DEPARTAMENTO DE MICROBIOLOGIA
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ICB USP

Patogênese viral: Infecções crônicas

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Vírus da Imunodeficiência humana

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 linfoadenopatia (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.

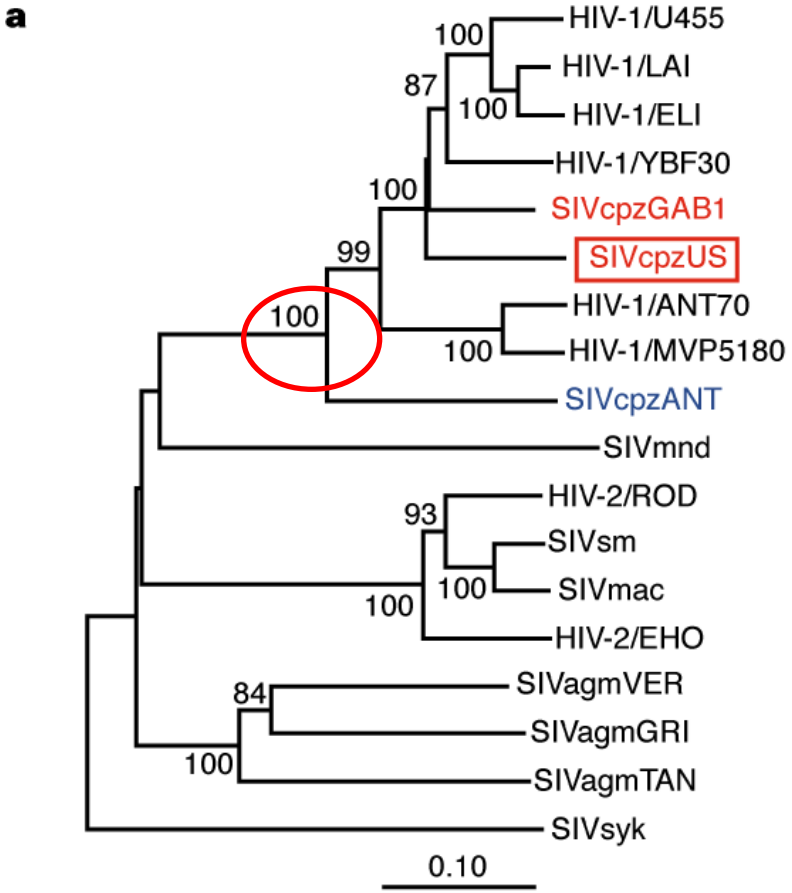
A Origem do HIV

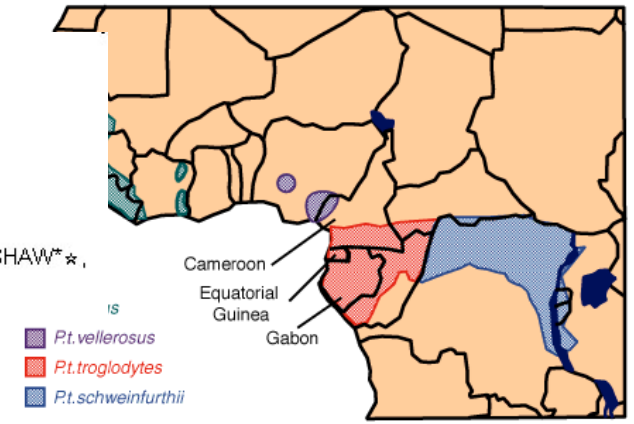
letters to nature

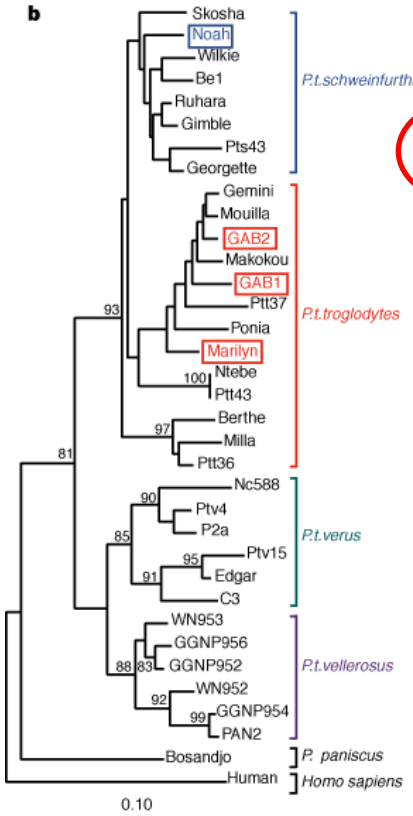
Nature 397, 436 - 441 (1999) © Macmillan Publishers Ltd.

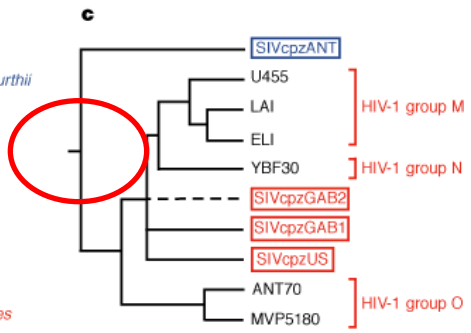
Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*

FENG GAO*, ELIZABETH BAILES†, 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*

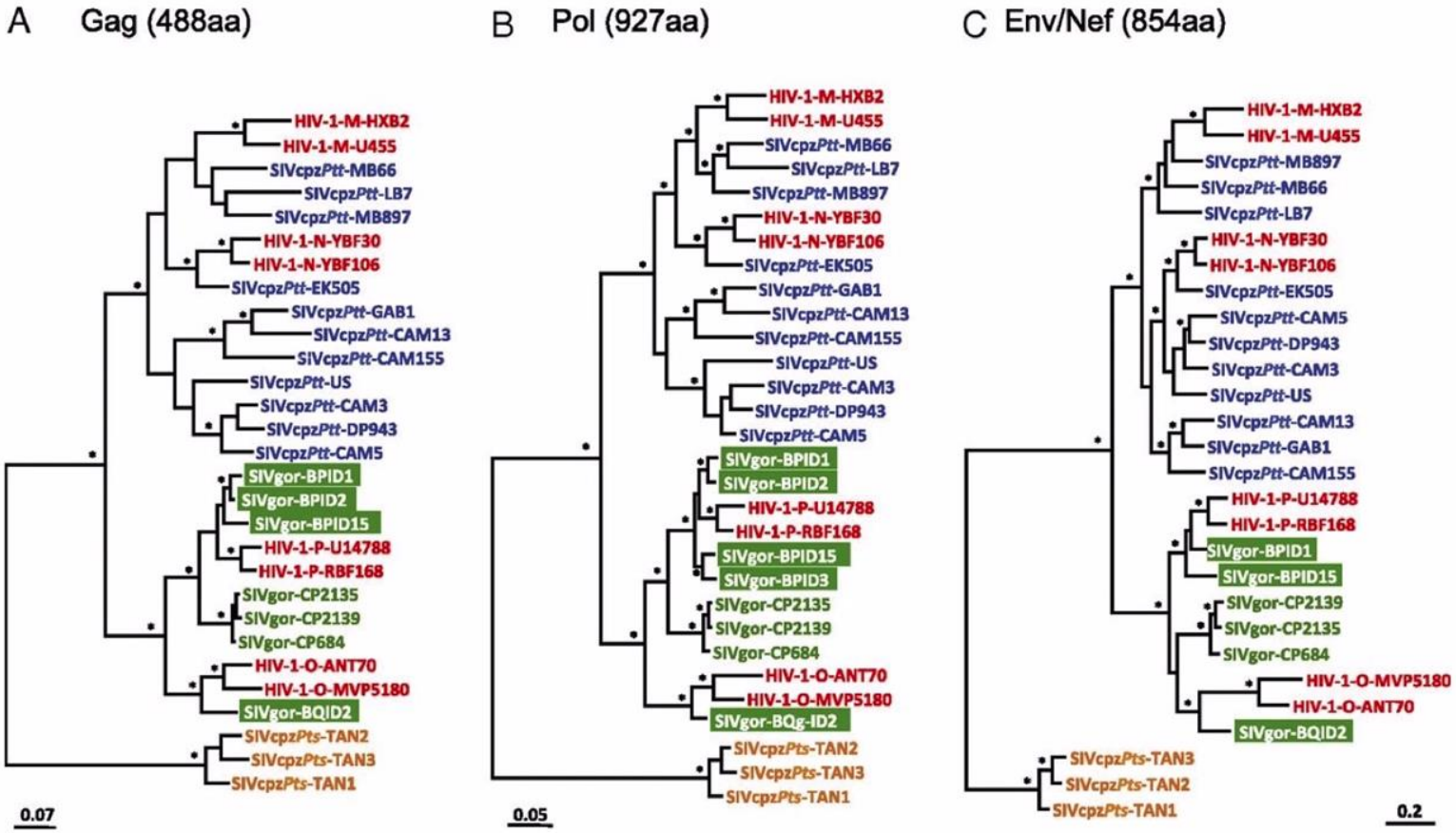






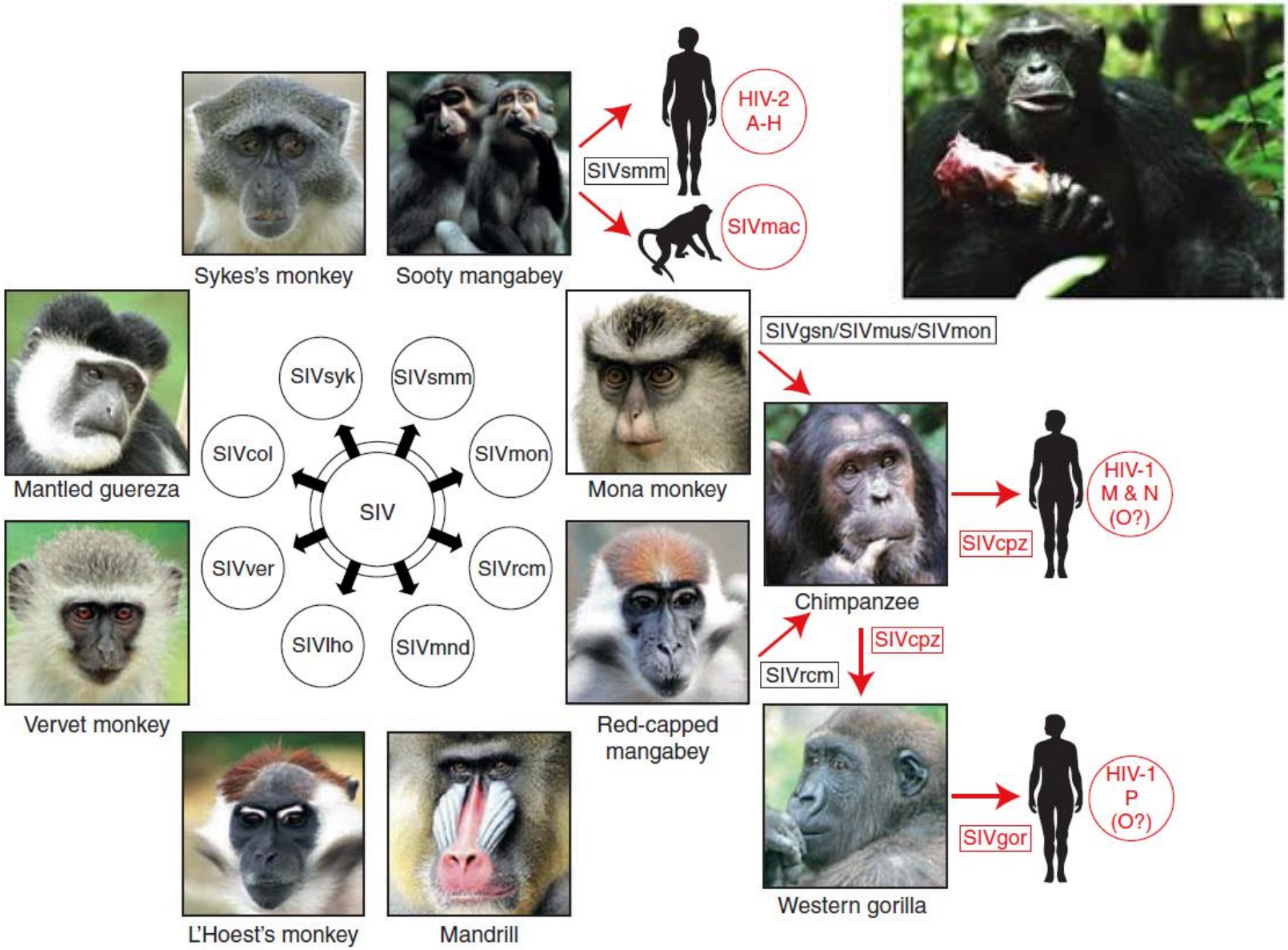


A Origem do HIV



PNAS 112(2015) doi: 10.1073/pnas.1502022112

A Origem do HIV



Cold Spring Harb Perspect Med 2011;1:a006841

A Origem do HIV

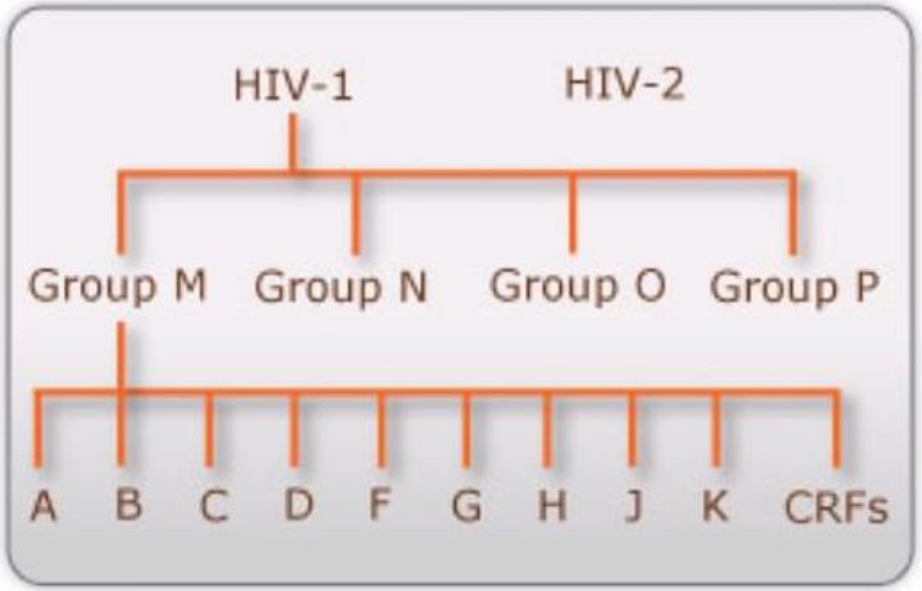
↓ SIV

~1921: Patient zero

↓ HIV

78,000,000 infections
35,000,000 deaths

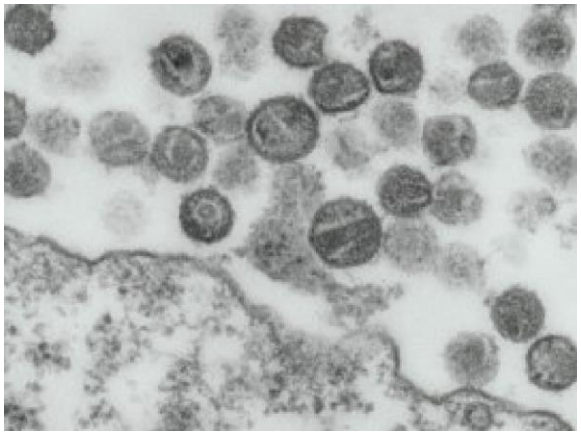
A Origem do HIV e sua diversidade

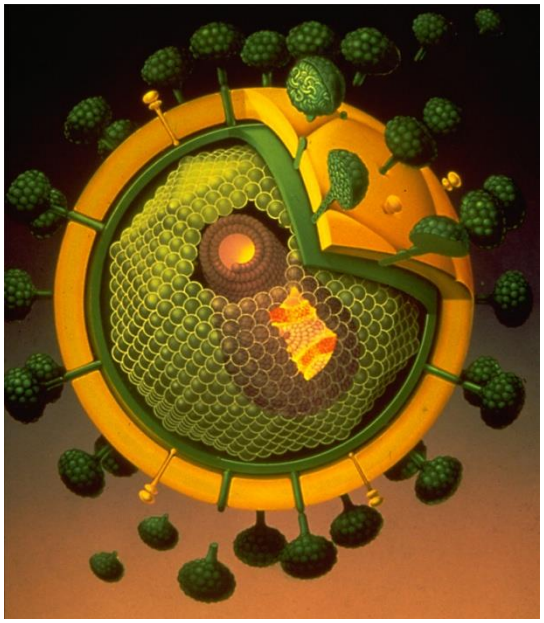


- O grupo M se divide em 9 subtipos
- Indivíduos de alto risco podem ser reinfectados e gerar recombinantes
- Subtipos vs AIDS, não existe diferença clara (infectados com subtipo D morrem mais rápido)
- Subtipo C é liberado em maior quantidade no trato reprodutor feminino.

O vírus

Vírus da imunodeficiência Humana (HIV)





Família : *Retroviridae*
Gênero: Lentivírus

Vírus pequenos de RNA envelopados

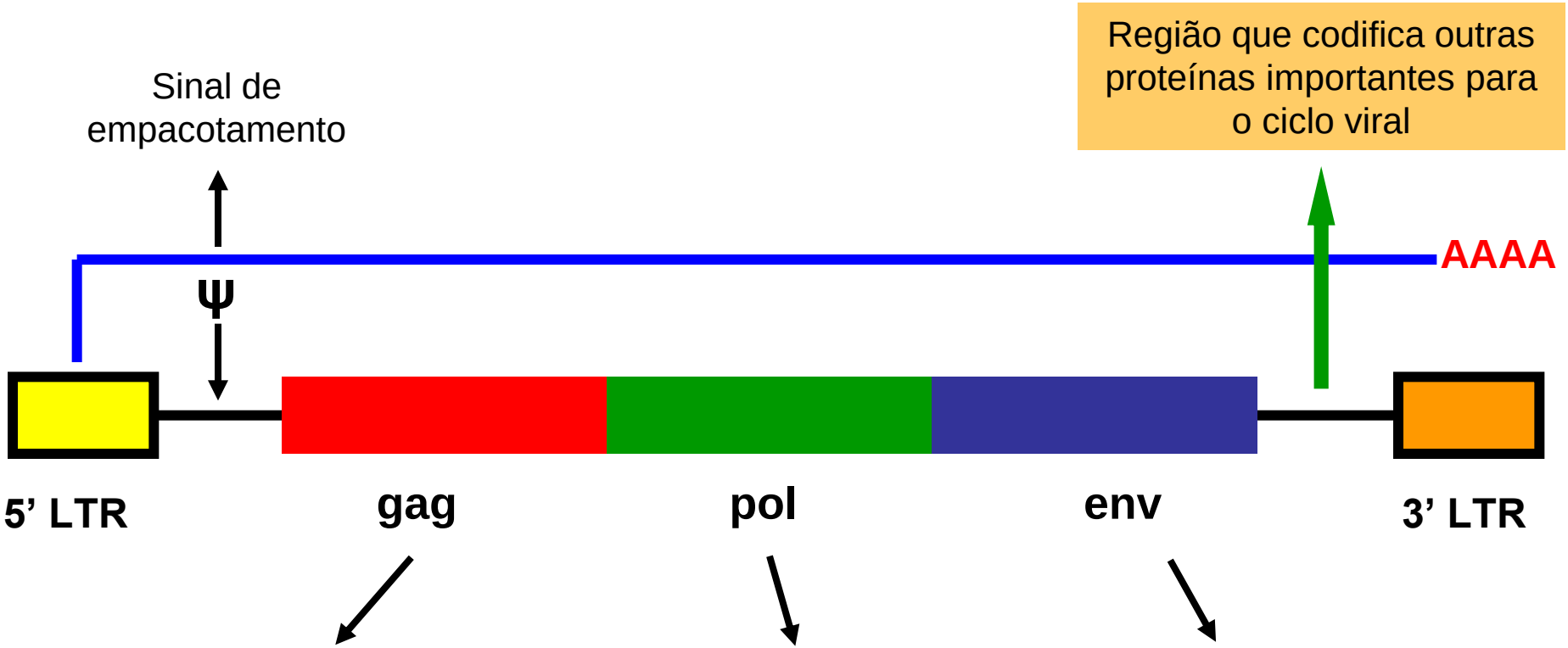
RNA linear simples-fita (~9,3 kb)

Célula alvo: Linfócitos T $CD4^+$

Etiologicamente associado com:

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

O HIV é um retrovírus complexo

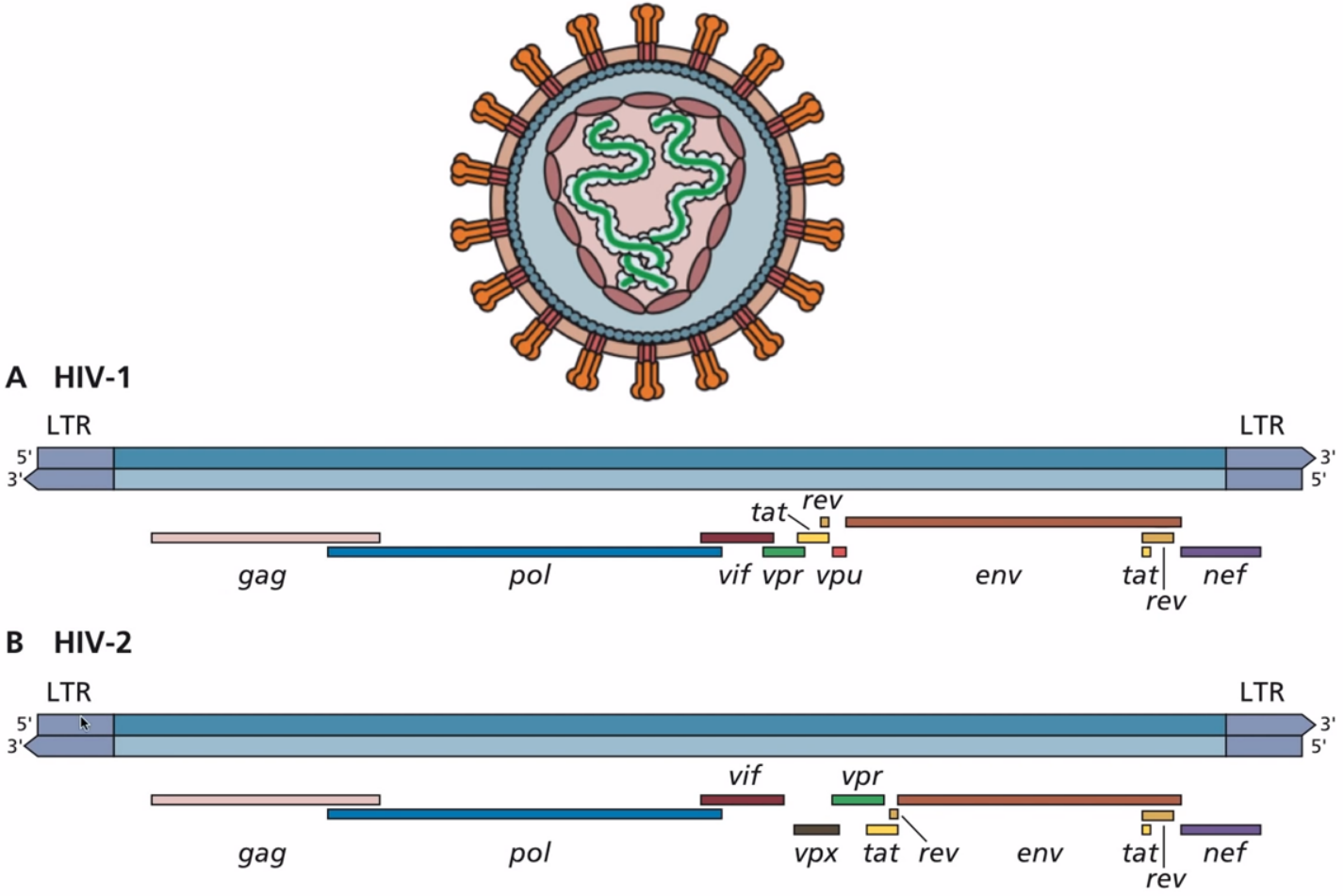


Proteína associada à membrana (MA)
Proteína do capsídeo (CA)
Proteína associada ao RNA (NC)

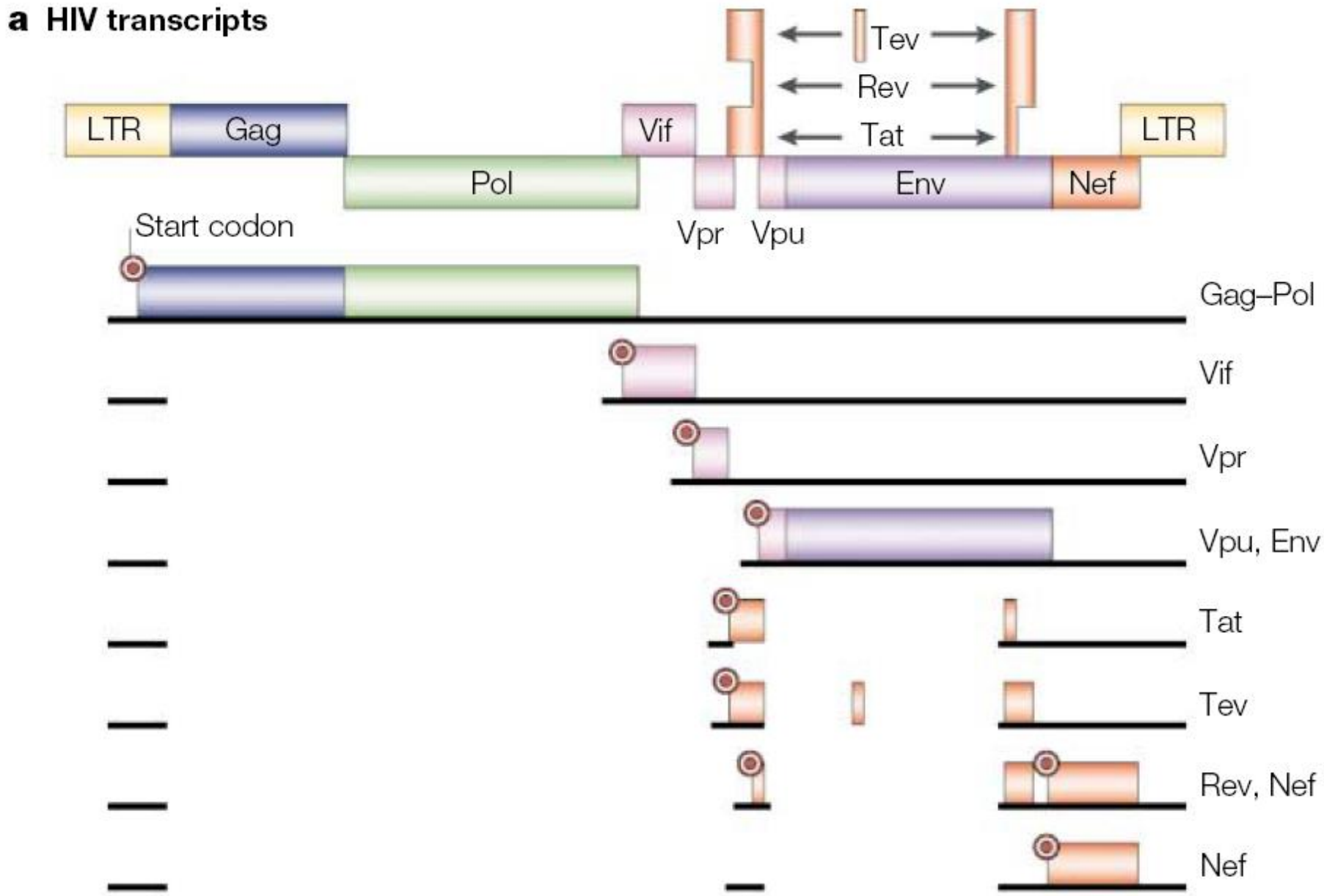
Transcriptase reversa
RNase H
Integrase

Proteína do envelope
Determina o tropismo do vírus

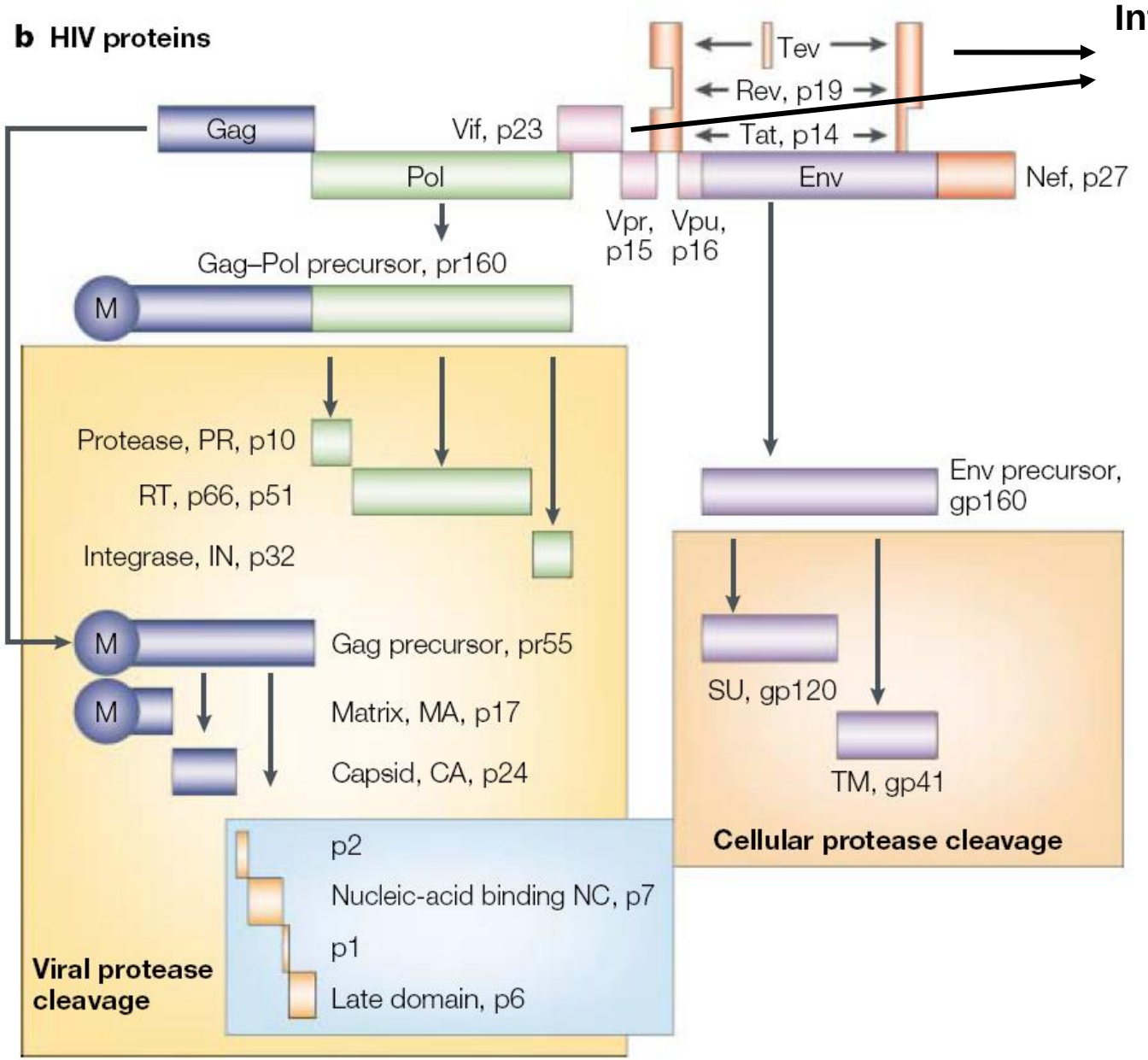
O HIV é um retrovírus complexo



Genoma e transcritos do HIV



Proteínas do HIV



Proteínas do HIV

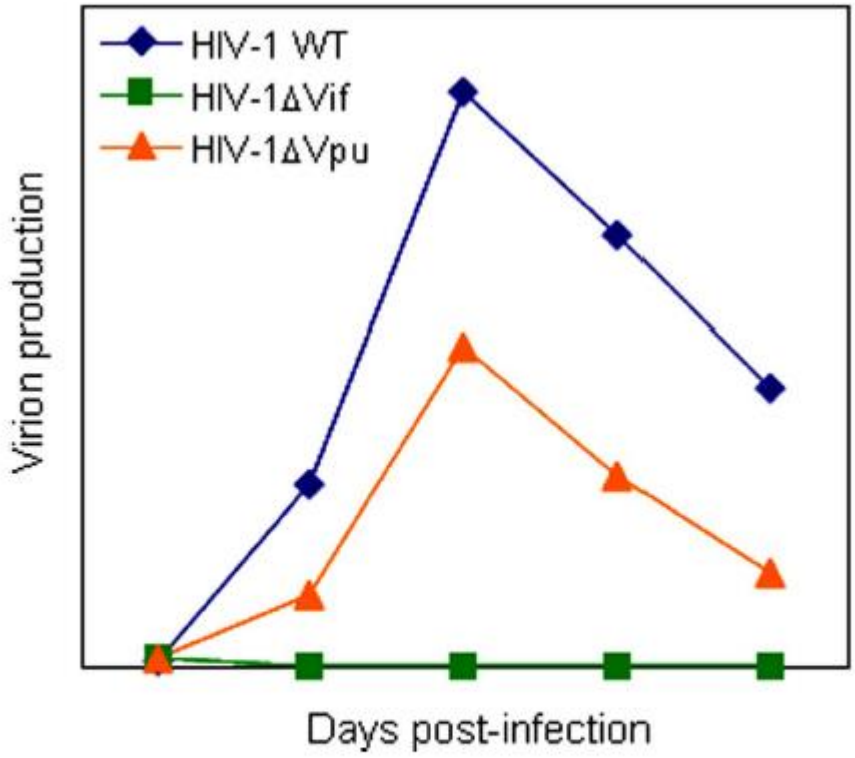
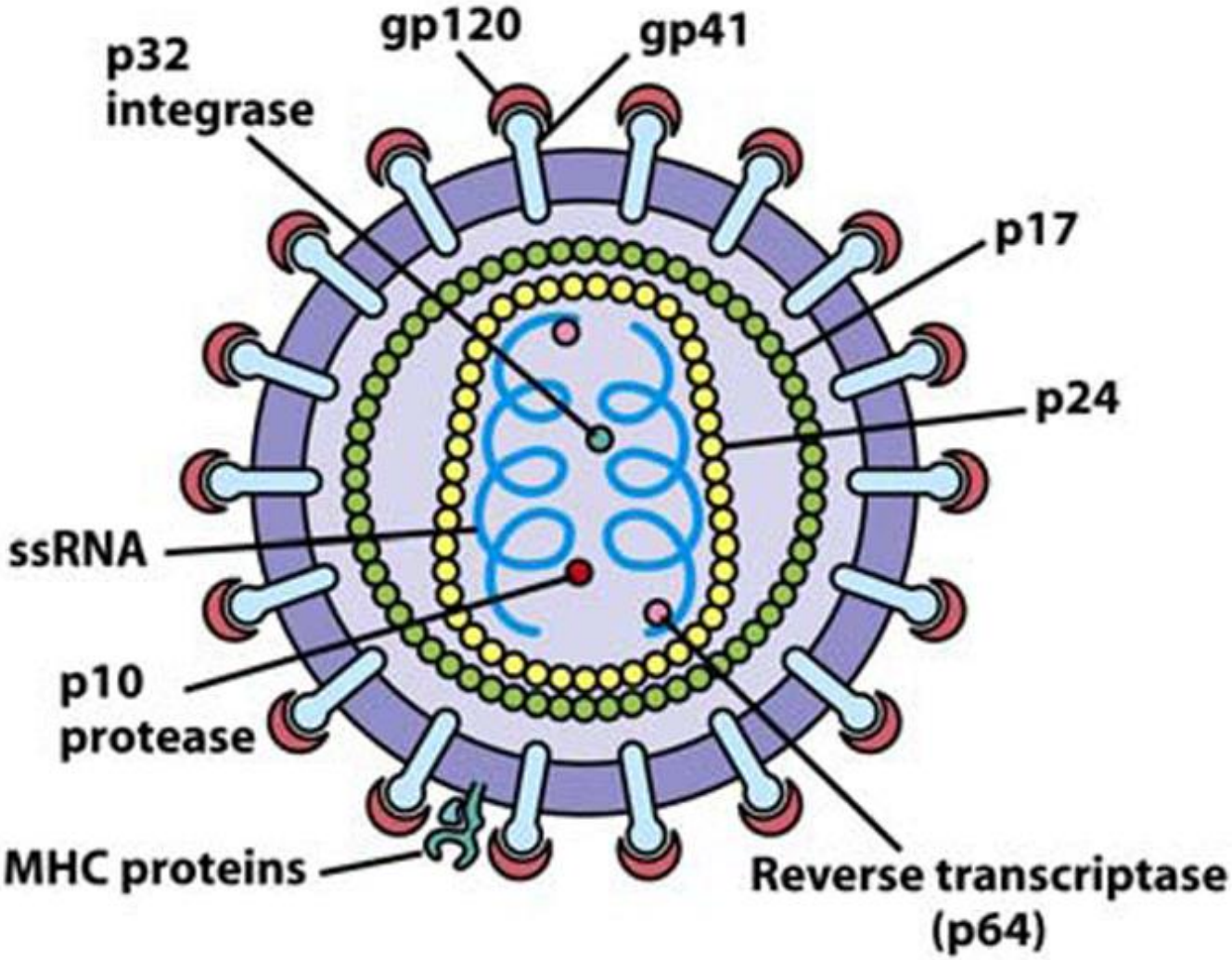


FIGURE 2 | A schema of replication kinetics by HIV-1 wild-type and mutant viruses. Viral growth properties in cells are illustrated based on numerous infection experiments in our laboratory. WT, wild-type.

Estrutura do HIV



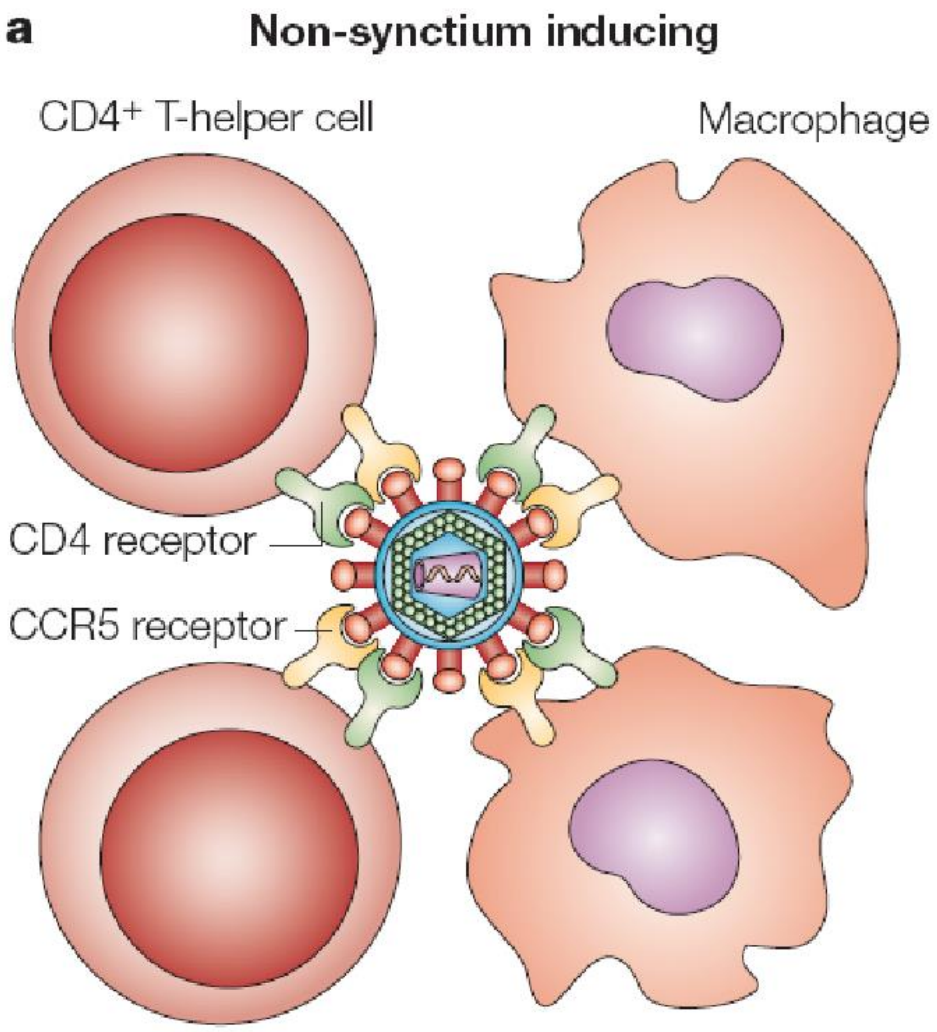
O ciclo viral

Células alvo do HIV

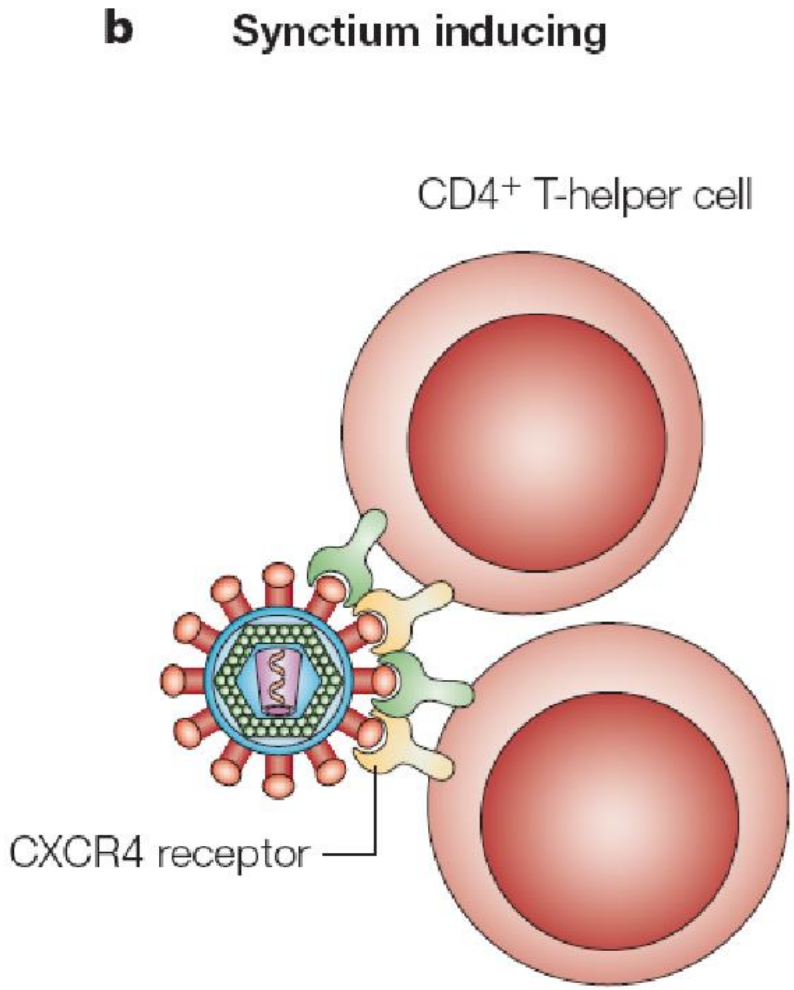
Células que apresentam o Receptor CD4 e os Co-receptores CXCR4 ou CCR5, entre elas:

- Linfócito T Auxiliar CD4+
- Macrófagos
- Células Dendríticas

Receptores do HIV

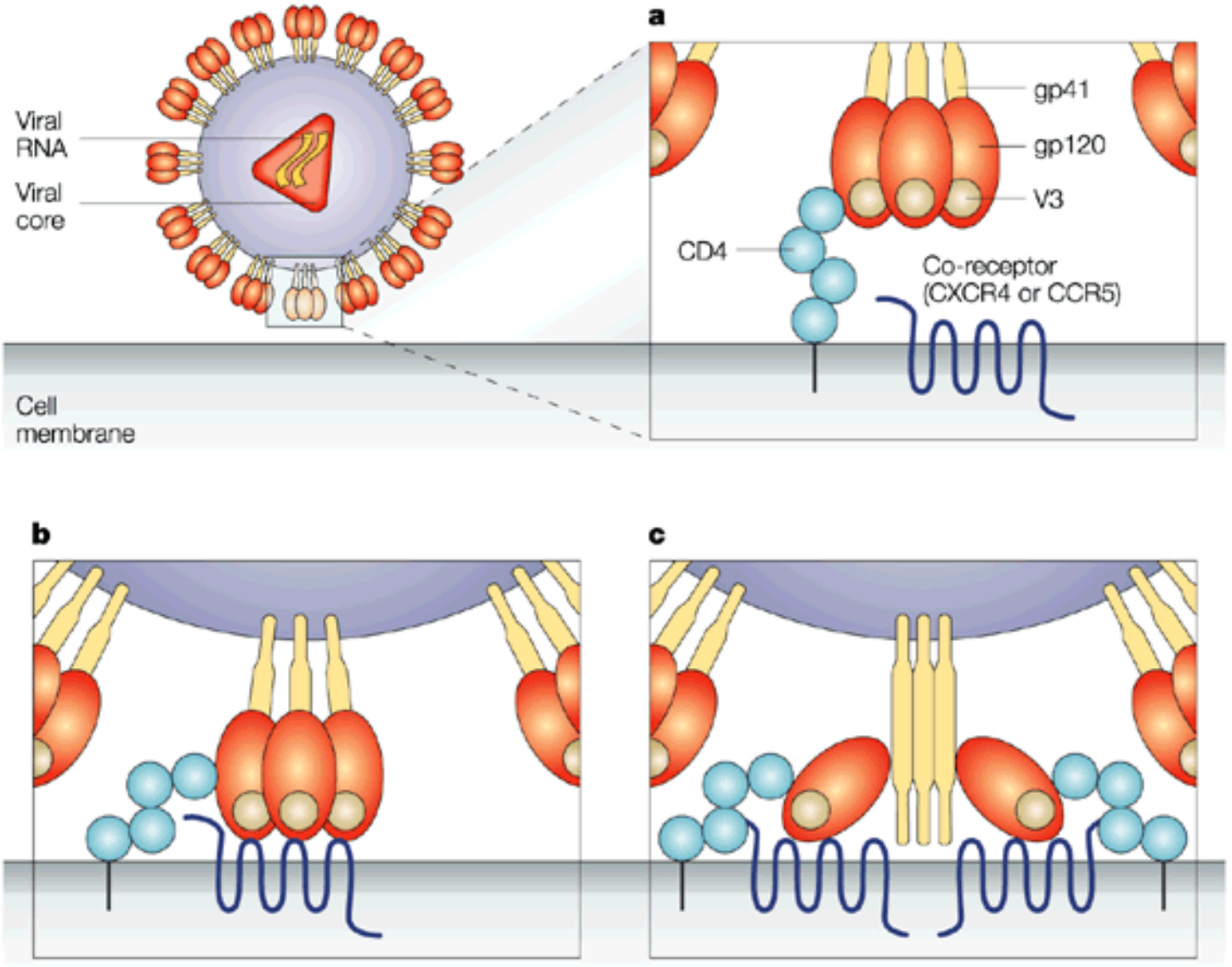


Cepas “R5”

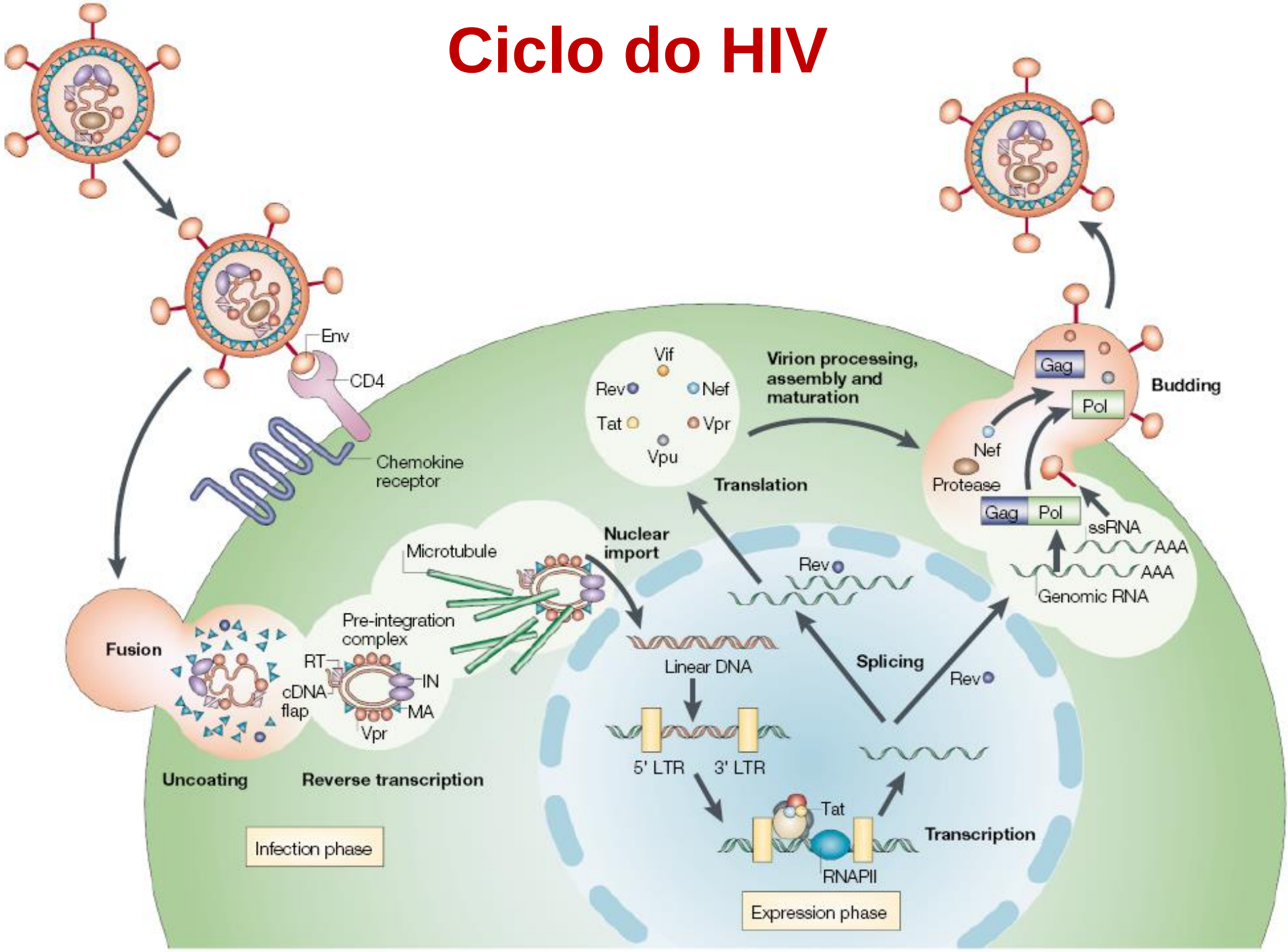


Cepas “X4”

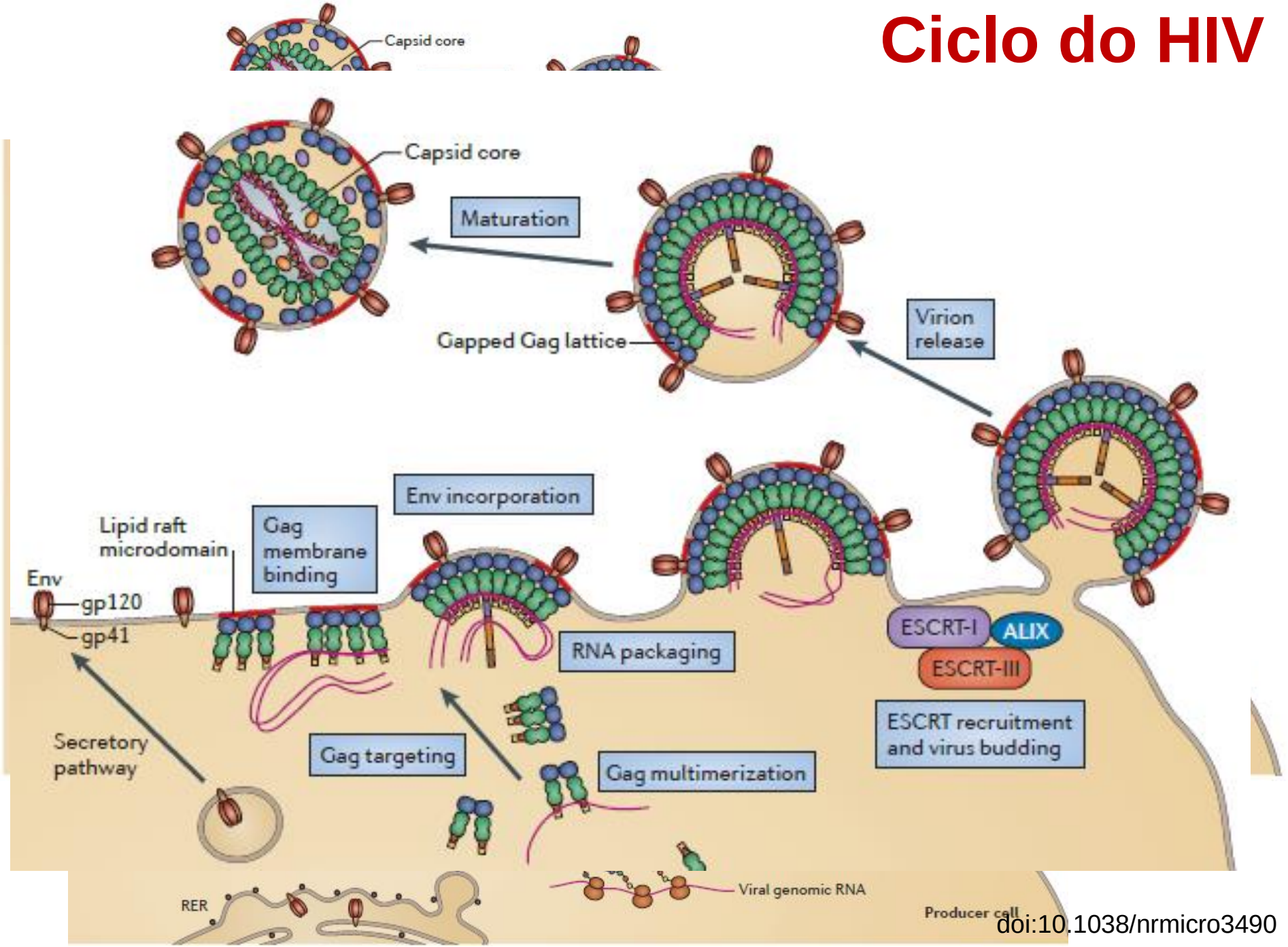
Receptores do HIV



Ciclo do HIV


Env
CD4
Chemokine receptor
Fusion
Uncoating
Microtubule
Pre-integration complex
RT
IN
cDNA flap
MA
Vpr
Reverse transcription
Infection phase
Nuclear import
Vif
Rev
Nef
Tat
Vpr
Vpu
Translation
Virion processing, assembly and maturation
Linear DNA
5' LTR
3' LTR
Tat
RNAPII
Transcription
Expression phase
Splicing
Rev
Rev
Gag
Pol
Nef
Protease
Gag
Pol
ssRNA
AAA
AAA
Genomic RNA
Budding

Ciclo do HIV

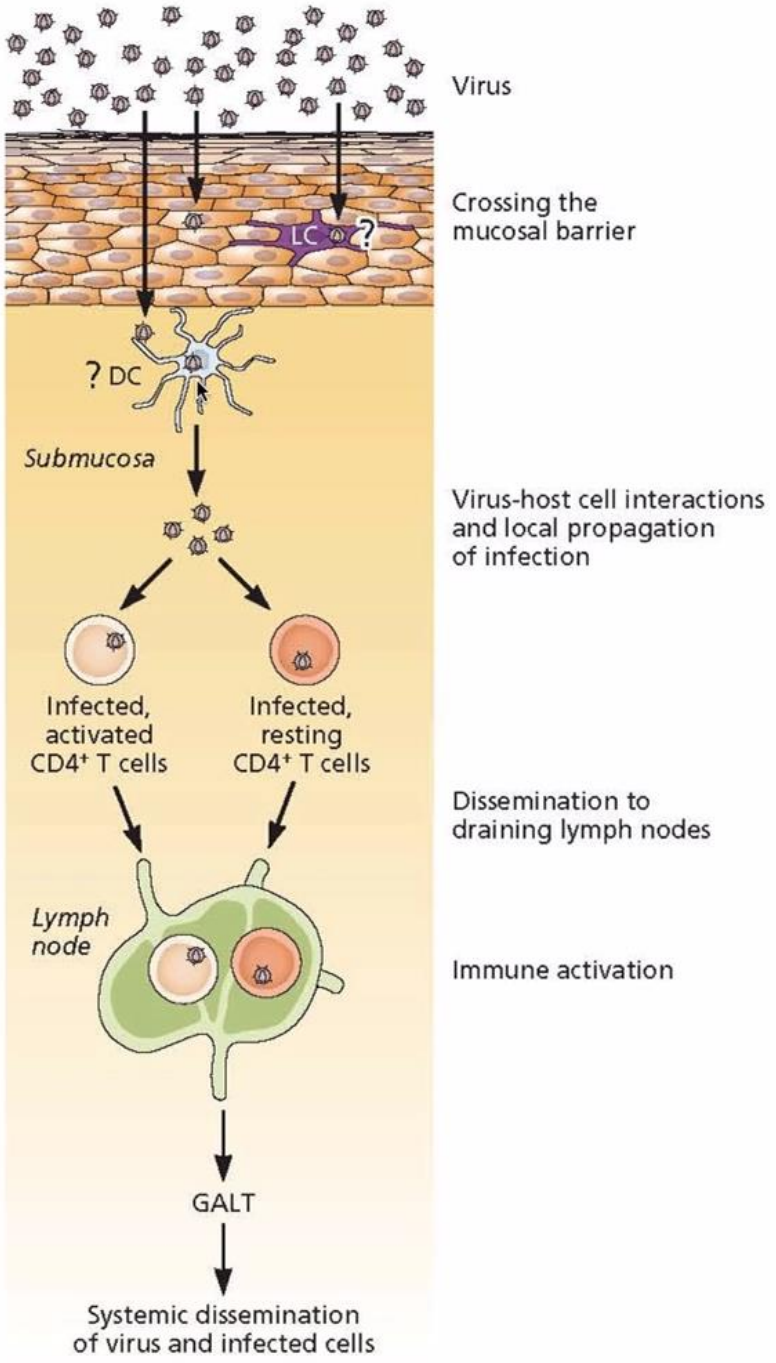


doi:10.1038/nrmicro3490

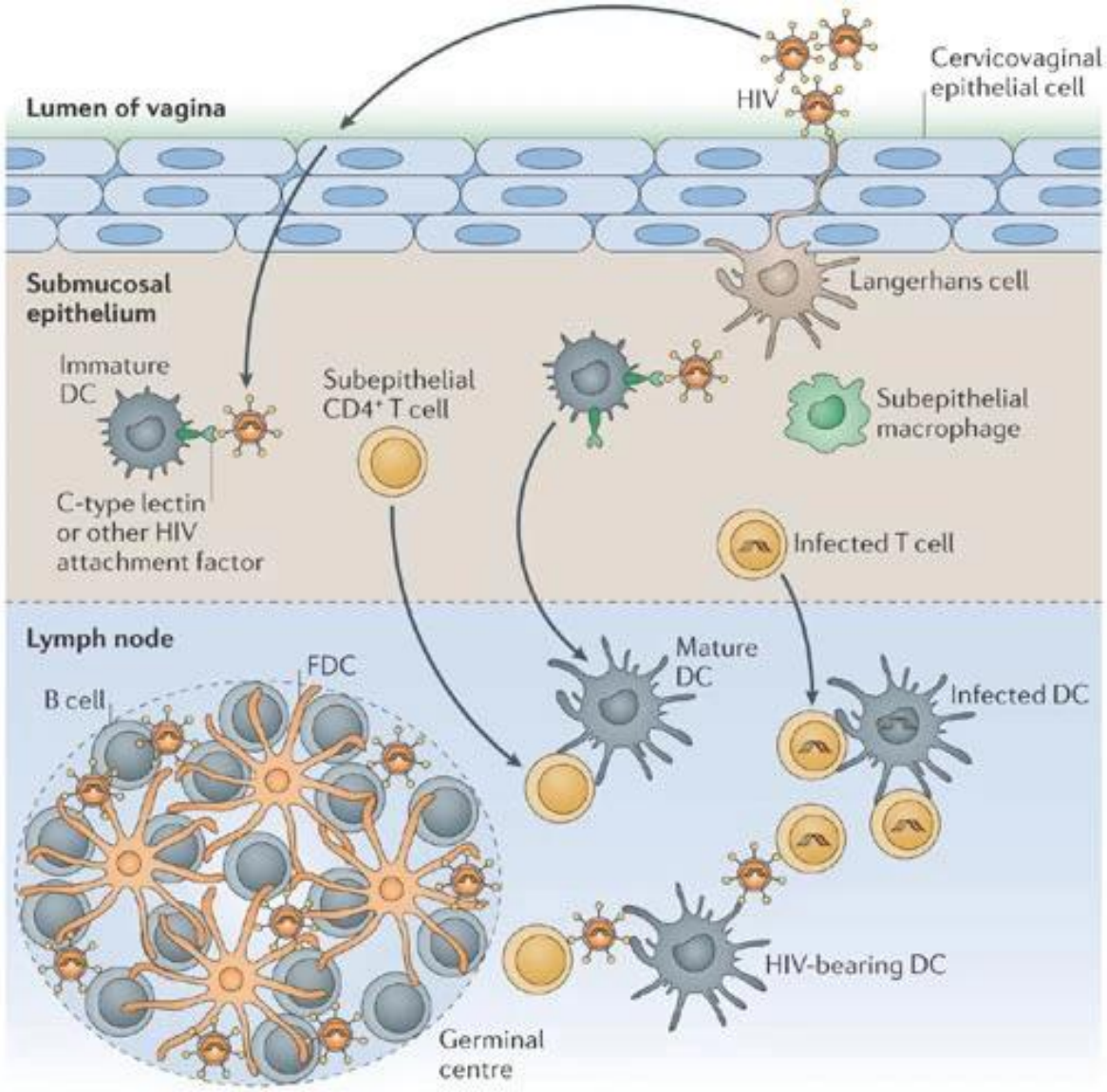
Infecção

HIV: Infecção primária

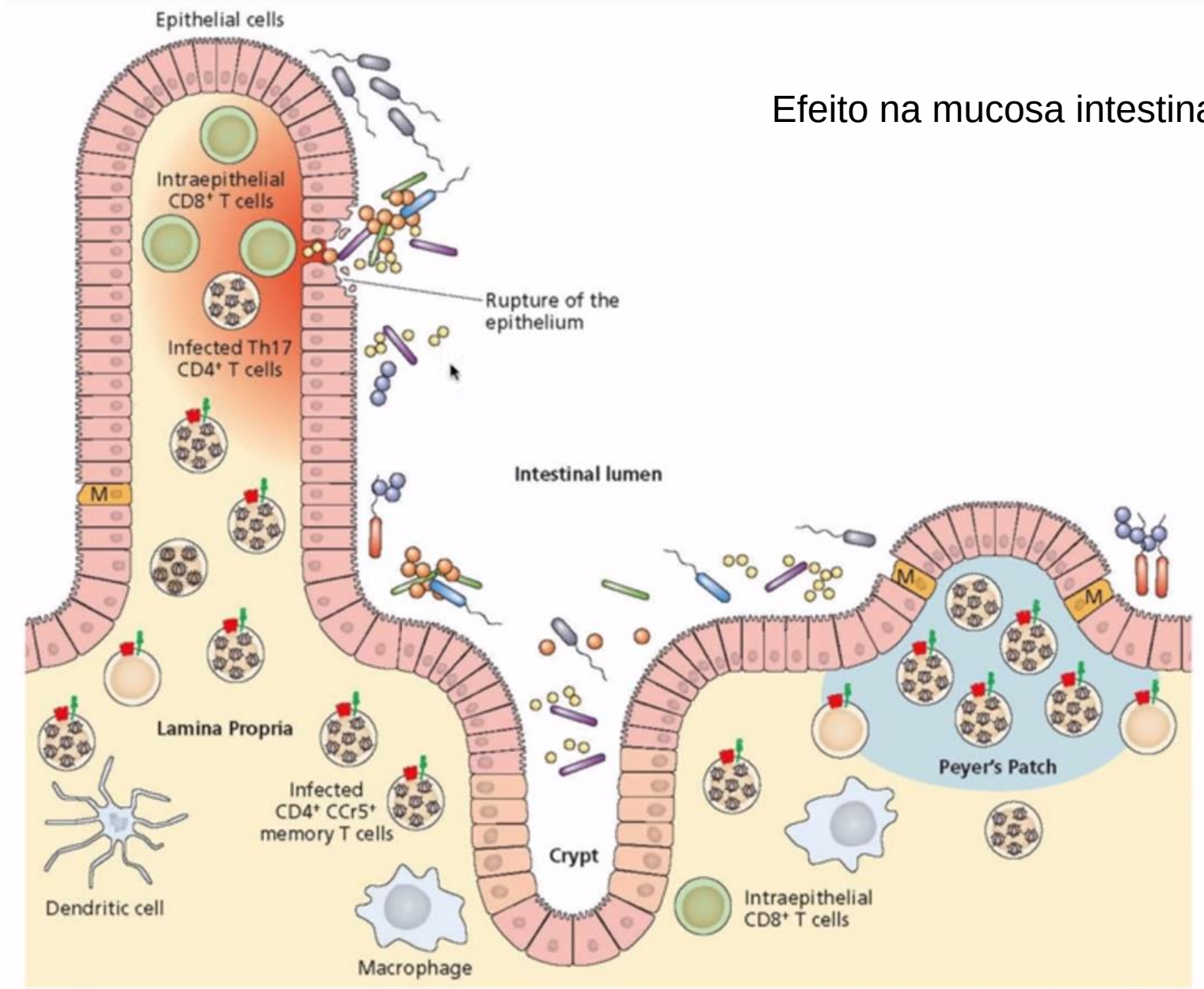
- DC-SIGN (*dendritic cell-specific, Icam-3 grabbing nonintegrin*) como carregador de HIV



Receptores:HIV



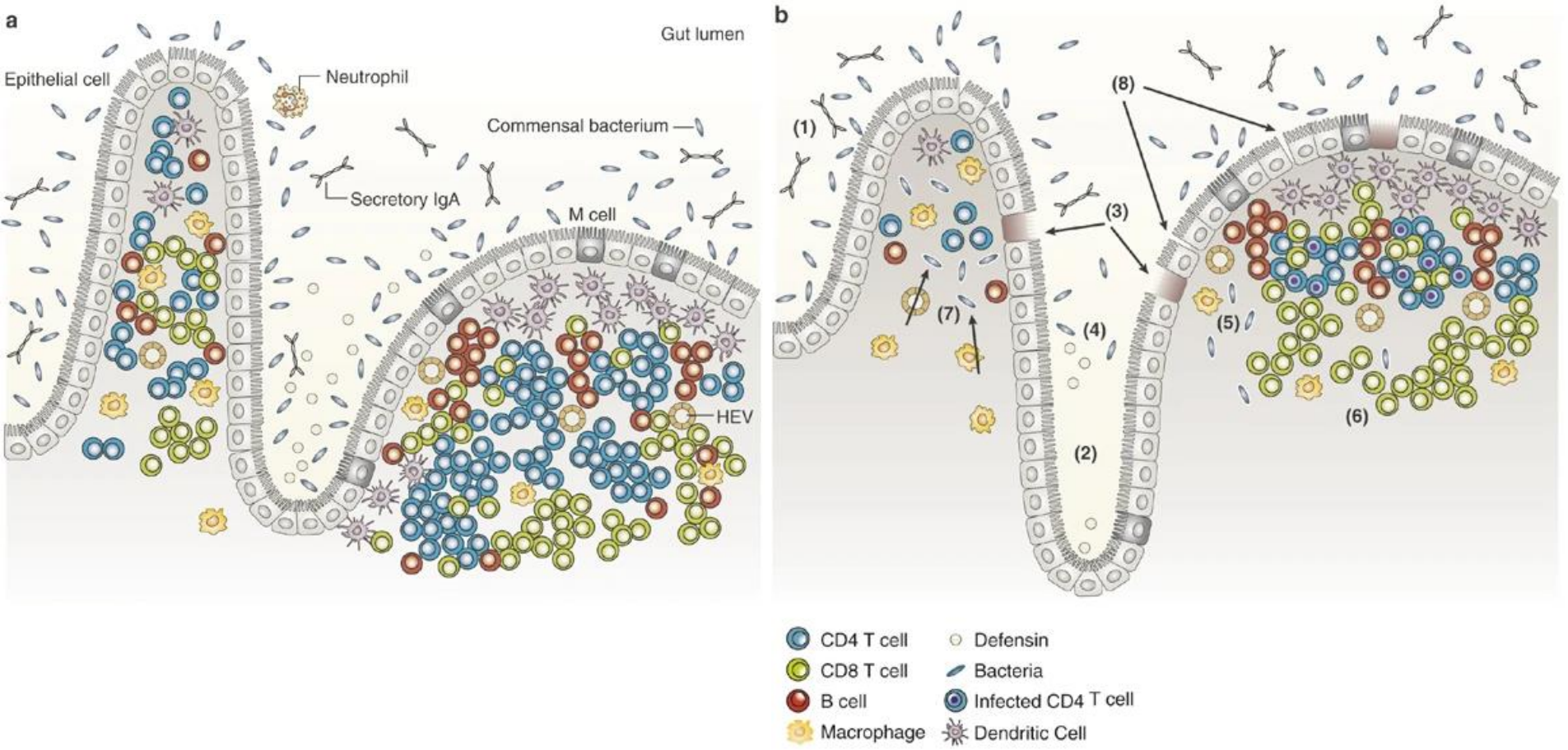
HIV: Infecção primária



Efeito na mucosa intestinal

HIV: Infecção crônica

Efeito na mucosa intestinal



Receptores:HIV

TABLE 3 - Human Cells Susceptible to HIV

Hematopoietic	Bowel
T-lymphocytes	Fetal adrenal cells
B-lymphocytes	Columnar and goblet cells
Macrophages	Enterochromaffin cells
NK cells	Colon carcinoma cells
Megakaryocytes	
Dendritic cells	**Other**
Promyelocytes	
Stem cells	Myocardium
Thymic epithelium	Renal tubular cells
Follicular dendritic cells	Synovial membrane
Bone marrow endothelial cells	Hepatocytes
	Hepatic sinusoid endothelium
Skin	Hepatic carcinoma cells
	Kupffer cells
Langerhans cells	Pulmonary fibroblasts
Fibroblasts	Adrenal carcinoma cells
	Retinal cells
Brain	Cervix-derived epithelial cells
	Cervix
Capillary endothelial cells	Prostate
Astocytes	Testes
Macrophages (microglia)	Osteosarcoma cells
Oligodendrocytes	Rhabdomyosarcoma cells
Choroid plexus ganglia cells	Fetal chorionic villi
Neuroblastoma cells	Trophoblast cells
Glioma cell lines (Neurons)	
Dental pulp fibroblasts	

Adv Dent Res 19:10-16, April, 2006

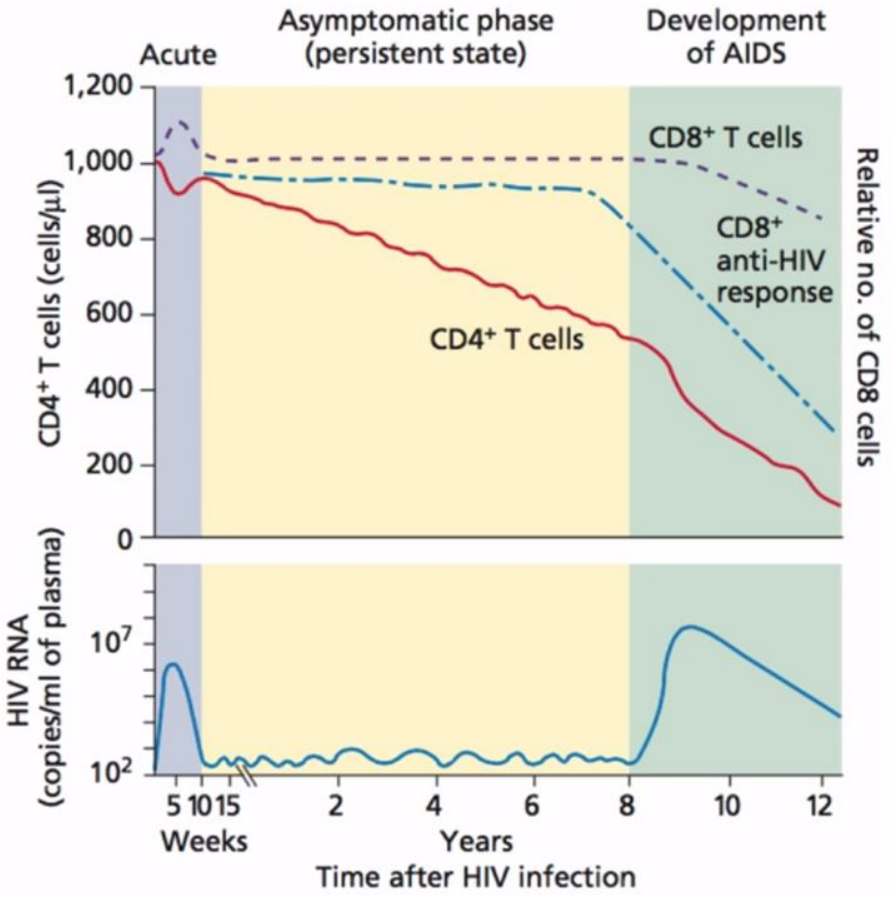
HIV: isolamento de partículas infecciosas

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: isolamento de partículas infecciosas

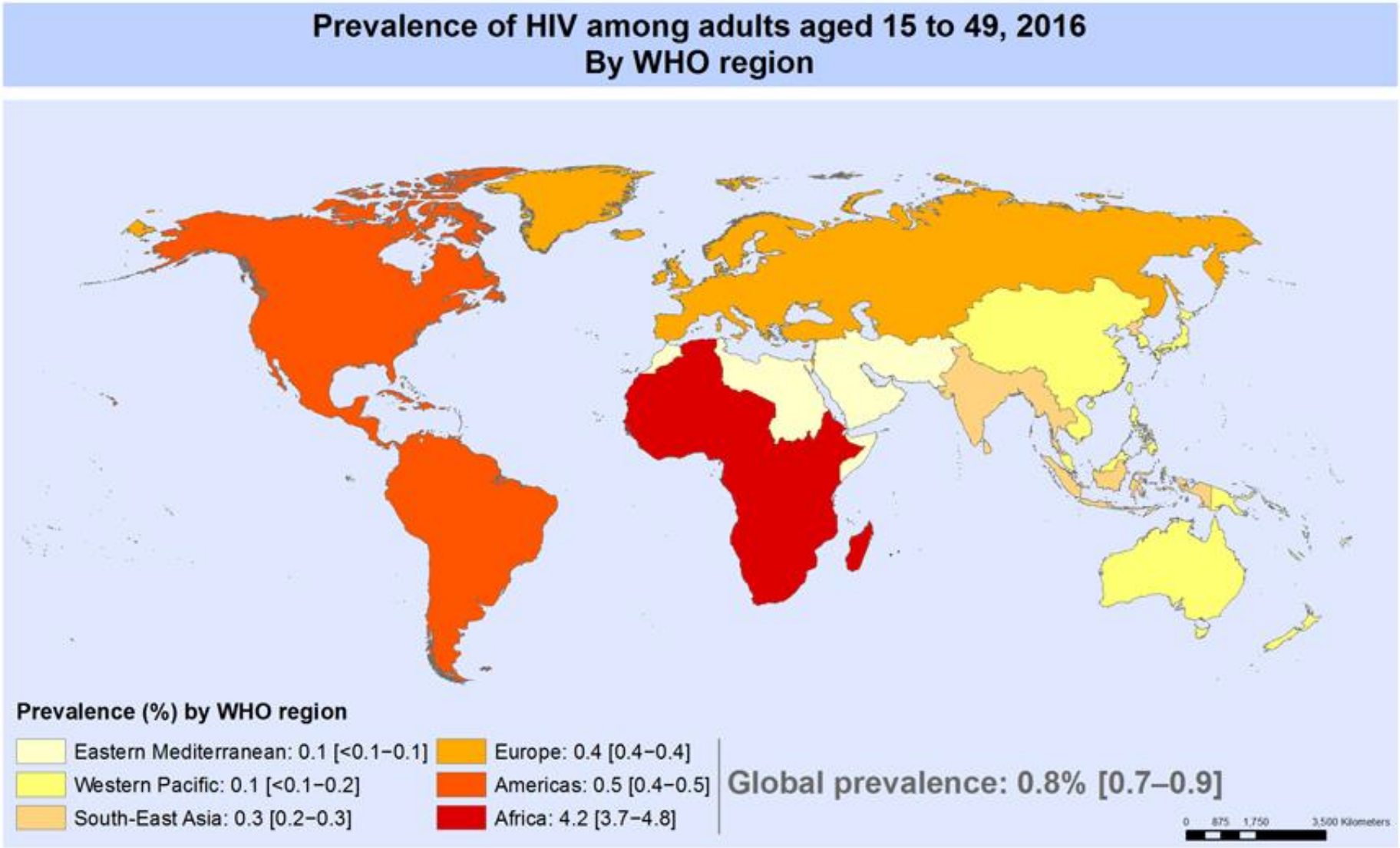
- Active viral replication throughout course of disease
- Major reservoirs of infection exist outside of blood
  - Lymphoreticular tissues (bone marrow, lymph nodes, spleen, MALT)
  - Central nervous system
  - Genital tract
- At least 10 x 10^9 virions produced and destroyed each day
- $T_{1/2}$ of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



Principles of Virology, ASM Press

Epidemiologia

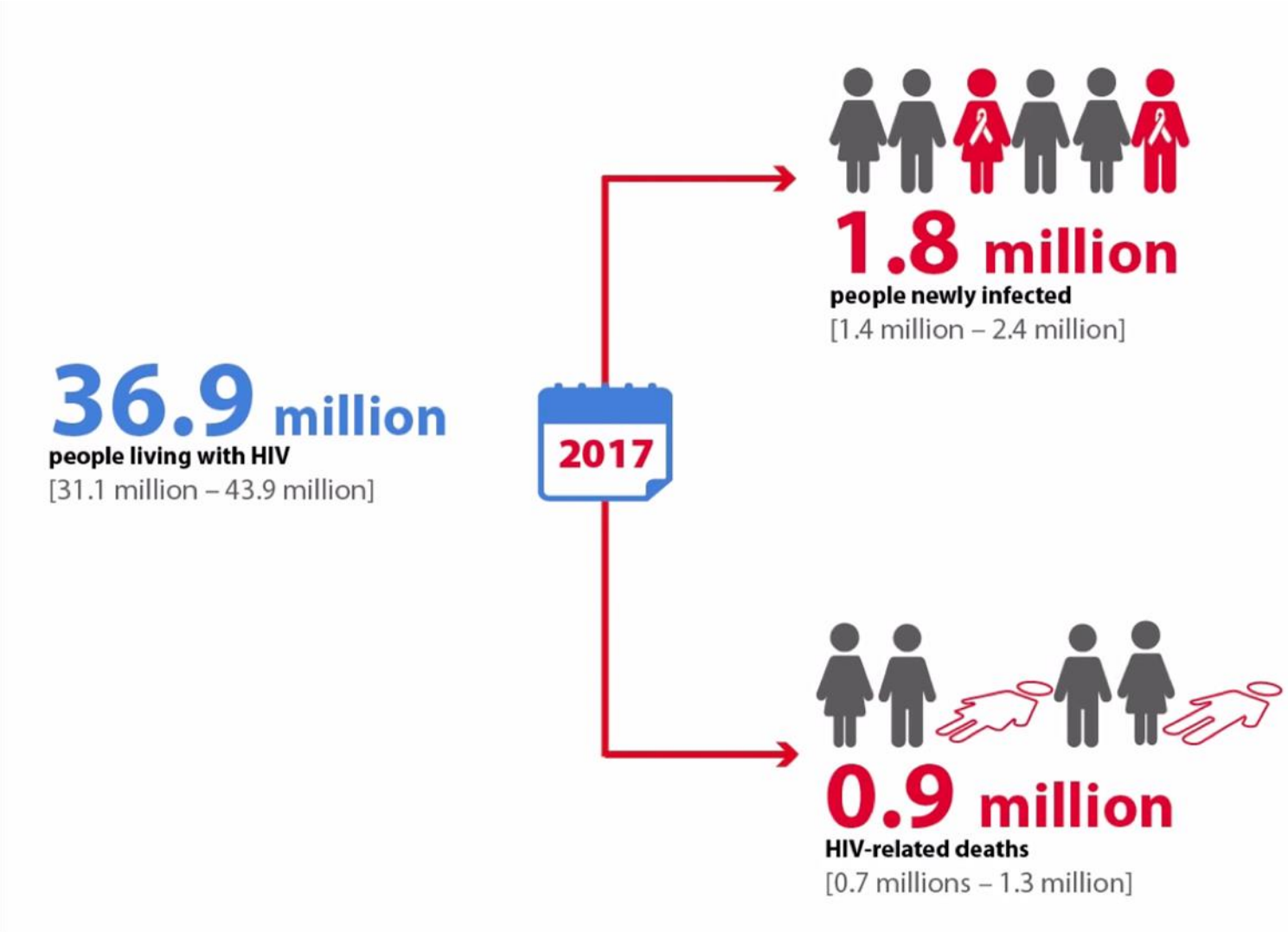
HIV no mundo



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

World Health Organization

HIV no mundo



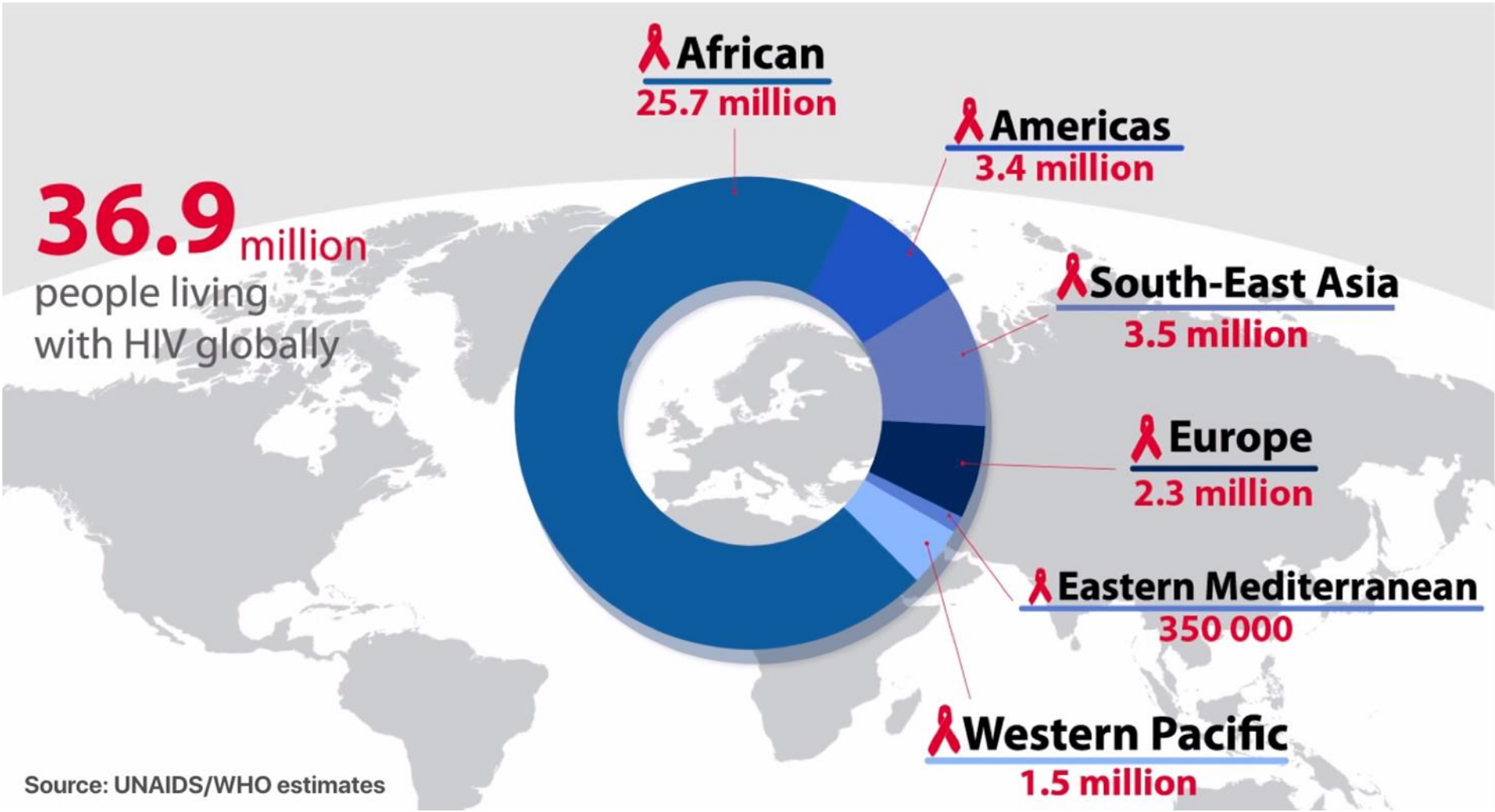
WHO 2017

HIV no mundo

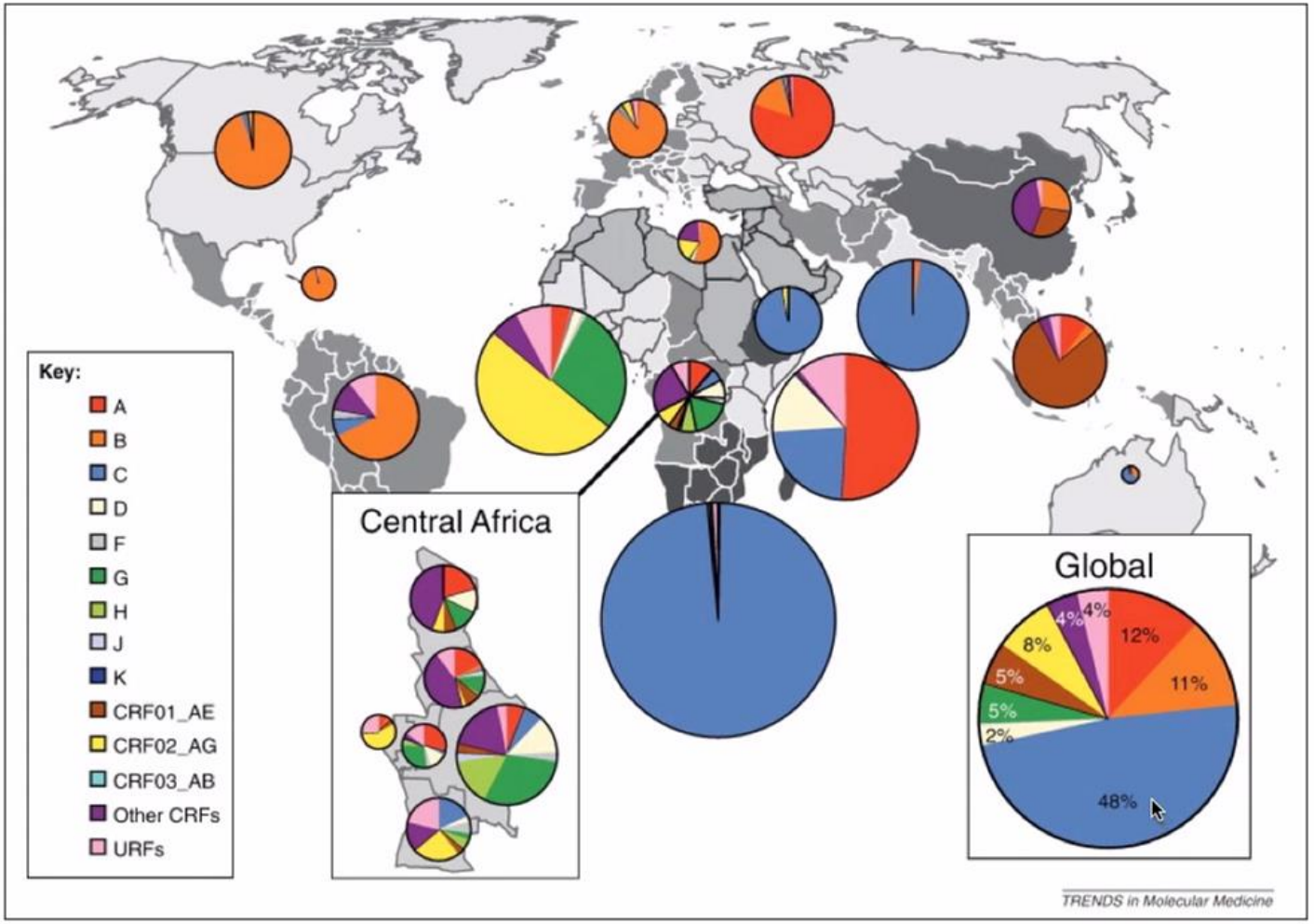
	People living with HIV in 2017	People newly infected with HIV in 2017	HIV-related deaths 2017
Total	36.9 million [31.1 million – 43.9 million]	1.8 million [1.4 million – 2.4 million]	940 000 [670 000 – 1.3 million]
Adults	35.1 million [29.6 million – 41.7 million]	1.6 million [1.3 million – 2.1 million]	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


African
25.7 million
Americas
3.4 million
South-East Asia
3.5 million
Europe
2.3 million
Eastern Mediterranean
350 000
Western Pacific
1.5 million
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

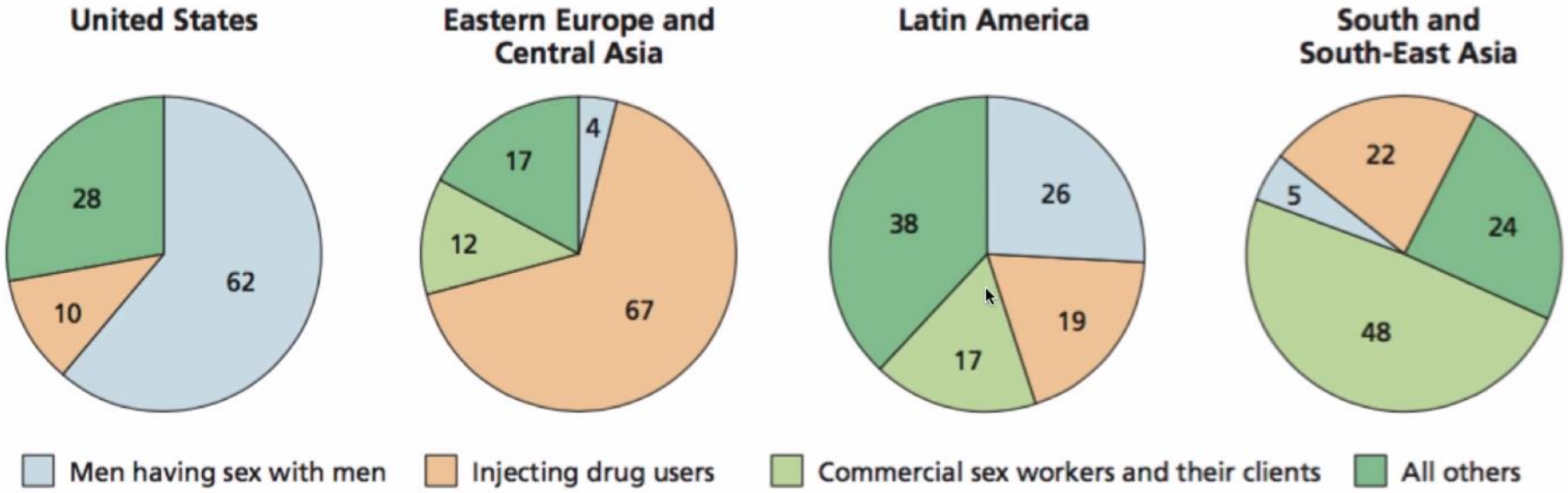
Vias de transmissão

- 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

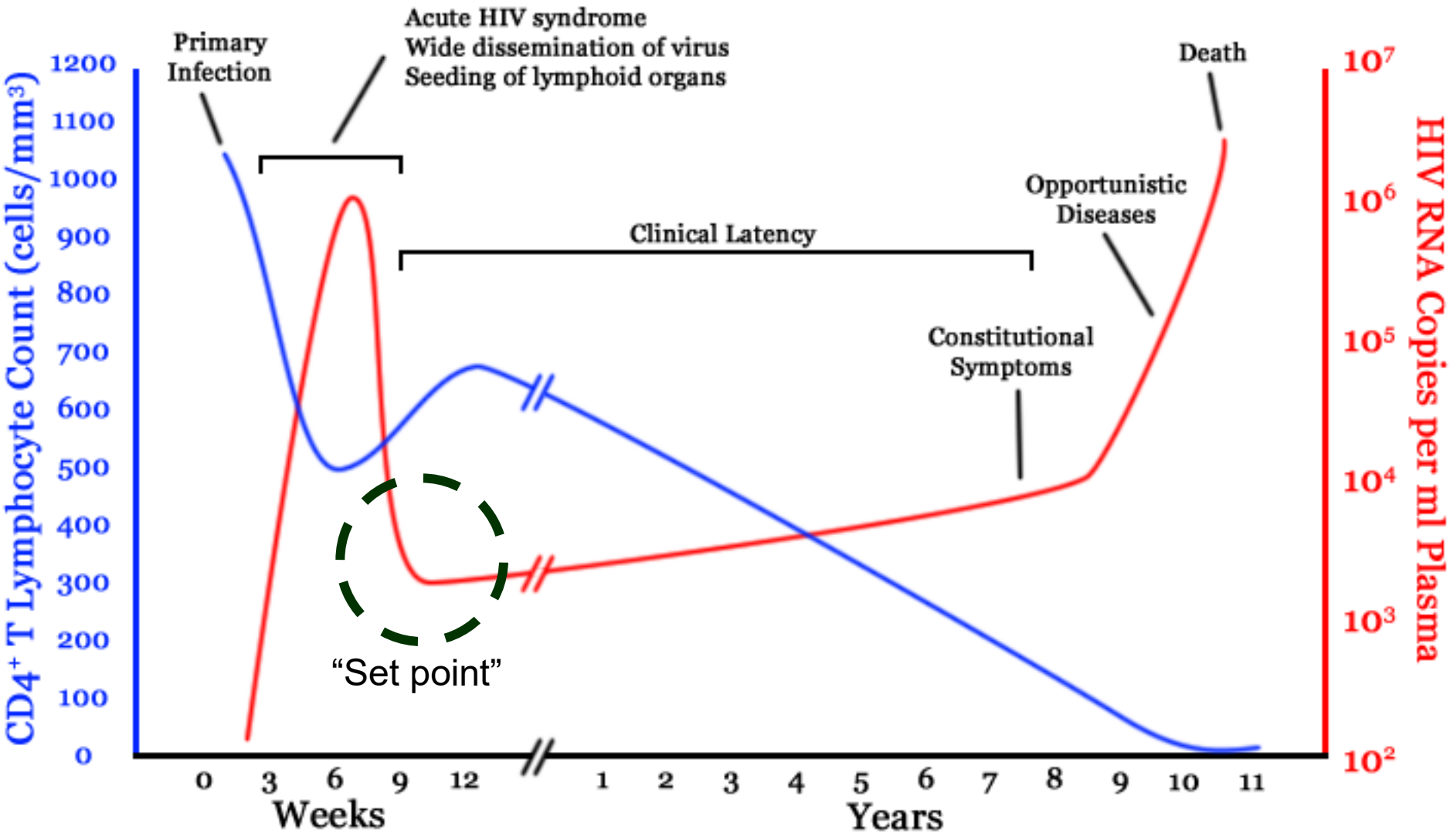
Principal forma de transmissão do HIV no Brasil e no Mundo;

Fatores que aumentam o risco de transmissão relação heterossexual são:

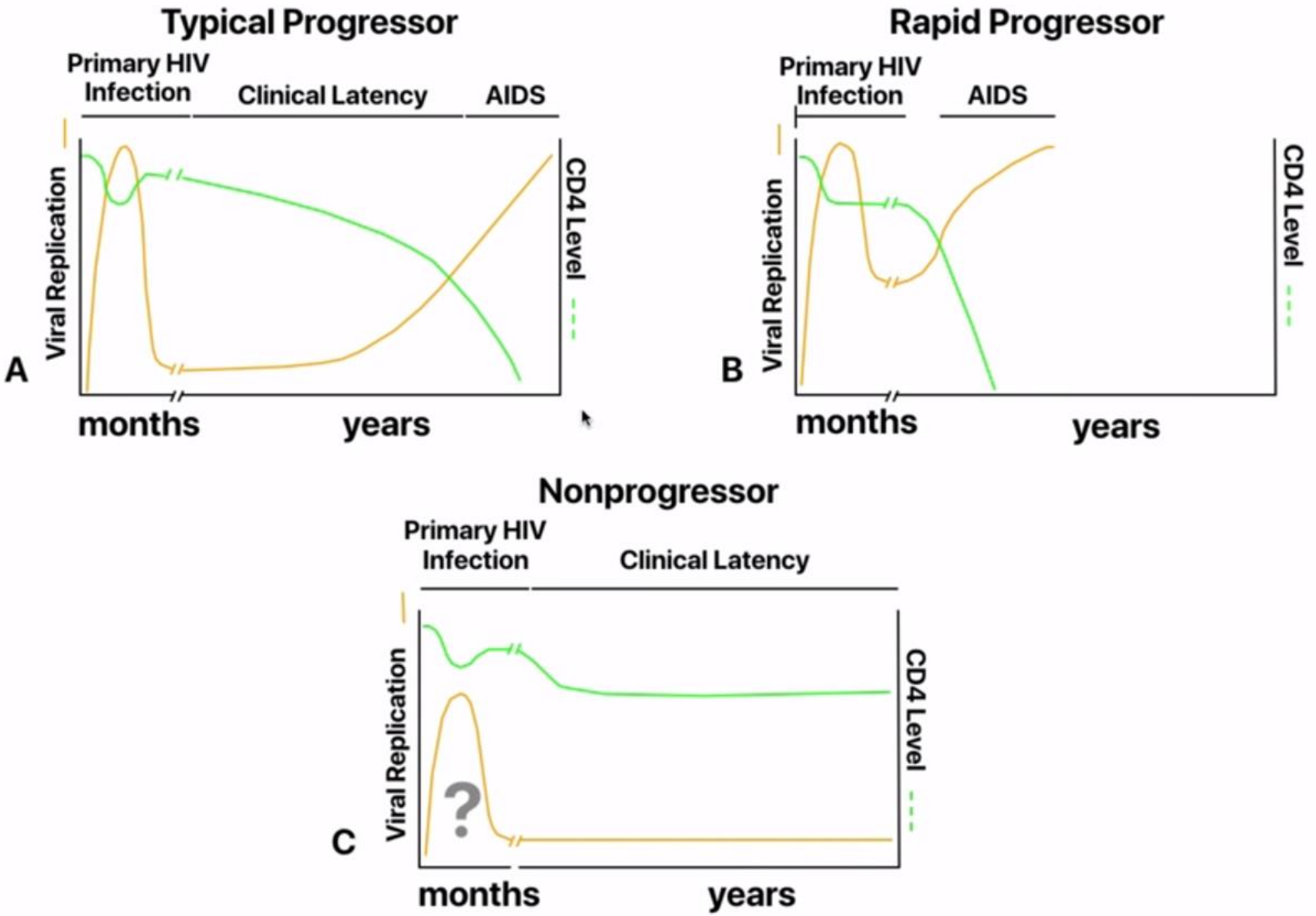
- Alta viremia;
- anal receptiva;
- Relação sexual durante a menstruação;
- Presença de outra DST

Patogênese

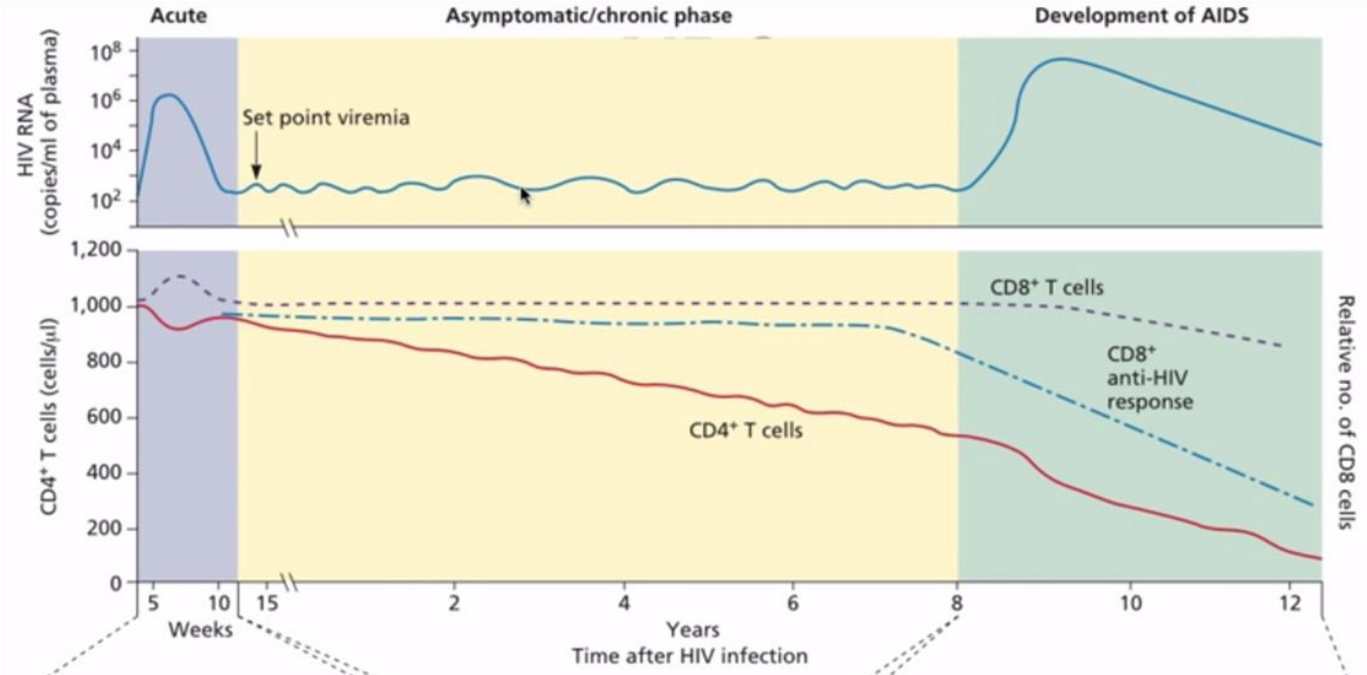
Curso da infecção por HIV



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

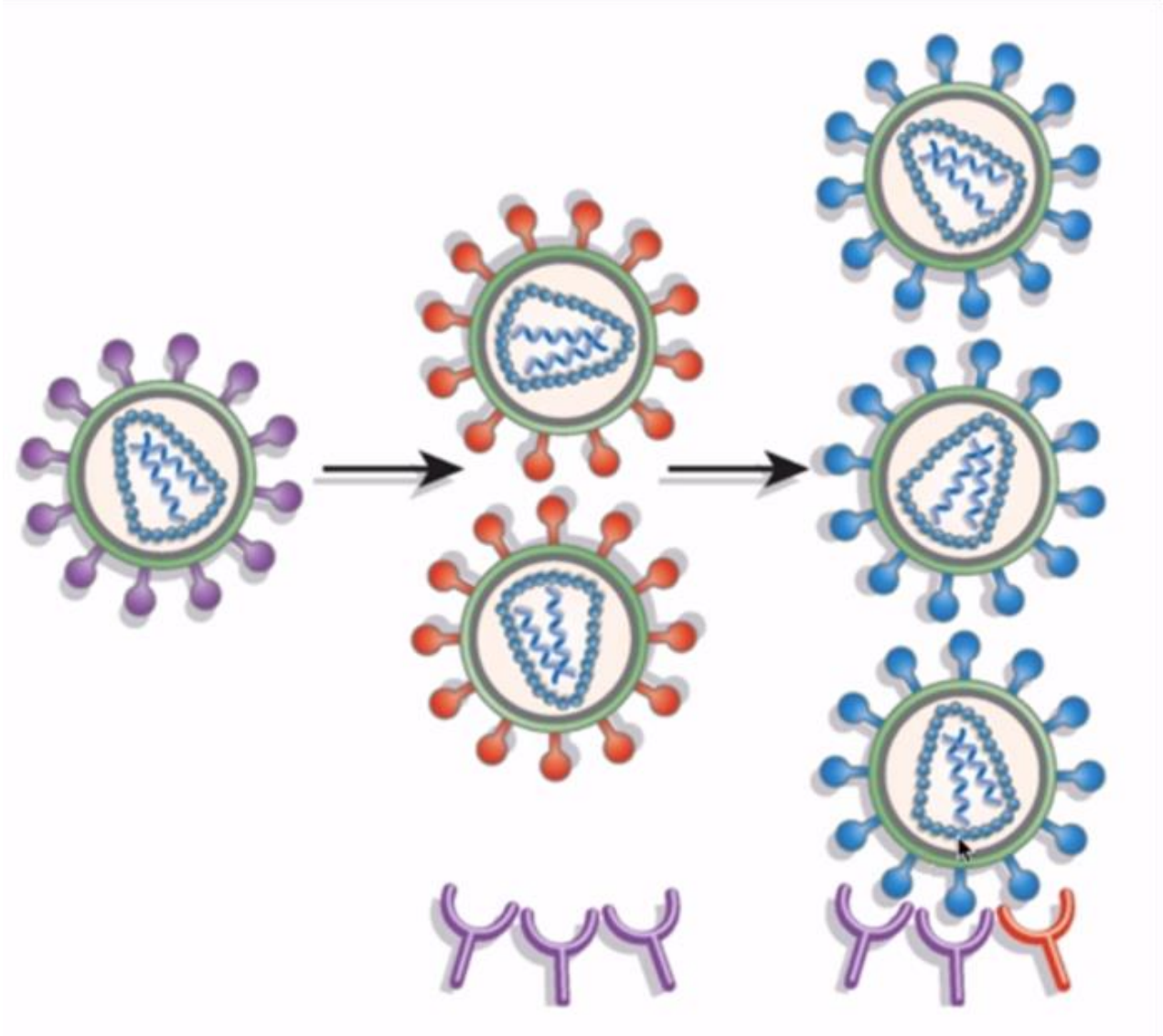
Symptoms
200-500 CD4⁺ T cells/ml
Oral/skin lesions
Genital warts
Development of Kaposis sarcoma
Reactivation of latent Mycobacterium tuberculosis

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

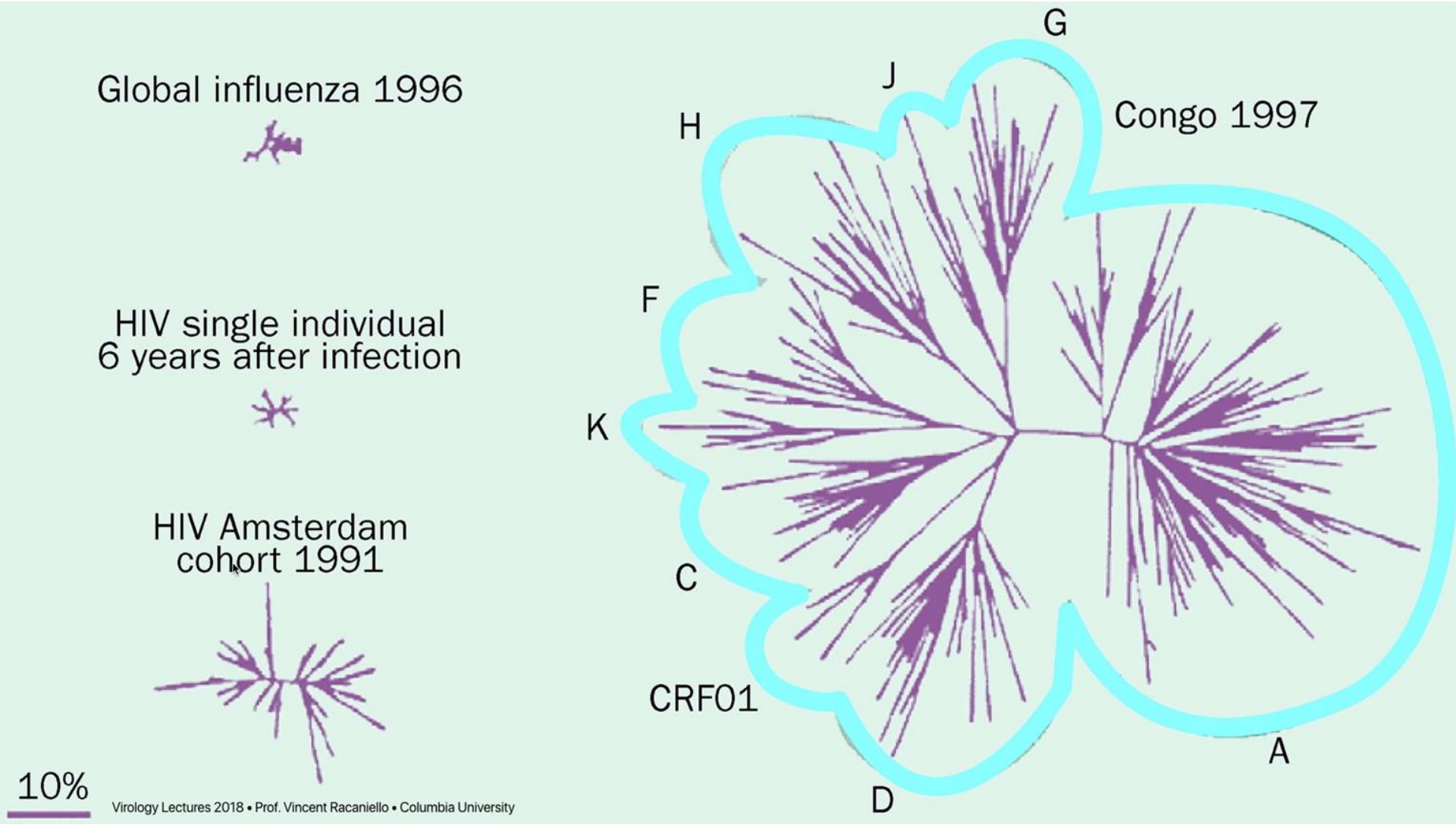
At cellular level
CD4⁺ T cell depletion, loss of helper function
HIV-1-specific CD4⁺/CD8⁺ T cell exhaustion
B cells: decrease/dysregulation
natural killer (NK) cells: impairment of function

• Columbia University

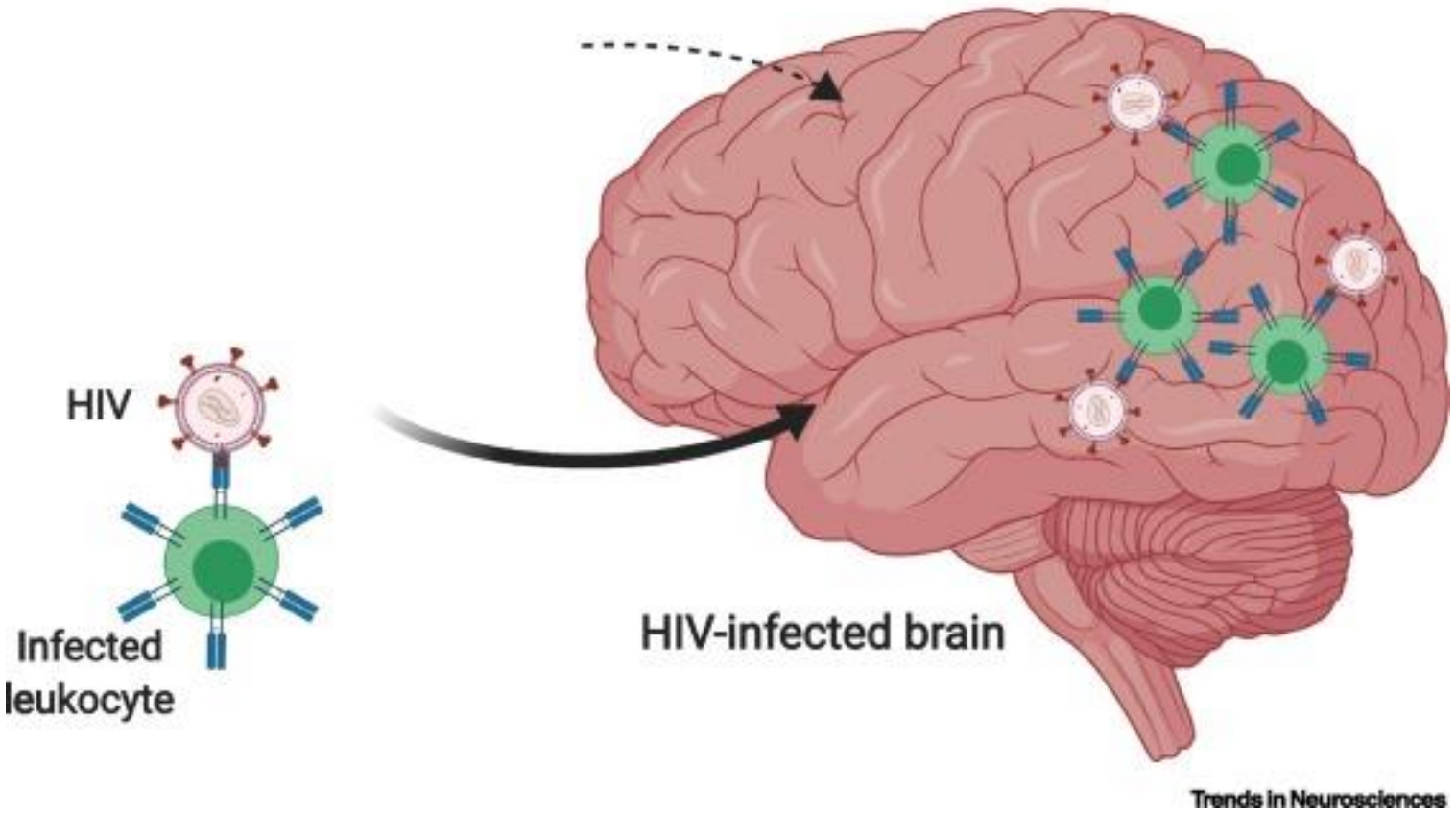
Escape da resposta imune



Escape da resposta imune

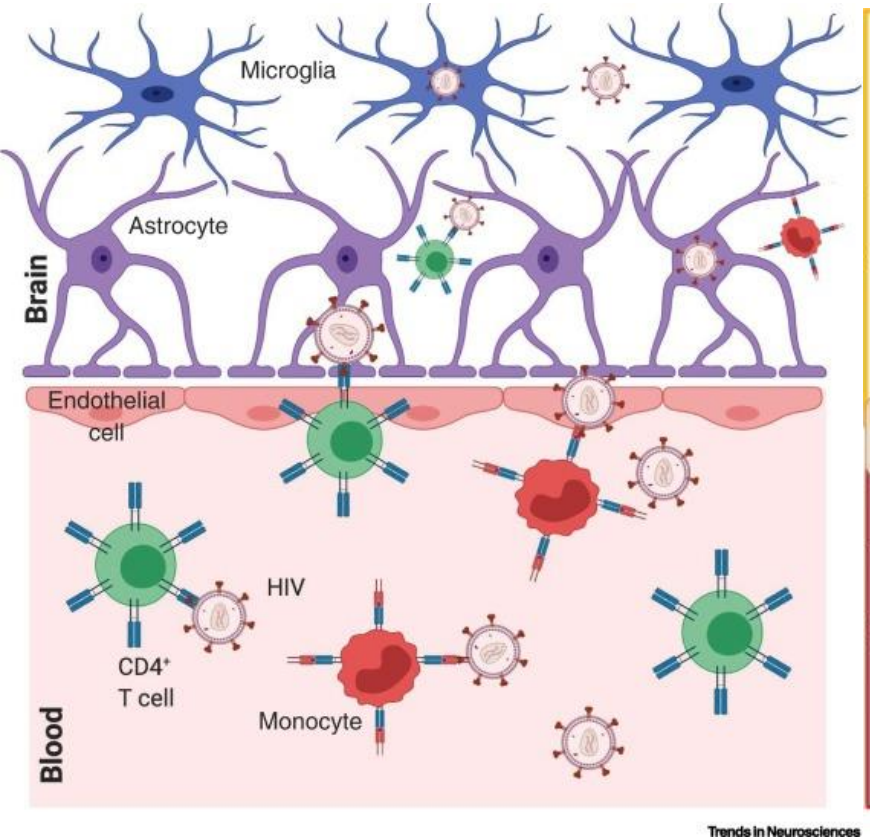


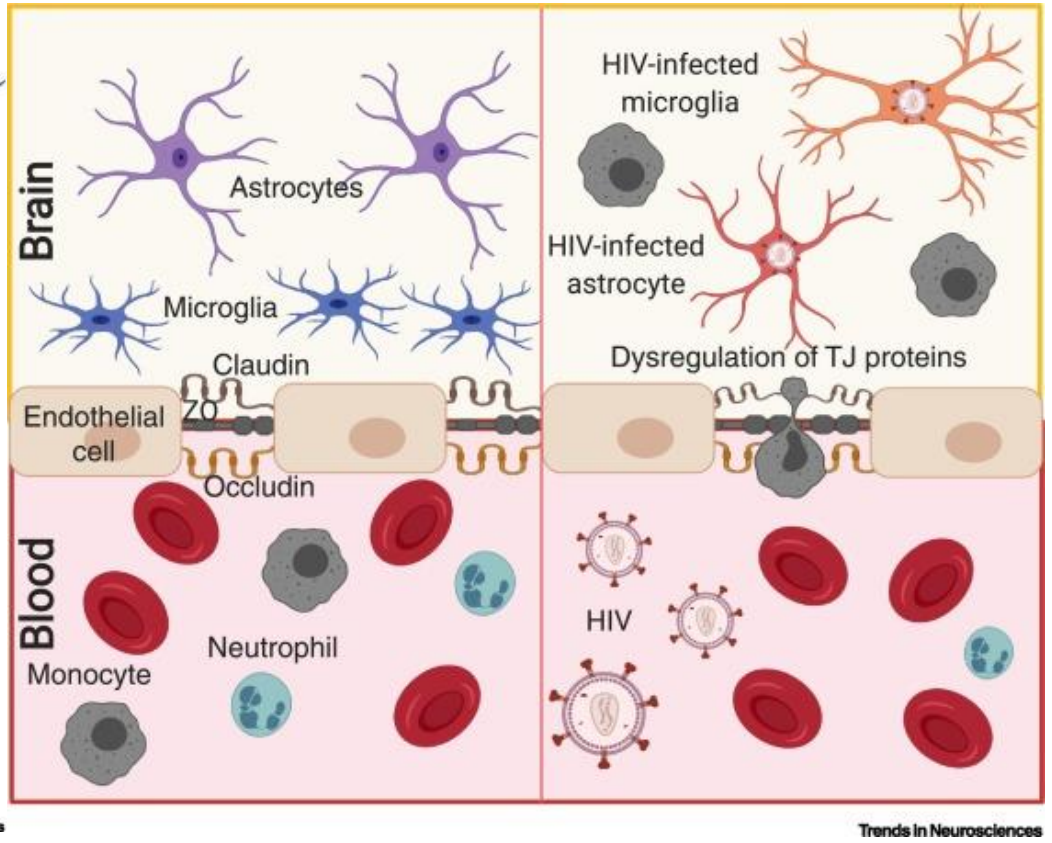
Sintomas neurológicos



DOI:https://doi.org/10.1016/j.tins.2020.06.007

Sintomas neurológicos





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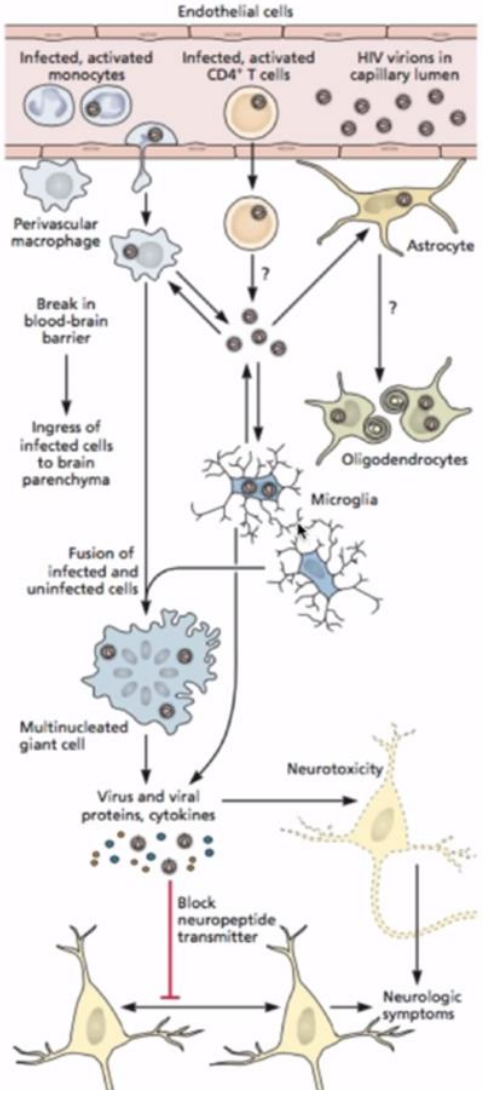
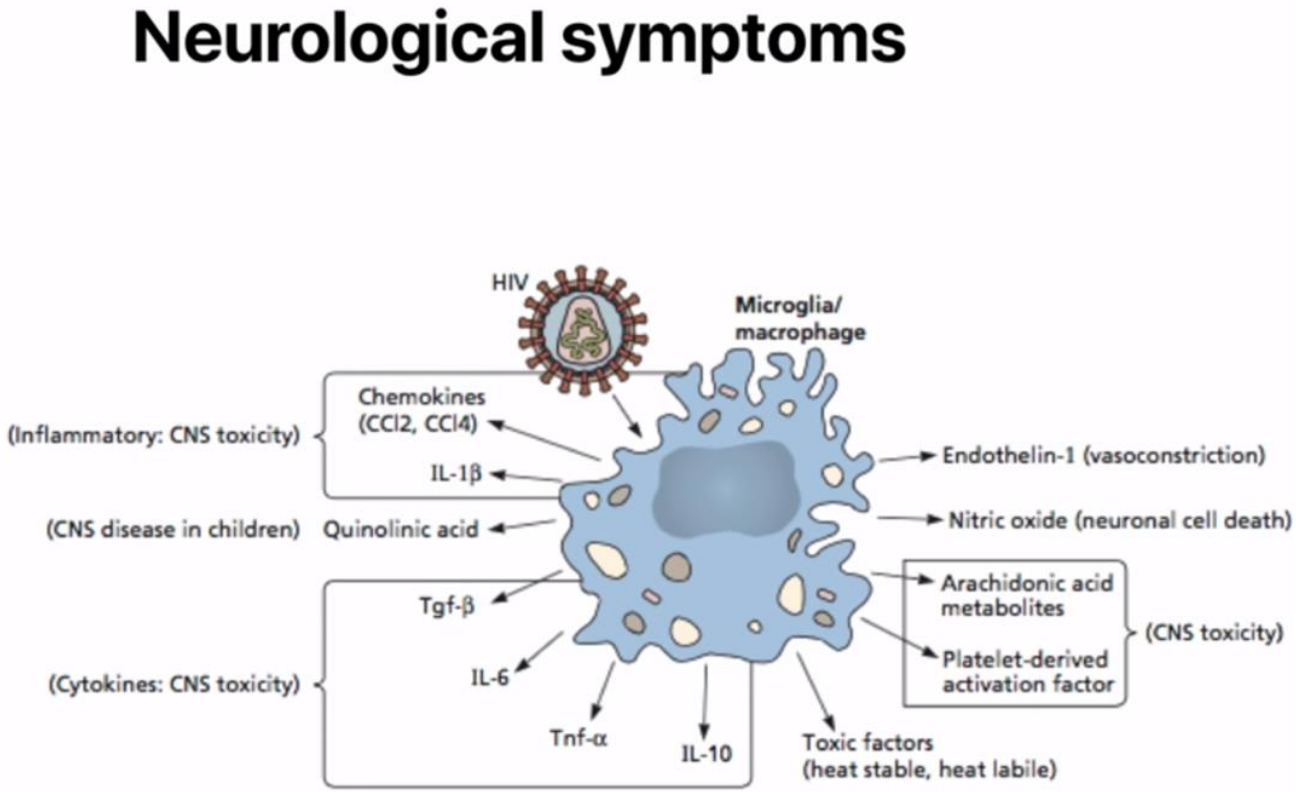
Sintomas neurológicos





DOI:https://doi.org/10.1016/j.tins.2020.06.007

Curso da infecção por HIV

Aids

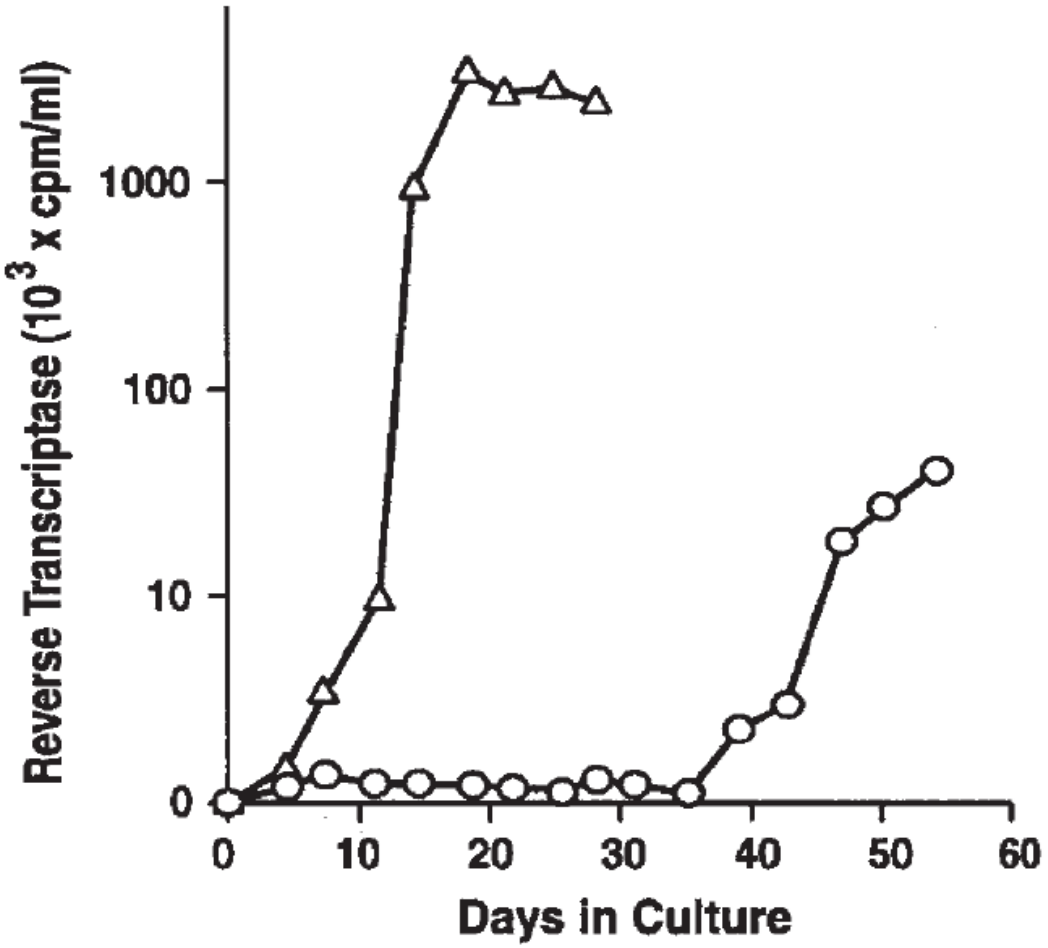
Curso da infecção por HIV

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



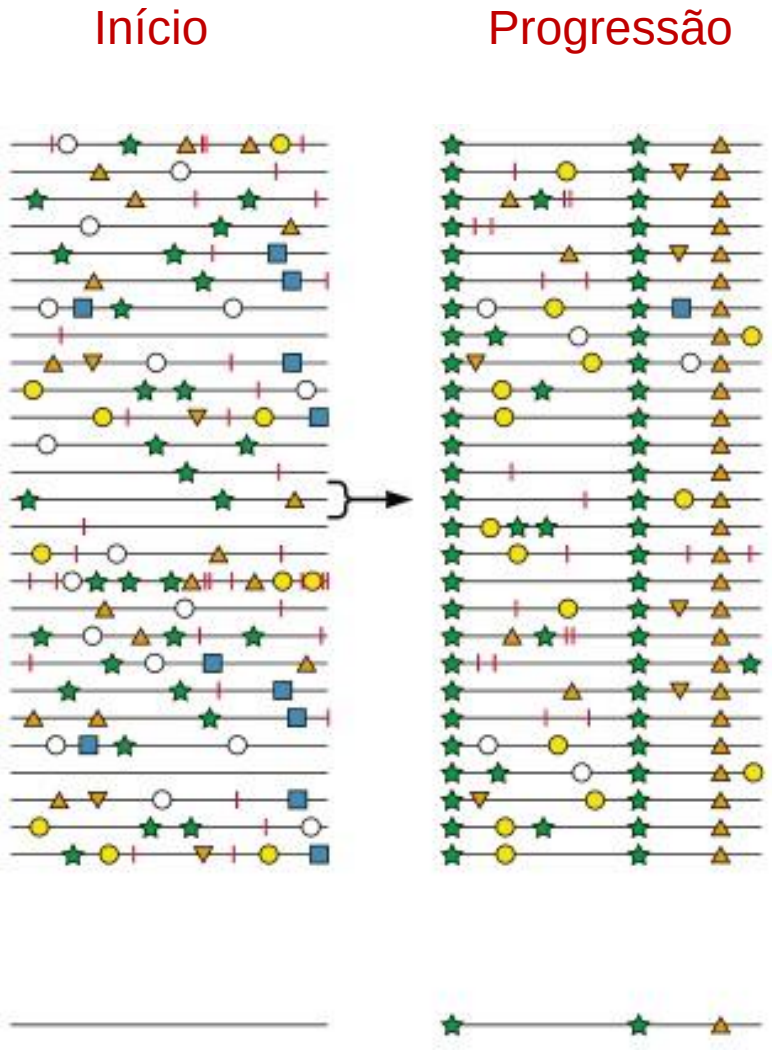


Fig. 4 - Differences in replication of HIV-1 recovered from an individual early in infection (○) and later, when he had progressed to disease (△) (Cheng-Mayer *et al.*, 1988b). Note that the early virus replicates at low titer, and peaks after a longer period of time than the faster-replicating virus,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

Curso da infecção por HIV

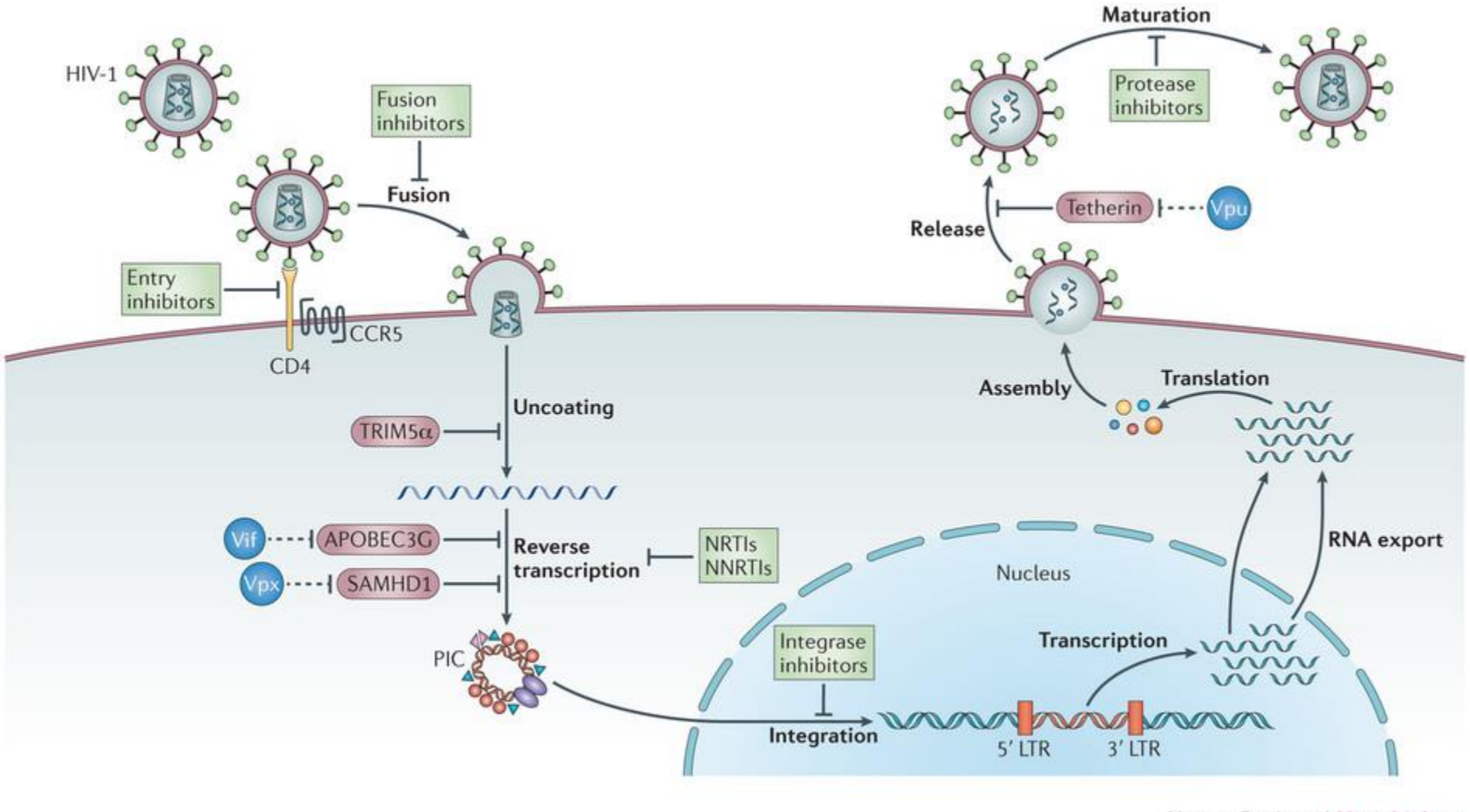
AIDS

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

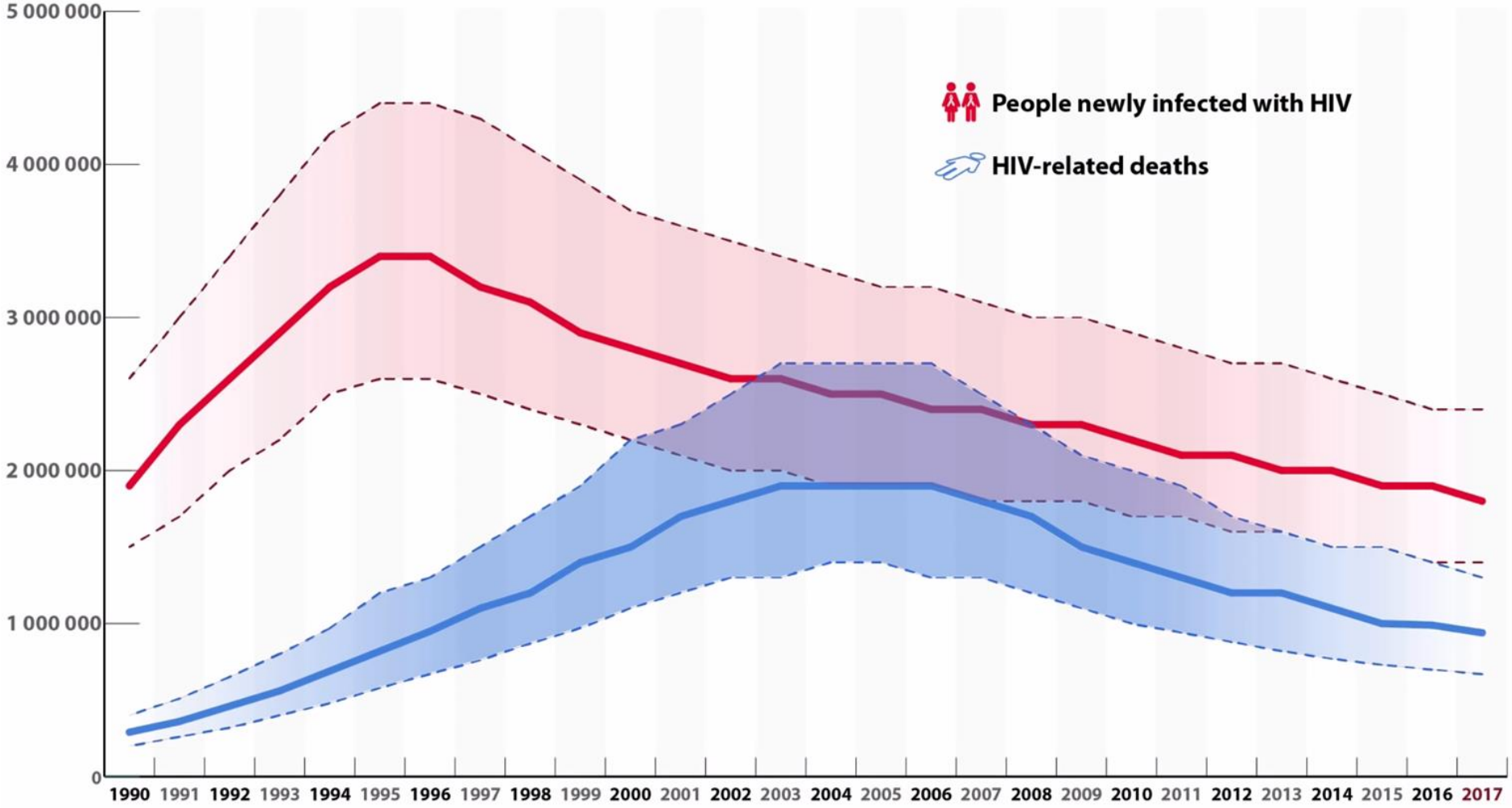
Processos virais como alvos terapêuticos



Nature Reviews | Microbiology

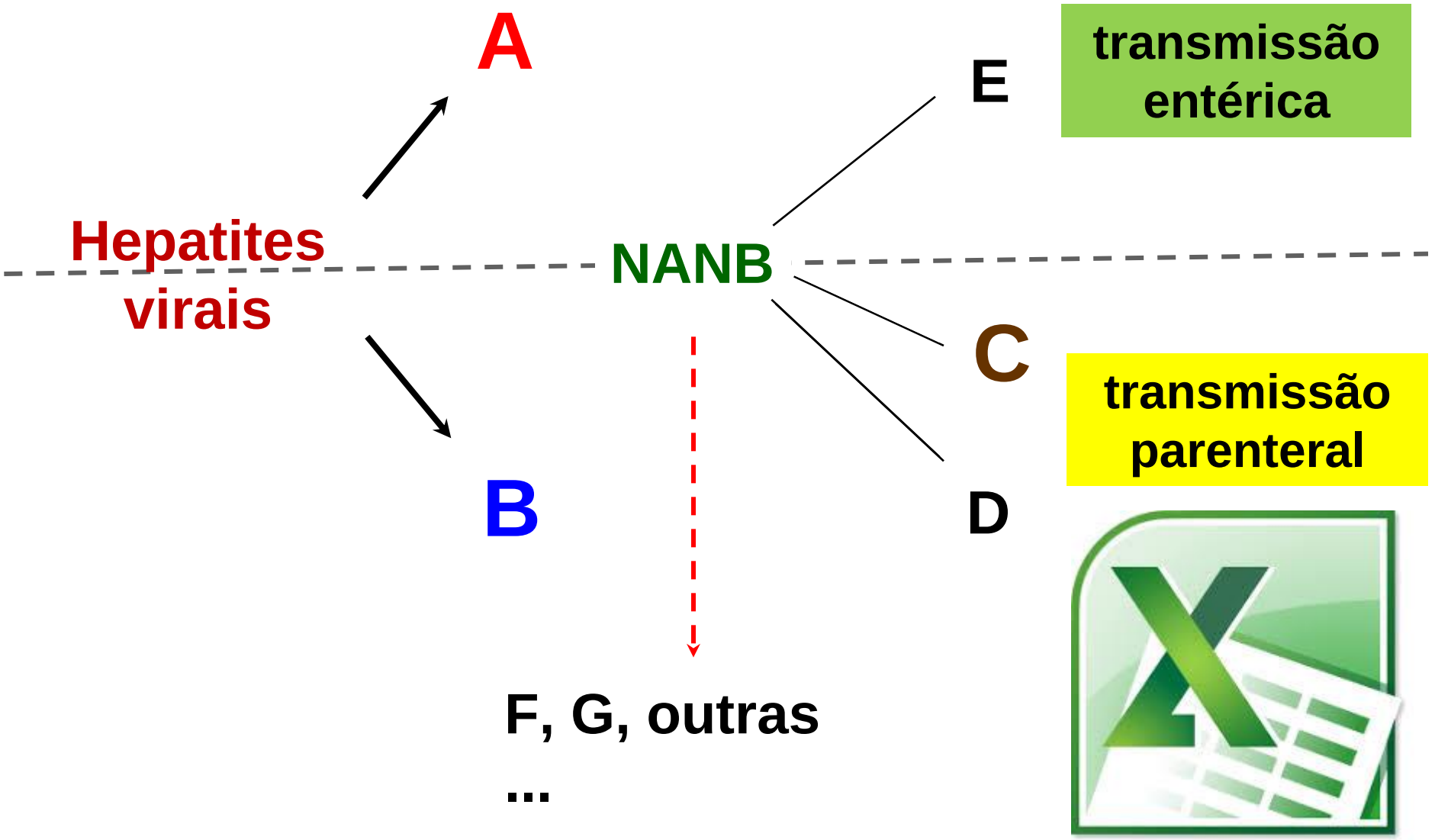
Curso da infecção por HIV

Processos virais como alvos terapêuticos



Hepatites Virais

É uma virose...


A
E
transmissão entérica
Hepatites virais
NANB
C
transmissão parenteral
B
D
F, G, outras
...

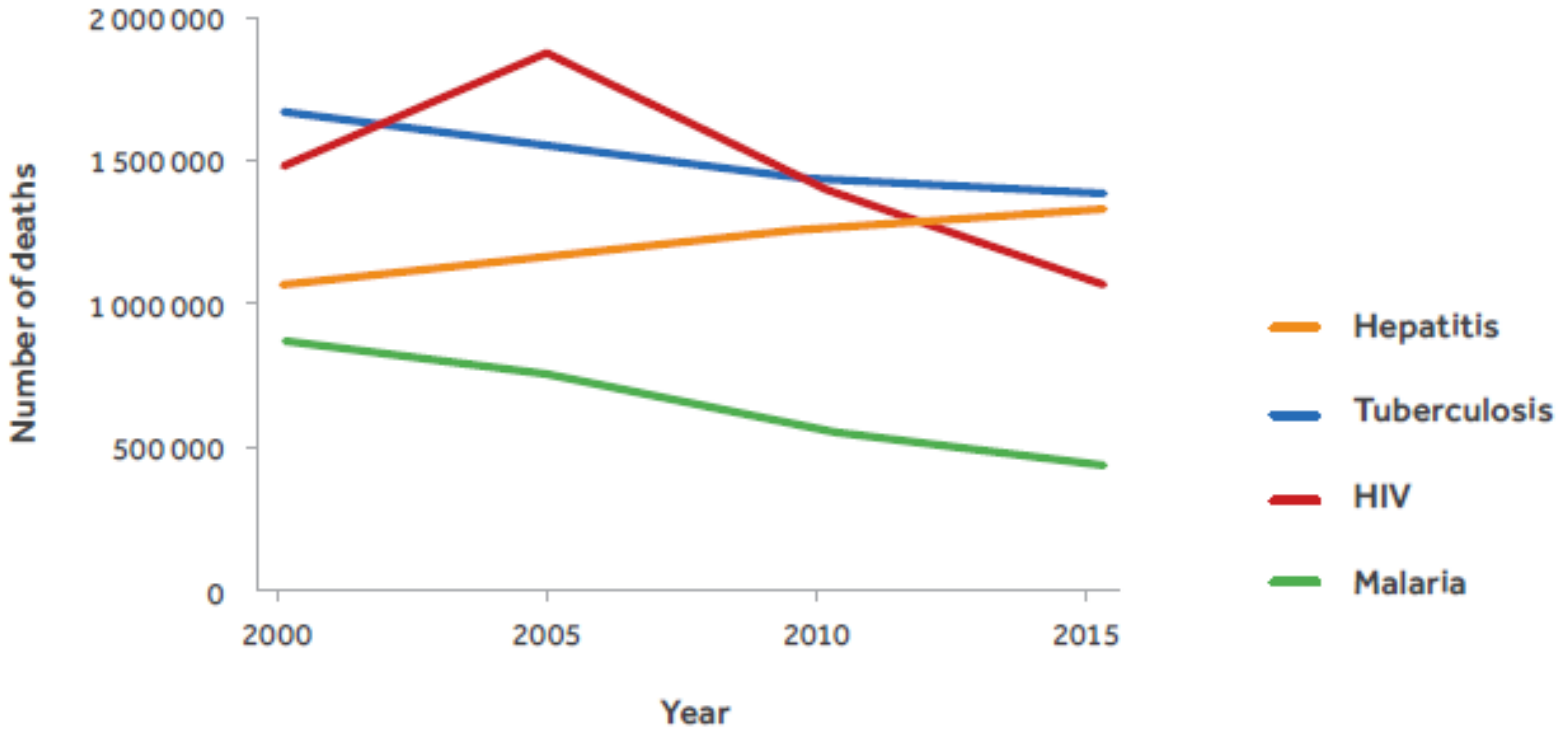
Hepatites Virais: impacto nas populações humanas

Estimativas da WHO (2015)

- 257 milhões de pessoas (3.5% da população mundial) estão infectados de maneira crônica pelo HBV.
- 5% das pessoas infectadas por HBV estão infectadas por HDV.
- 71 milhões de pessoas (1.0% da população mundial) estão infectados de maneira crônica pelo HCV.
- 20 milhões de pessoas/ano se infectam com o HEV (44.000 mortes em 2015 [3.3% das mortes por Hepatites virais]).
- Mais de 7.000 mortes por HAV em 2016 (taxa de hepatite fulminante varia de 0.14 – 0.35, portanto, 2 – 5 milhões de casos por ano).

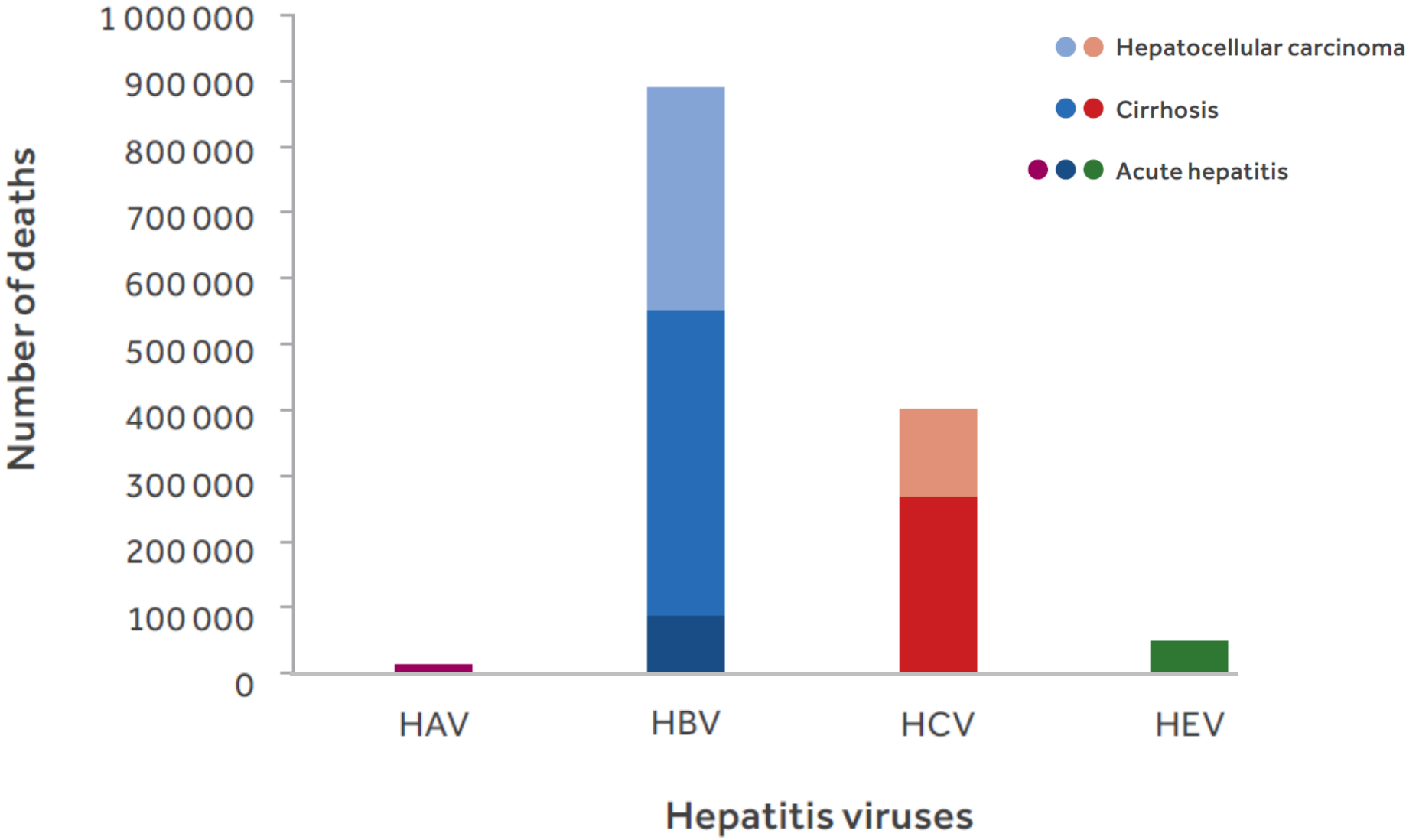
Hepatites Virais: impacto nas populações humanas

Fig. 2. Global annual mortality from hepatitis, HIV, tuberculosis and malaria, 2000–2015: unlike HIV, tuberculosis and malaria, the trend in mortality from viral hepatitis is increasing



Source: WHO global health estimates (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000-2015. Geneva: World Health Organization; 2016.)

Hepatites Virais: impacto nas populações humanas



HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virusSource: WHO global health estimates for 2015 published in 2016 (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000–2015. Geneva: World Health Organization; 2016.)

Hepatites Virais

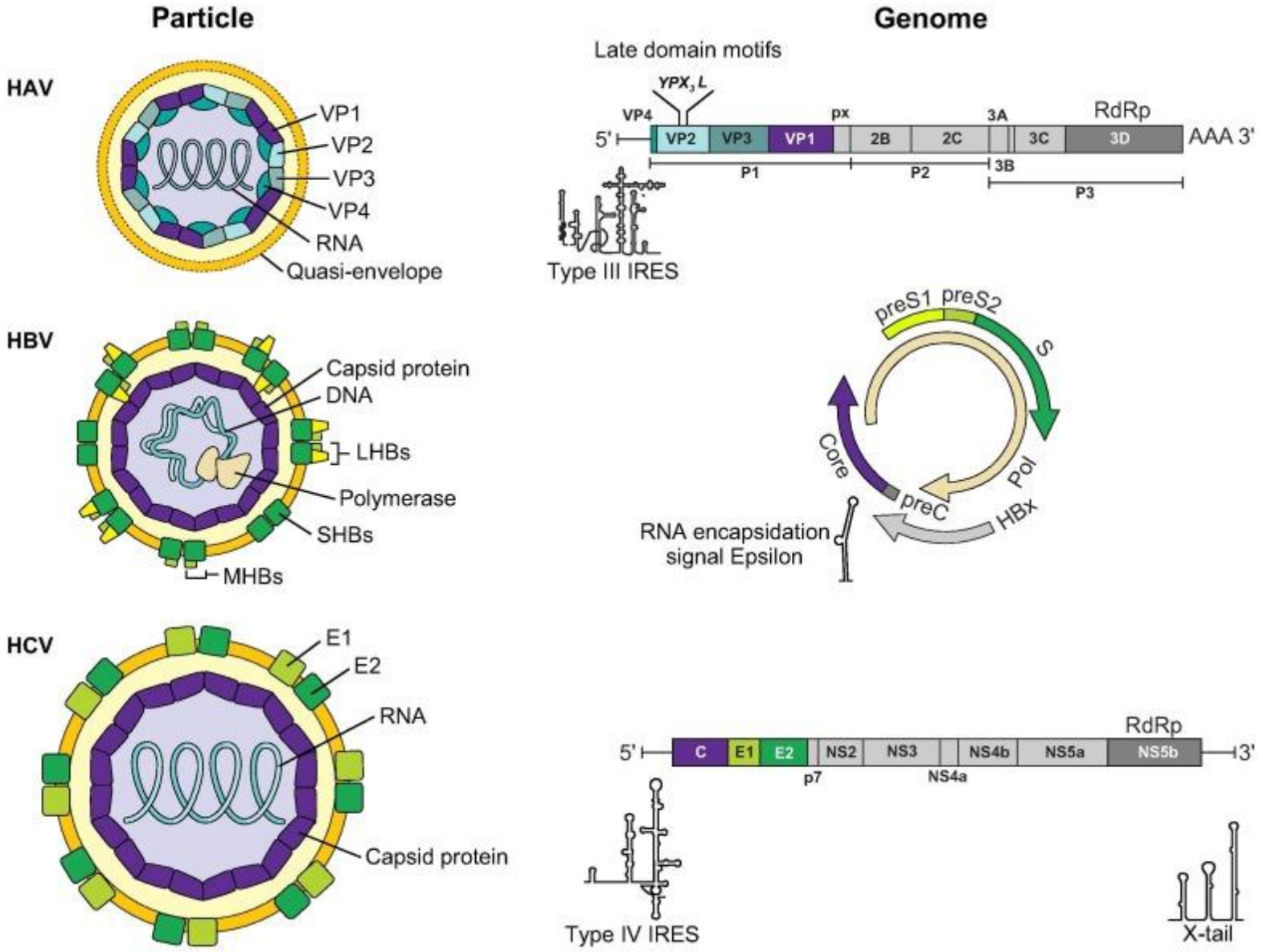
Table 1. Properties of human hepatitis viruses.

	HAV	HBV	HCV	HDV	HEV
Virus family, genus	*Picornaviridae, Hepatovirus*	*Hepadnaviridae, Orthohepadnavirus*	*Flaviviridae, Hepacivirus*	Unassigned, *Deltavirus*	*Hepeviridae, Orthohepevirus*
Genome type	Positive-sense linear ssRNA	Circular, partially dsDNA (full length negative-sense, partial positive-sense), replication via reverse transcription	Positive-sense linear ssRNA	Viroid-like, negative-sense circular ssRNA	Positive-sense linear ssRNA
Approx. genome length (nt)	7,500	3,200	9,600	1,700	7,200
Virion diameter (nm)	27–32	42	55–65	36–43	30–34
Envelope	No/quasi-enveloped	Yes	Yes	Yes	No/quasi-enveloped
Course of infection	Acute[61]	Acute/chronic (children 30–90%; adults <5%)[62]	Acute/chronic (80–85%)[63]	Acute/chronic (>80% if superinfection)[64]	Acute/chronic (<1%)[65]
Predominant transmission routes	Mainly faecal-oral, parenteral	Vertical, parenteral, sexual	Parenteral	Parenteral, sexual	Faecal-oral, food-borne, parenteral
Cellular receptor	Unknown[66]	NTCP, heparan sulfate proteoglycans[67,68]	CD81, SR-B1, LDL receptor, claudin-1, occludine[69–71]	NTCP, heparan sulfate proteoglycans[67,72]	Unknown

dsDNA, double-stranded DNA; nt, nucleotide; NTCP, sodium taurocholate co-transporting polypeptide; ssRNA, single-stranded RNA.

http://dx.doi.org/10.1016/j.jhep.2018.11.010

Hepatites Virais



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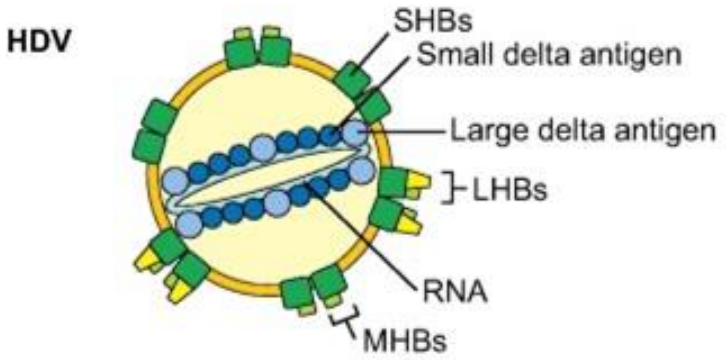
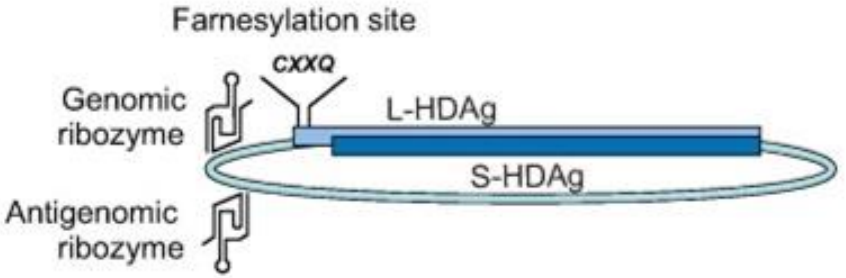
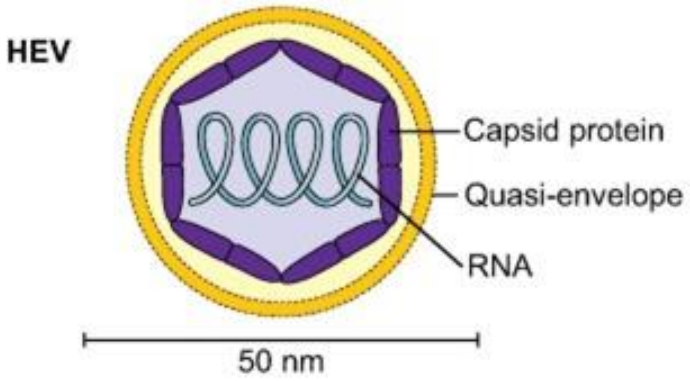
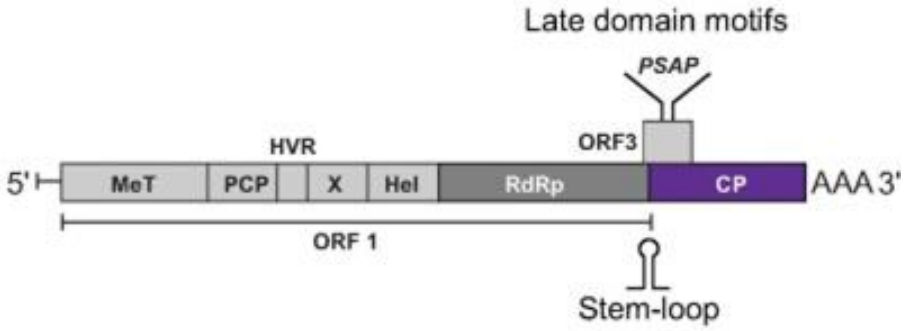
Hepatites Virais









http://dx.doi.org/10.1016/j.jhep.2018.11.010

Vírus de hepatite de transmissão parenteral (sexual?)

Hepatite B e C

Table 2 | **Virology of HBV and HCV**

Viral features	HBV	HCV
Molecular virology		
Structure	42 nm; enveloped nucleocapsid; partially double-stranded DNA genome	50 nm; enveloped nucleocapsid; positive-stranded RNA genome
Family	Hepadnaviridae family	Flaviviridae family; hepacivirus genus
Receptor	Unknown; there are several candidate HBV-binding proteins	Unknown; the receptor complex probably includes the tetraspanin CD81 and as-yet-unknown hepatocyte-specific factors; there are several other candidate HCV-binding proteins
Replication strategy	Replication of HBV DNA occurs by reverse transcription of an RNA intermediate within cytoplasmic nucleocapsids	Replication occurs by synthesis of a genome-length minus-strand RNA intermediate within cytoplasmic replication complexes that form a perinuclear membranous web
Mutation rate	Low (1 in 100,000 bases per year)	High (1 in 1,000 bases per year)
Genotypes	8 genotypes (8% intergroup divergence)	6 main genotypes (20–35% overall sequence difference); more than 50 subtypes (10–25% difference); quasispecies in every infected patient
Integration into host chromosome	Yes	No
Viral kinetics		
Viral half-life	2–3 days	3 hours
Viral production	10^{10}–10^{12} virions per day	10^{12} virions per day

References are provided in the online version of this Table (see online supplementary information S1). HBV, hepatitis B virus; HCV, hepatitis C virus.

Hepatite B e C

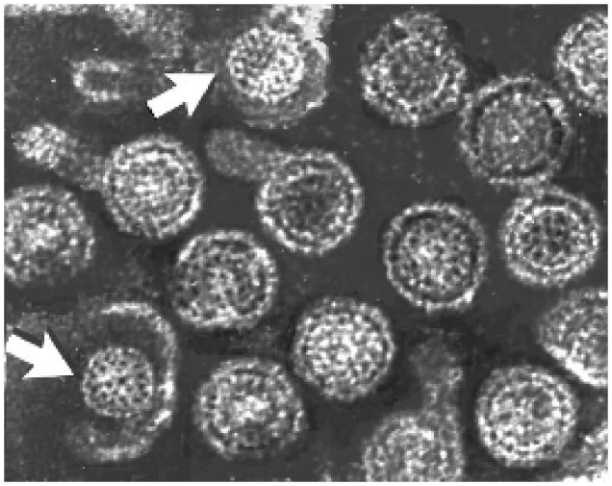
Table 1 | **Clinical features of hepatitis B and hepatitis C**

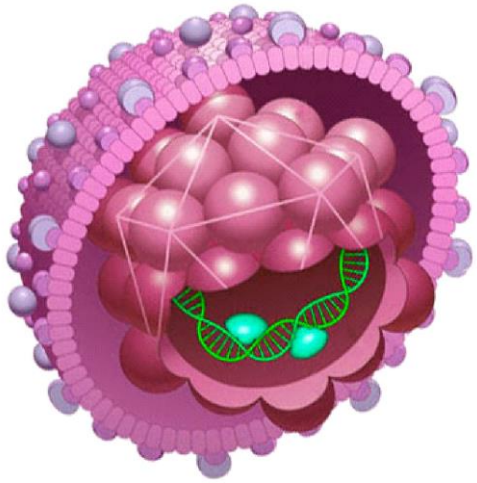
Feature	Hepatitis B	Hepatitis C
Public-health impact		
Worldwide	350 million people infected	170 million people infected
United States	1 million people infected; ~5,000 deaths per year	4 million people infected; leading cause of liver transplantation
Clinical course of infection		
Vertical (or perinatal) transmission	Most common from mother to neonate, followed by childhood infection	Rare
Horizontal transmission	Intravenous drug use, parenteral, sexual	Intravenous drug use, parenteral, sexual
Vertical (or perinatal) transmission: infection outcome	90% of individuals have chronically evolving hepatitis	–
Horizontal transmission: infection outcome	90% of individuals recover	60–80% of individuals have chronically evolving hepatitis; except those infected with genotype 2 HCV in Africa, which is cleared by 53% of individuals
Characteristic histological features of chronic hepatitis	Ground-glass inclusions of HBsAg in hepatocytes, appearing as pale, eosinophilic areas in the cytoplasm but not the nucleus	Lymphoid aggregates with organization similar to primary lymphoid follicles; steatosis (with genotype 3 HCV); reactive epithelial changes of bile ducts

Hepatite B e C

Hepatite B (HBV)

Hepatite B





Familia : *Hepadnaviridae*
Gênero: *Orthohepadnavírus*

- Pararetrovírus

Vírus pequenos de DNA envelopados (~45 nm)

DNA circular dupla-fita parcial (~3,5 kpb)

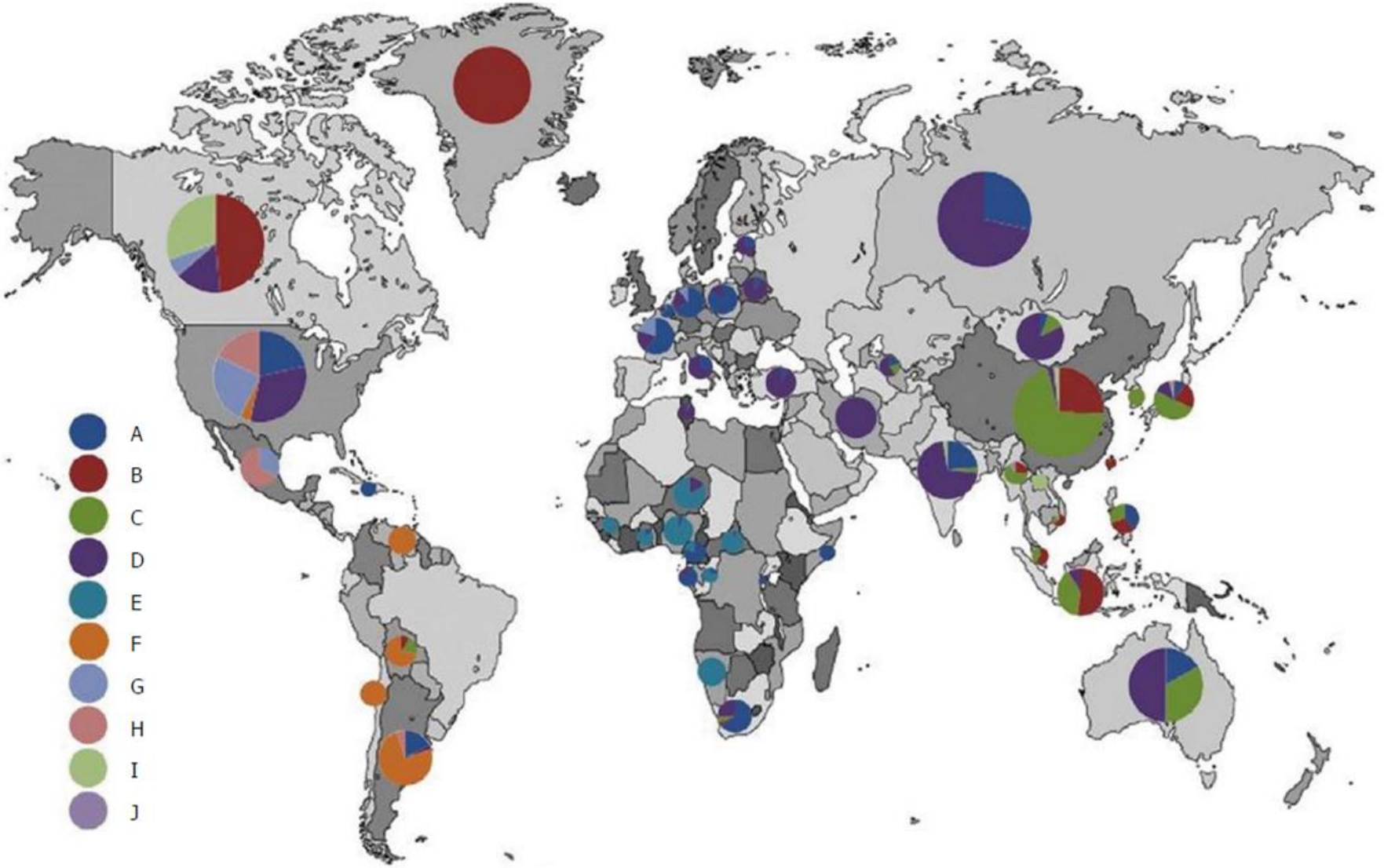
Célula alvo: hepatócitos

Etiologicamente associado com:

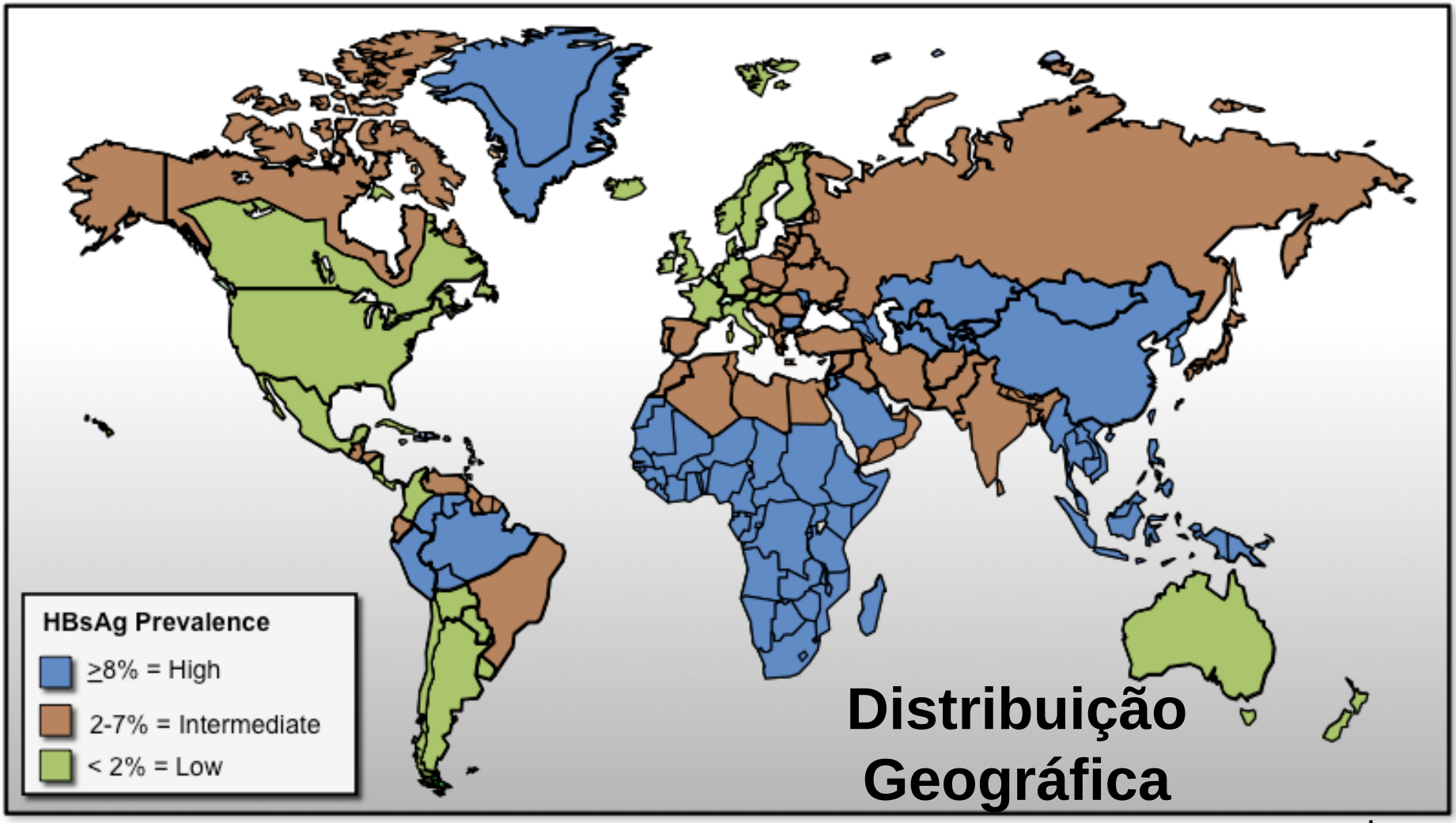
- Hepatite
- Cirrose
- Carcinoma hepatocelular

Hepatite B

Dez genótipos



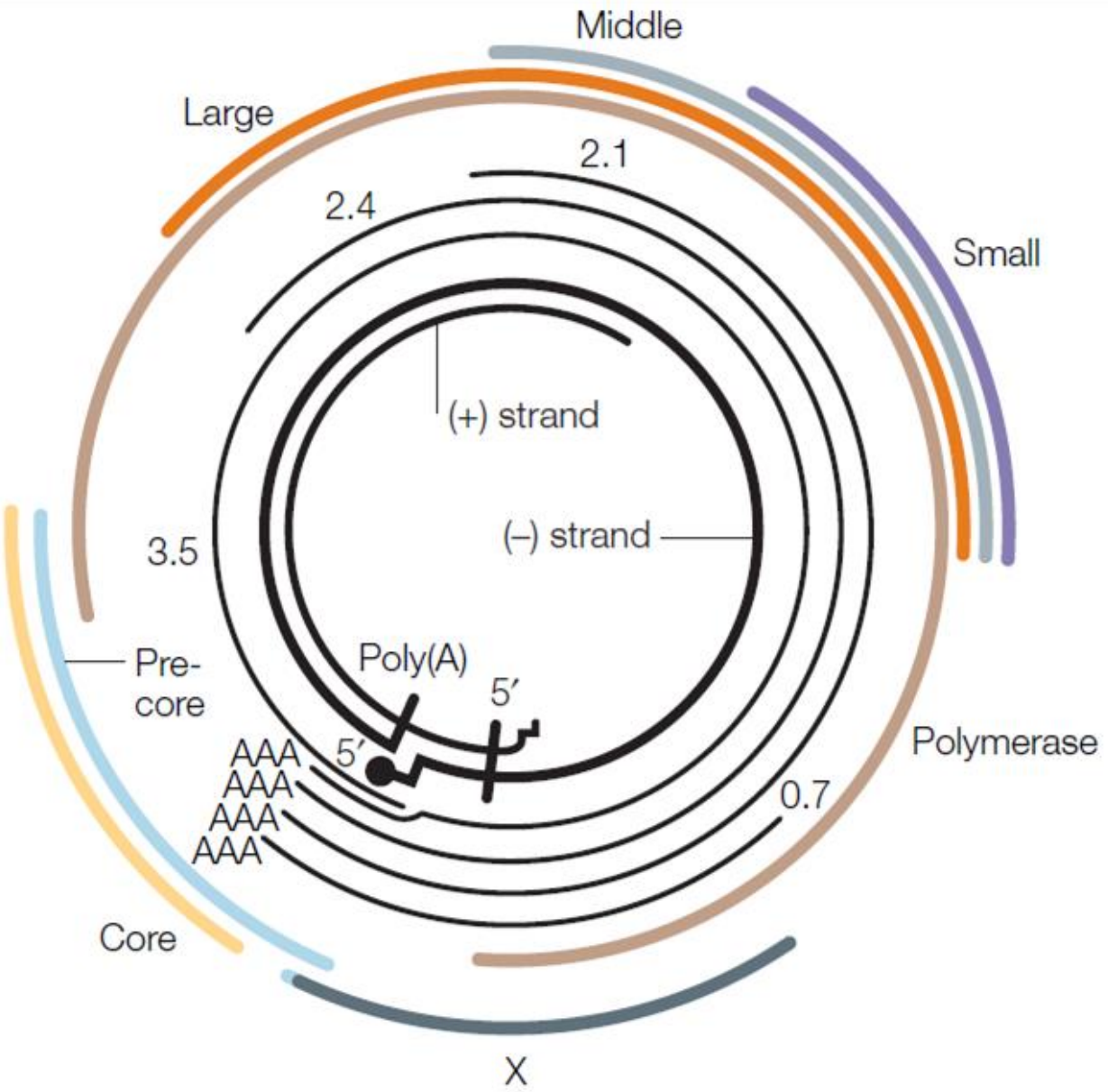
Hepatite B



www.cdc.gov

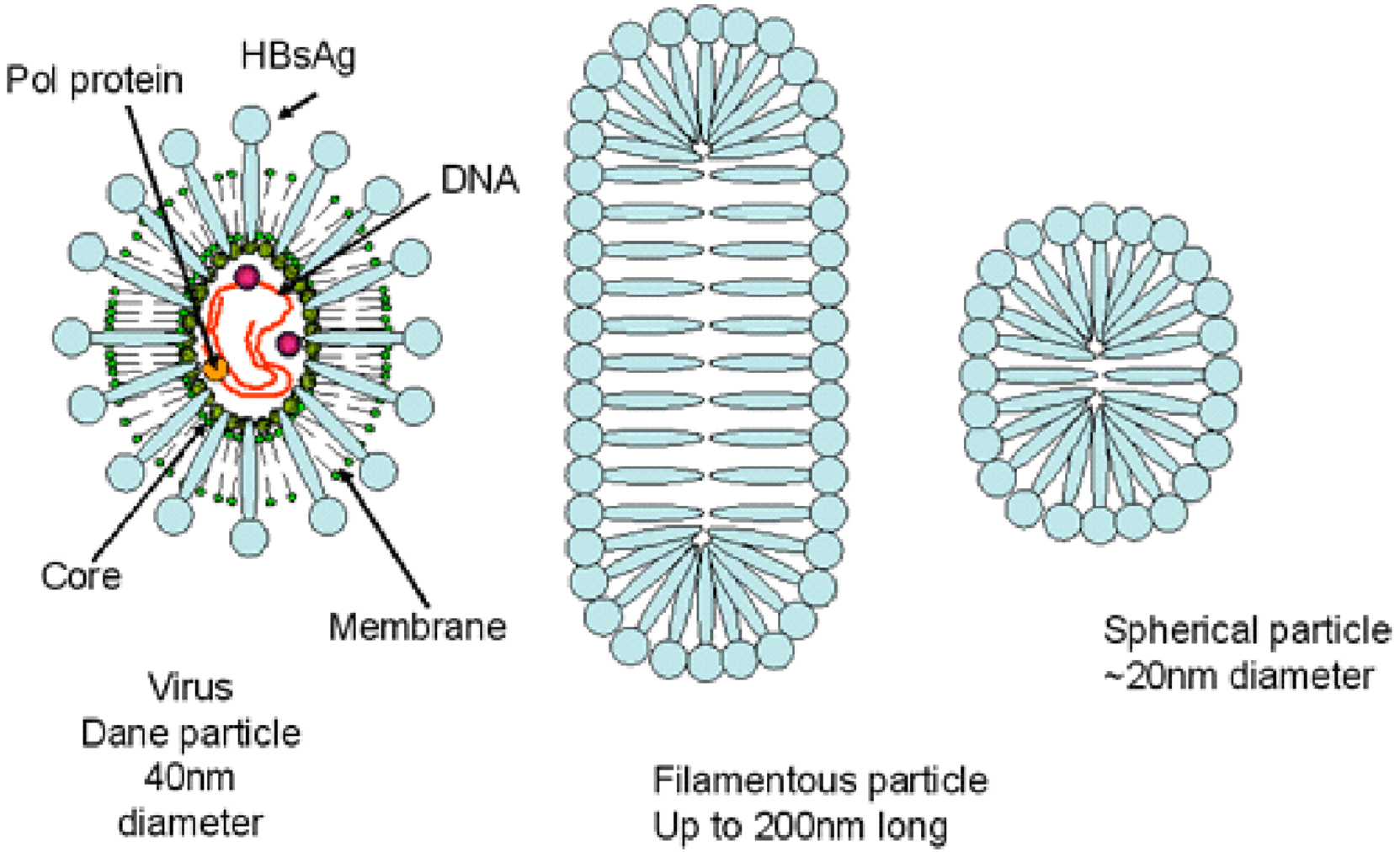
Hepatite B

Organização genômica



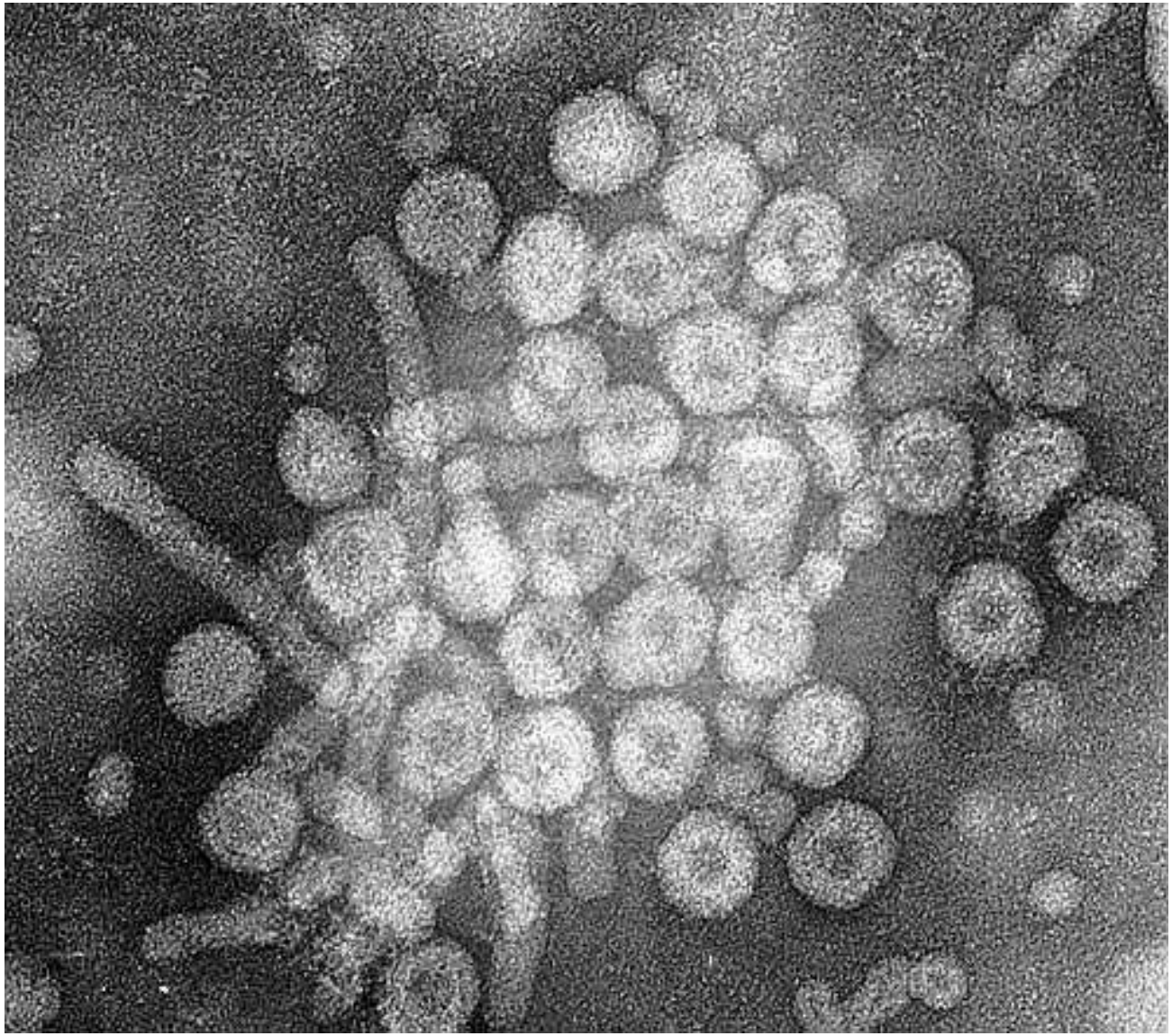
Hepatite B

Antígenos virais



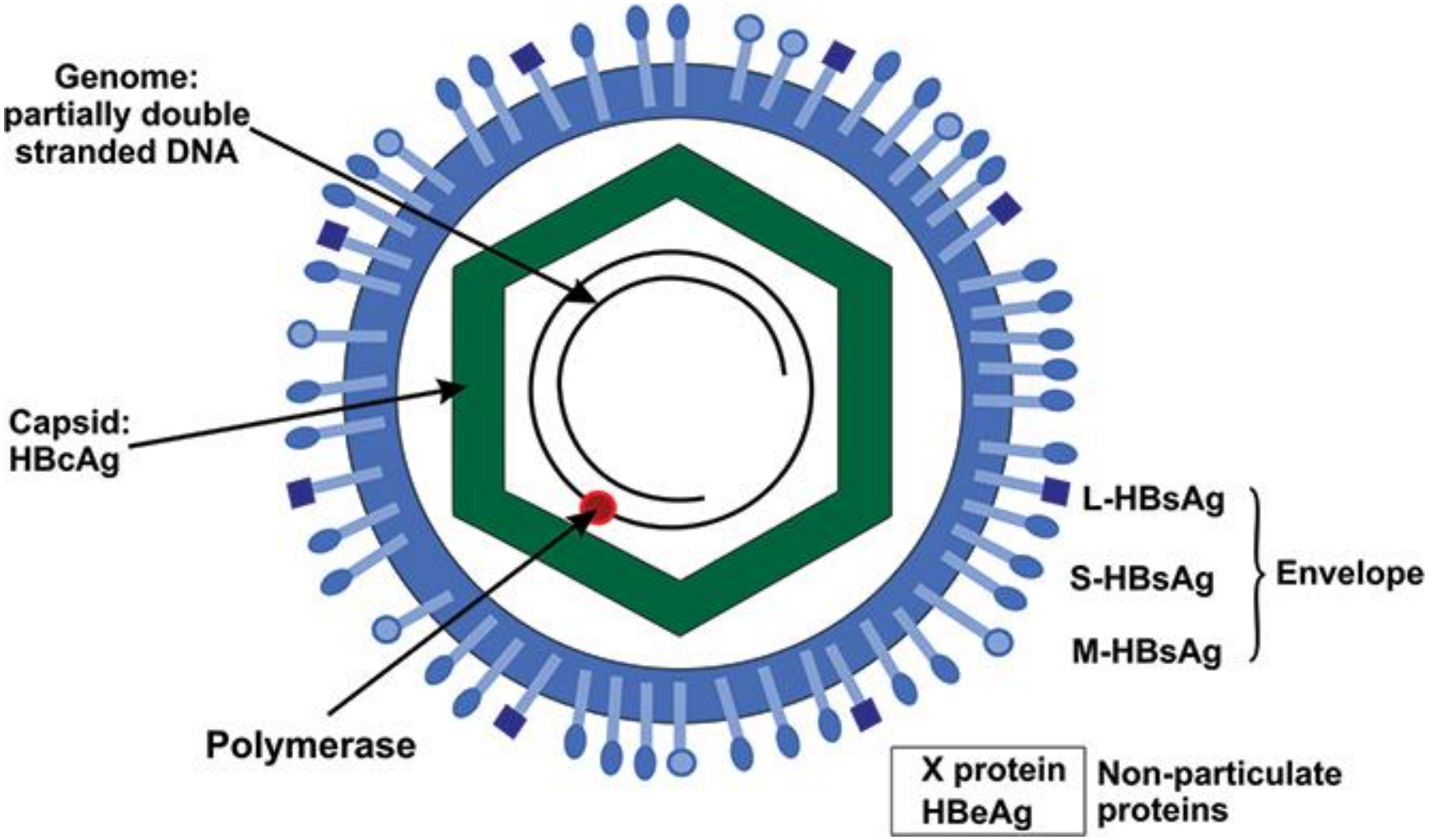
Hepatite B

Antígenos virais



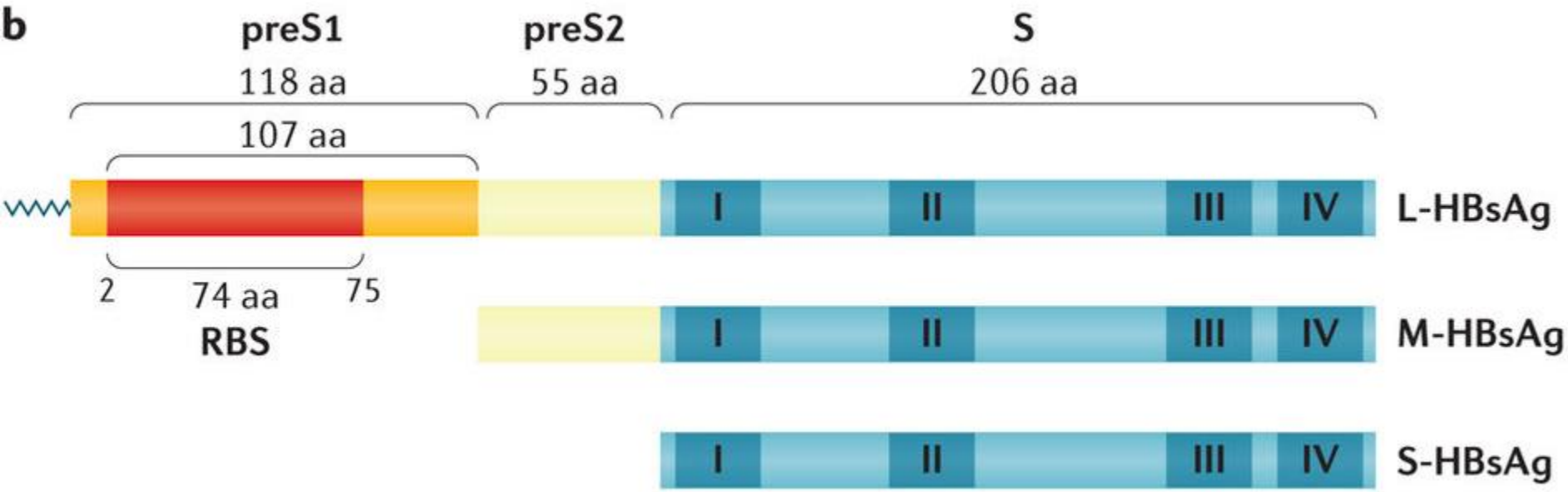
Hepatite B

Antígenos virais



Hepatite B

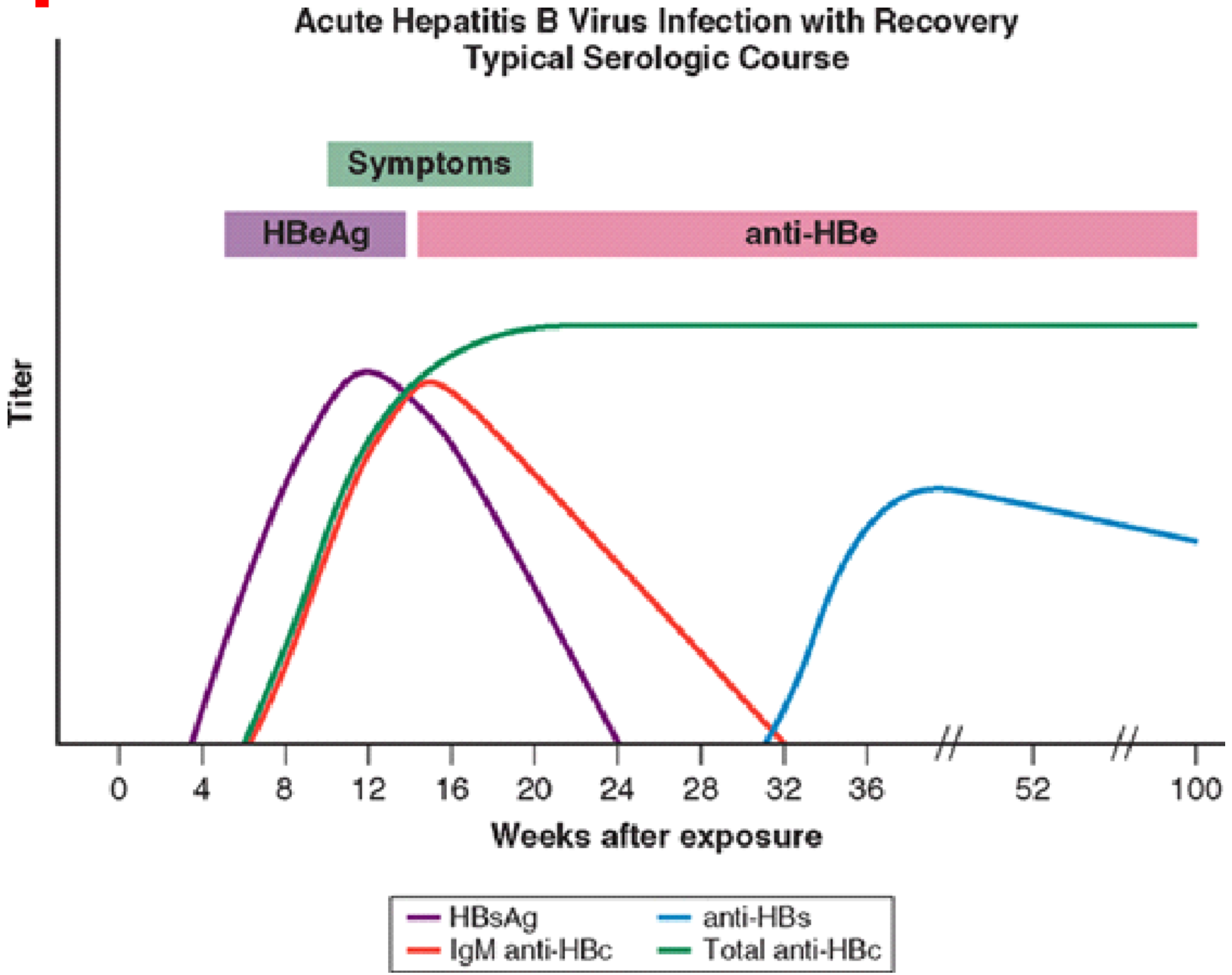
Antígenos virais



doi:10.1038/nrgastro.2016.126

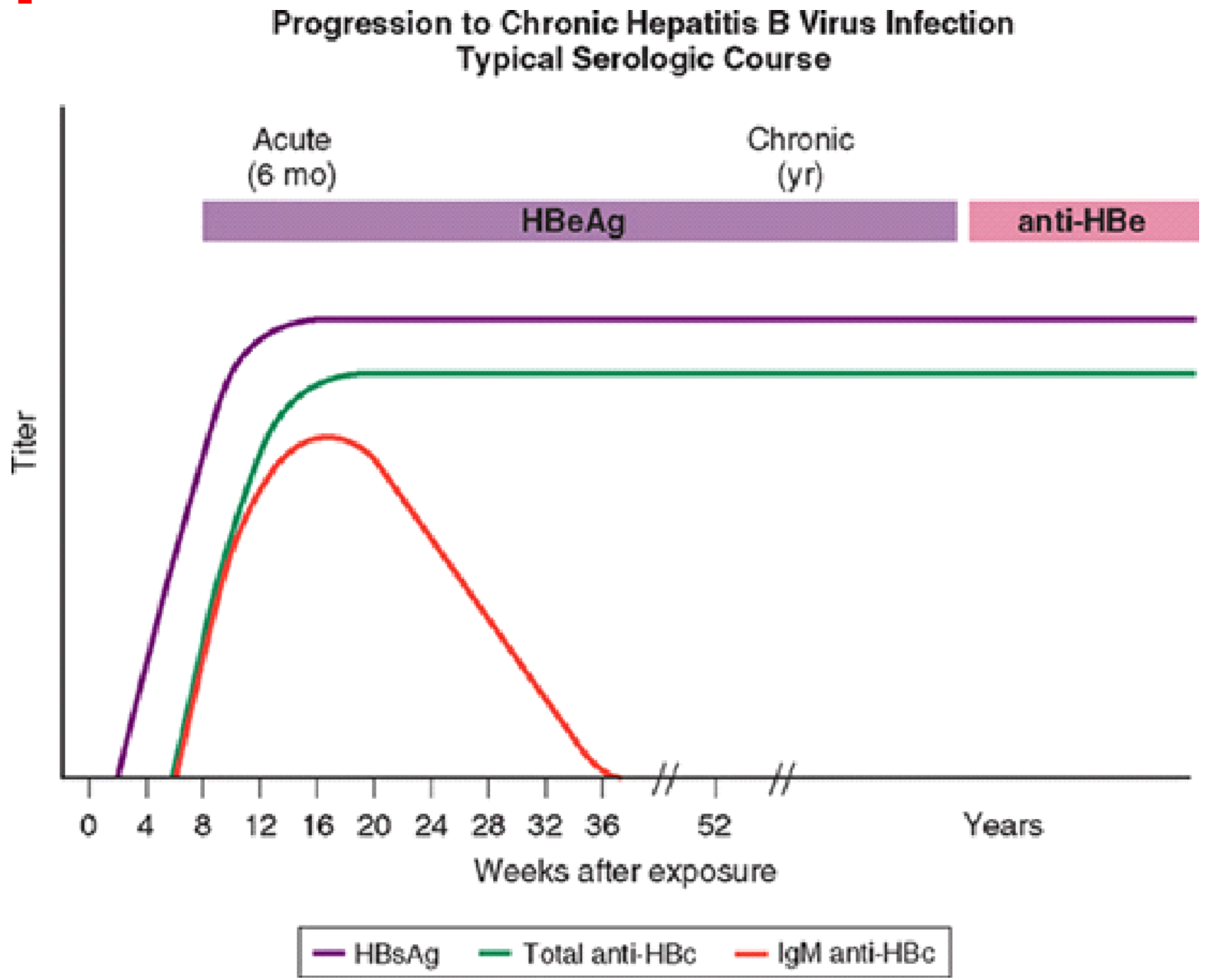
Hepatite B

Antígenos virais



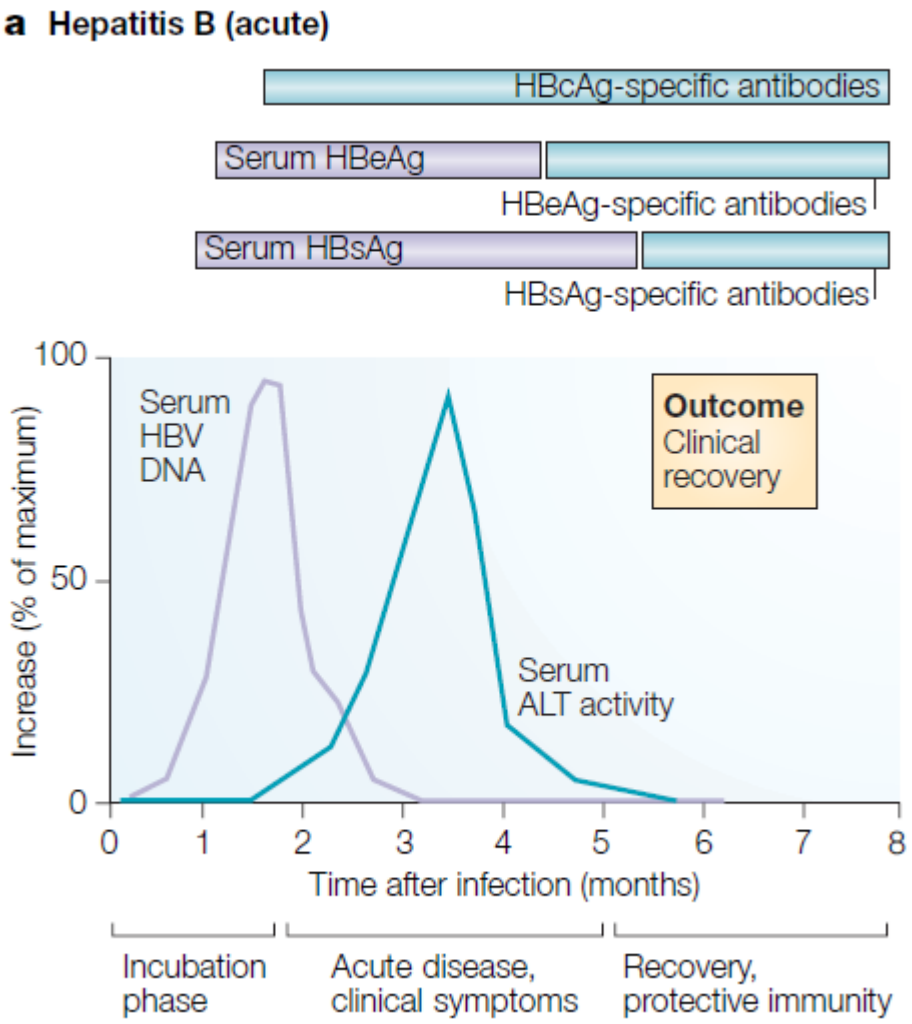
Hepatite B

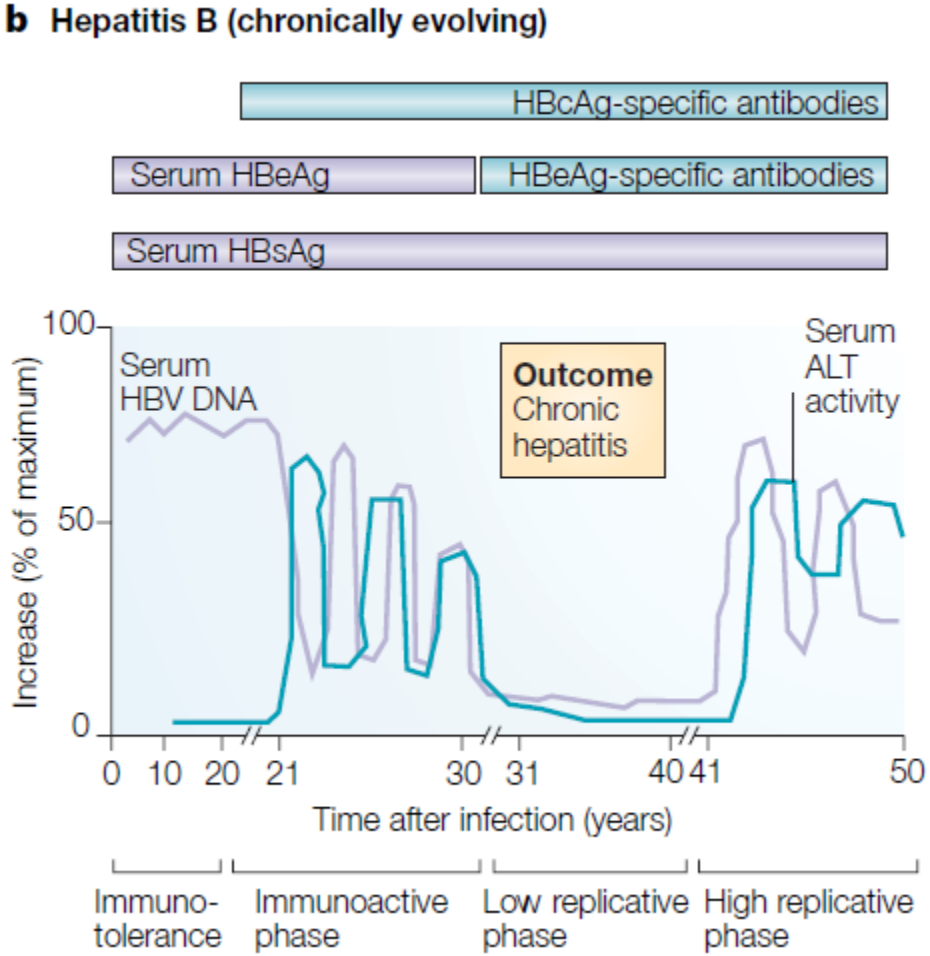
Antígenos virais



Hepatite B

Antígenos virais





Interpretation of Hepatitis B Serologic Tests

Tests	Results	Interpretation
HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible
HBsAg anti-HBc anti-HBs	Negative Negative Positive with ≥10mIU/mL*	Immune due to vaccination
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune due to natural infection
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative	Chronically infected
HBsAg anti-HBc anti-HBs	Negative Positive Negative	Four interpretations possible†

*Postvaccination testing, when it is recommended, should be performed 1-2 months following dose #3.

† 1. May be recovering from acute HBV infection.
2. May be distantly immune and the test is not sensitive enough to detect a very low level of anti-HBs in serum.
3. May be susceptible with a false positive anti-HBc.
4. May be chronically infected and have an undetectable level of HBsAg present in the serum.

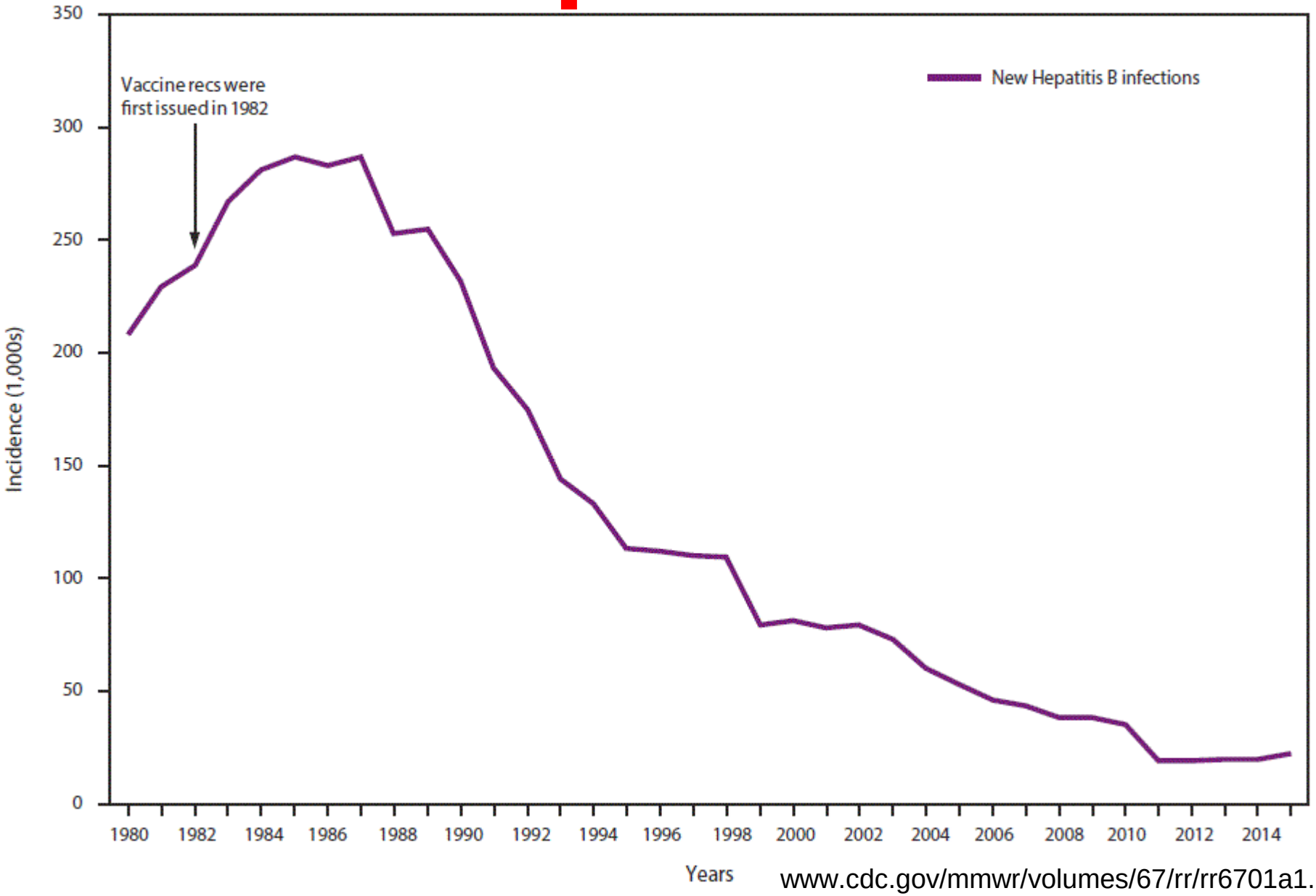
Hepatite B

1984 – Taiwan – prevalência de positividade para HBsAg passou 9.8% a 1.3% em 1994 em crianças <15 anos de idade.

1987 – Long'an – Incidência de CHC caiu 94.8% no grupo de 0-19 anos de idade. A incidência média na população geral passou de 48/100000 (1969 – 1988) a 28/100000 (1996 – 2002).

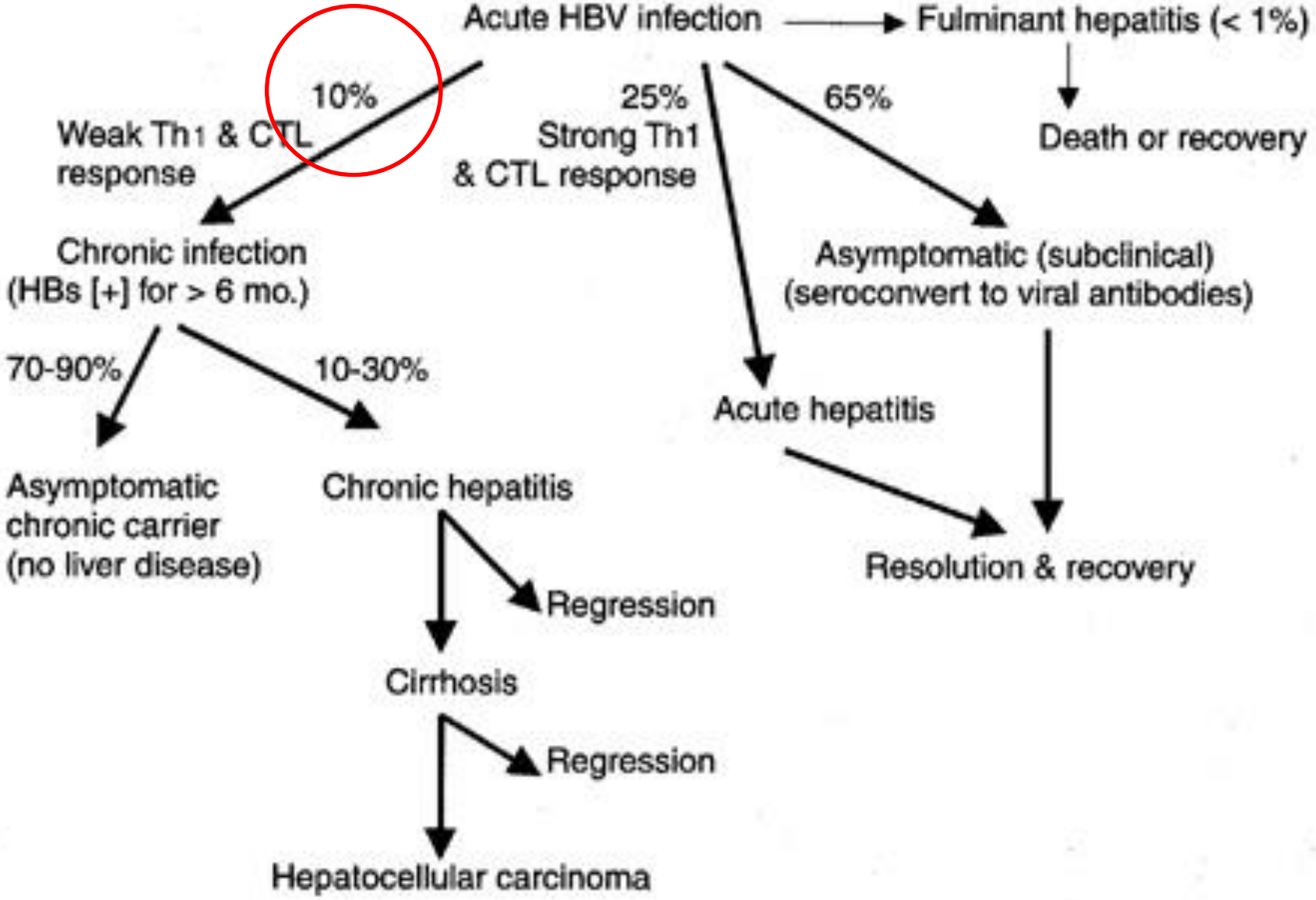
Hou et al., *Int J Med Sci* 2005; 2:50-57

Hepatite B



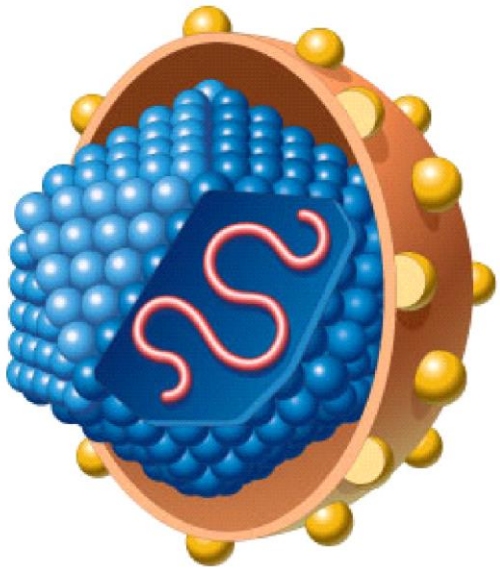
www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm

Hepatite B


Acute HBV infection
Fulminant hepatitis (< 1%)
Death or recovery
10%
Weak Th1 & CTL response
25%
Strong Th1 & CTL response
65%
Chronic infection (HBs [+] for > 6 mo.)
Asymptomatic (subclinical) (seroconvert to viral antibodies)
70-90%
10-30%
Acute hepatitis
Asymptomatic chronic carrier (no liver disease)
Chronic hepatitis
Resolution & recovery
Regression
Cirrhosis
Regression
Hepatocellular carcinoma

Hepatite C (HCV)

Hepatite C



Familia : *Flaviviridae*
Gênero: *Hepacivírus*

Vírus pequenos de RNA envelopados (~45 nm)

RNA linear simples-fita (~9,4 kpb)

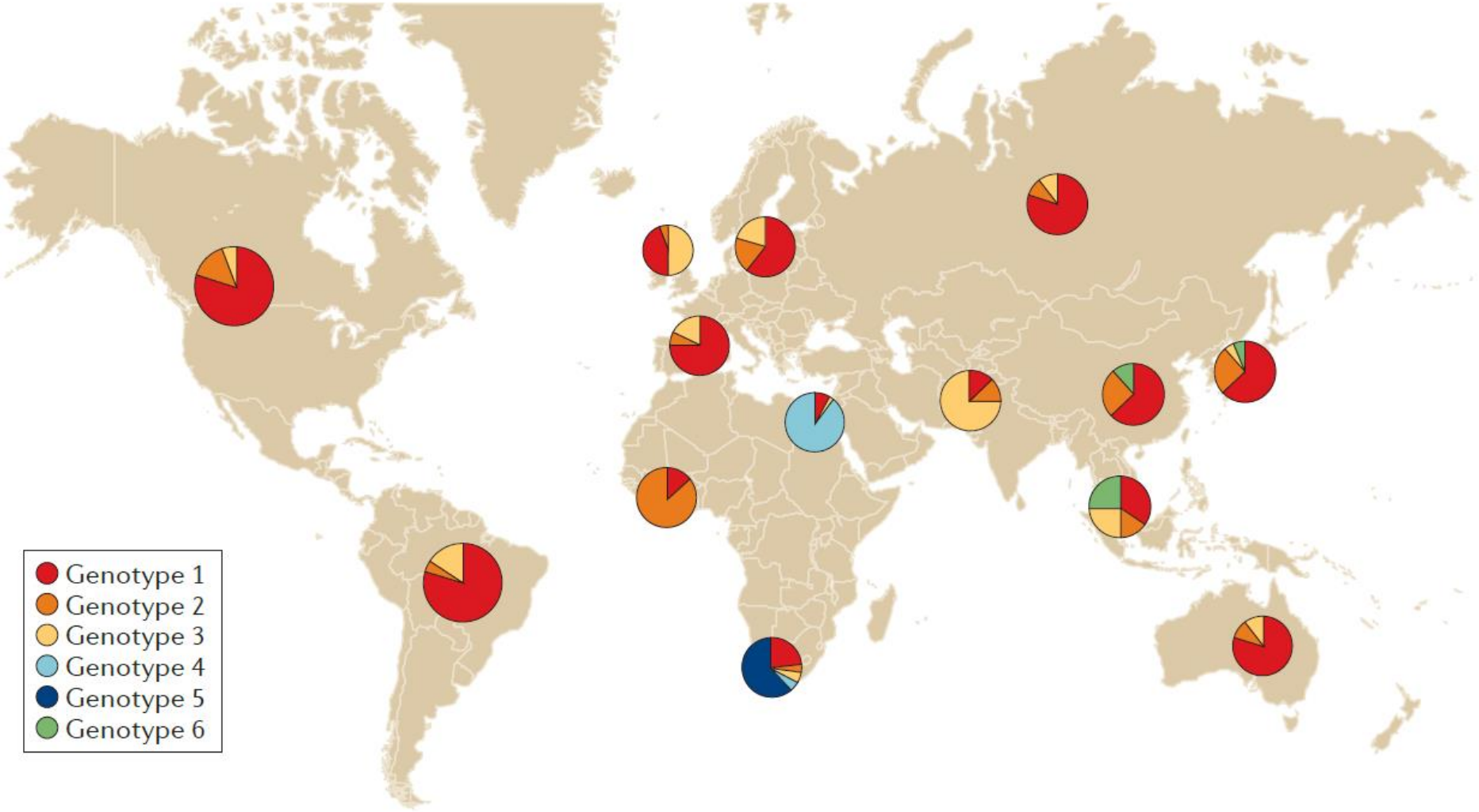
Célular alvo: hepatócitos

Etiologicamente associado com:

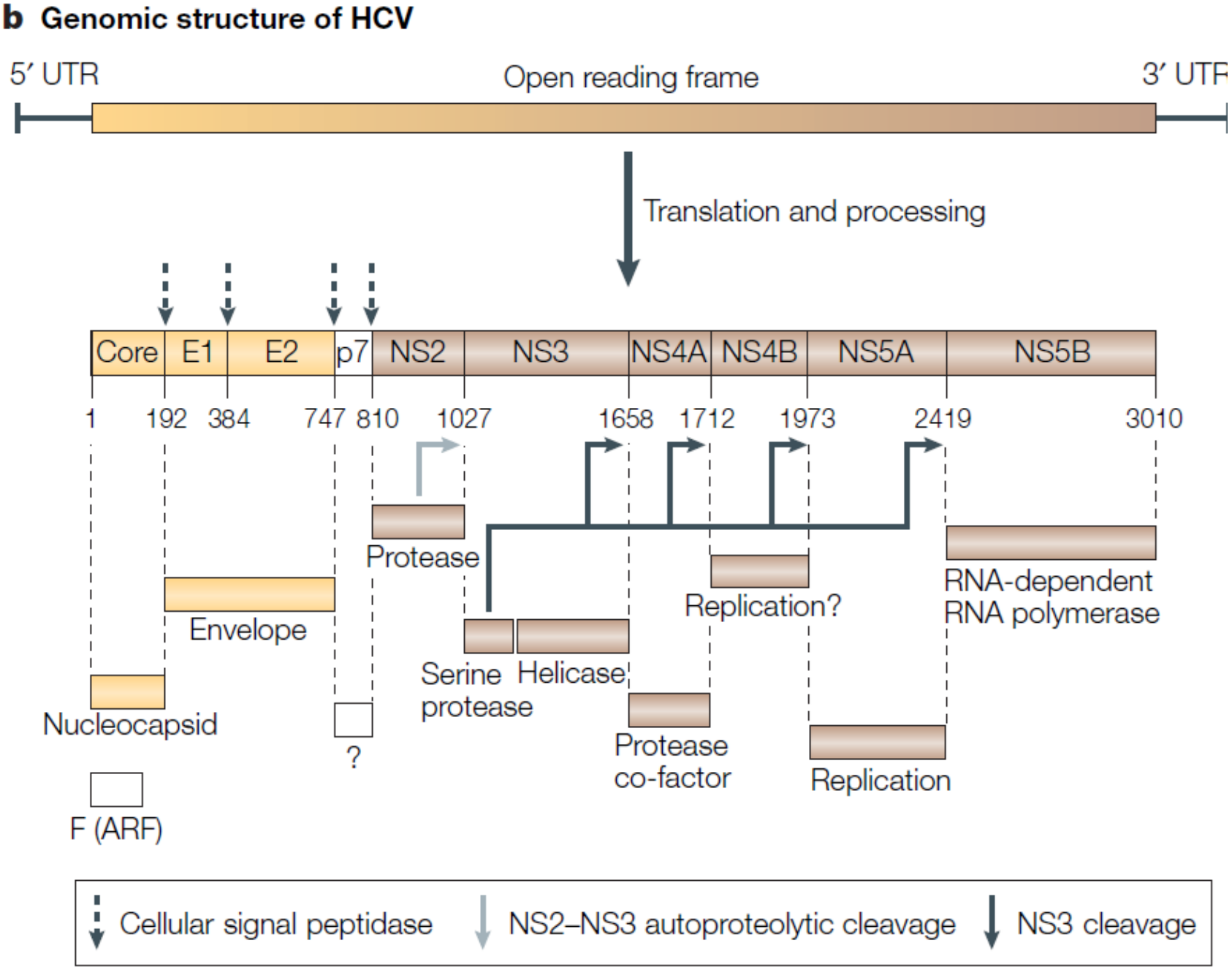
- Hepatite
- Cirrose
- Carcinoma hepatocelular

Hepatite C

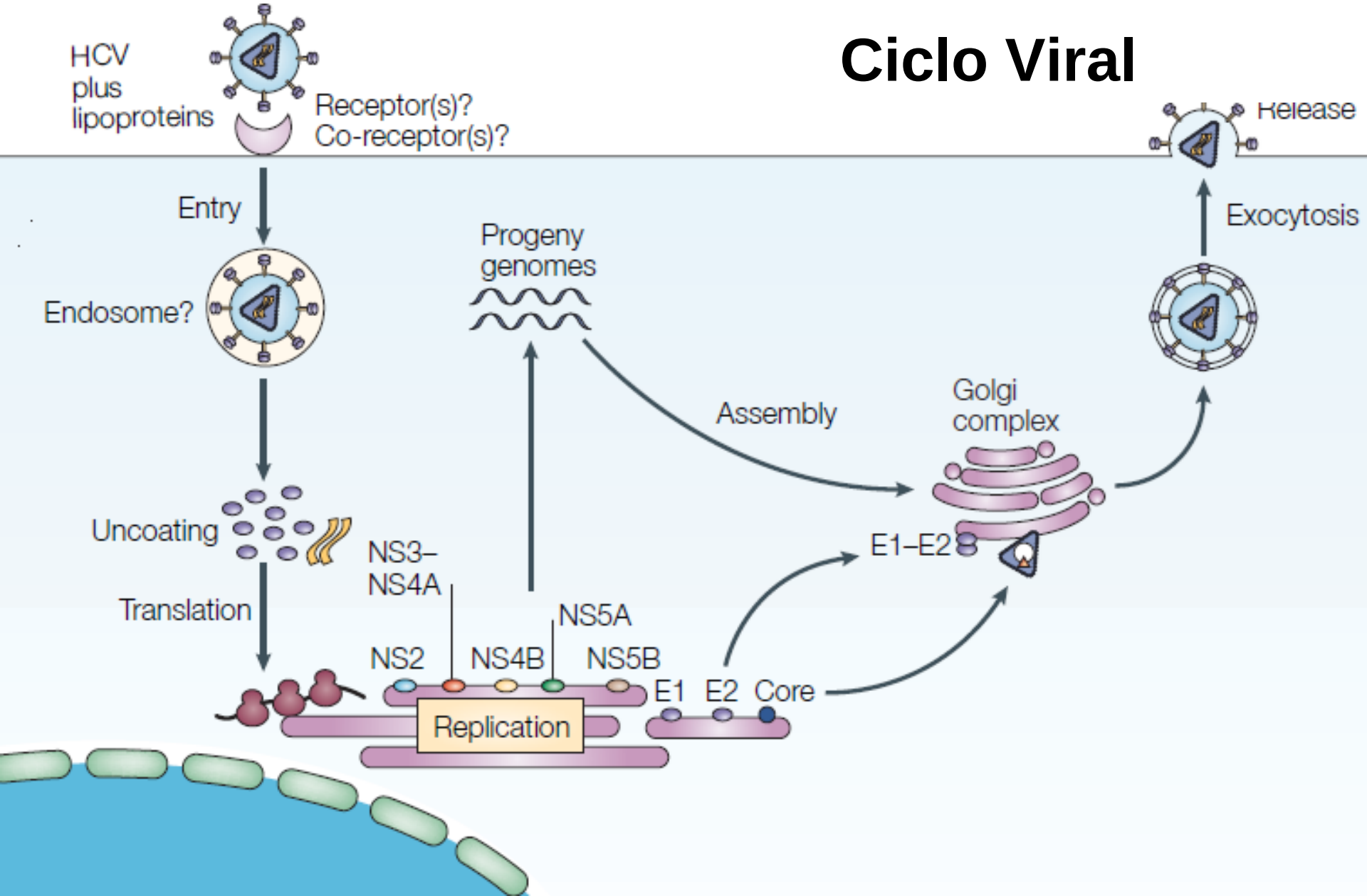
~71 milhões de portadores no Mundo todo



Vírus da Hepatite C

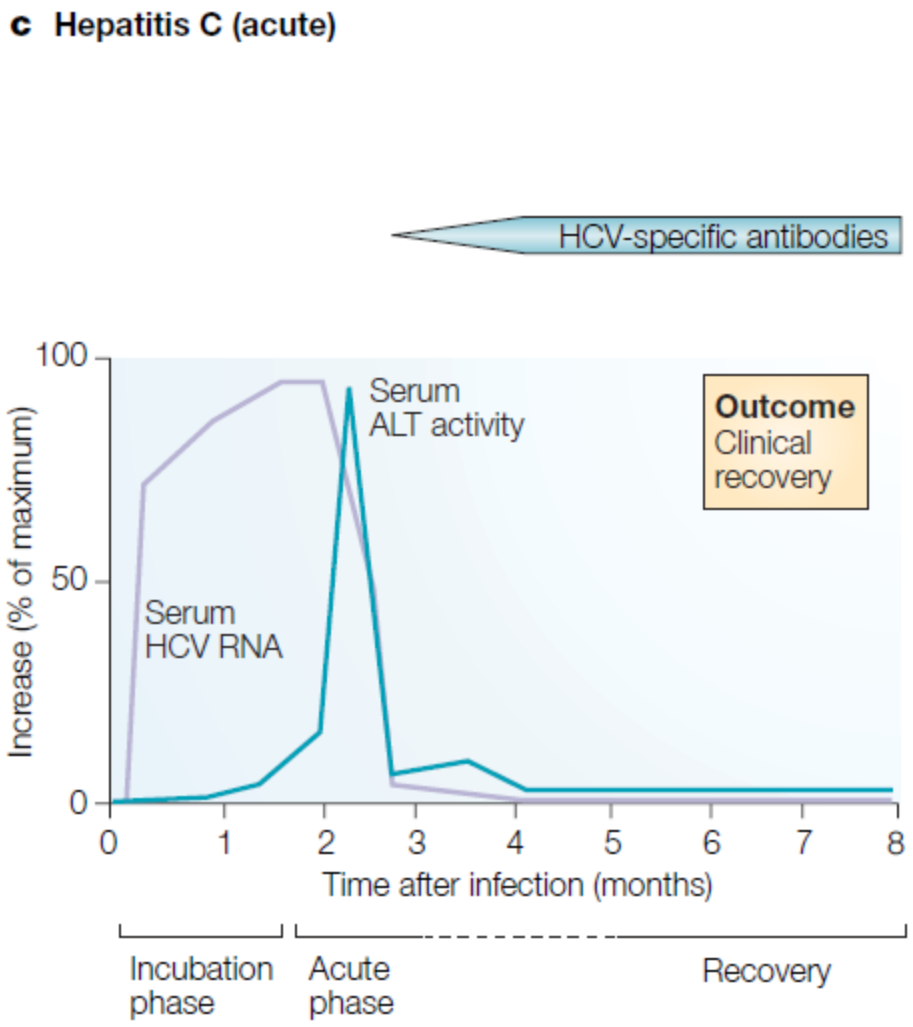


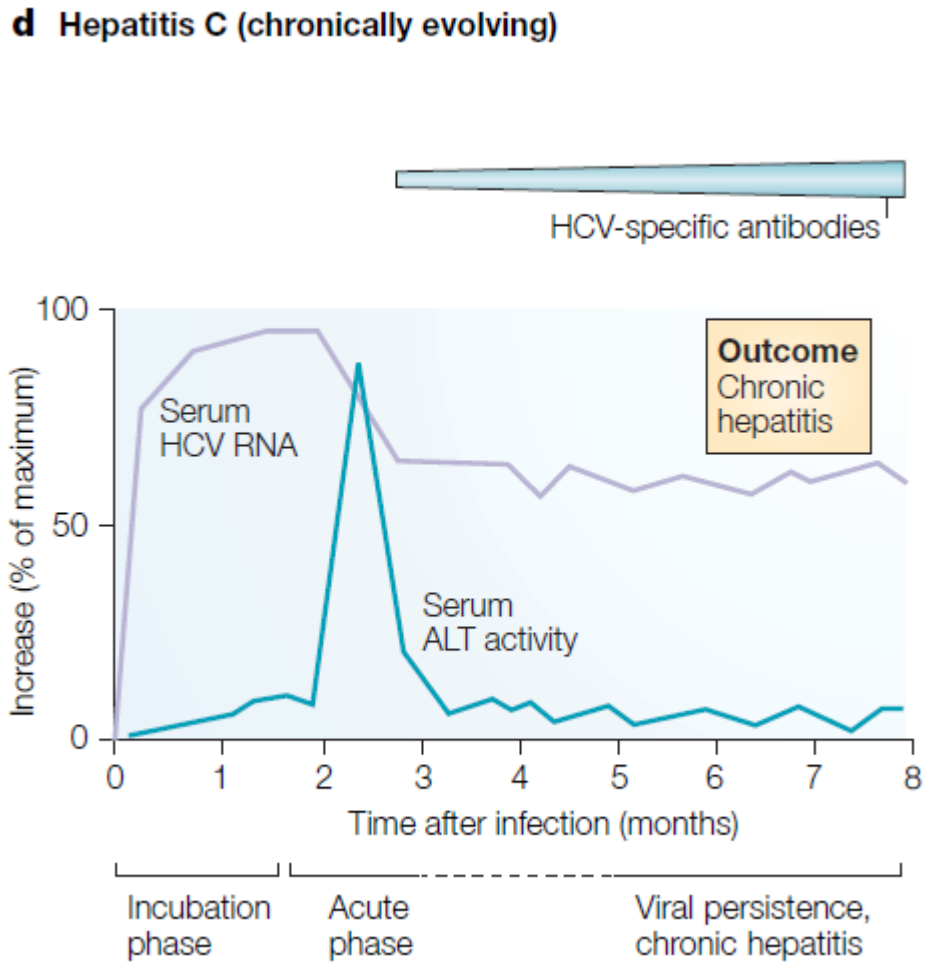
Vírus da Hepatite C



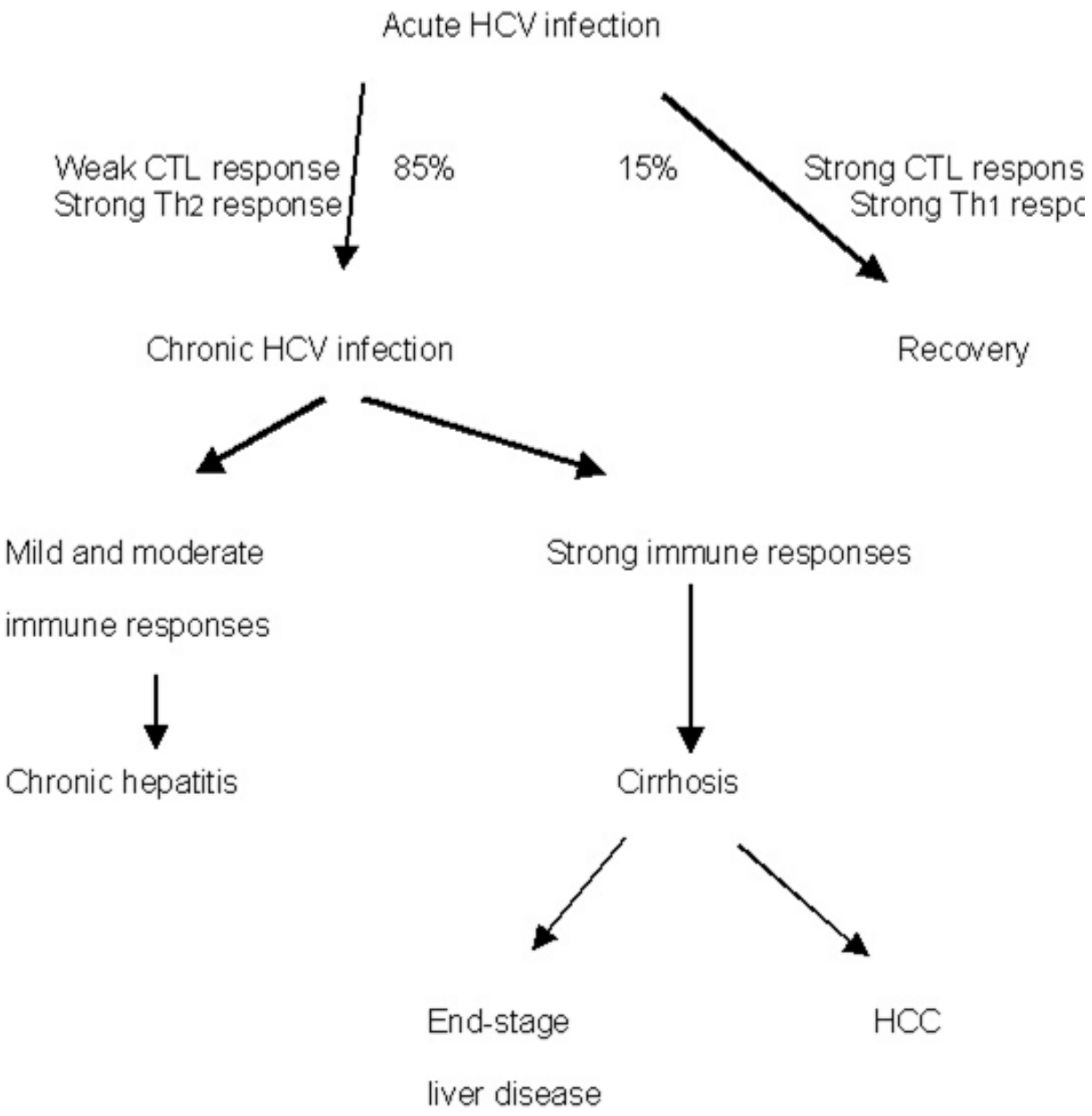
Vírus da Hepatite C

Antígenos virais

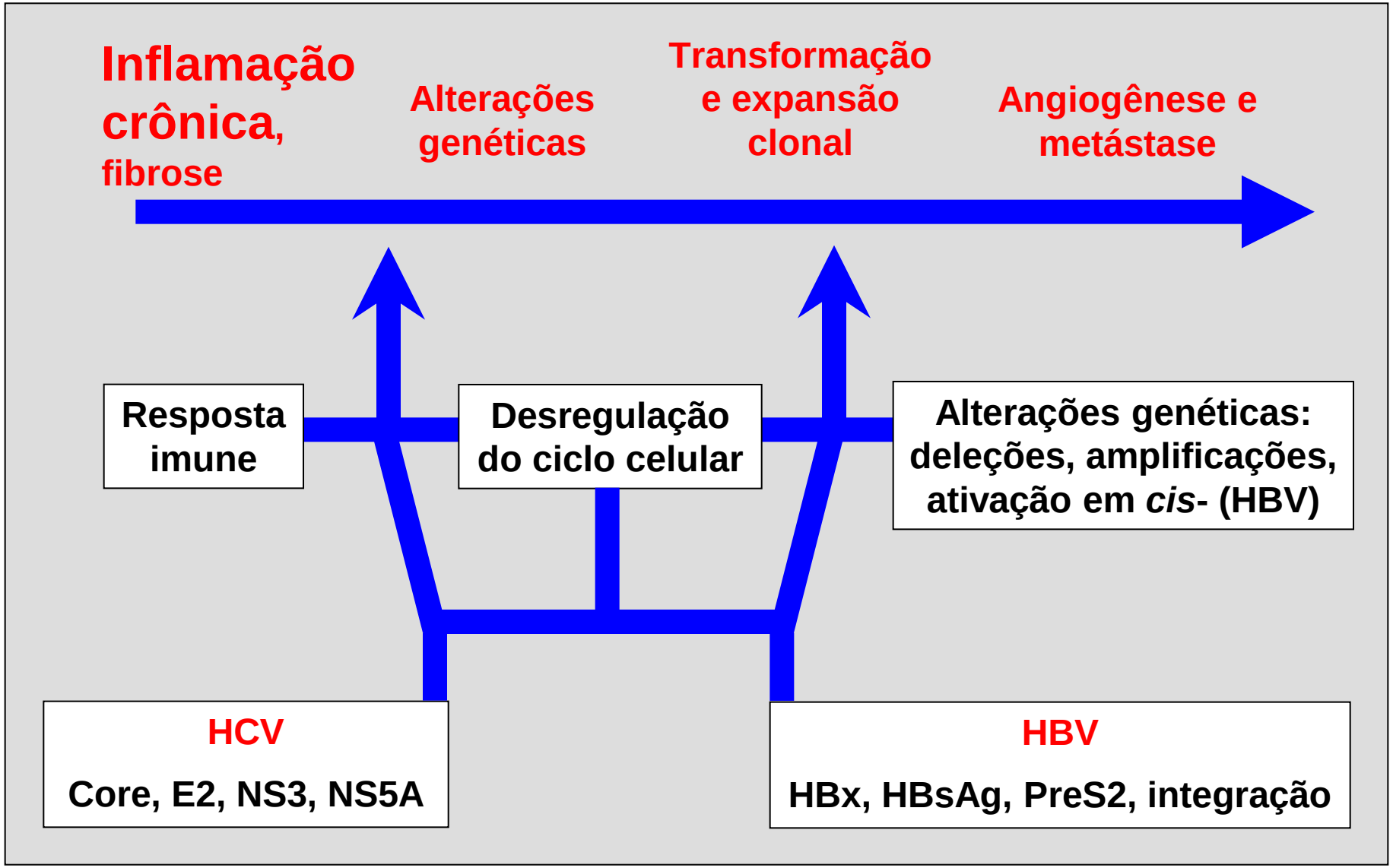




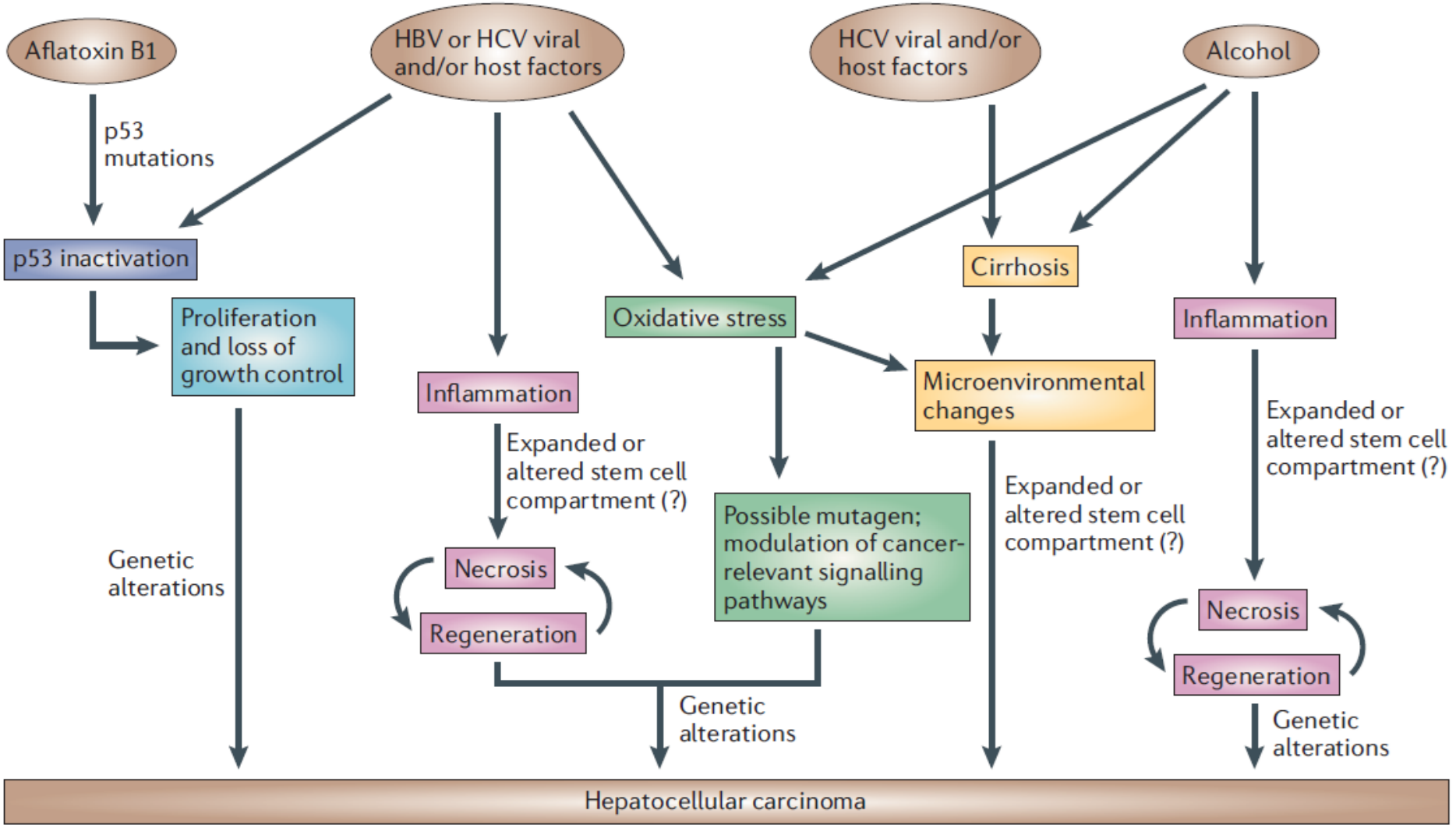
Vírus da Hepatite C



Transformação celular por HBV e HCV



HCC: Co-fatores

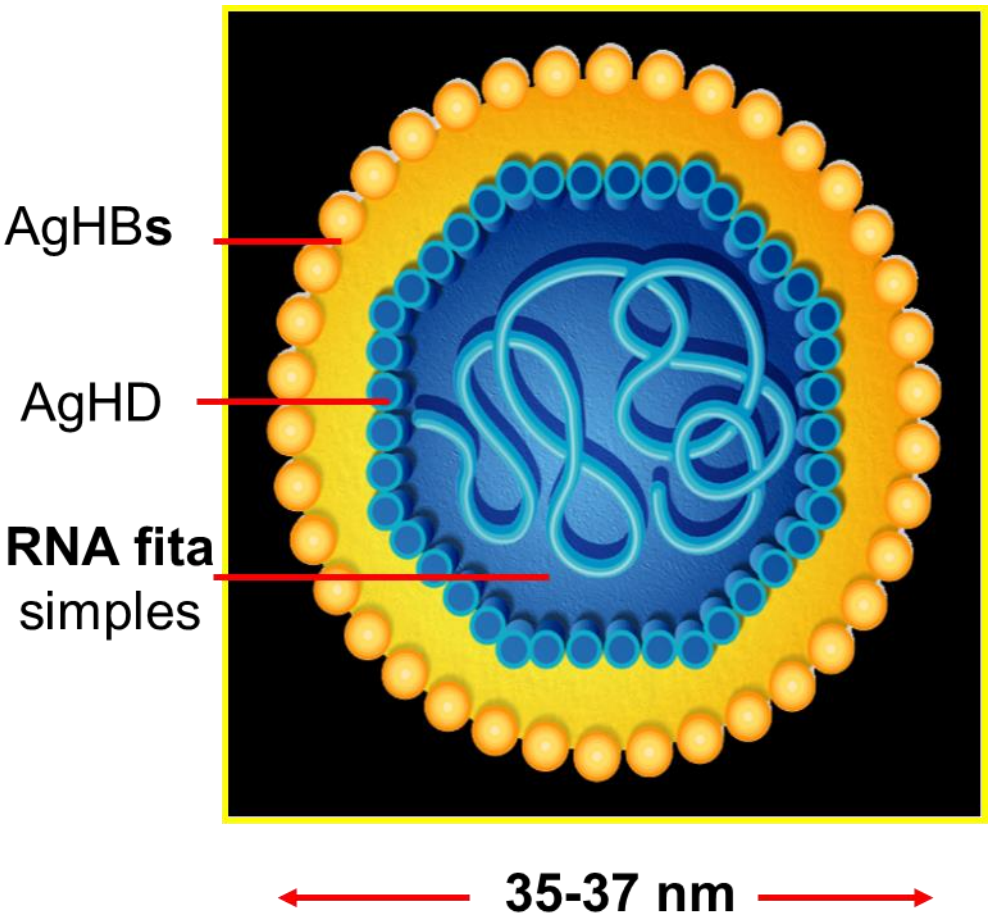


Hepatite Delta (HDV)

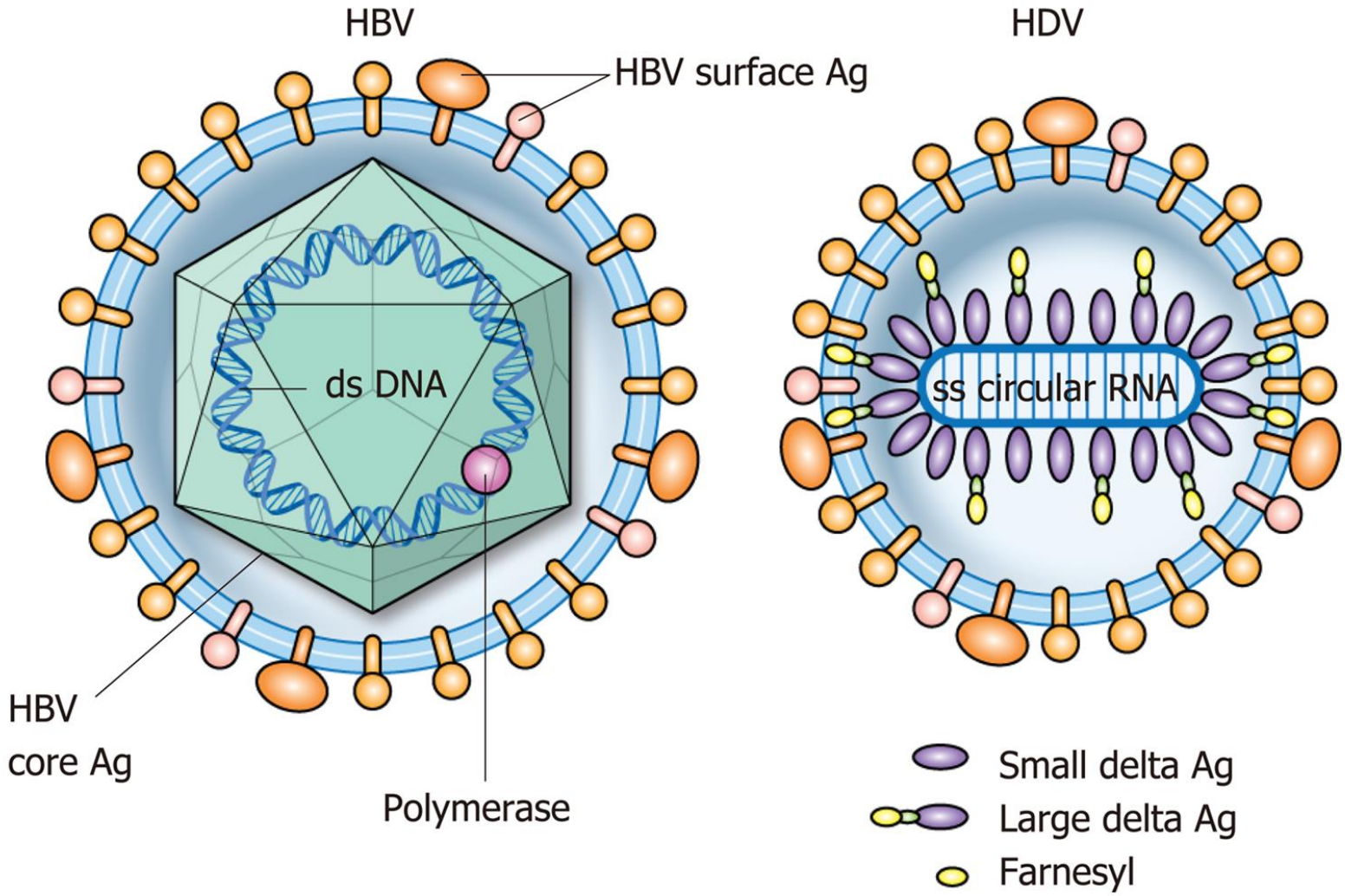
Hepatite D

- Similar a viróides de plantas
- codifica proteínas (S-HDAg/replicação e L-HDAg/montagem)
- RNA com 1,7Kb, circular, negativo, dobrado sobre si mesmo
- Infecção concomitante com HBV, mas com multiplicação independente
- Citopático, 3 genótipos
- Antígeno + RNA envelopado por capsídeo codificada por HBsAg

Hepatite D

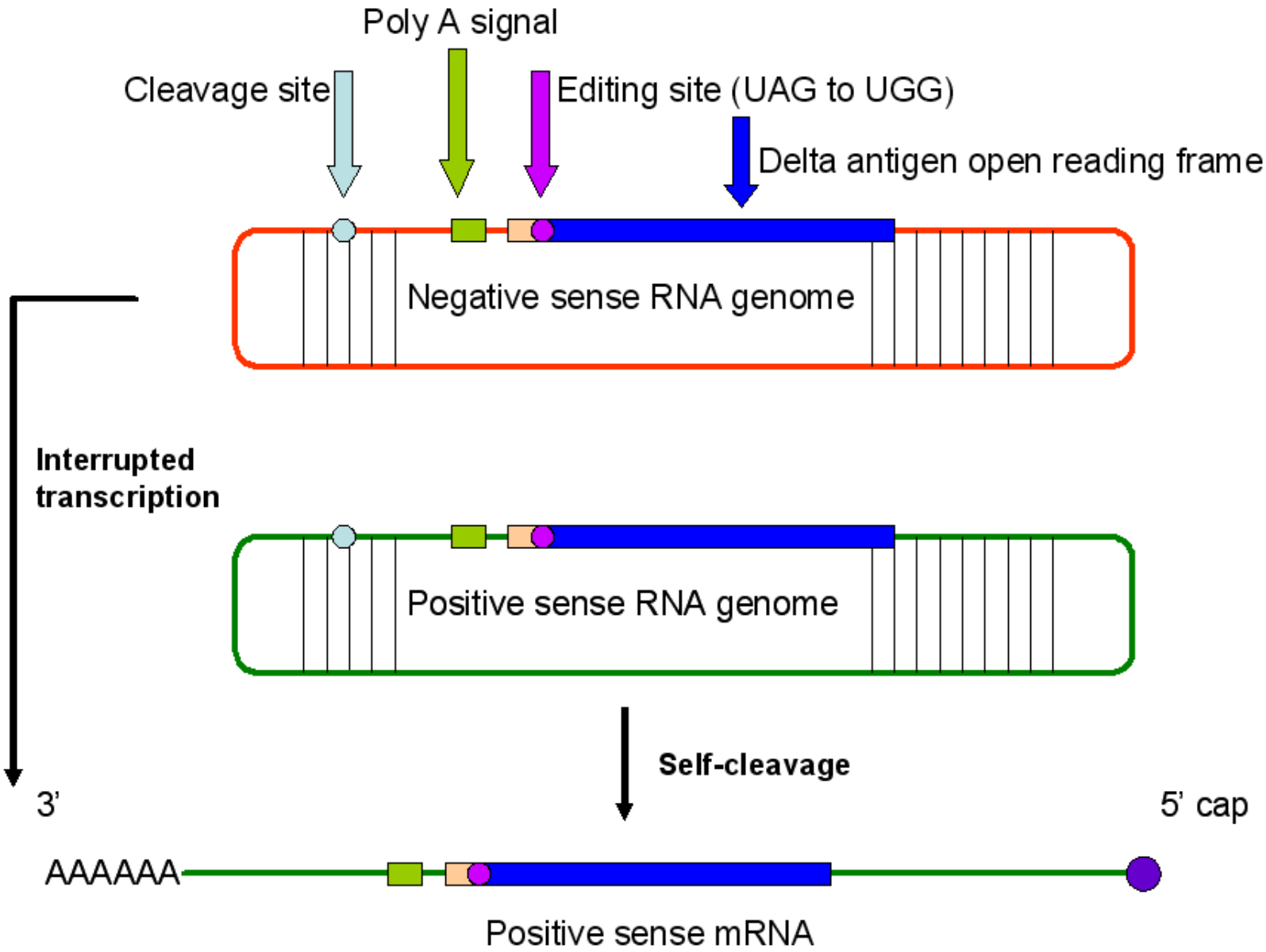


Hepatite D


HBV
HBV surface Ag
ds DNA
HBV
core Ag
Polymerase
HDV
ss circular RNA
Small delta Ag
Large delta Ag
Farnesyl

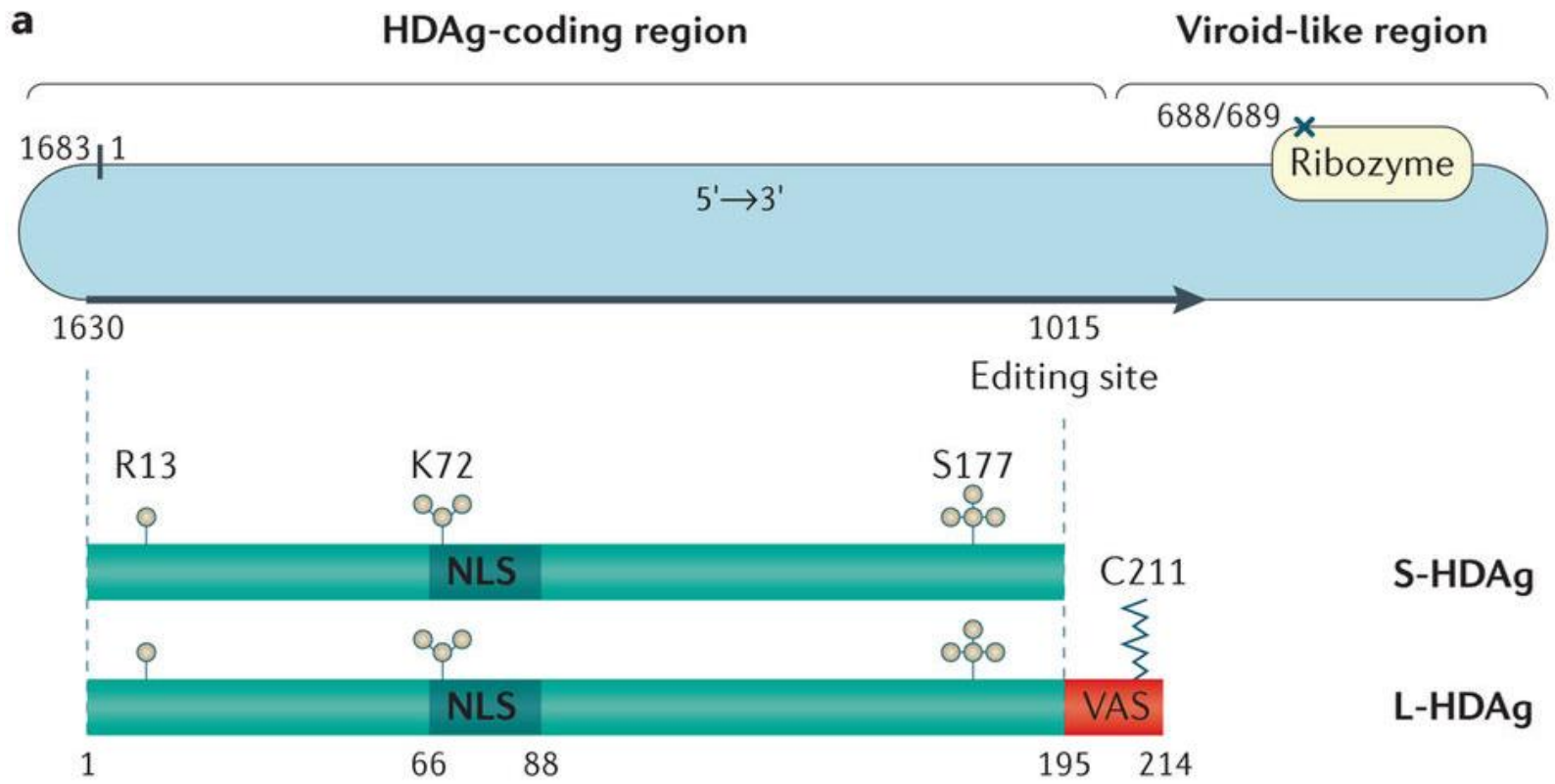
Hepatite D

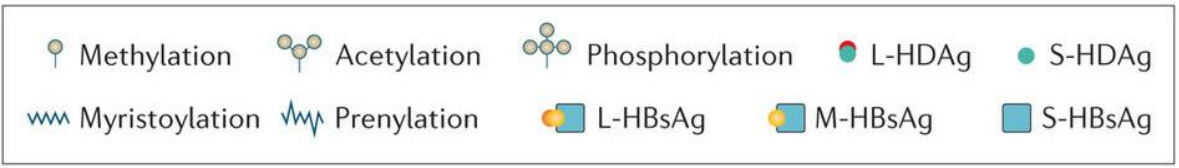
Organização genômica



Hepatite D

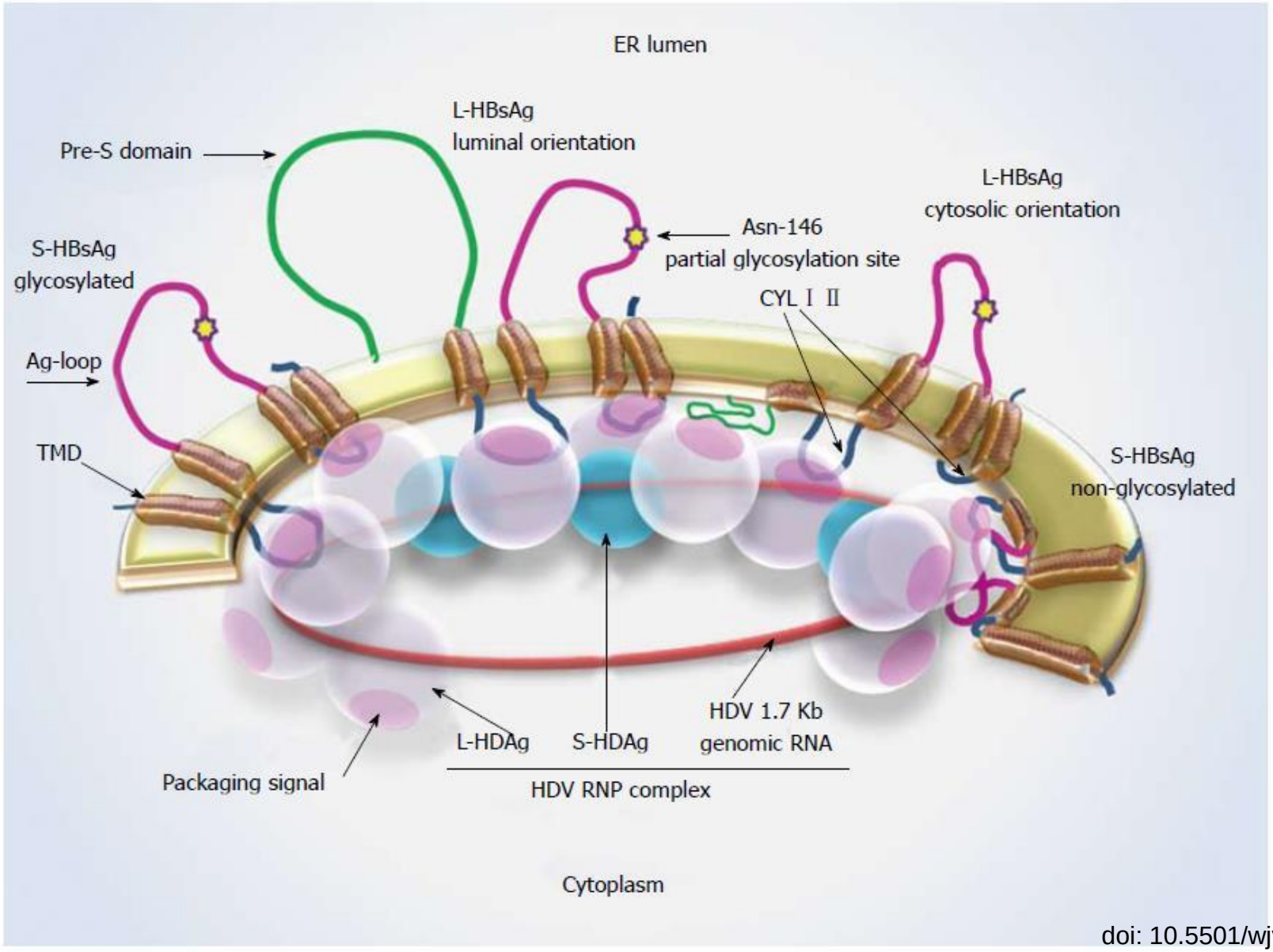
Organização genômica





doi:10.1038/nrgastro.2016.126

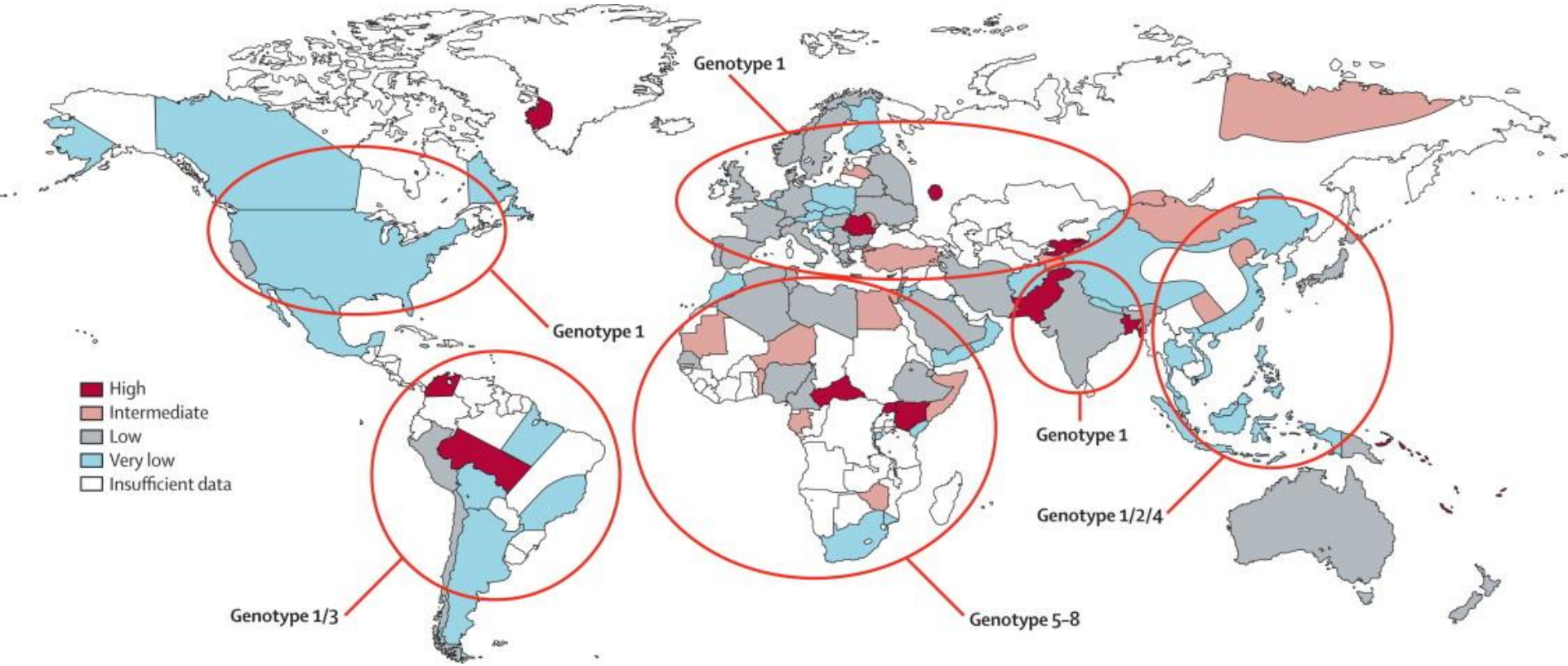
Hepatite D



doi: 10.5501/wjv.v4.i2.36

Hepatite D

Oito genótipos



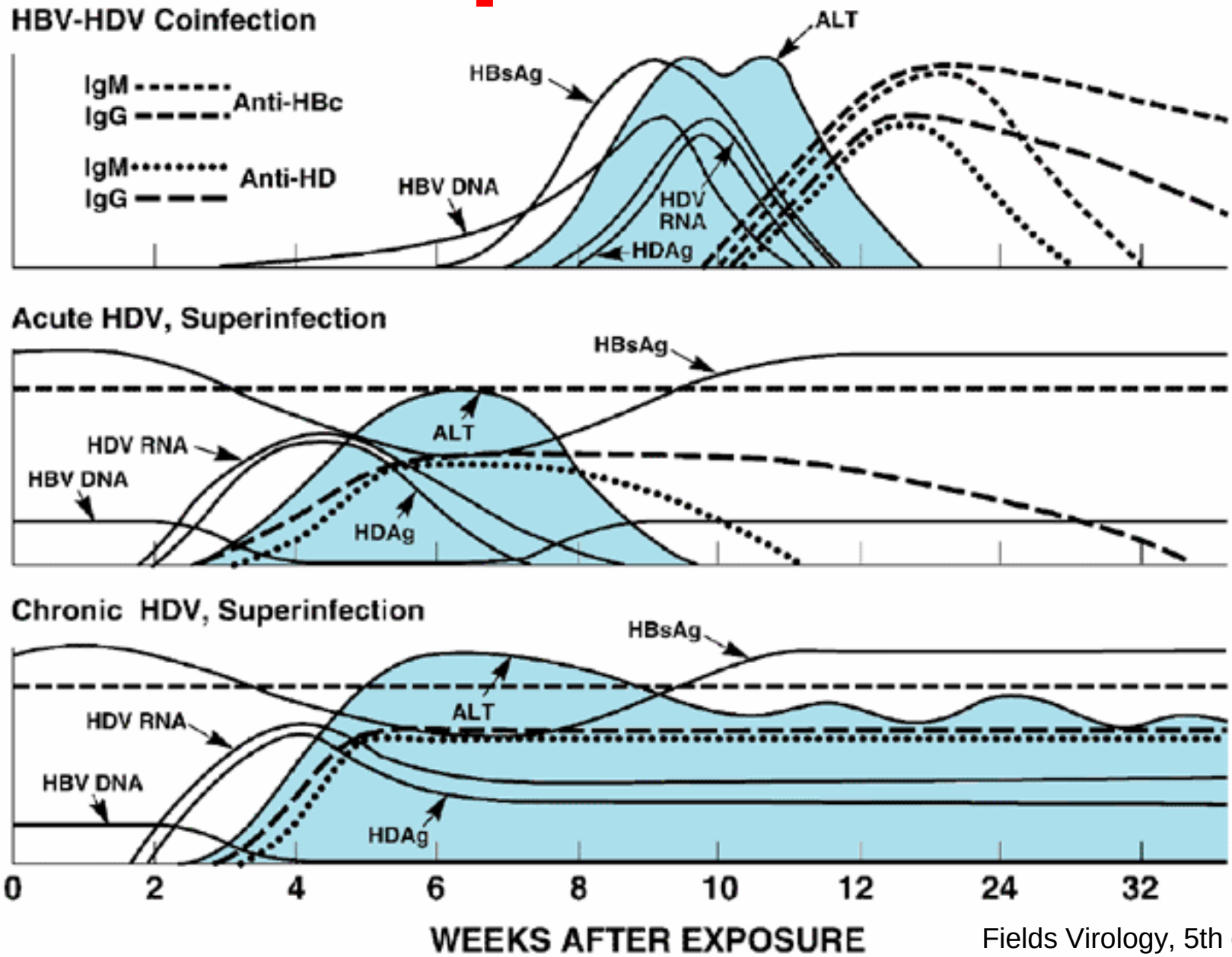
Hepatite D

Características clínicas

- Co-infecção
  - Doença aguda severa - hepatite fulminante
  - Baixo risco de infecção crônica

- Super-infecção
  - Geralmente desenvolve infecção crônica por HDV
  - Alto risco de doença crônica grave

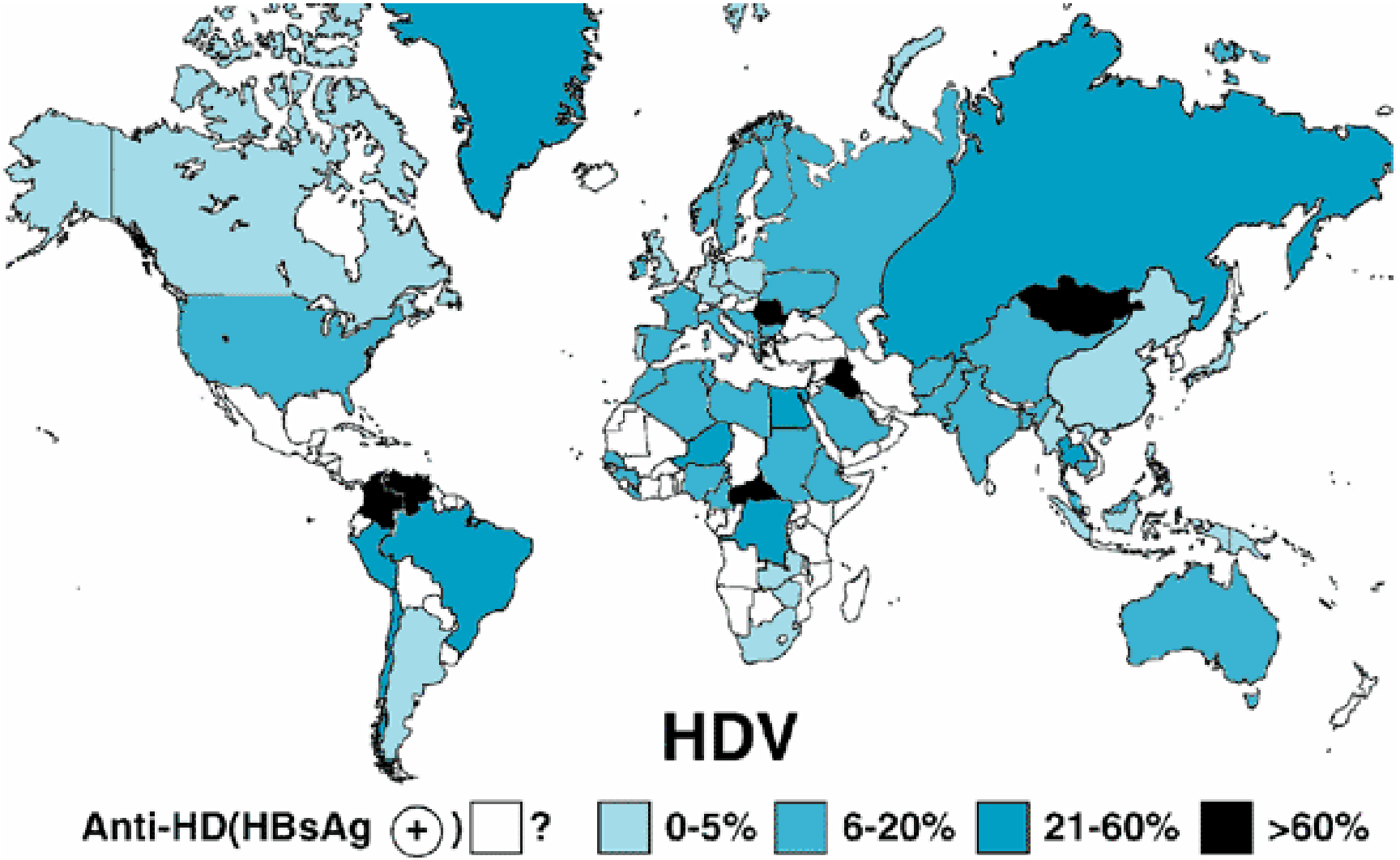
Hepatite D



Fields Virology, 5th ed

Hepatite D

Prevalência de anti-HD em indivíduos positivos para HBsAg



Fields Virology, 5th ed

Hepatite D

Diagnóstico Laboratorial

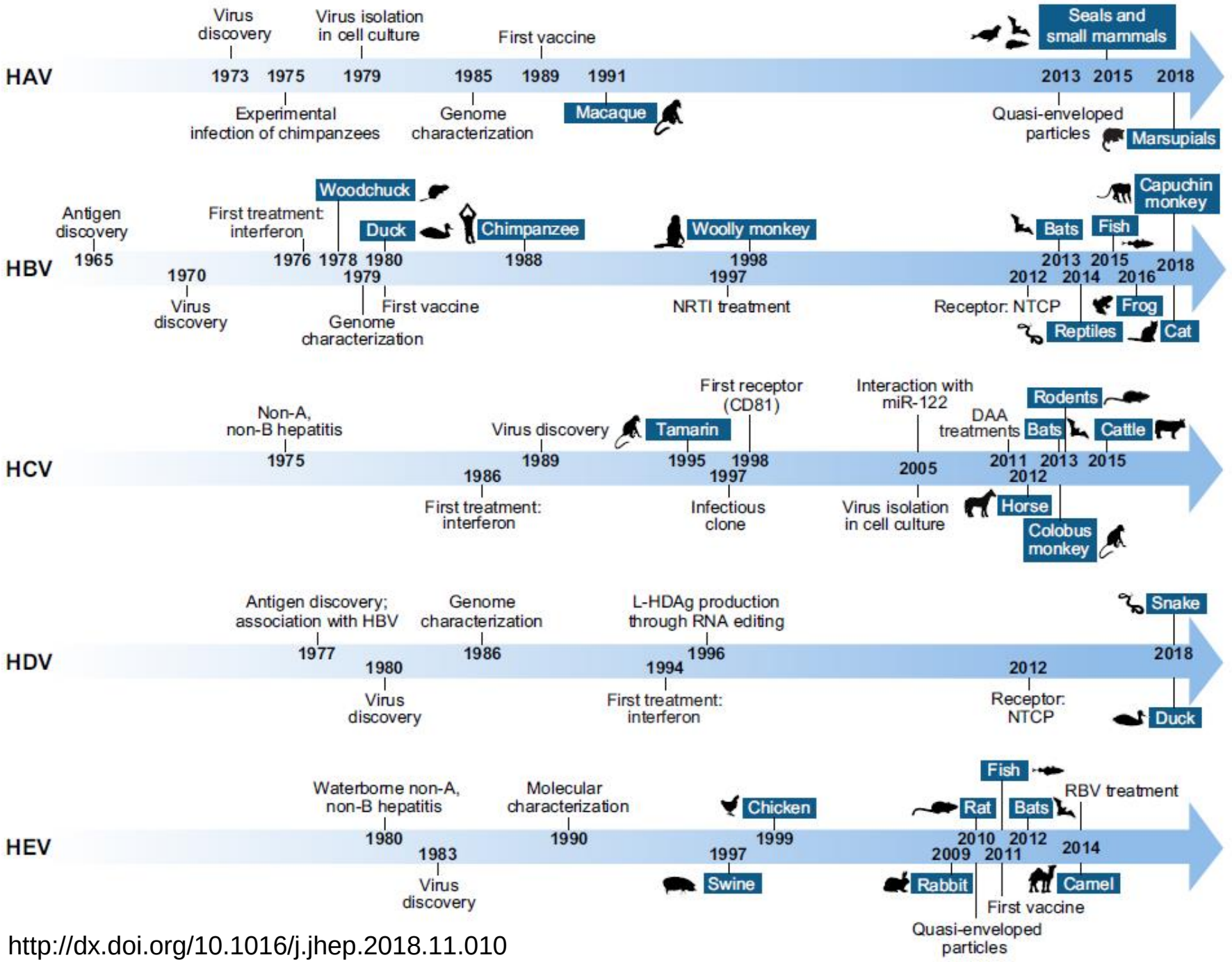
- Marcador Sorológico:
  - VHB (Ag e Ac)
  - Anti-VHD IgM
  - Anti-VHD IgG
- Marcador Molecular: RNA
  - RT-PCR / “nested” PCR

Table 1 | A summary of diagnostic tests for the evaluation of patients with HDV infection

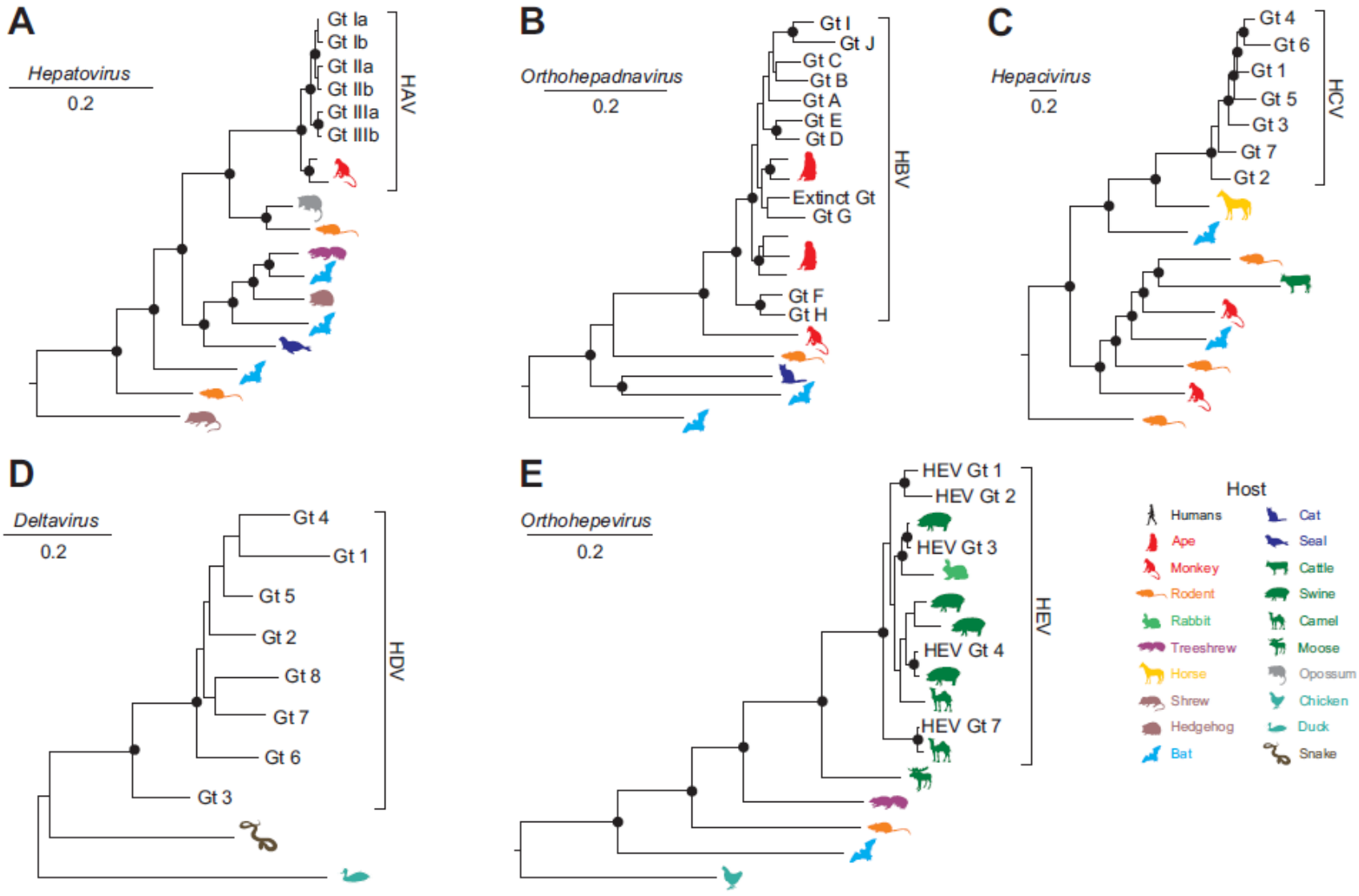
Test	Purpose	Remarks
Anti-HDV IgG antibody	Detects IgG antibodies against HDV, indicates previous or ongoing contact with HDV	Should be the first diagnostic screening test employed and should be performed in all HBsAg-positive patients
Anti-HDV IgM antibody	Detects IgM antibodies against HDV, indicates acute HDV infection or chronic HDV infection with disease activity	Can be used to determine disease activity in patients who test positive for anti-HDV IgG antibodies. Available tests are not standardized
HDV RNA qualitative	Detects HDV RNA Indicates HDV replication and active infection	Gold standard to determine HDV infection. Test can be false-negative if primers are not optimized for all HDV genotypes
HDV RNA quantitative	Determines the level of HDV RNA in the blood	Can be useful in the context of antiviral treatment to predict treatment response. There is no association between serum HDV RNA levels and the grade or stage of liver disease
HDV genotyping	Determines the HDV genotype	Different HDV genotypes may be associated with distinct clinical courses
HBsAg quantitative	Determines the level of HBsAg in the blood	HBsAg is associated with HDV RNA levels. HBsAg clearance is associated with HDV eradication and thus HBsAg monitoring can be useful during antiviral treatment
HBeAg/anti-HBe antibody	Determines the presence of the HBeAg and the presence of anti-HBe antibodies	About 15–20% of patients with HDV infection test positive for HBeAg, which can be associated with HBV replication. Treatment with HBV polymerase inhibitors might be indicated if IFN-α treatment is not possible
HBV DNA quantitative	Determines the level of HBV DNA in the blood	Indication for treatment with HBV polymerase inhibitors depends on the amount of HBV DNA detectable in the blood
Anti-HCV antibody/HCV RNA	Determines the presence of the antibodies against HCV and the presence of HCV RNA	Up to one third of patients in Europe with HDV infection are coinfected with HCV. Screening for HCV should be performed at least once. HCV RNA is frequently suppressed by coinfection
Liver biopsy	Histological evaluation of and grading or staging of liver disease	Should be performed in all patients with hepatitis D as noninvasive markers of liver fibrosis are not proven to be able to accurately predict the stage of liver disease in patients with HDV infection

Abbreviations: HBsAg, hepatitis B surface antigen; HBe; hepatitis B early antigen; HBeAg, hepatitis B e antigen; HDV, hepatitis D virus.

Vírus das hepatites...
De onde eles vêm?



http://dx.doi.org/10.1016/j.jhep.2018.11.010



http://dx.doi.org/10.1016/j.jhep.2018.11.010

Herpesvírus

HERPESVÍRUS

- São uma das principais causas de doenças humanas associadas a vírus.
- Quando a infecção acontece é para a vida toda do indivíduo.

O termo *Herpes* vem do grego e significa latente, crônico.

HERPESVÍRUS

- Vírus envelopados, com capsídeo icosahédrico.
- Partícula de diâmetro entre 180-200nm.
- Genomas de DNA dupla fita, linear, grandes (até 235kbp)
- São vírus complexos (vírions com ~35 proteínas diferentes)
- Codificam uma variedade de enzimas envolvidas no metabolismo e síntese de DNA e no processamento de proteínas.
- Os tipos diferem na sequência do seu genoma e suas proteínas, mas são semelhantes em termos de estrutura do vírion e organização genômica.
- **Replicação: Nuclear.**
- **Montagem: Nuclear.**

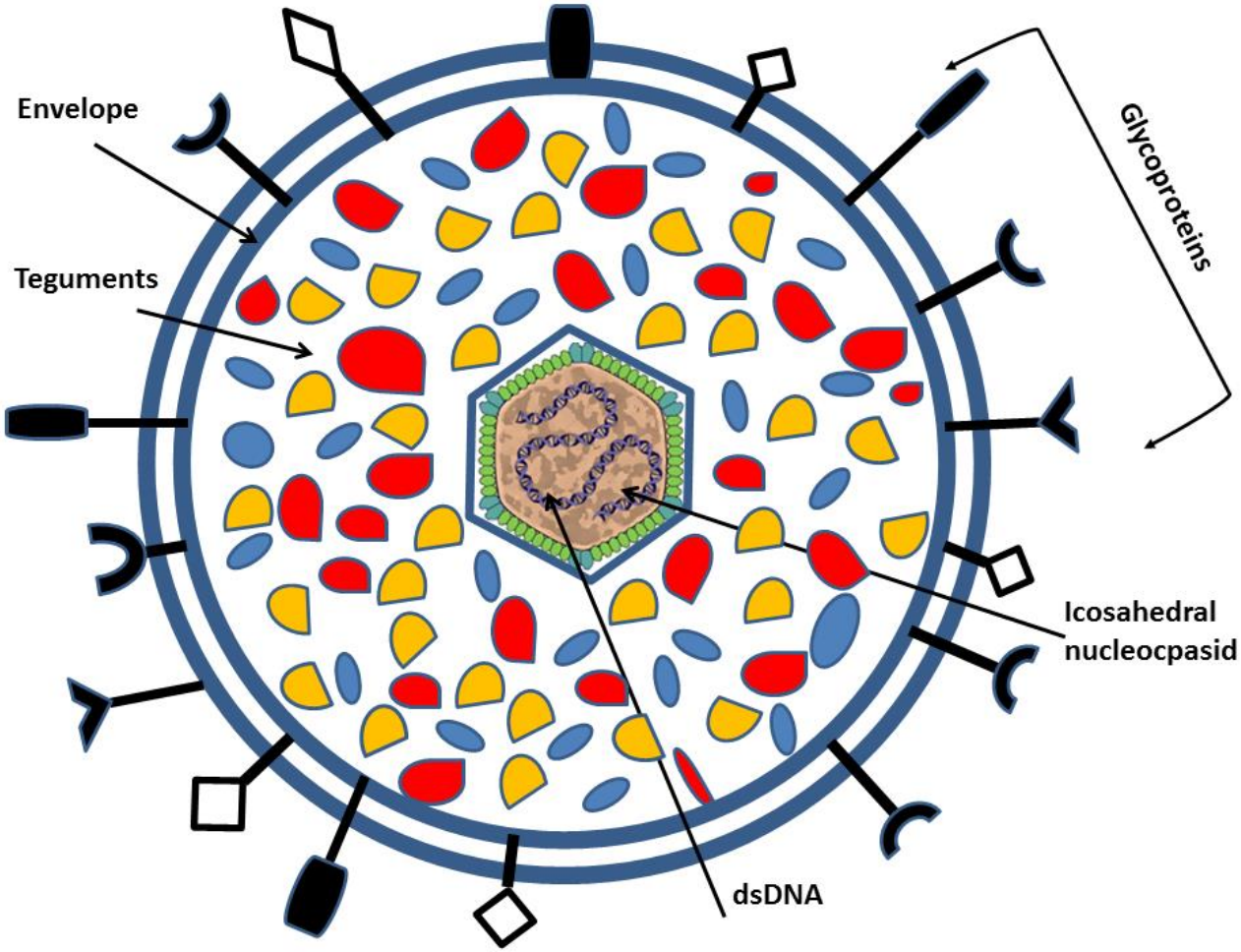
HERPESVÍRUS

- **Order:** *Herpesvirales* (3 Families) history
  - **Family:** *Alloherpesviridae* (4 Genera) history → Peixes e anfíbios
  - **Family:** *Herpesviridae* (3 Subfamilies) history
    - **Subfamily:** *Alphaherpesvirinae* (5 Genera) history
      - **Genus:** *Iltovirus* (2 Species) history
      - **Genus:** *Mardivirus* (5 Species) history
      - **Genus:** *Scutavirus* (1 Species) history
      - **Genus:** *Simplexvirus* (11 Species) history
      - **Genus:** Unassigned (1 Species) history
      - **Genus:** *Varicellovirus* (17 Species) history
    - **Subfamily:** *Betaherpesvirinae* (4 Genera) history
      - **Genus:** *Cytomegalovirus* (8 Species) history
      - **Genus:** *Muromegalovirus* (3 Species) history
      - **Genus:** *Proboscivirus* (1 Species) history
      - **Genus:** *Roseolovirus* (3 Species) history
      - **Genus:** Unassigned (3 Species) history
    - **Subfamily:** *Gammaherpesvirinae* (4 Genera) history
      - **Genus:** *Lymphocryptovirus* (8 Species) history
      - **Genus:** *Macavirus* (9 Species) history
      - **Genus:** *Percavirus* (3 Species) history
      - **Genus:** *Rhadinovirus* (9 Species) history
      - **Genus:** Unassigned (3 Species) history
    - **Genus:** Unassigned (1 Species) history

Mamíferos, aves e répteis

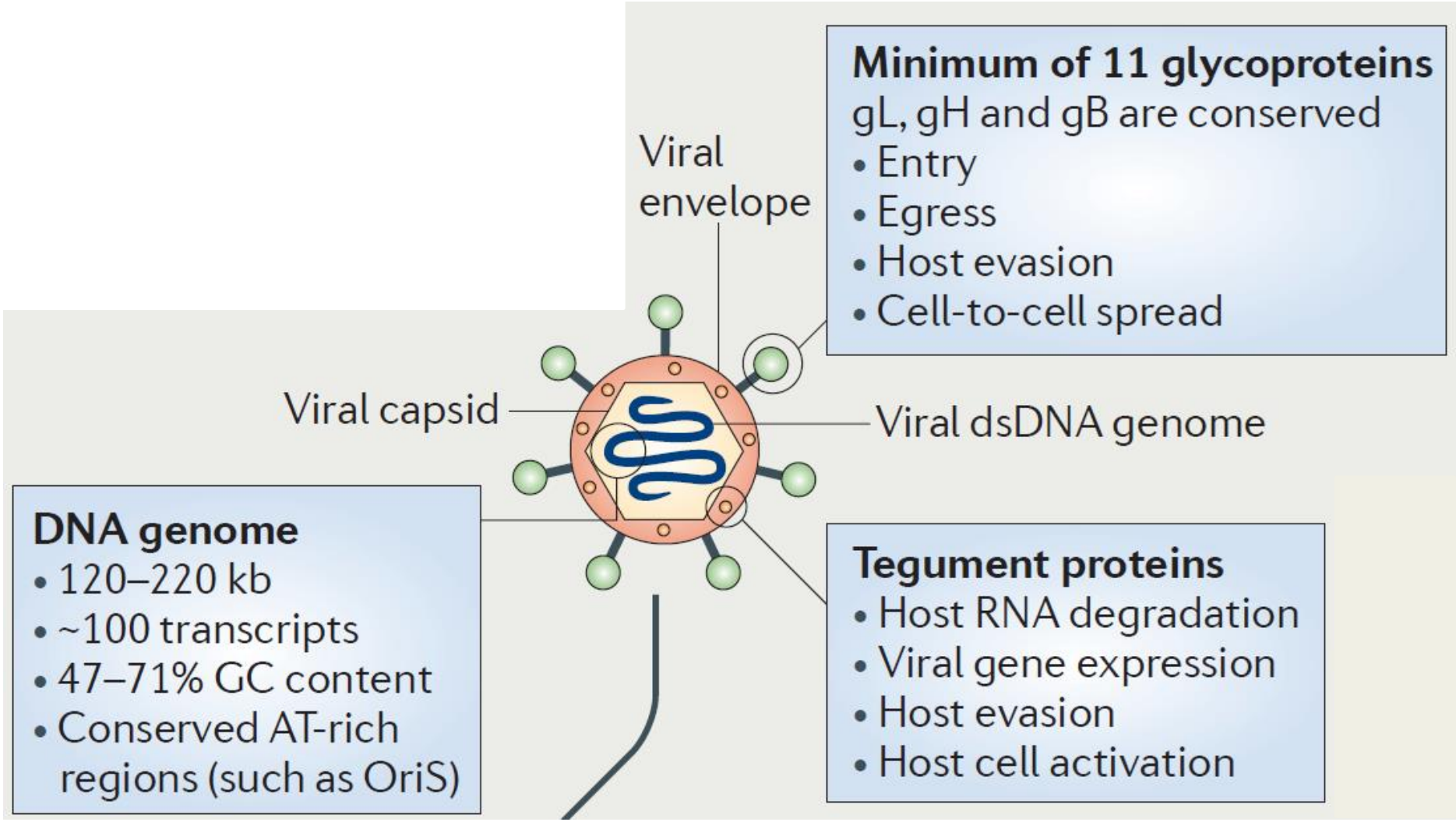
  - **Family:** *Malacoherpesviridae* (2 Genera) history → Bivalves

HERPESVÍRUS



Herpesvírus

HERPESVÍRUS



HERPESVÍRUS

- Organização do genoma

- Genoma formado por fragmento curtos e longos, orientados em “qualquer” direção, gerando 4 isômeros
- Sete blocos de genes conservados.

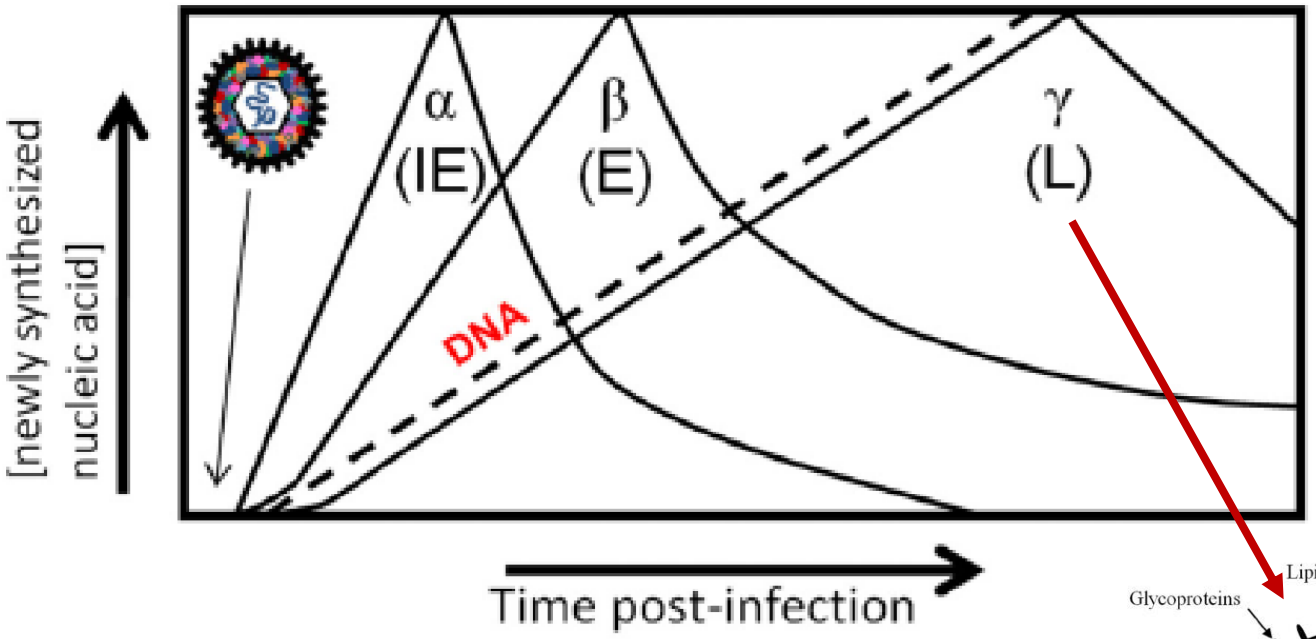
Pergunta de prova!!!!

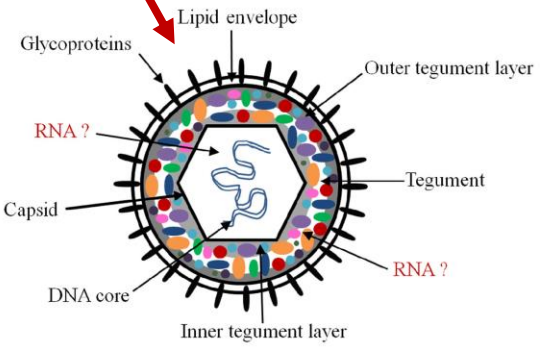
Viruses 2009, 1(3), 420-440; doi:10.3390/v1030420

HERPESVÍRUS

Ciclo viral

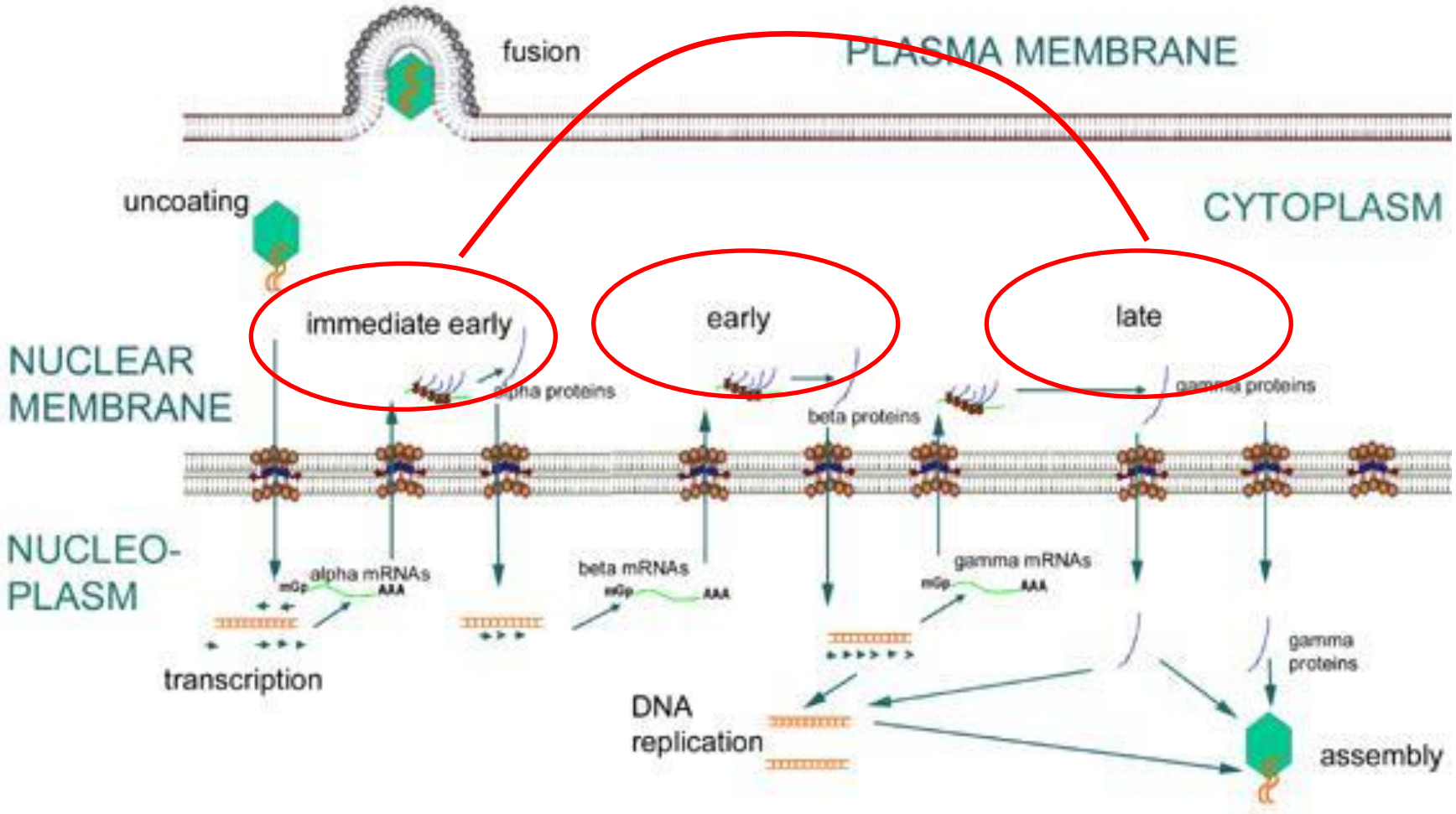
- Expressão dos genes precoces imediatos, precoces e tardios





HERPESVÍRUS

- **Ciclo viral**
  - Expressão dos genes precoces imediatos, precoces e tardios



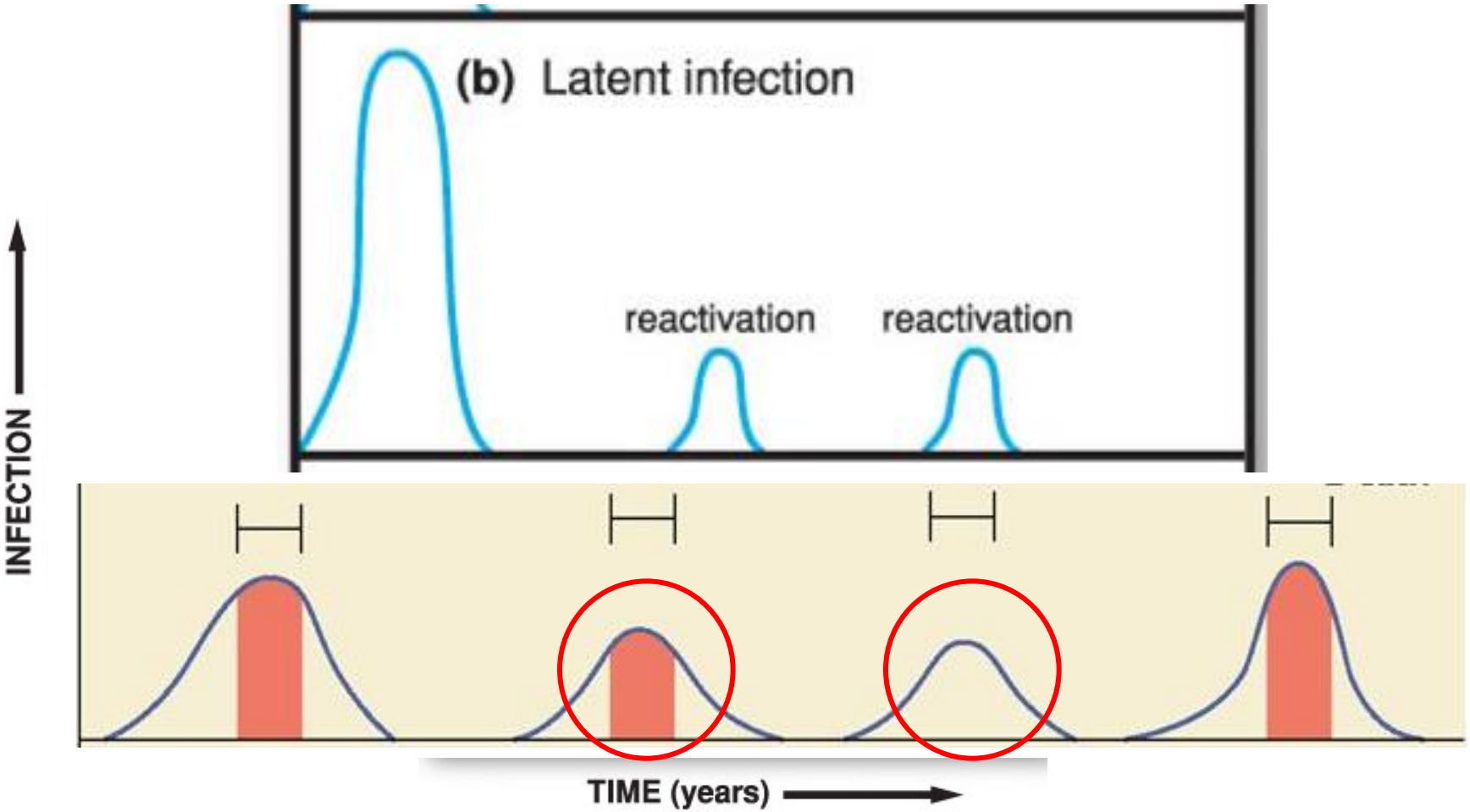
HERPESVÍRUS

- Três subfamílias (Patogénicos em humanos):
  - Alphaherpesviruses (HSV-1/HHV1; HHV2/HSV-2; VZV/HHV-3)
  - Betaherpesviruses (HCMV/HHV-5; HHV-6; HHV-7)
  - Gammaherpesviruses (EBV/HHV-4; HHV-8/KSHV)
- Estabelecem infecções latentes e persistentes após a infecção primária.
- A reativação acontece principalmente em períodos de imunossupressão.
- A infecção primária e a reativação são mais graves em indivíduos imunossuprimidos.

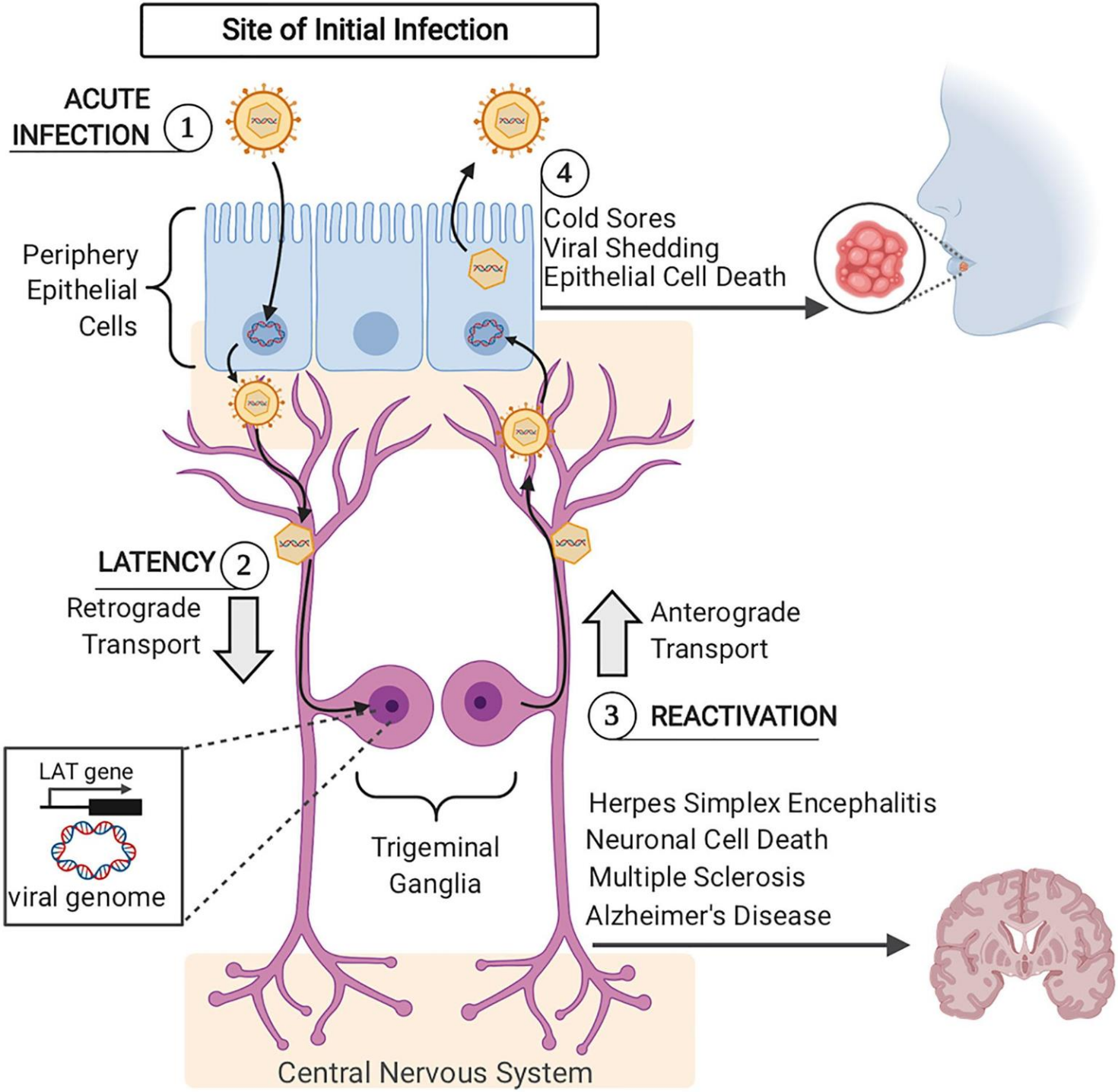
HERPESVÍRUS

INFECÇÃO LATENTE

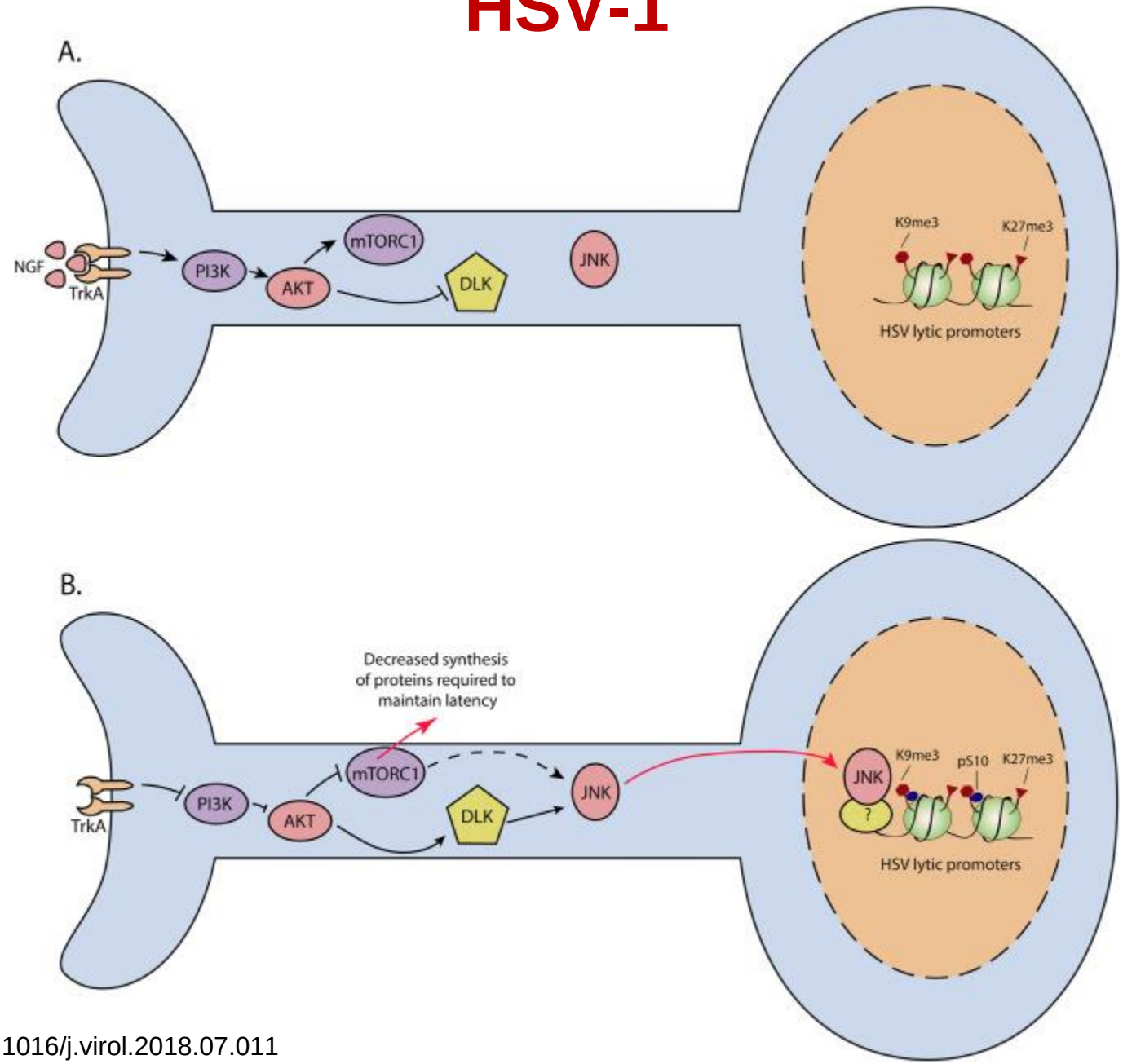
Latência - Estado transcricional e traducional único do vírus. O ciclo produtivo não funciona mas pode ser ativado a qualquer momento.



Herpes simples (Herpesvírus 1)


Site of Initial Infection
ACUTE INFECTION
1
Periphery Epithelial Cells
4
Cold Sores
Viral Shedding
Epithelial Cell Death
LATENCY
2
Retrograde Transport
Anterograde Transport
3
REACTIVATION
LAT gene
viral genome
Trigeminal Ganglia
Herpes Simplex Encephalitis
Neuronal Cell Death
Multiple Sclerosis
Alzheimer's Disease
Central Nervous System

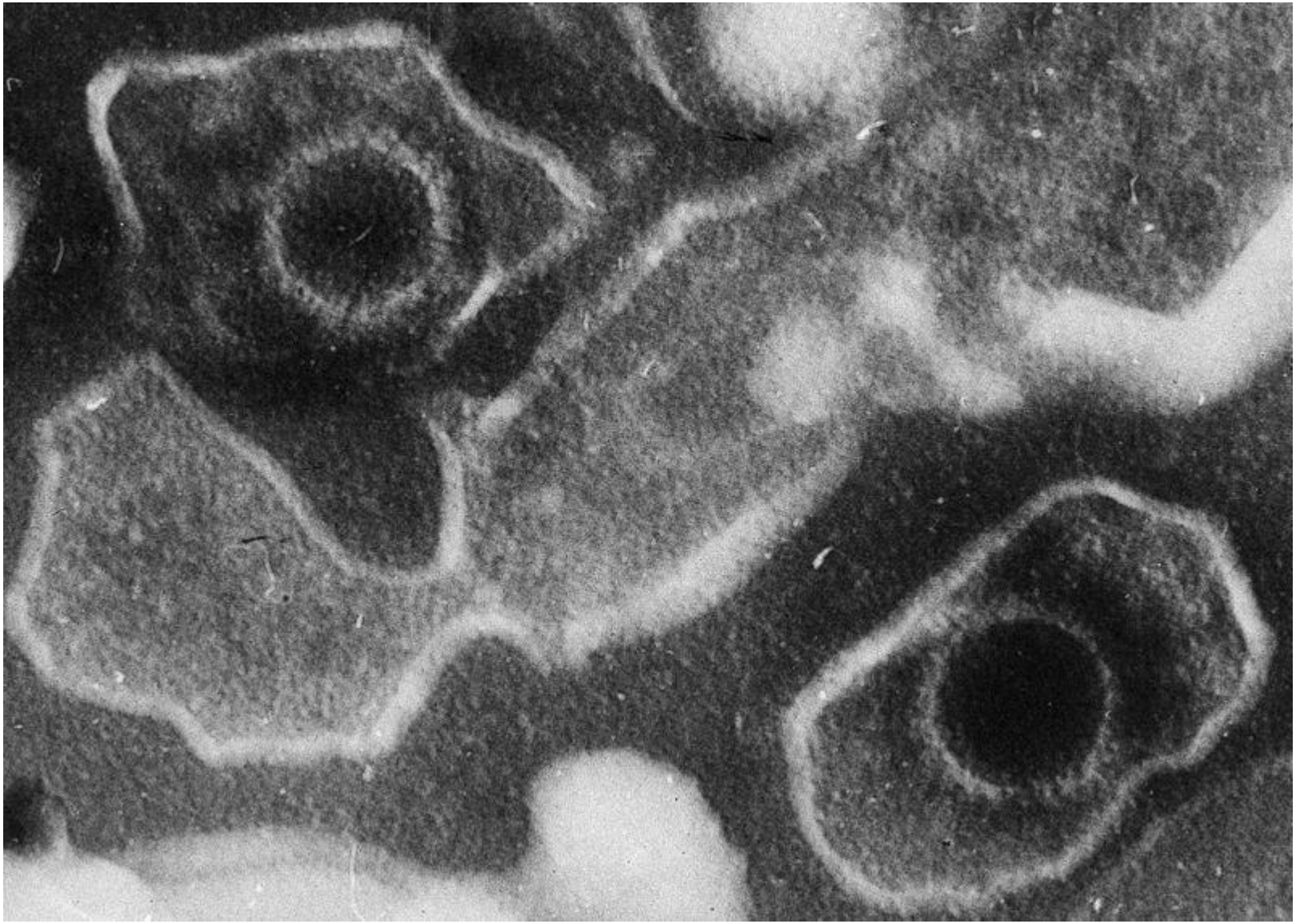
HSV-1



https://doi.org/10.1016/j.virol.2018.07.011

Vírus Epstein-Barr (Herpesvírus 4)

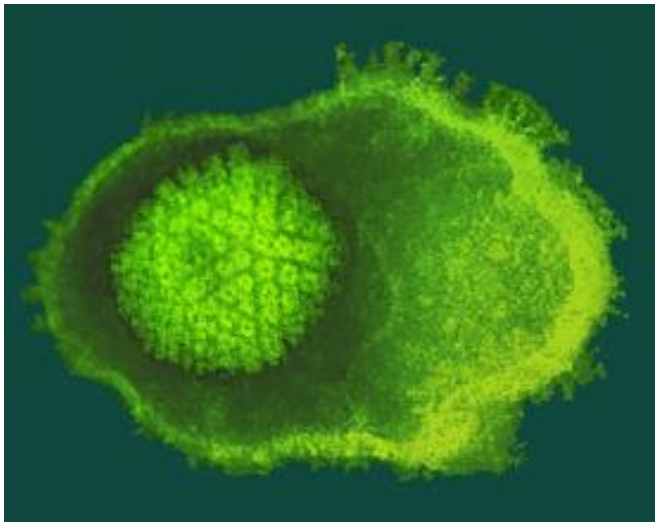
Vírus Epstein-Barr (EBV)

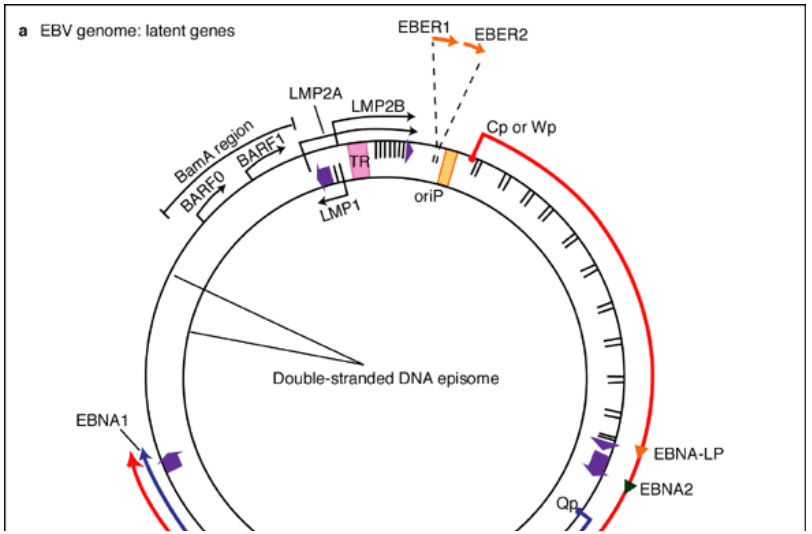


Vírus Epstein-Barr (EBV)

Receptor: CD21 (linfócitos B e células epiteliais da naso- e orofaringe)

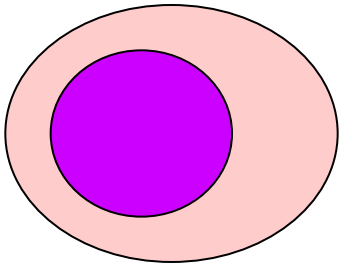
- Mais de 90% da população mundial esta infectada por este vírus.
- É transmitido pela saliva infectando as células epiteliais de orofaringe e linfócitos B.



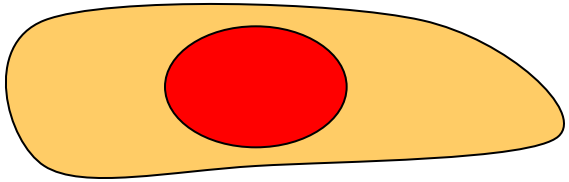


- Etiologicamente associado com:
- Mononucleose
- Linfoma de Burkitt,
- Doença de Hodgkin
- Carcinoma naso-faríngeo

Vírus Epstein-Barr (EBV)



Os linfócitos B são semipermissivos para a replicação viral. A infecção pode ser **latente** ou as células podem ser estimuladas e, eventualmente, transformadas pelo vírus.



As células epiteliais permitem o ciclo lítico completo.

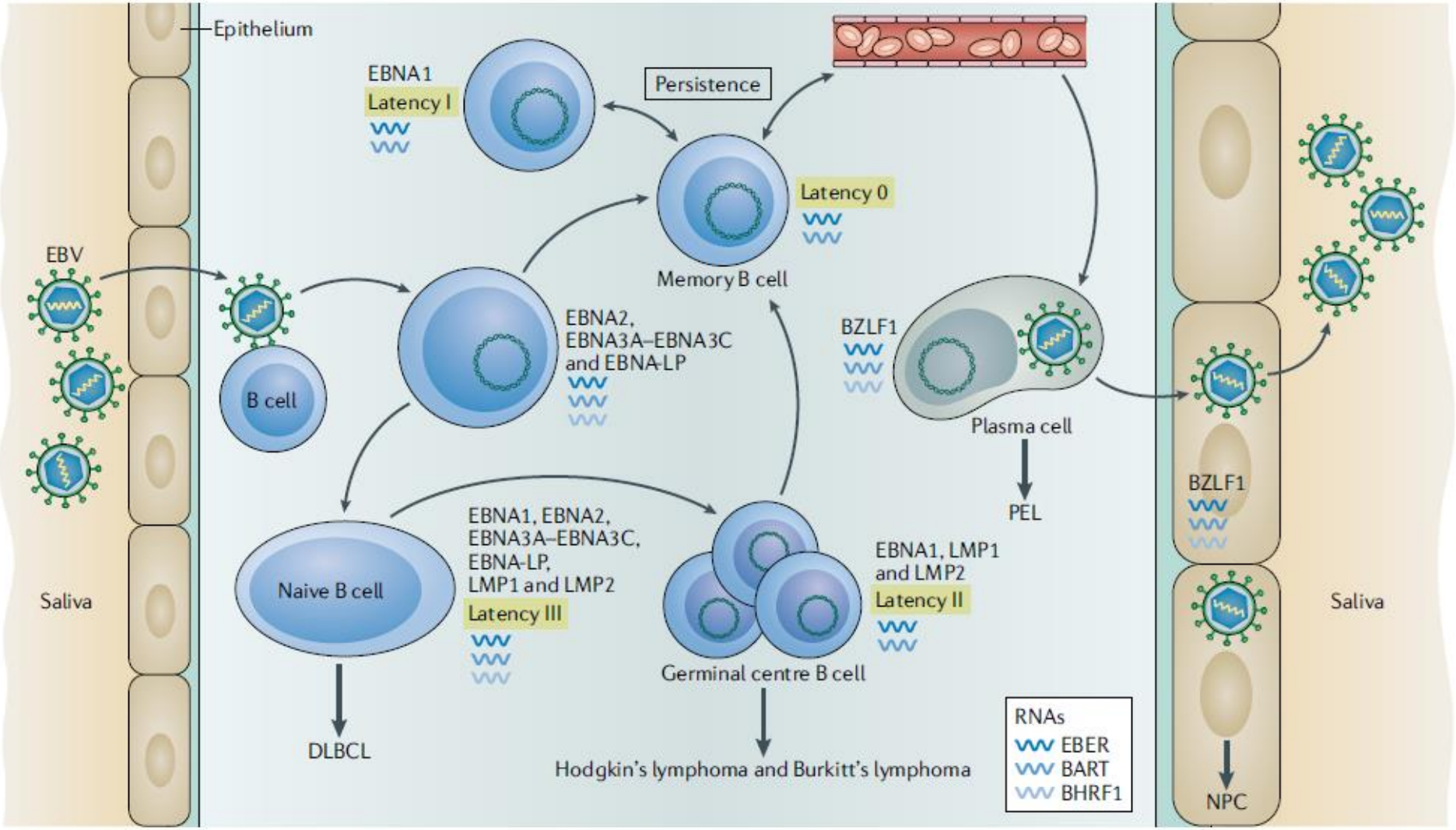
HERPESVÍRUS

Table 1 | **Human herpesviruses**

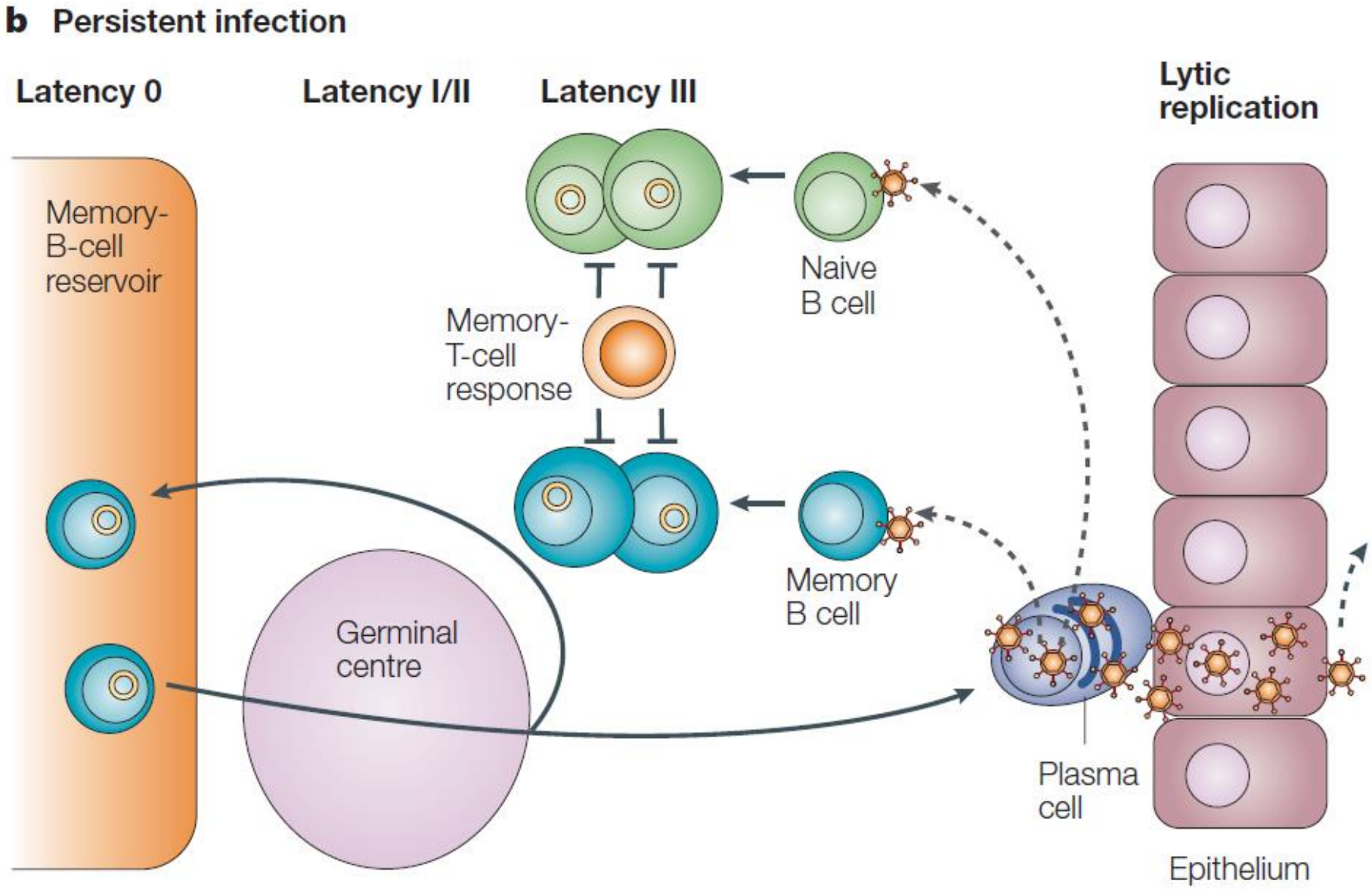
Name	Subfamily	Sequence characteristics		Cell types infected		Pathophysiology
		GC content	% coding	Lytic infection	Latent infection	
HSV-1 (HHV1)	α	68%	79	Epithelial cells	Neurons	Orofacial infections, encephalitis
HSV-2 (HHV2)	α	70%	79	Epithelial cells	Neurons	Genital and neonatal infections
VZV (HHV3)	α	46%	89	Epithelial cells	Neurons	Chickenpox, shingles
EBV (HHV4)	γ	59%	68	B cells, epithelial cells	B cells	Infectious mononucleosis, lymphoma, carcinoma
CMV (HHV5)	β	57%	79	Macrophages, lymphocytes, epithelial cells	Macrophages, lymphocytes, epithelial cells	Congenital infection, retinitis, hepatitis
HHV6	β	42%	79 (subtype A); 82 (subtype B)	$CD4^+$ T cells	Monocytes, macrophages	Exanthem subitum
HHV7	β	36%	79	T cells	T cells	Exanthem subitum
HHV8	γ	53%	83	Lymphocytes	Lymphocytes	Kaposi's sarcoma

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

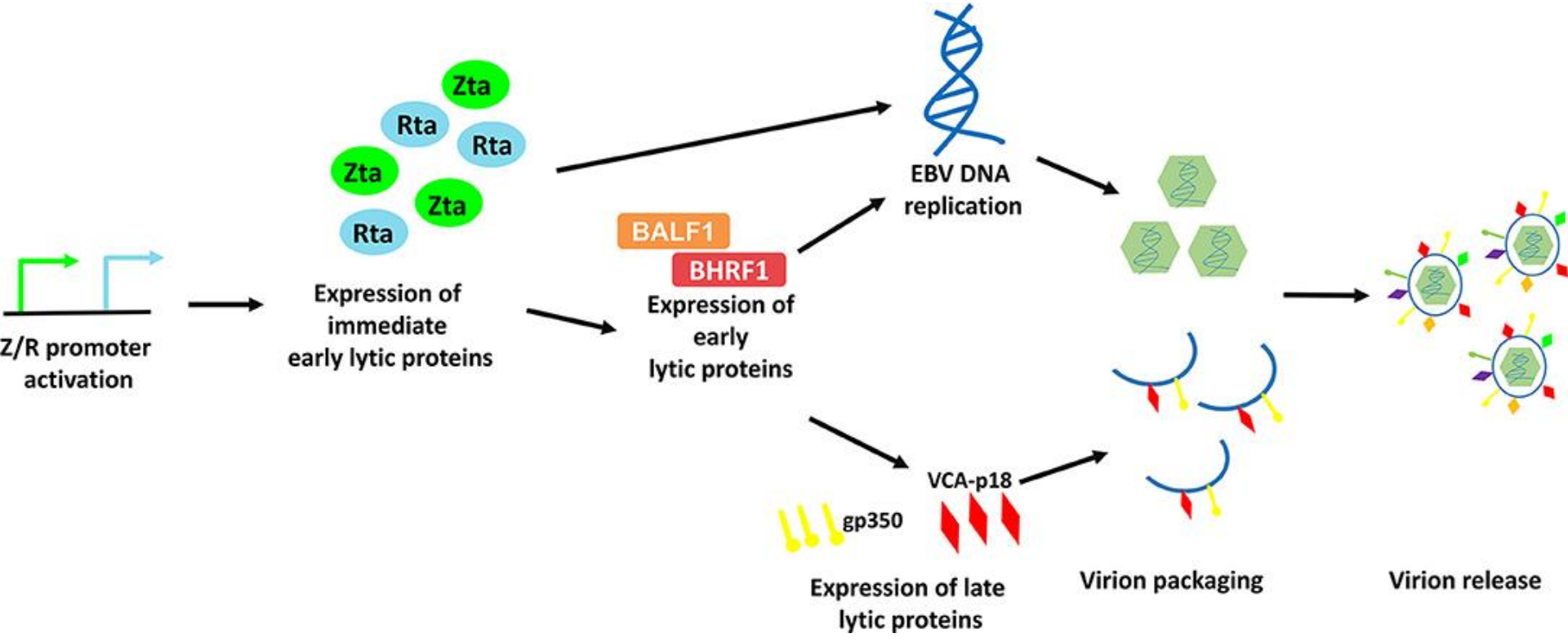
Vírus Epstein-Barr (EBV)



Vírus Epstein-Barr (EBV)

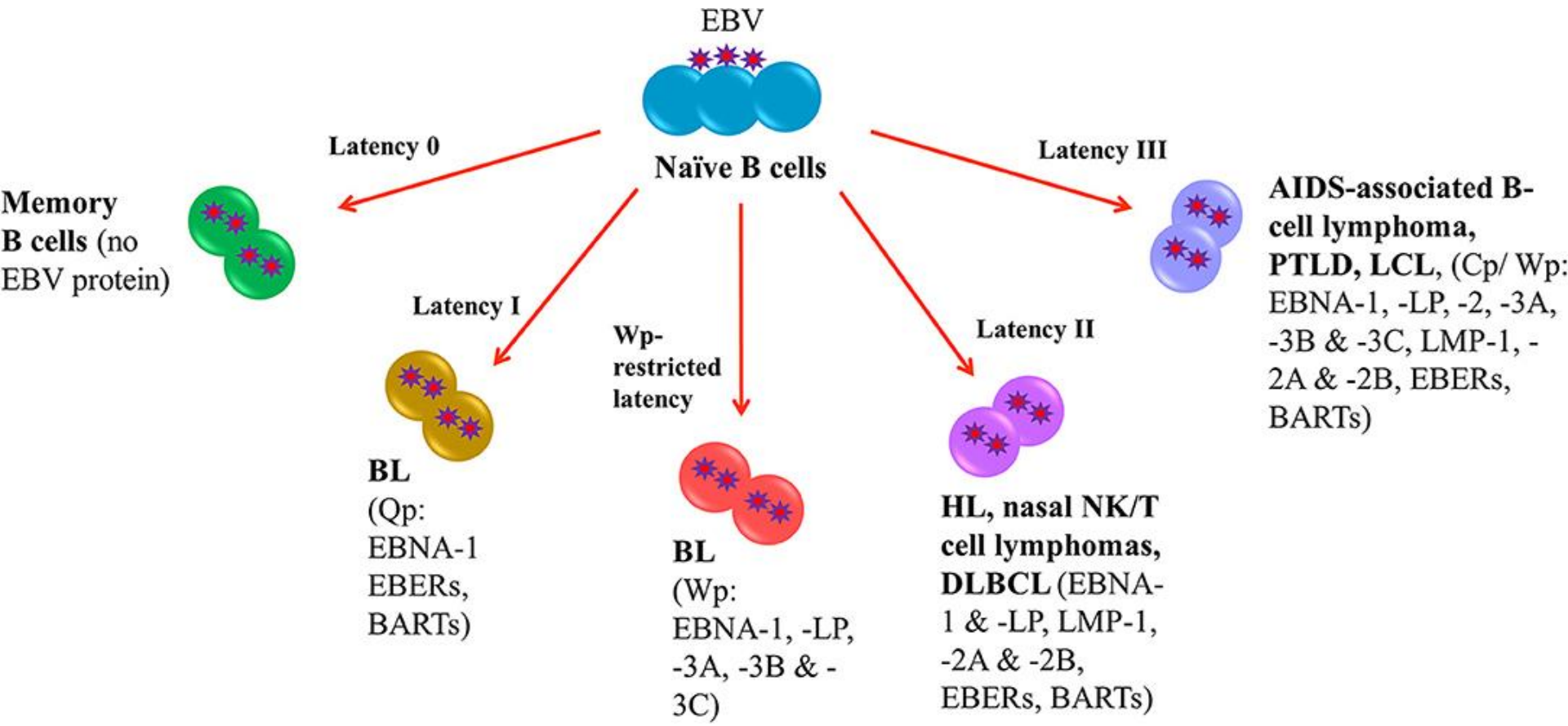


Vírus Epstein-Barr (EBV)



https://doi.org/10.3389/fonc.2019.00081

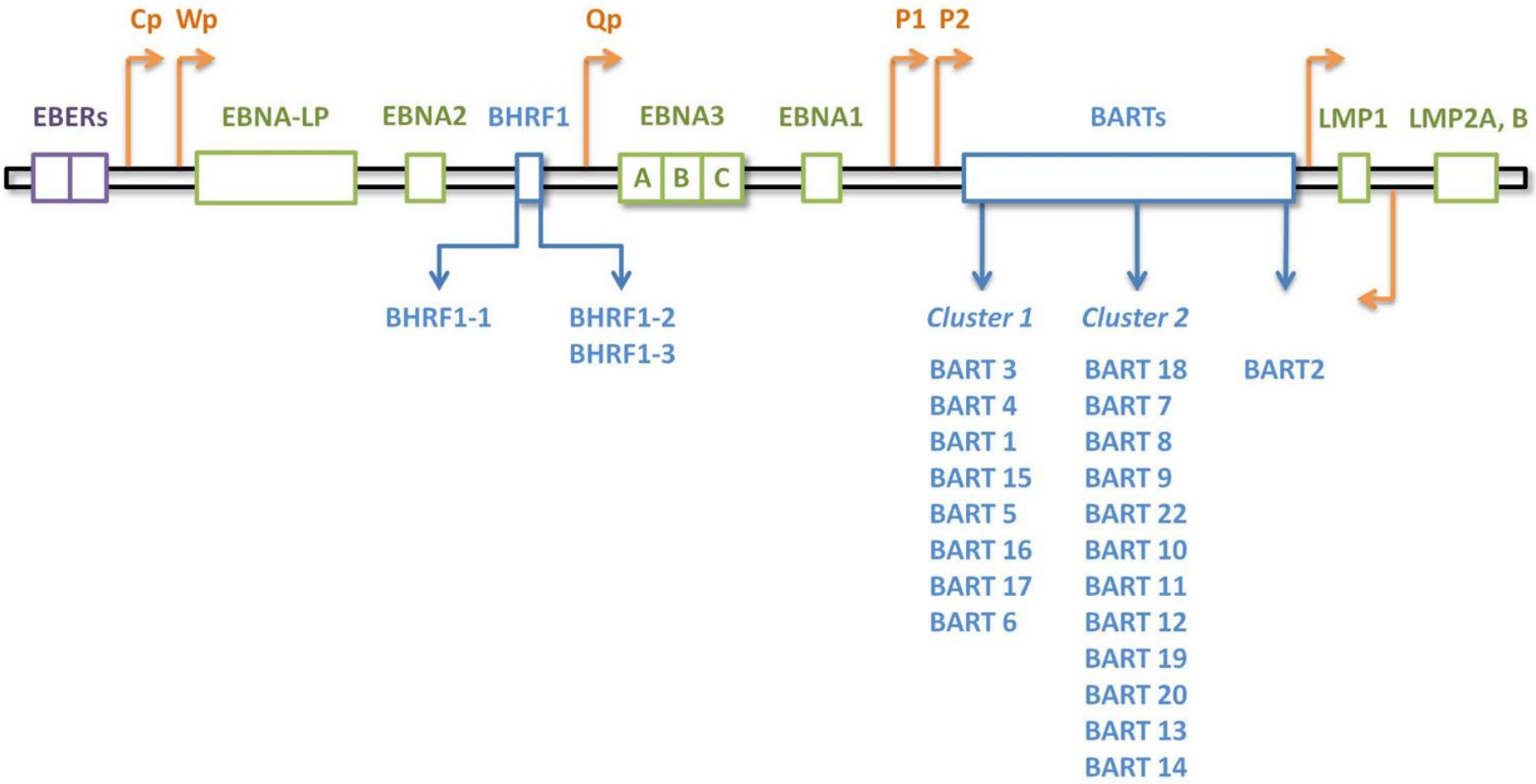
Vírus Epstein-Barr (EBV)



(**EBV**)-encoded small RNAs (**EBERs**)

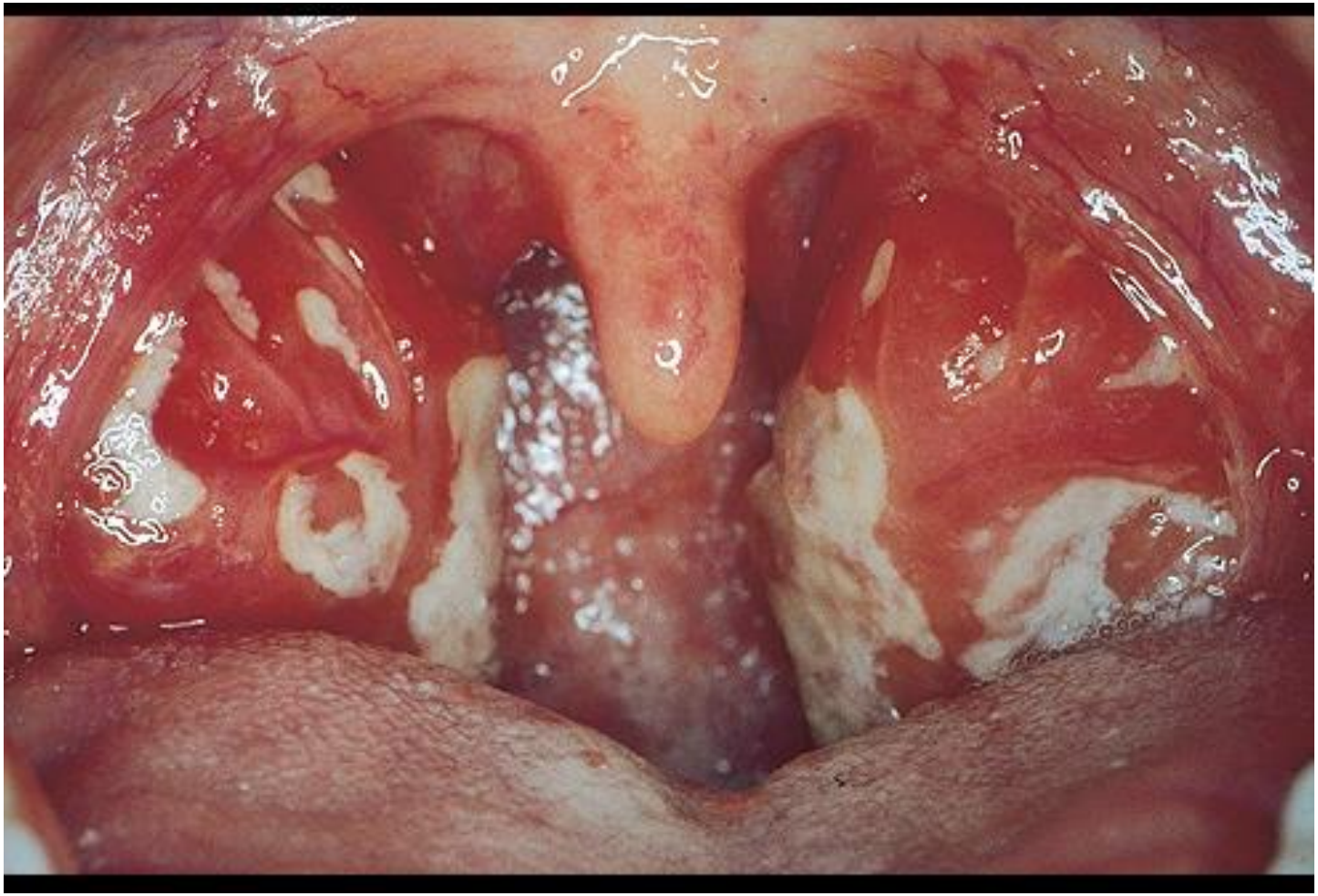
https://doi.org/10.3389/fonc.2019.00081

Vírus Epstein-Barr (EBV)



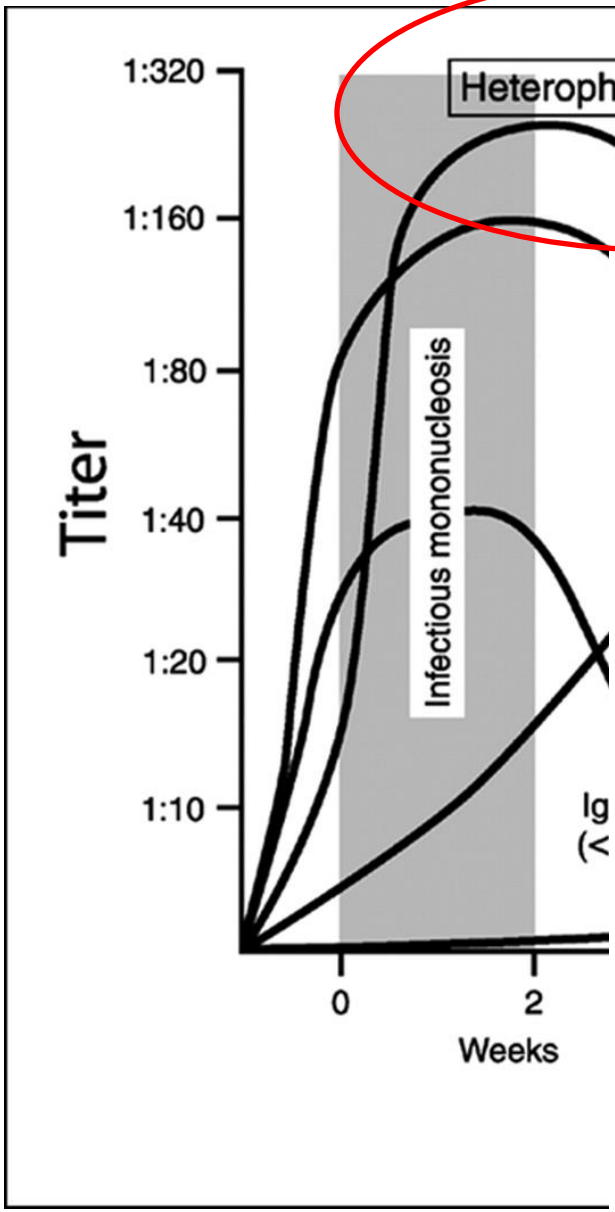
Vírus Epstein-Barr (EBV)

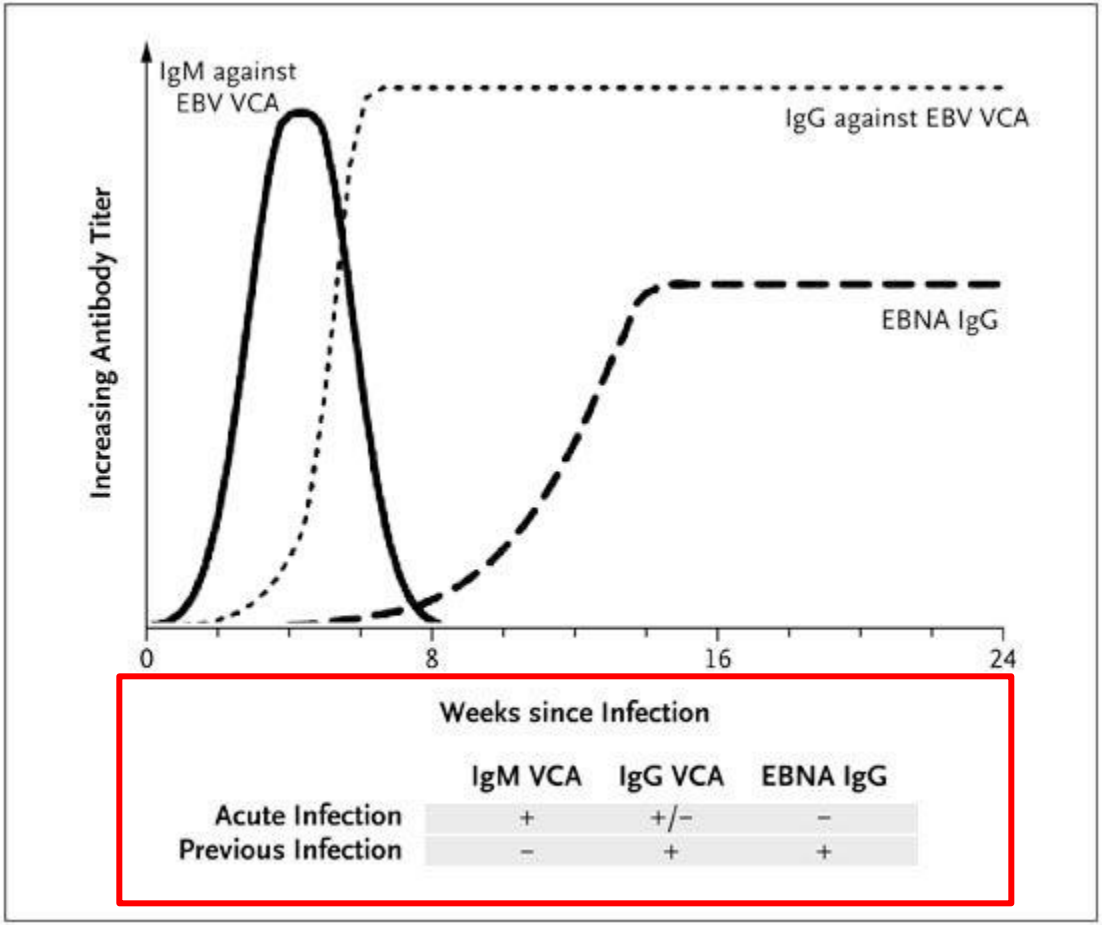
- **Mononucleose**



- Faringite e adenopatias...

DIAGNÓSTICO





	IgM VCA	IgG VCA	EBNA IgG
Acute Infection	+	+/–	–
Previous Infection	–	+	+

“Síndrome da mononucleose”

- Citomegalovírus (segunda causa viral mais importante)
- VZV
- HHV6
- Hepatite A ou B
- Rubéola
- HIV

Diagnóstico Laboratorial:

- Sorologia (anticorpos contra proteínas de superfície, anticorpos **Heterófilos**)
- PCR
- Biopsia

Vírus Epstein-Barr (EBV)

Linfoma de Burkitt

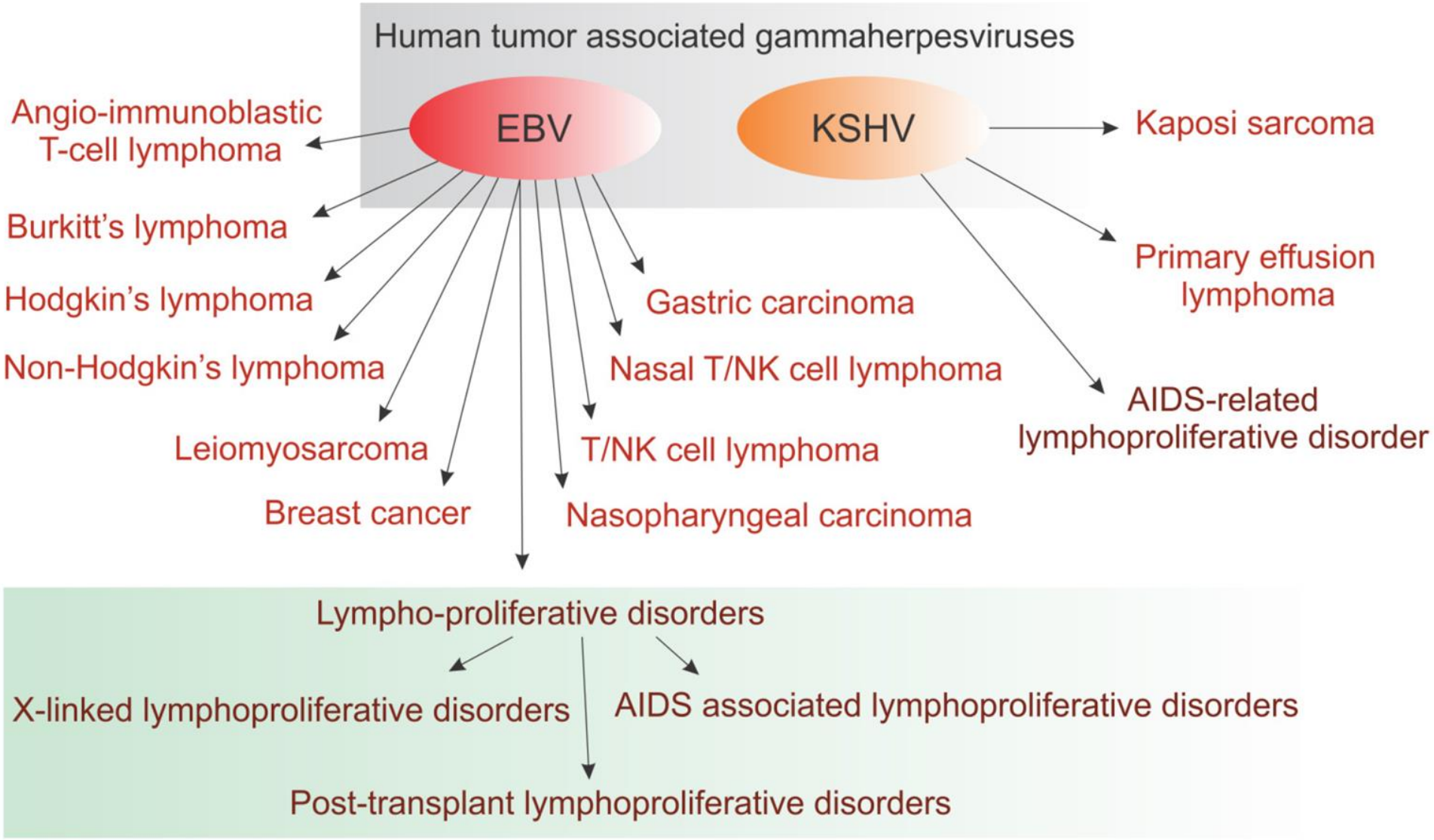
Vírus Epstein-Barr (EBV)

Leucoplasia pilosa

Vírus Epstein-Barr (EBV)

Leucoplasia pilosa

HERPESVÍRUS



Vírus Epstein-Barr (EBV)

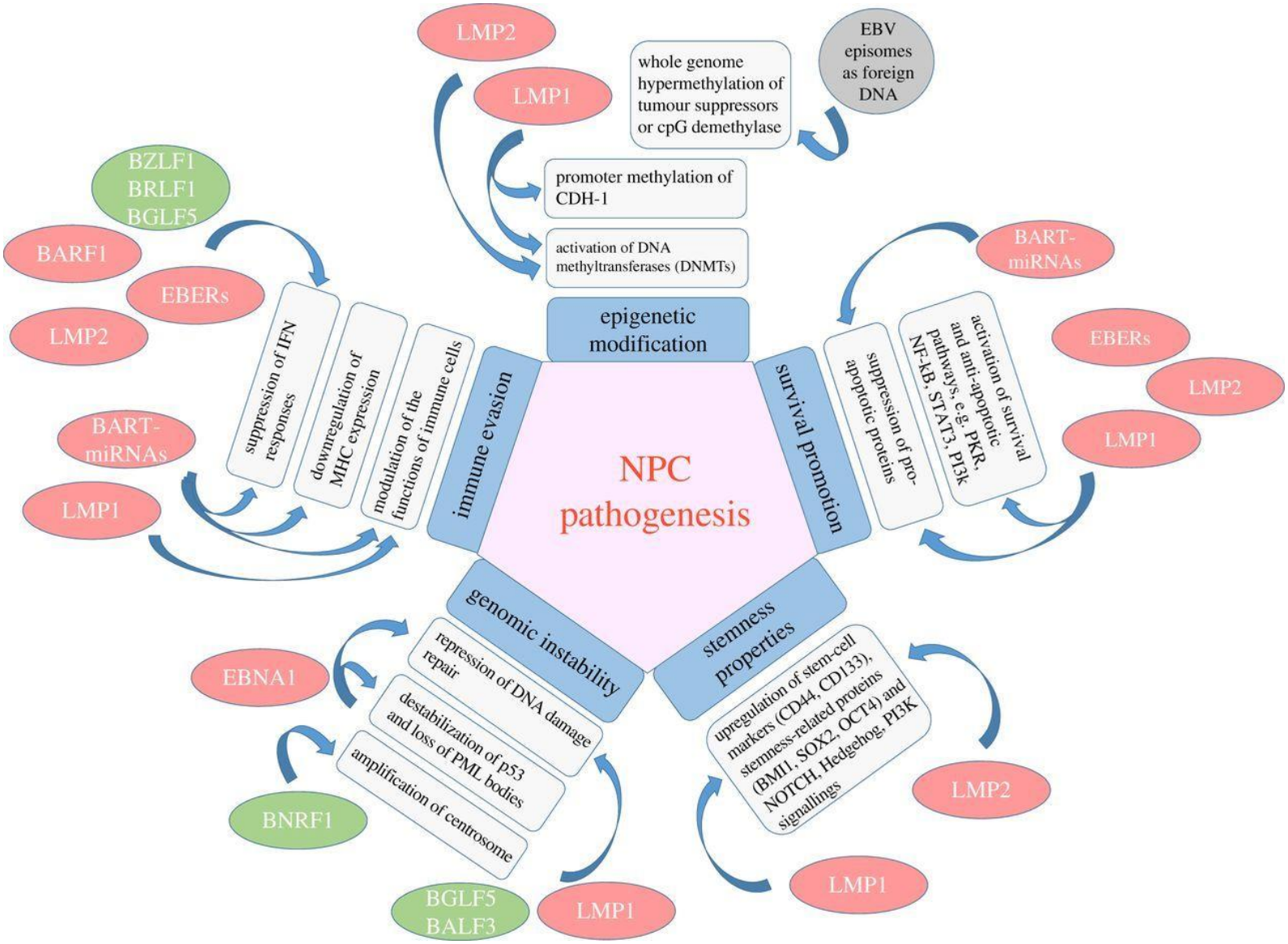
Carcinoma nasofaringeo

Carcinoma da nasofaringe (NPC):

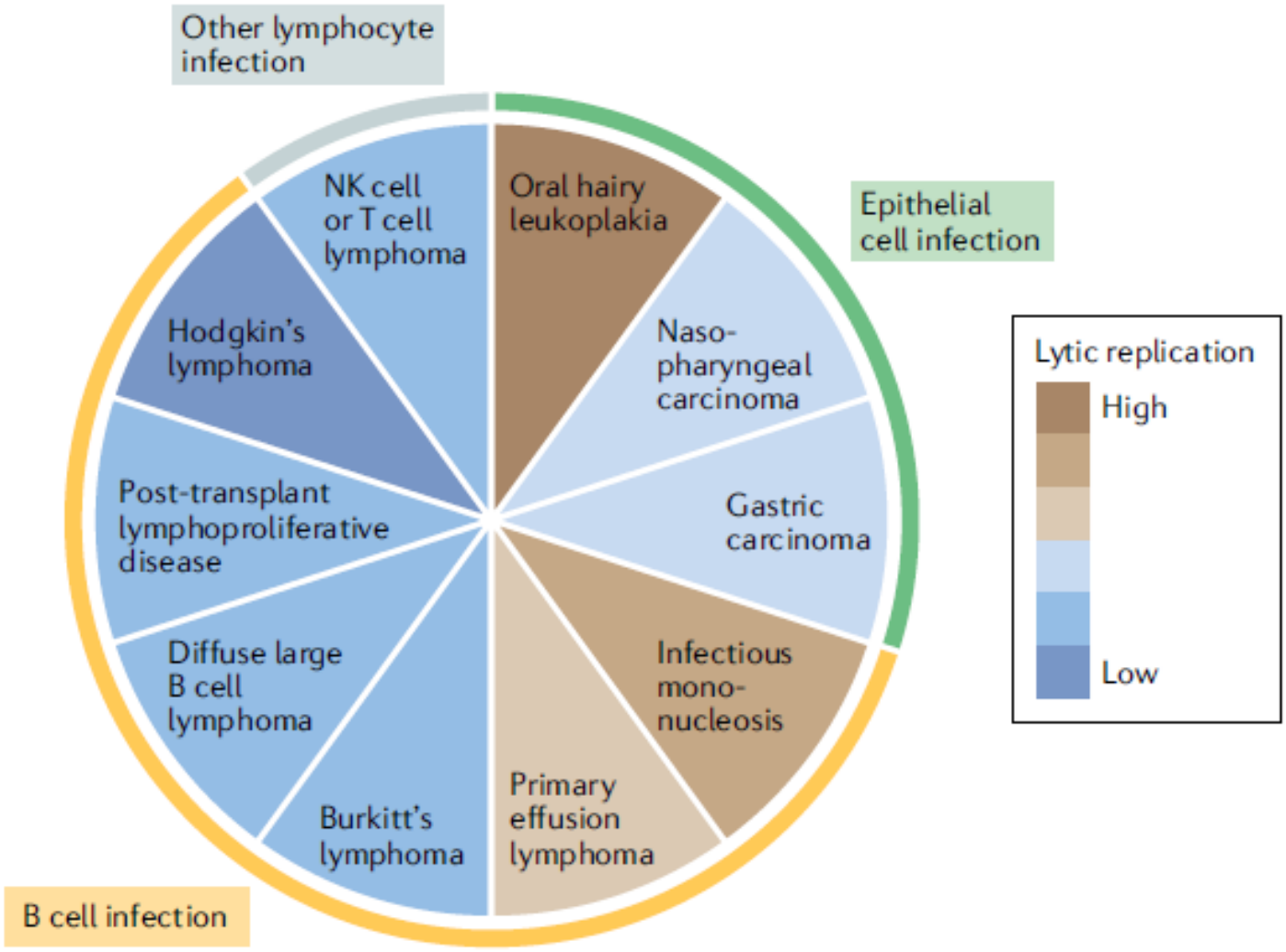
- Tumor maligno do epitélio escamoso da nasofaringe.
- A forma mais indiferenciada está sempre associada à infecção por EBV.

- Cópias de EBV podem ser detectadas nas células malignas de todos os NPC indiferenciados.
- As células malignas expressam EBNA-1 (algumas LMP).
- Linhagens celulares derivadas de NPC produzem partículas virais infecciosas

EBV: Carcinoma nasofaringeo

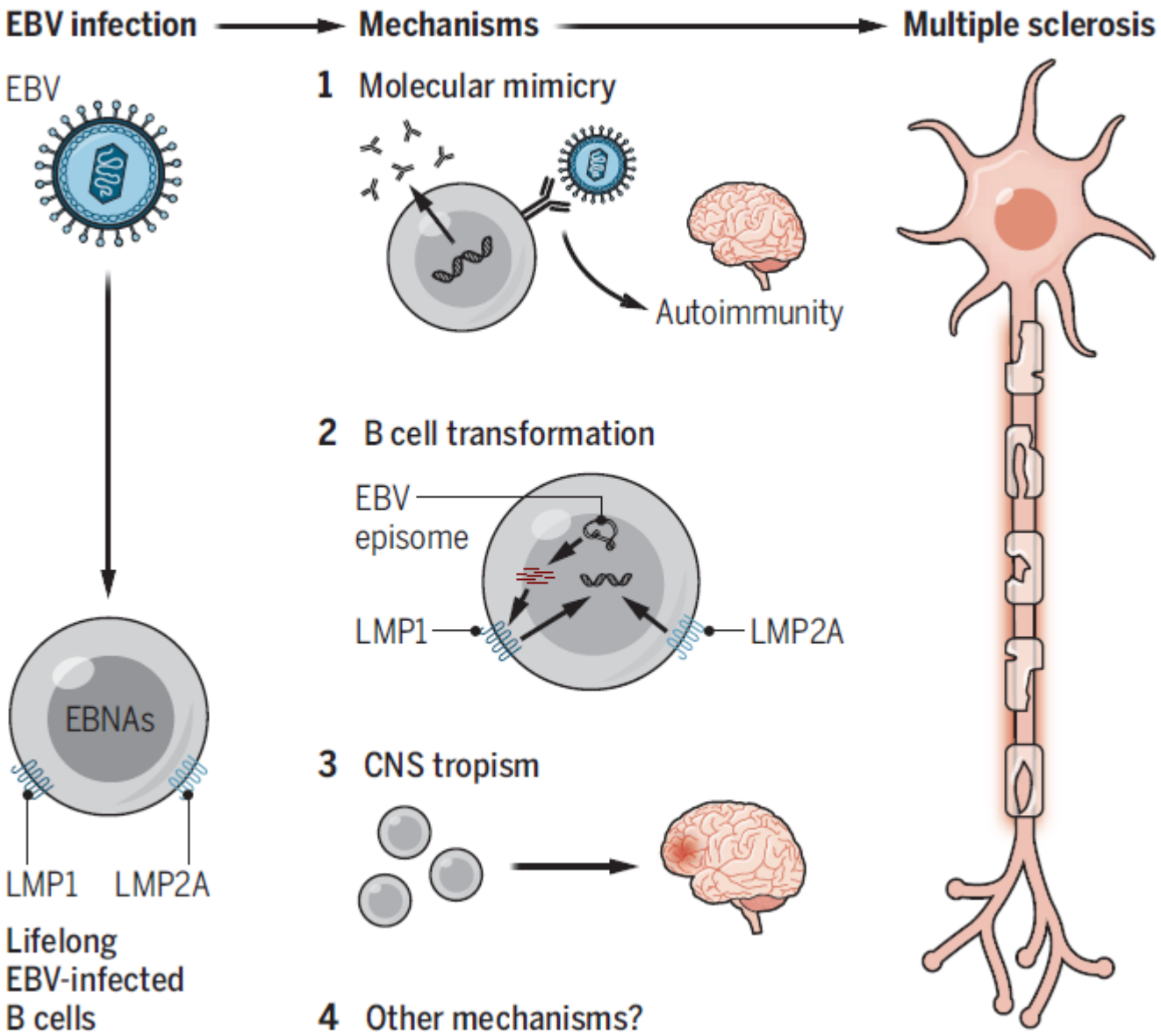


Vírus Epstein-Barr (EBV)



https://doi.org/10.1038/s41579-019-0249-7

Vírus Epstein-Barr (EBV)



Herpesvírus 8
(KSHV)

HERPESVÍRUS: KSHV

Obrigado!!!