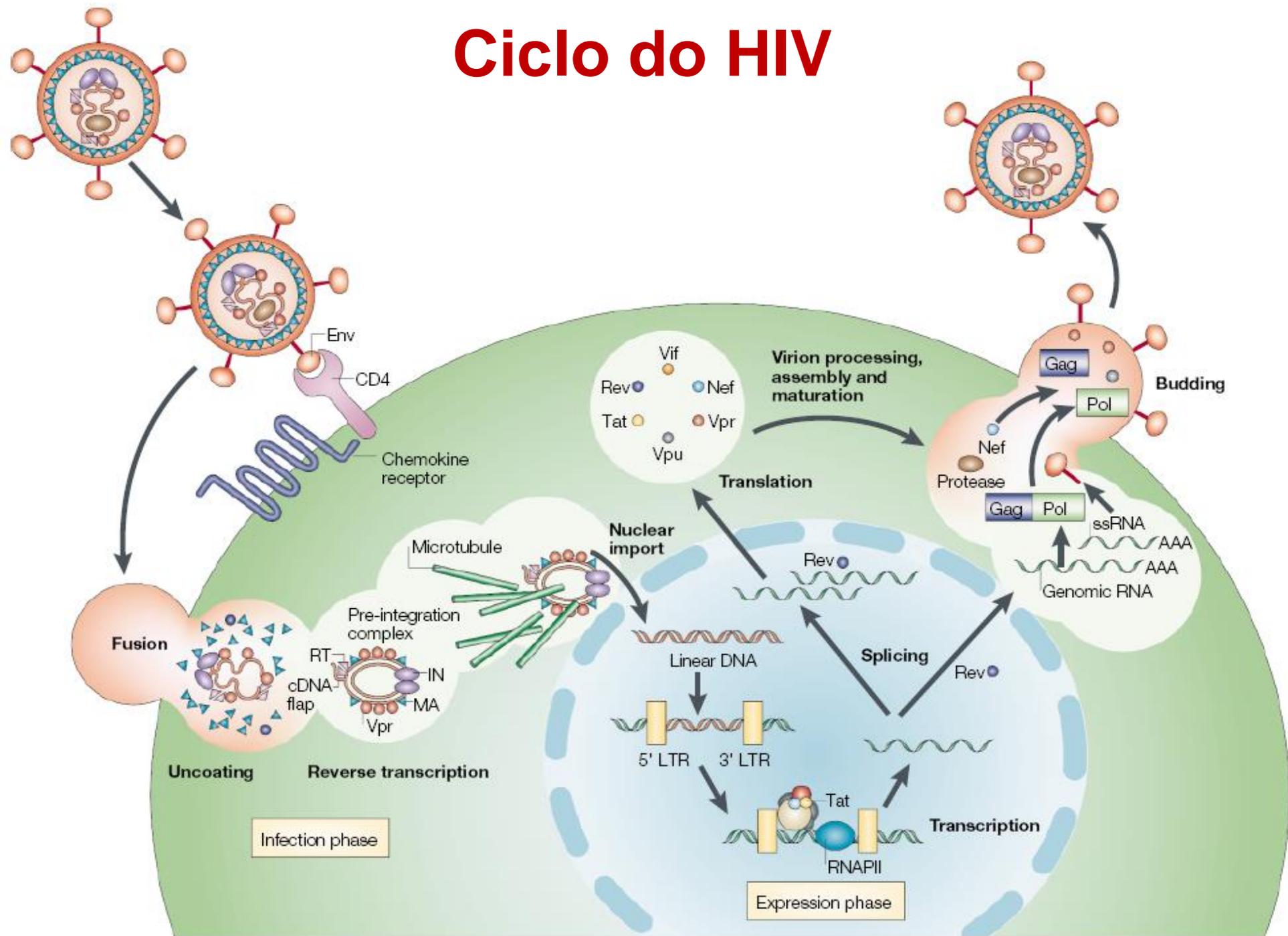


Cepas "X4"

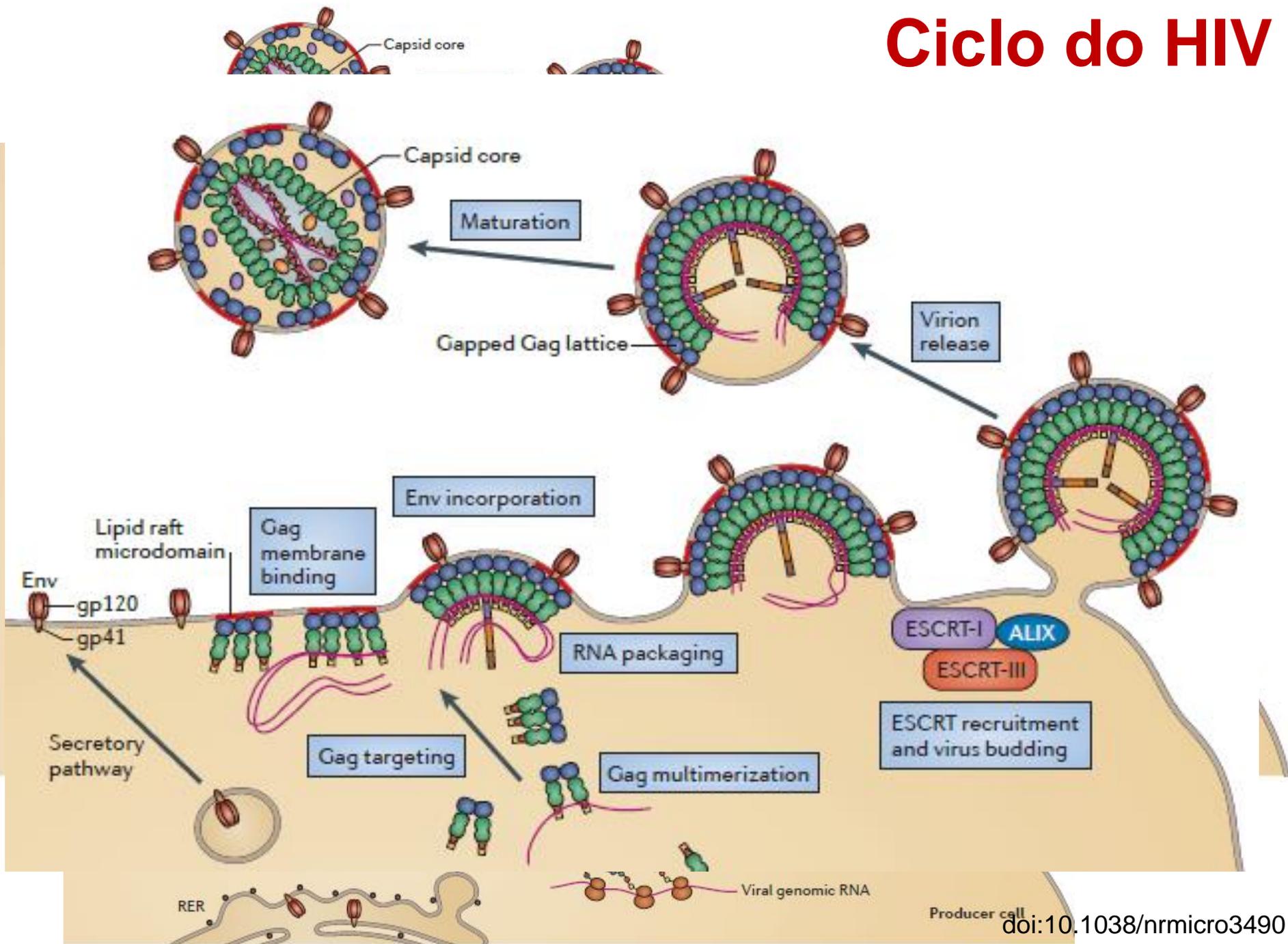
Receptores do HIV



Ciclo do HIV



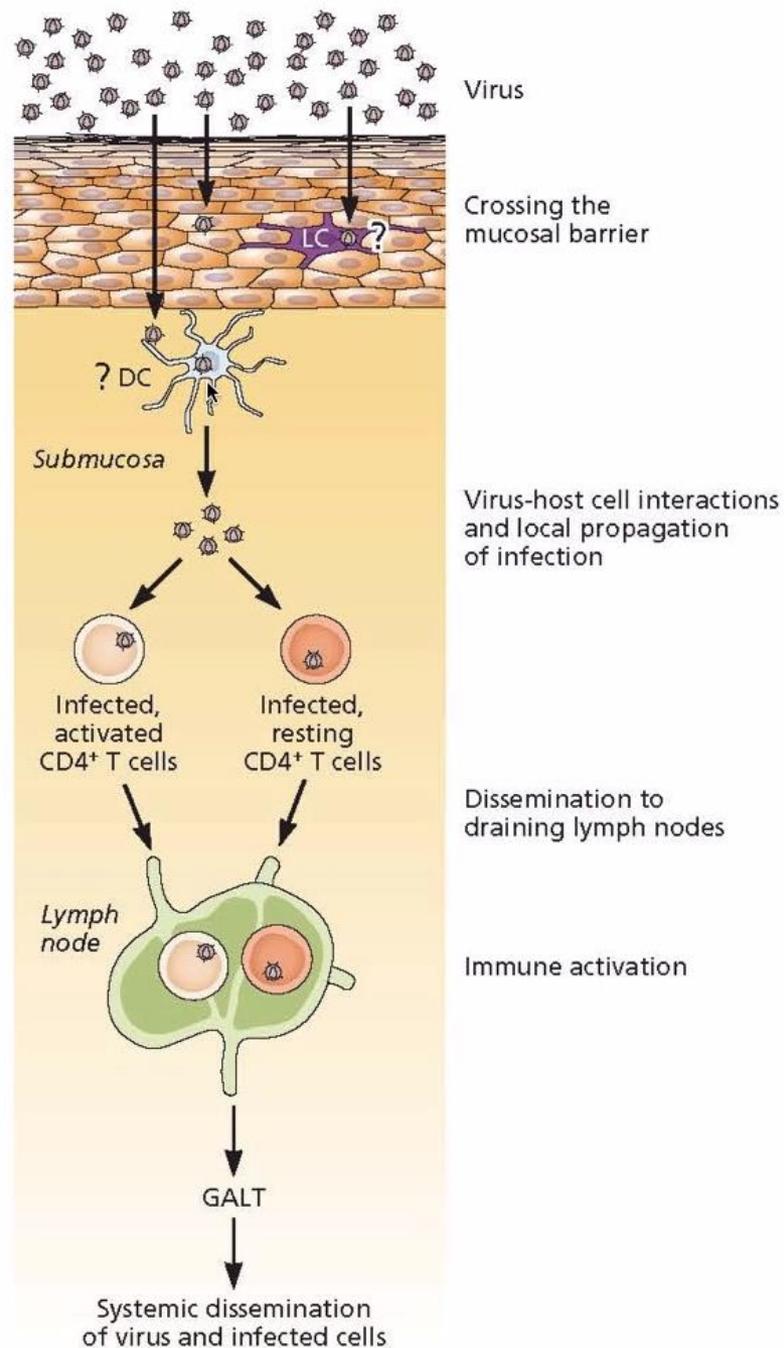
Ciclo do HIV



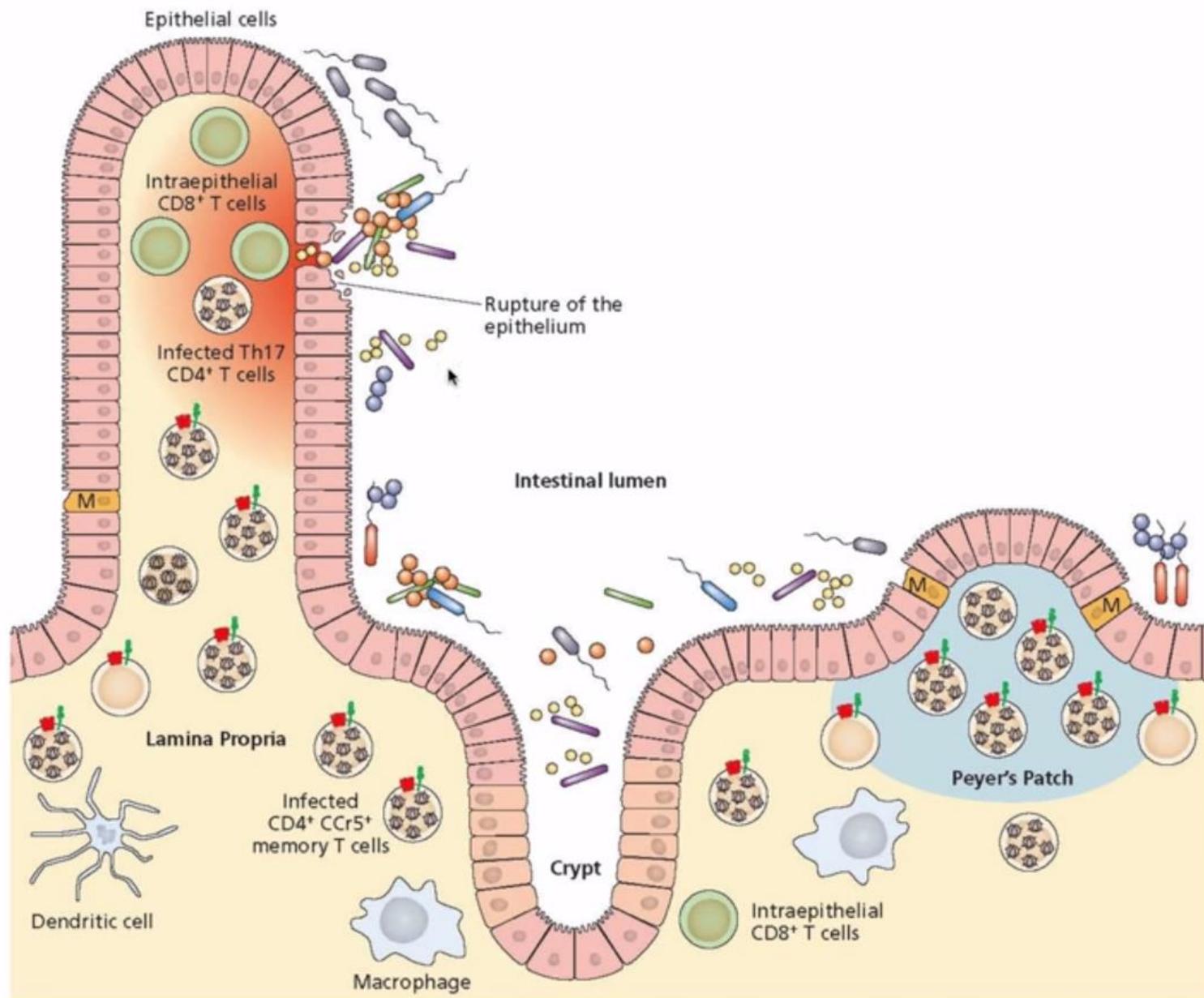
Infeção

HIV: Infecção primária

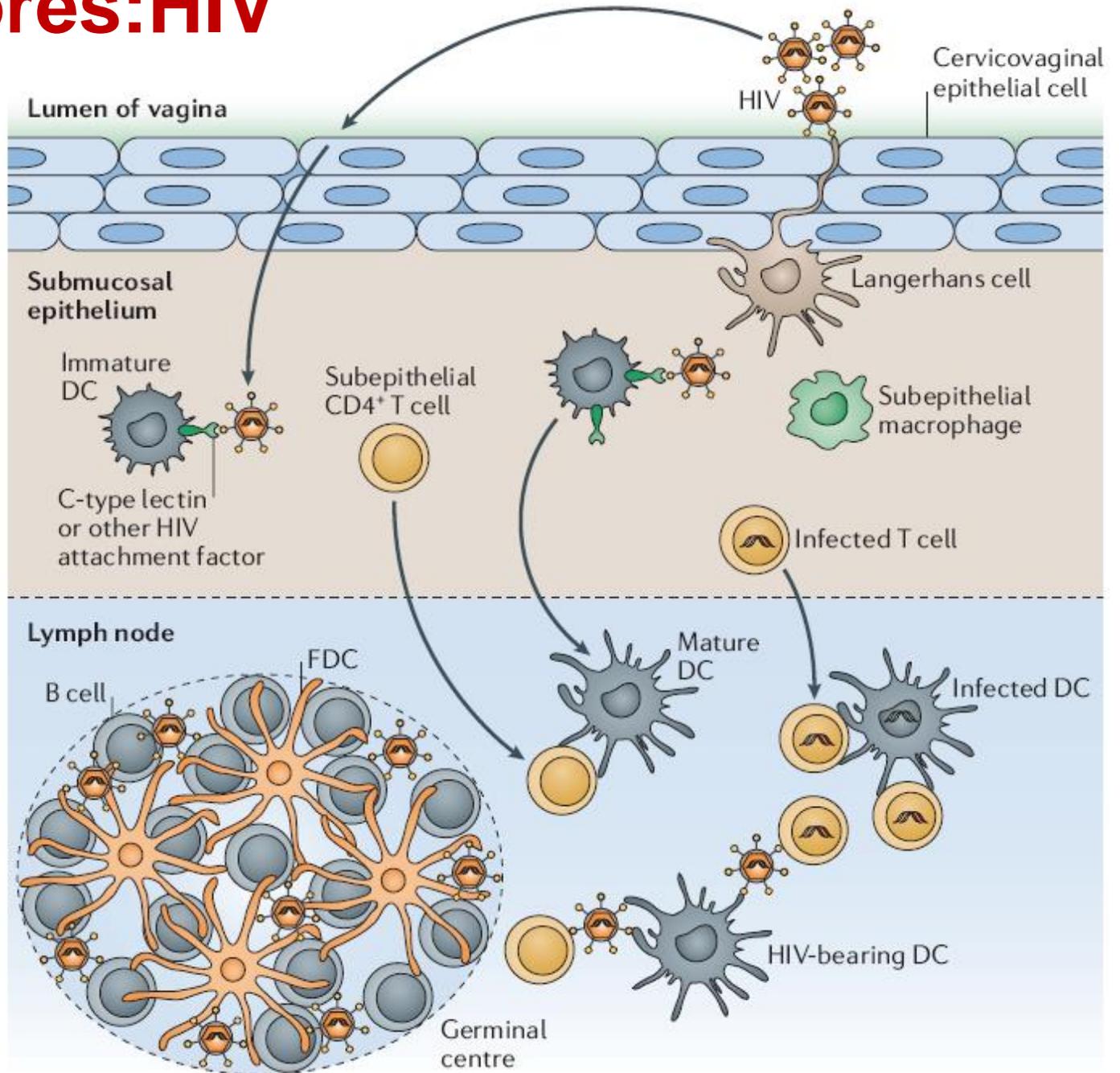
- DC-SIGN (*dendritic cell-specific, Icam-3 grabbing nonintegrin*) como carregador de HIV



HIV: Infecção primária



Receptores:HIV



Receptores:HIV

TABLE 3 - Human Cells Susceptible to HIV

Hematopoietic

T-lymphocytes
B-lymphocytes
Macrophages
NK cells
Megakaryocytes
Dendritic cells
Promyelocytes
Stem cells
Thymic epithelium
Follicular dendritic cells
Bone marrow endothelial cells

Skin

Langerhans cells
Fibroblasts

Brain

Capillary endothelial cells
Astocytes
Macrophages (microglia)
Oligodendrocytes
Choroid plexus ganglia cells
Neuroblastoma cells
Glioma cell lines (Neurons)
Dental pulp fibroblasts

Bowel

Fetal adrenal cells
Columnar and goblet cells
Enterochromaffin cells
Colon carcinoma cells

Other

Myocardium
Renal tubular cells
Synovial membrane
Hepatocytes
Hepatic sinusoid endothelium
Hepatic carcinoma cells
Kupffer cells
Pulmonary fibroblasts
Adrenal carcinoma cells
Retinal cells
Cervix-derived epithelial cells
Cervix
Prostate
Testes
Osteosarcoma cells
Rhabdomyosarcoma cells
Fetal chorionic villi
Trophoblast cells

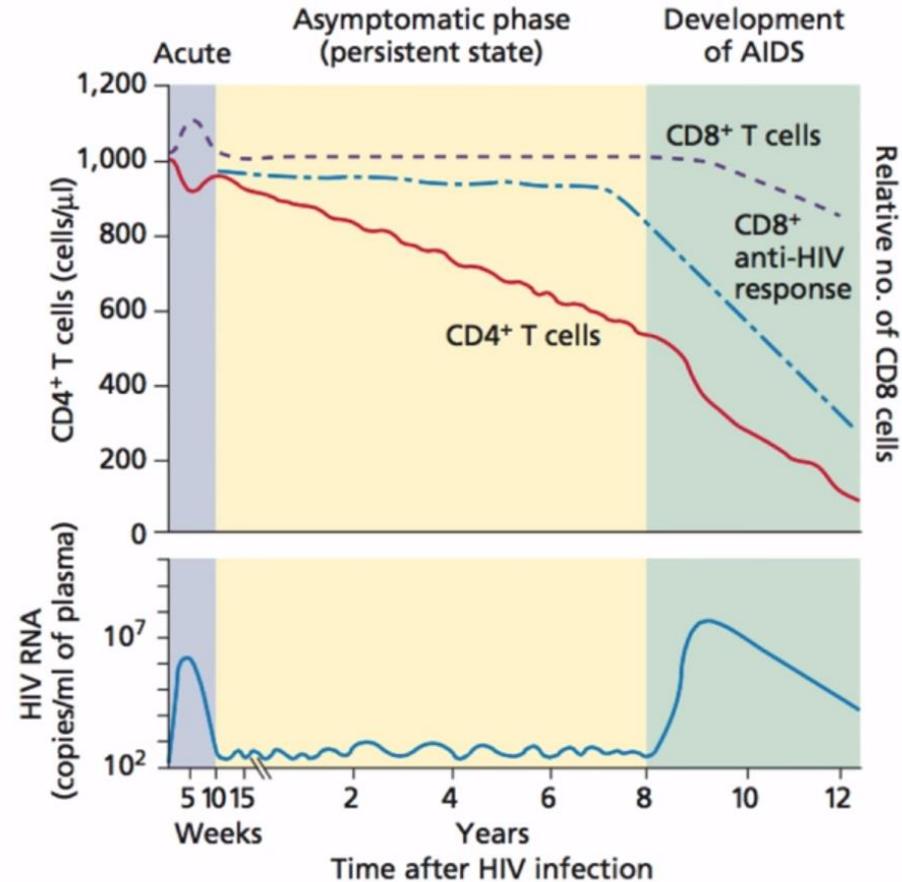
HIV: isolamento de partículas infecciosas

	Fluid	Virus isolation^b	Estimated quantity of virus^c
	Cell-free fluid		
	Cerebrospinal fluid	21/40	10–10,000
	Ear secretions	1/8	5–10
	Feces	0/2	None detected
	Milk	1/5	<1
	Plasma	33/33	1–5,000 ^d
	Saliva	3/55	<1
	Semen	5/15	10–50
	Sweat	0/2	None detected
	Tears	2/5	<1
	Urine	1/5	<1
	Vaginal-cervical	5/16	<1
	Infected cells		
	Bronchial fluid	3/24	Not determined
	PBMC	89/92	0.001–1% ^d
	Saliva	4/11	<0.01%
	Semen	11/28	0.01–5%
	Vaginal-cervical fluid	7/16	Not determined

Partículas infecciosas por mL ou % de células que liberam vírus.

HIV: aislamiento de partículas infecciosas

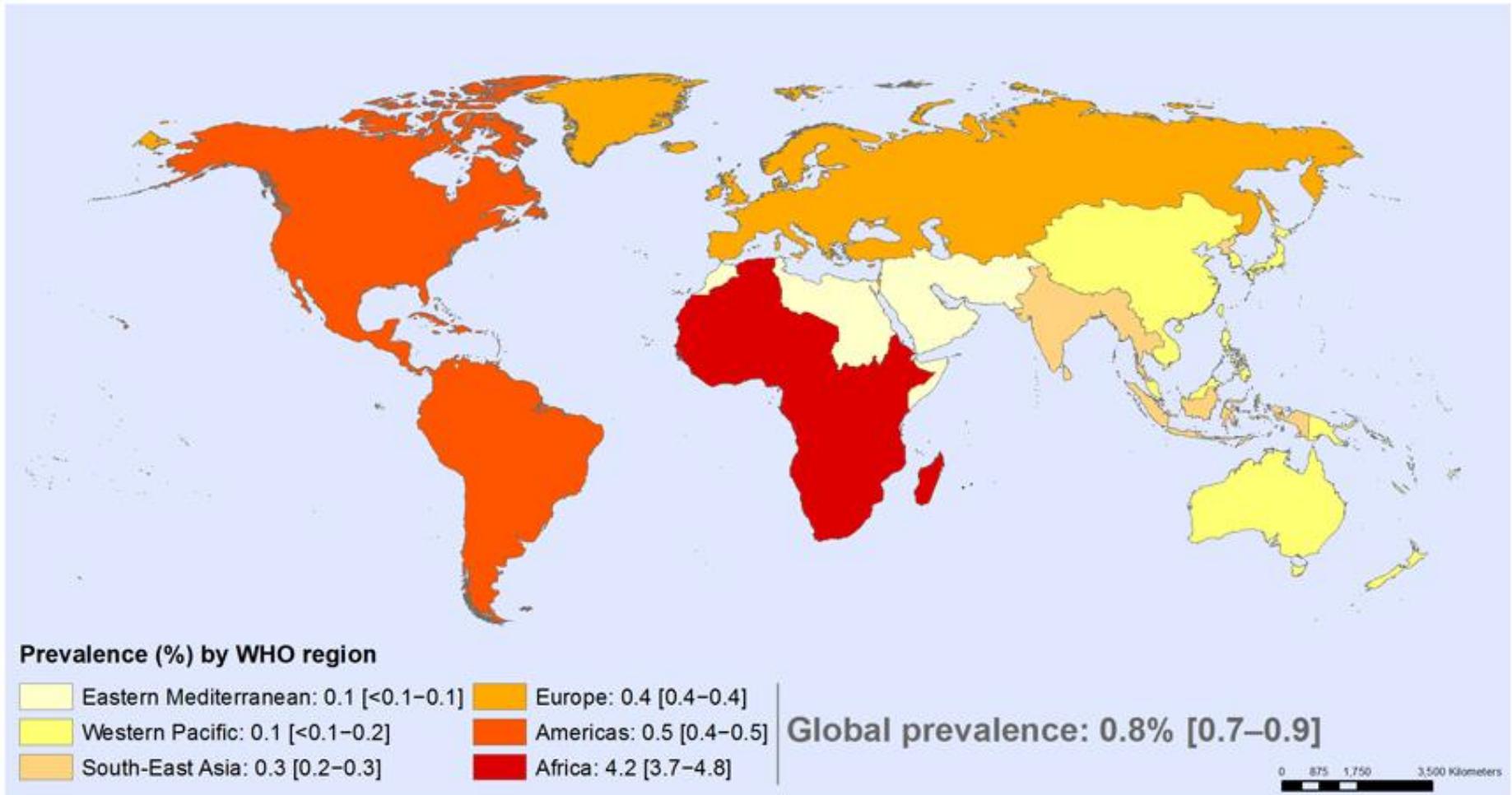
- Active viral replication throughout course of disease
- Major reservoirs of infection exist outside of blood
 - Lymphoreticular tissues (bone marrow, lymph nodes, spleen, MALT)
 - Central nervous system
 - Genital tract
- At least 10×10^9 virions produced and destroyed each day
- $T_{1/2}$ of HIV in plasma is <6 h and may be as short as 30 min



Epidemiologia

HIV no mundo

Prevalence of HIV among adults aged 15 to 49, 2016 By WHO region



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization



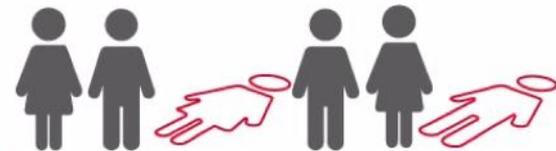
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HIV no mundo

36.9 million
people living with HIV
[31.1 million – 43.9 million]



1.8 million
people newly infected
[1.4 million – 2.4 million]



0.9 million
HIV-related deaths
[0.7 millions – 1.3 million]

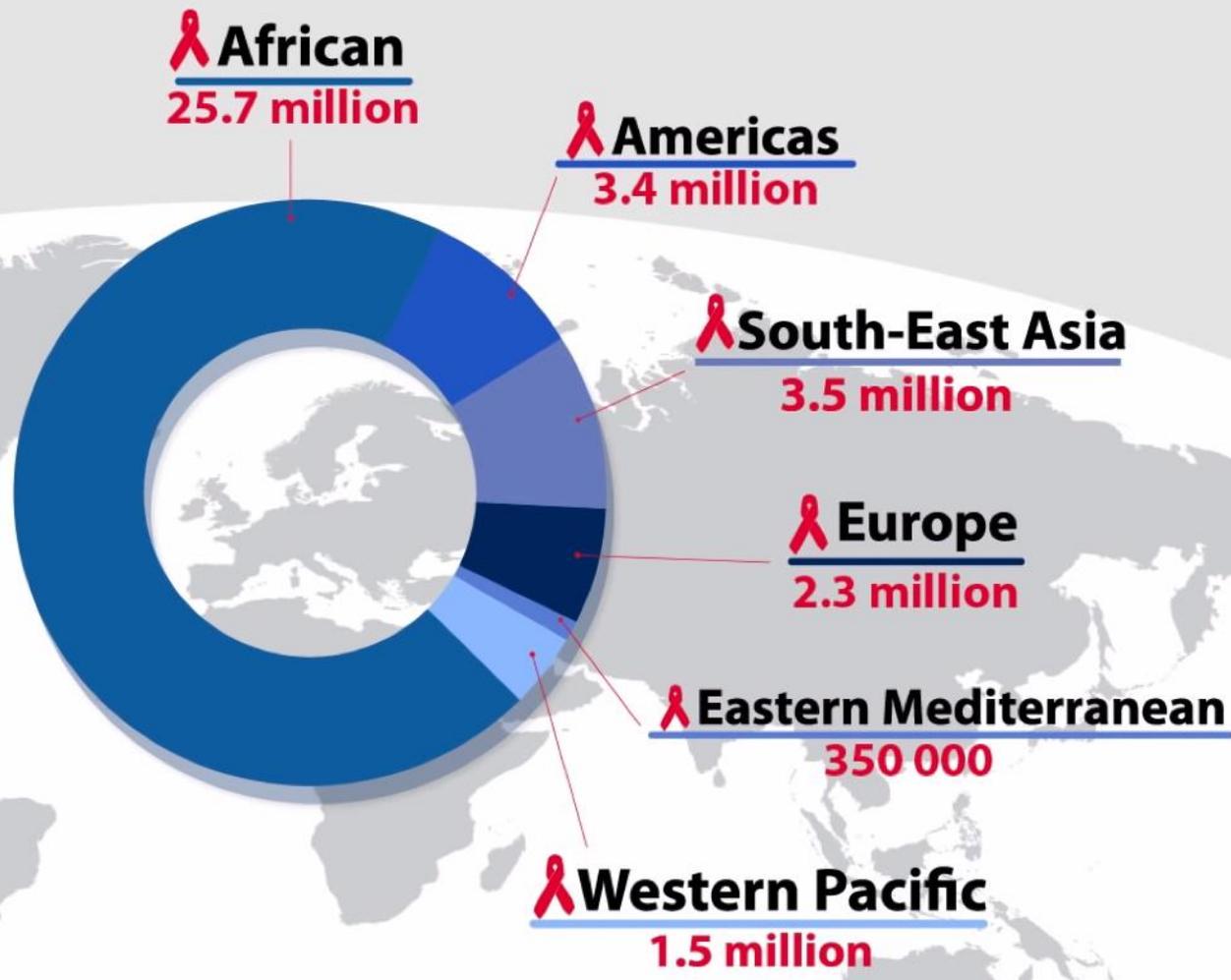
HIV no mundo

	People living with HIV in 2017	People newly infected with HIV in 2017	HIV-related deaths 2017
 Total	36.9 million [31.1 million – 43.9 million]	1.8 million [1.4 million – 2.4 million]	940 000 [670 000 – 1.3 million]
 Adults	35.1 million [29.6 million – 41.7 million]	1.6 million [1.3 million – 2.1 million]	830 000 [590 000 – 1.2 million]
 Women	18.2 million [15.6 million – 21.4 million]	–	–
 Men	16.8 million [13.9 million – 20.4 million]	–	–
 Children (<15 years)	1.8 million [1.3 million – 2.4 million]	180 000 [110 000 – 260 000]	110 000 [63 000 – 160 000]

Source: UNAIDS/WHO estimates

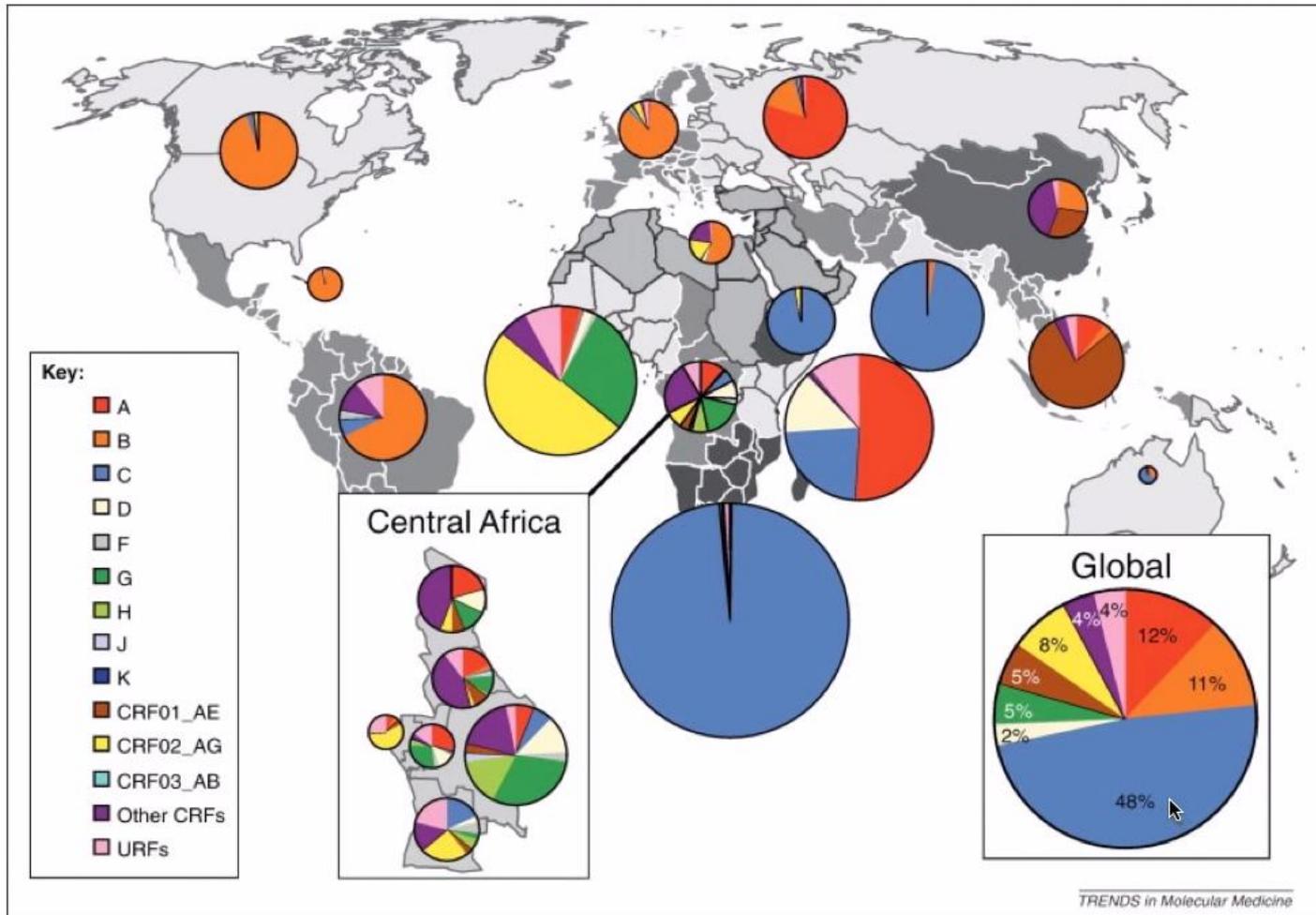
HIV no mundo

36.9 million
people living
with HIV globally



Source: UNAIDS/WHO estimates

HIV no mundo



- Subtipo C (50%), B e A (10-12%), G (6%), CRF02_AG (5%), CRF01_AE (5%), D (2,5%) do total de infecções por HIV-1.
- Subtipos F, H, J, K transmissão limitada (<1%)

Epidemiologia do HIV

Vias de transmissão

- Sexual

- Sanguínea (transfusão e compartilhamento de drogas injetáveis);

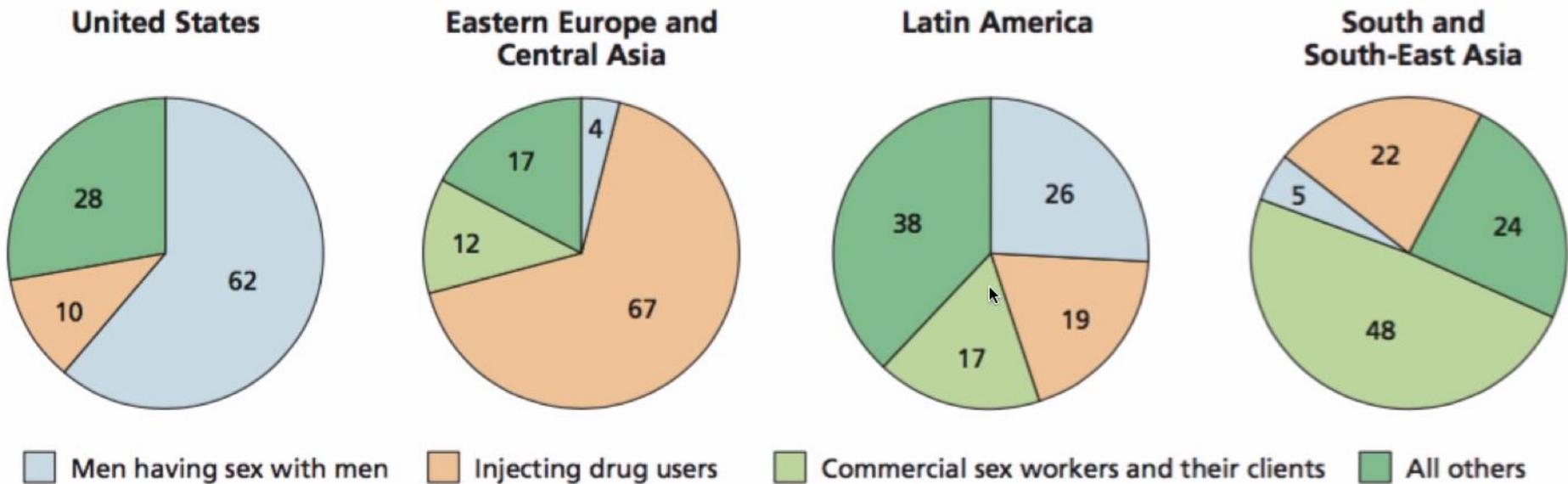
- Vertical (mãe para filho);

- Ocupacional (materiais perfurocortantes).

- As vias de transmissão podem variar segundo a região.

Epidemiologia do HIV

Vias de transmissão



Mother to child at birth, ~5%

Epidemiologia do HIV

Transmissão sexual

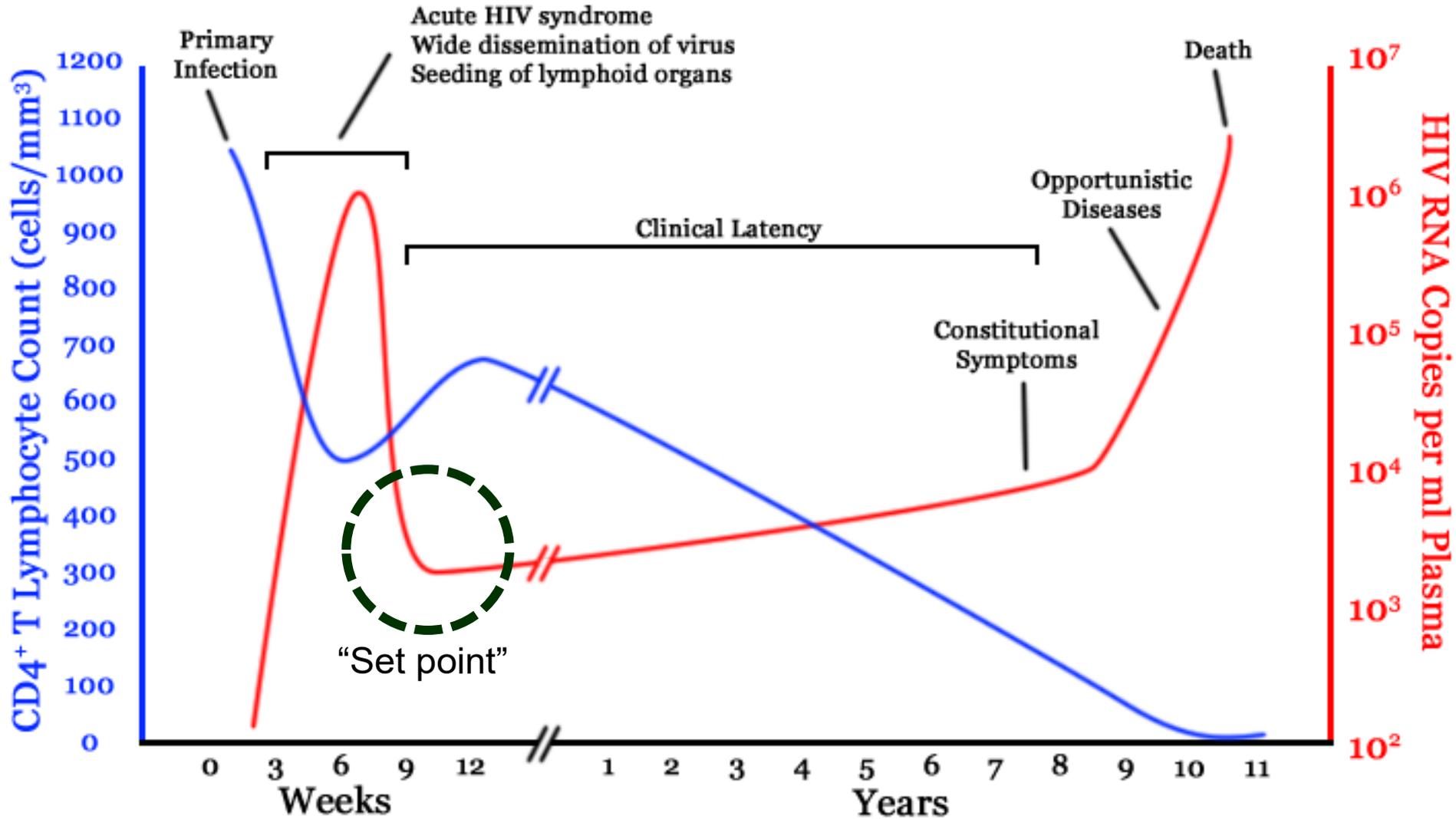
Principal forma de transmissão do HIV no Brasil e no Mundo;

Fatores que aumentam o risco de transmissão relação heterossexual são:

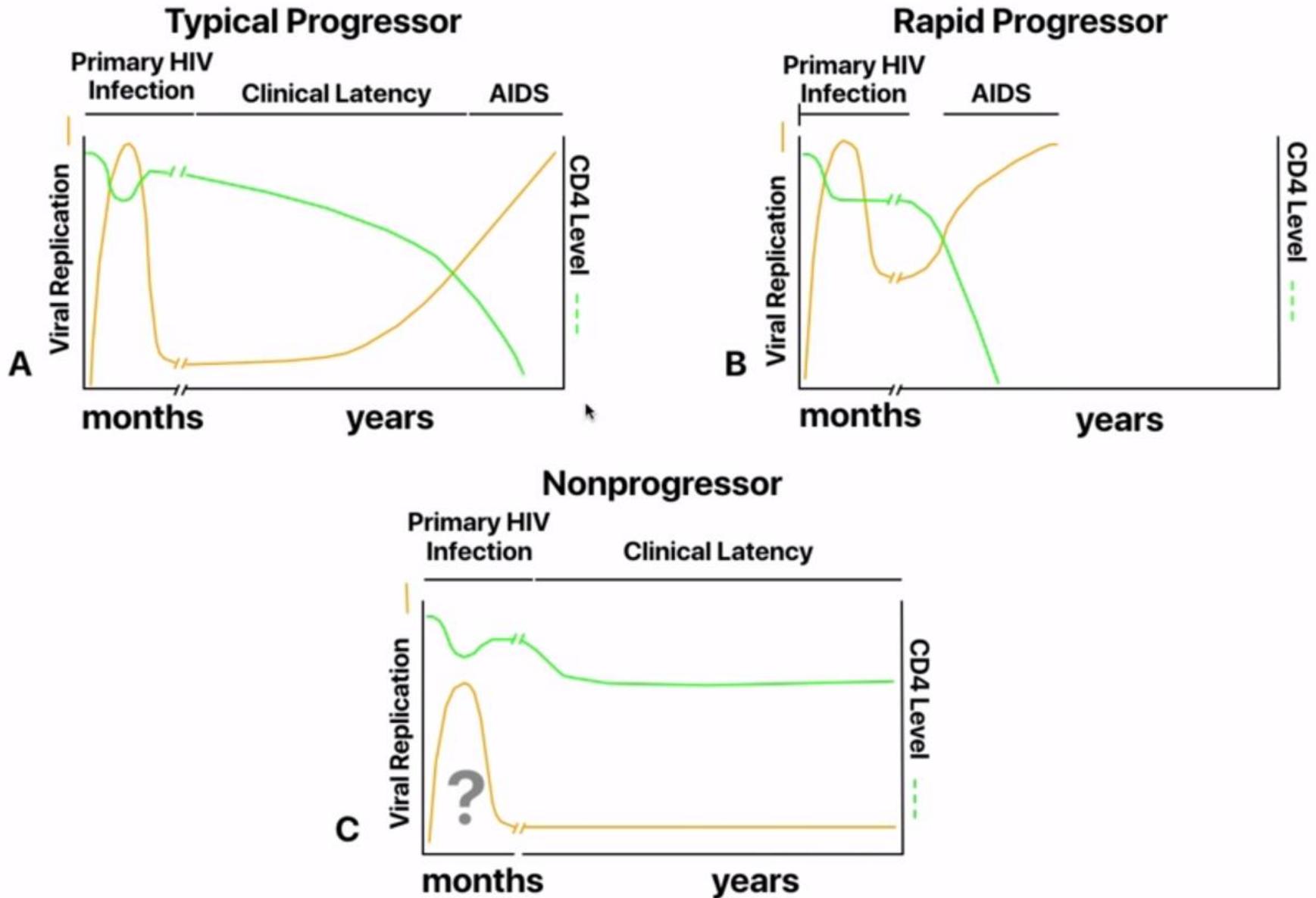
- Alta viremia;
- anal receptiva;
- Relação sexual durante a menstruação;
- Presença de outra DST

Patogênese

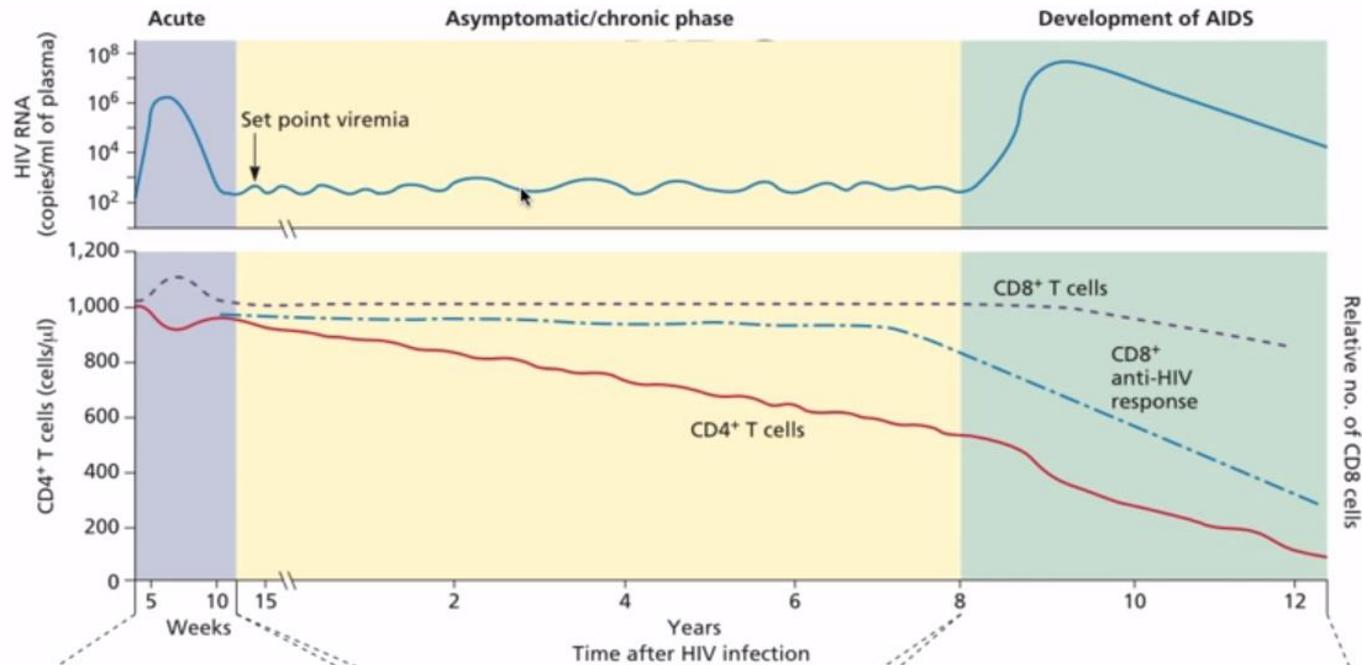
Curso da infecção por HIV



Curso da infecção por HIV



Curso da infecção por HIV



Acute phase

Symptoms
Swollen lymph nodes (Lymphadenopathy)
Fever
Diarrhea

At cellular level
CD4+ T cells decline temporarily
CD8+ T cells increase temporarily (homeostasis) & anti-HIV-1 CTLs increase temporarily
B cells: anti-HIV-1 antibodies appear

Chronic phase

Symptoms
Usually: no symptoms
Sporadically: fatigue, mild weight loss, generalized lymphadenopathy, rash, shingles

At cellular level
CD4+ T cells gradually decline
CD8+ T cells: levels largely unaffected and CTL responses evolve
B cells: co-evolution of anti-viral antibodies and viral antigens
Acquisition of macrophage tropism
Infection of central nervous system (in some patients)

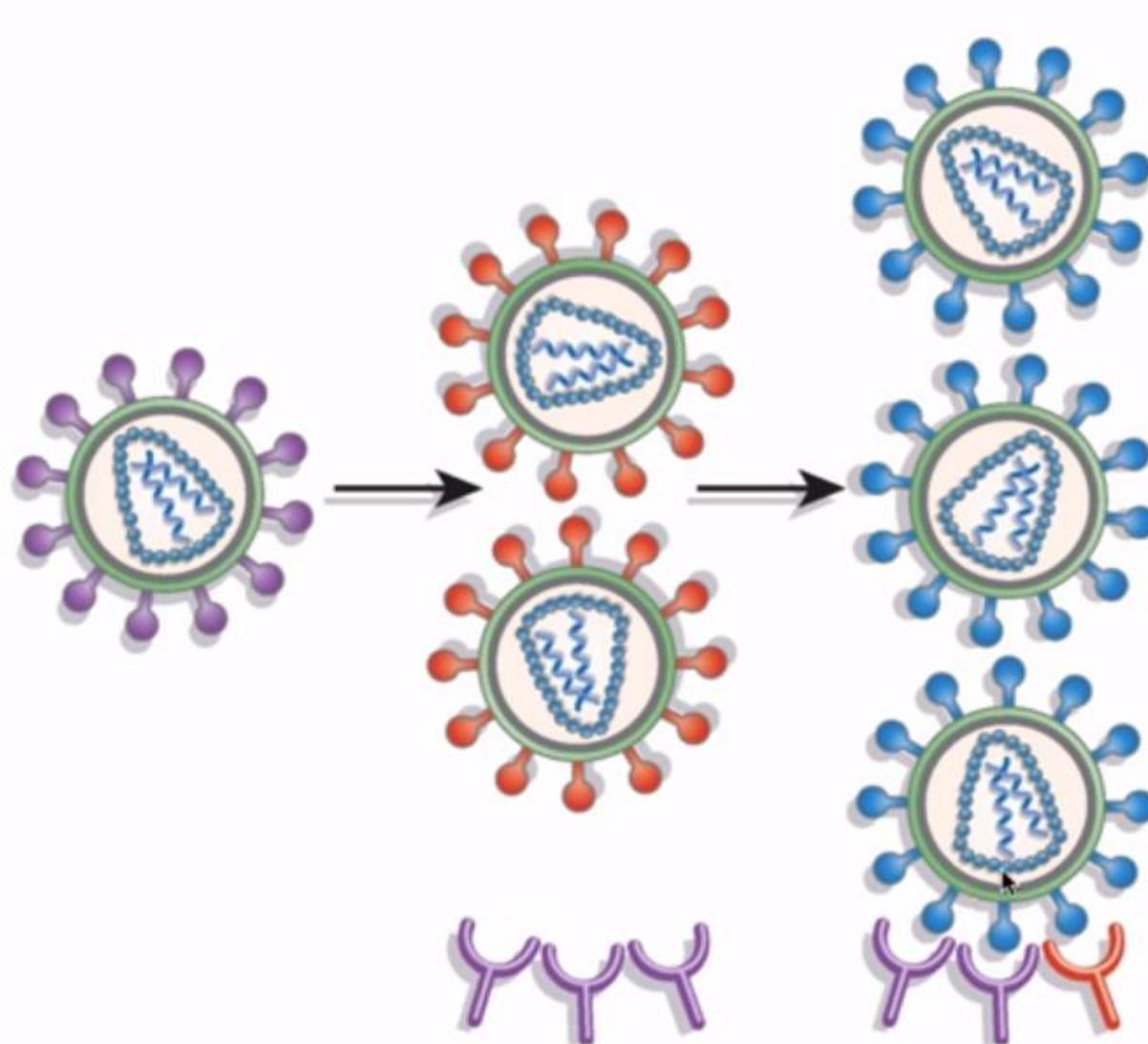
Symptomatic phase

Symptoms
200-500 CD4+ T cells/ml
Oral/skin lesions
Genital warts
Development of Kaposi sarcoma
Reactivation of latent Mycobacterium tuberculosis

<200 CD4+ T cells/ml
Opportunistic infections by protozoa/bacteria/fungi/viruses
Weight loss
Malignancies
Neurological symptoms

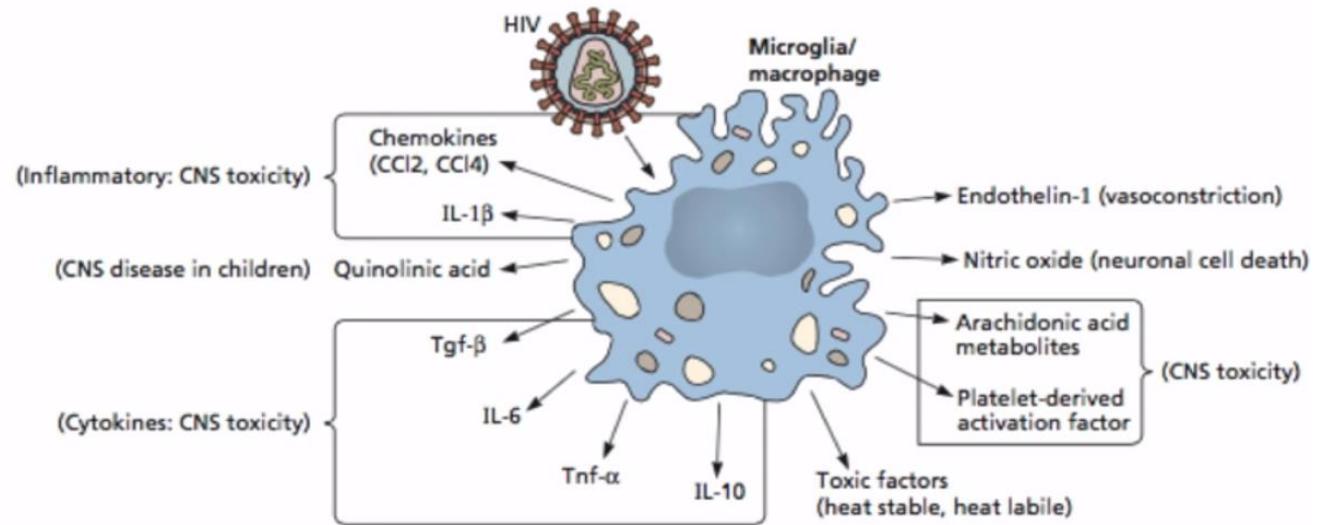
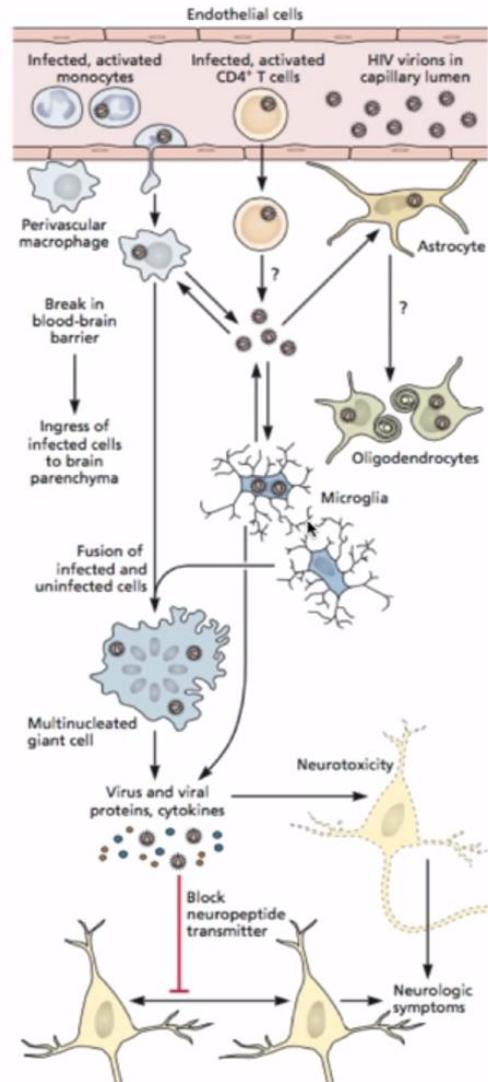
At cellular level
CD4+ T cell depletion, loss of helper function
HIV-1-specific CD4+/CD8+ T cell exhaustion
B cells: decrease/dysregulation
natural killer (NK) cells: impairment of function

Escape da resposta imune



Sintomas neurológicos

Neurological symptoms



Curso da infecção por HIV

Aids

Curso da infecção por HIV

AIDS

- Número de linfócitos T CD4+ < 200 céls/mm³;
- Aumento da carga viral (alta viremia);
- ~~Destruição do tecido linfóide;~~
- População viral homogênea;

Curso da infecção por HIV

AIDS

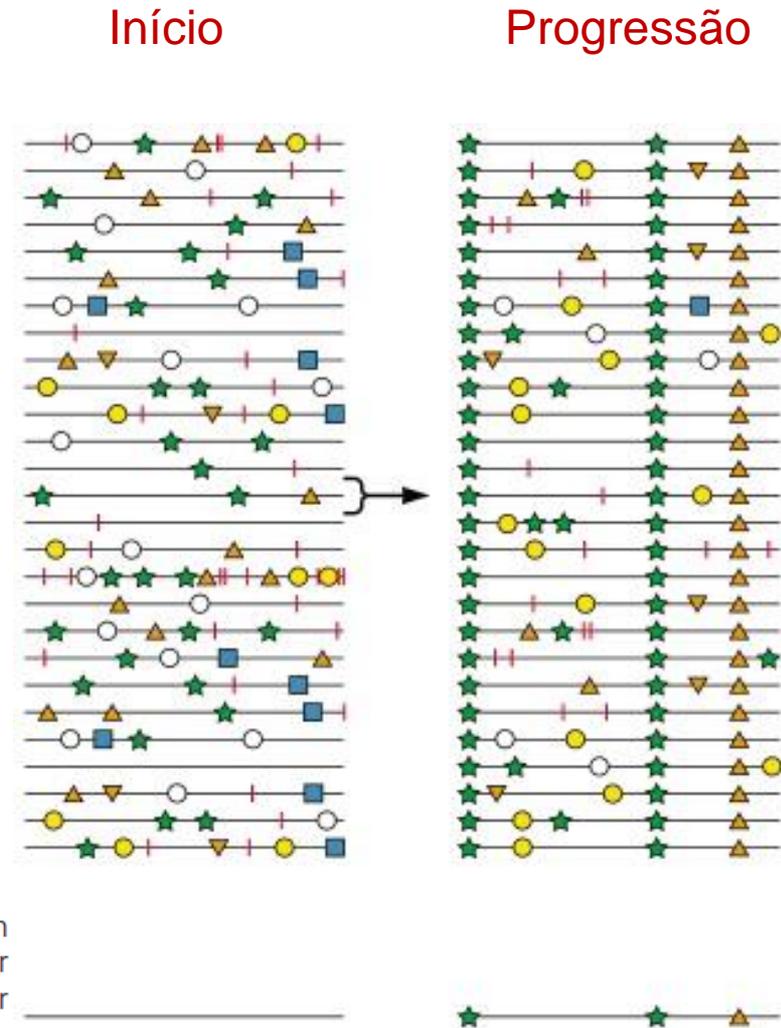
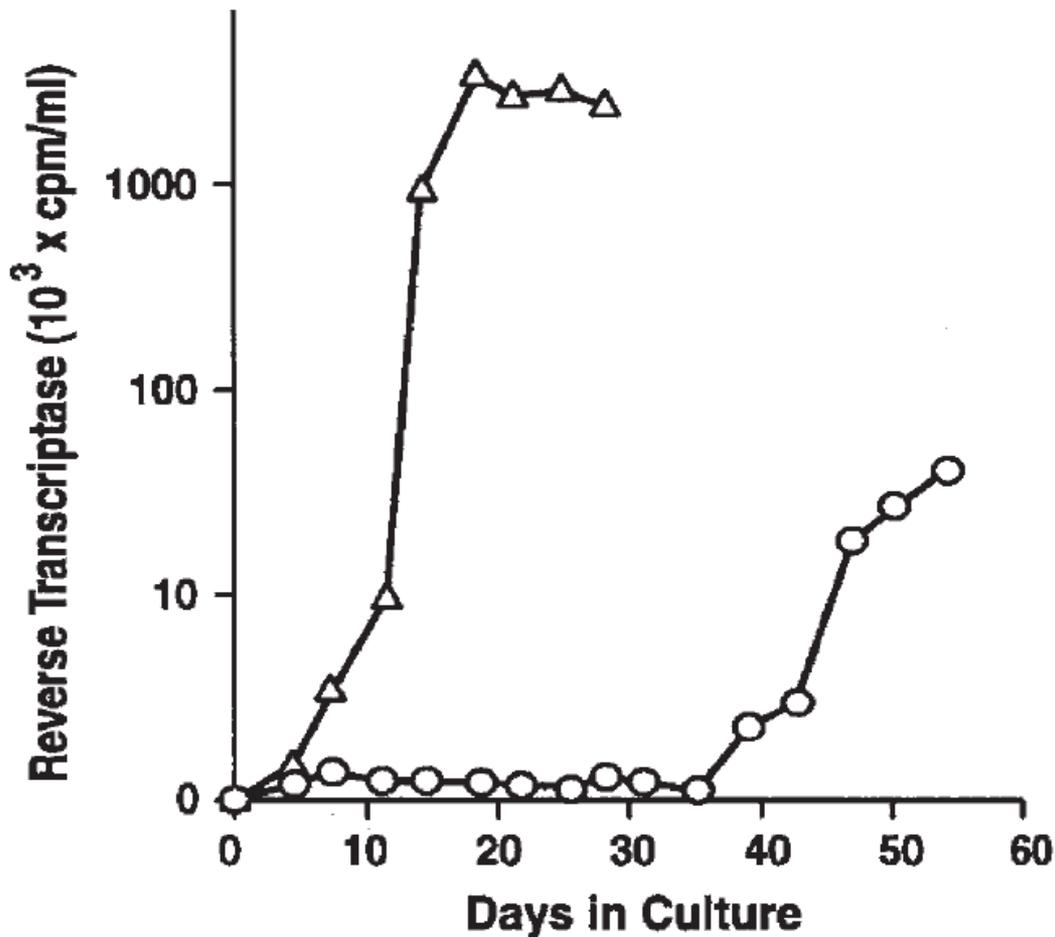


Fig. 4 - Differences in replication of HIV-1 recovered from an individual early in infection (○) and later, when he had progressed to disease (△) (Cheng-Mayer *et al.*, 1988b). Note that the early virus replicates at low titer, and peaks after a longer period of time than the faster-replicating virus, recovered later at the time of disease.

Curso da infecção por HIV

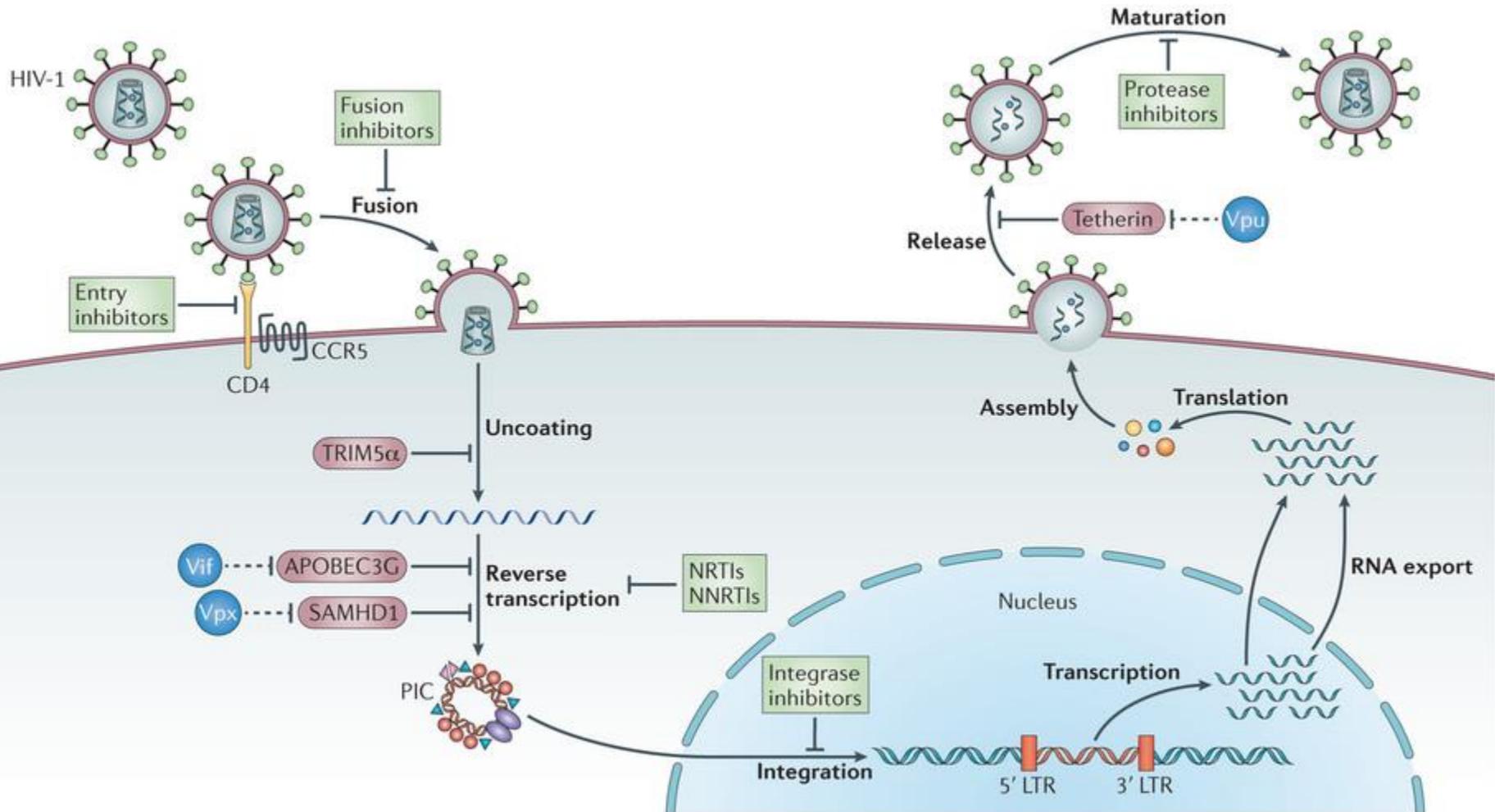
AIDS

Desenvolvimento de:

- **infecções oportunistas**
- **tumores** (possível envolvimento de mecanismos diretos)
- **alterações neurológicas:** Neurotropismo bastante acentuado (cepa viral) que, frequentemente, leva ao aparecimento de síndromes neurológicas específicas

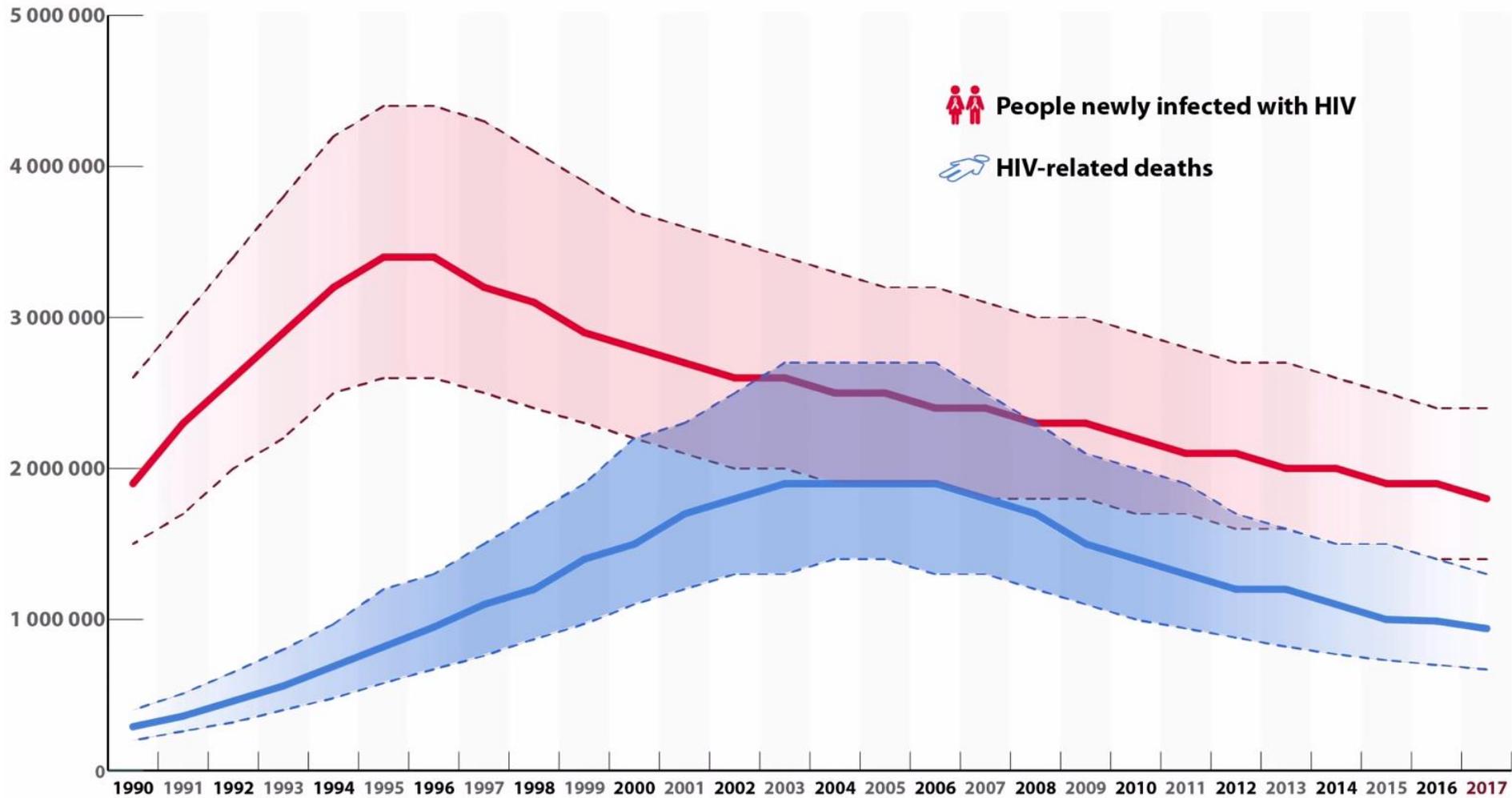
Curso da infecção por HIV

Processos virais como alvos terapêuticos



Curso da infecção por HIV

Processos virais como alvos terapêuticos



Source: UNAIDS/WHO estimates

**TESTES
DIAGNÓSTICOS PARA
HIV**

TESTES DIAGNÓSTICOS PARA HIV

DETECÇÃO DE ANTICORPOS (**ELISA**, IMUNOBLOT, WESTERN BLOT)

- Triagem inicial;
- Detectam a resposta do hospedeiro contra o vírus (os anticorpos) e não o próprio vírus;
- Presença dos anticorpos - 6 a 12 semanas após a infecção;
- Não é recomendado para menores de 2 anos – presença dos anticorpos maternos adquiridos durante a gestação.

DETECÇÃO DO VÍRUS (BIOLOGIA MOLECULAR E CULTIVO VIRAL)

- Detecta diretamente o vírus;
- Usado em algumas situações: esclarecimento de exames sorológicos indeterminados, acompanhamento laboratorial de pacientes e mensuração da carga viral para controle de tratamento;
- Recomendado para o diagnóstico em crianças menores de 2 anos (biologia molecular).

TESTES DIAGNÓSTICOS PARA HIV

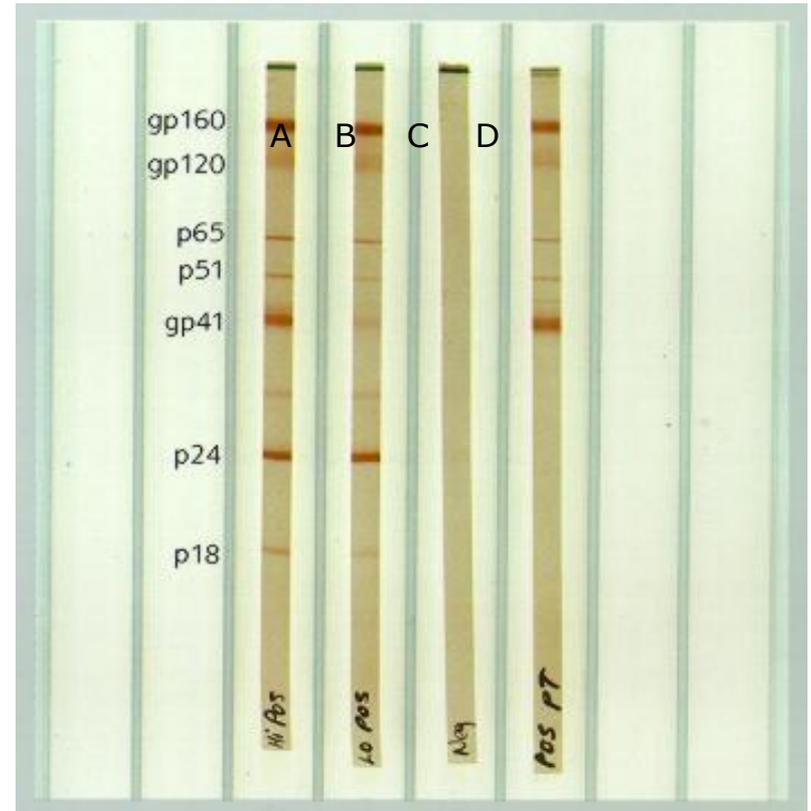
Testes de detecção de anticorpos do hospedeiro:

- ELISA e Western-blot

ELISA



Western-blot



Obrigado!!!