



DEPARTAMENTO DE
MICROBiologia
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Herpesviridae

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HERPESVÍRUS

- São uma das principais causas de doenças humanas associadas a virus (*mononucleose infecciosa*).
- 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 icosaédrico.
- Partícula com 125nm de diâmetro.
- Genomas: dsDNA, linear, grandes (124-295 kb)
- São vírus complexos (virions 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 virion e organização genômica.
- **Replicação: Nuclear.**
- **Montagem: Nuclear.**

HERPESVÍRUS



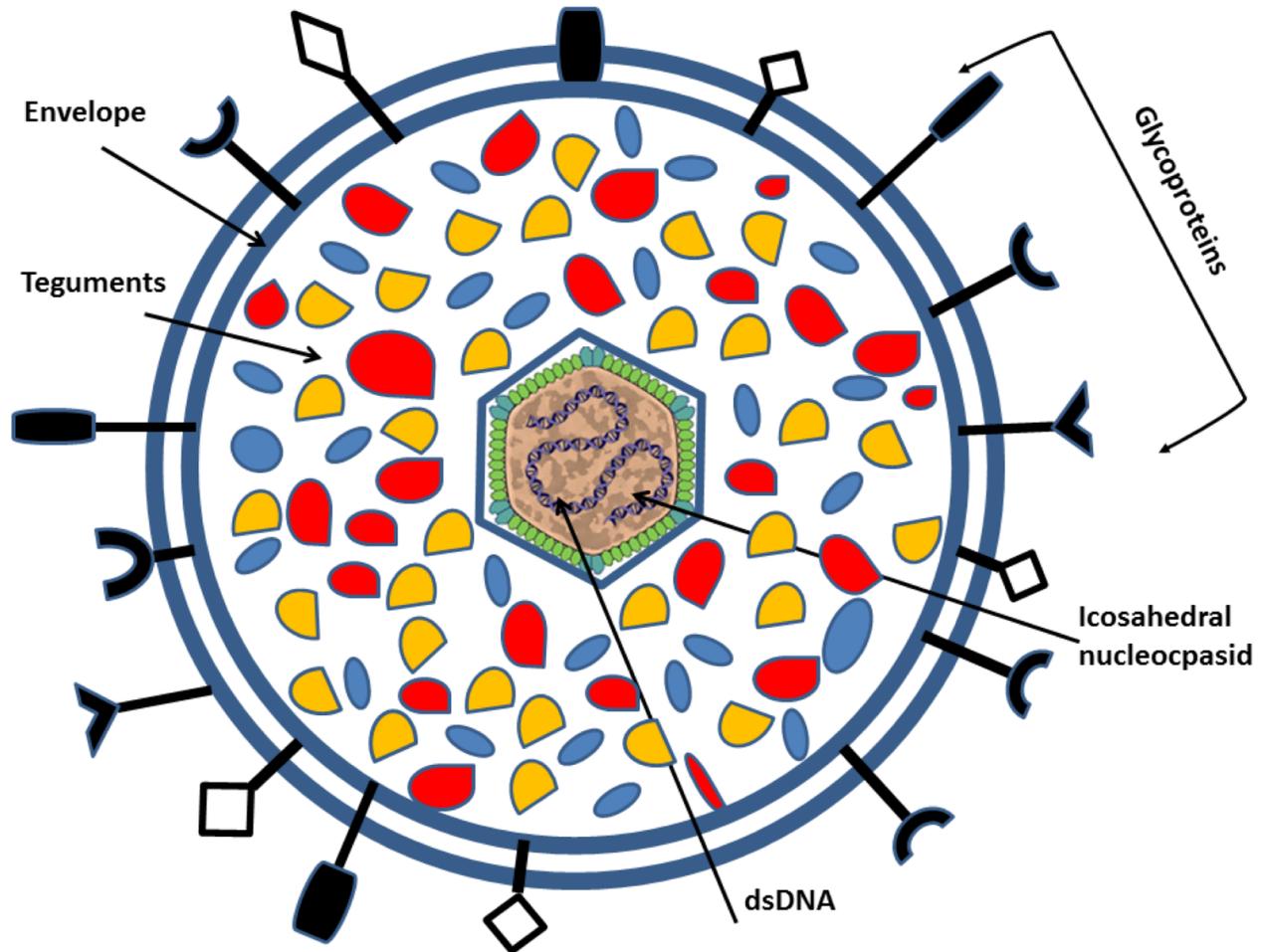
Order: <i>Herpesvirales</i>	(3 Families) < history >
Family: <i>Alloherpesviridae</i>	(4 Genera) < history >
Family: <i>Herpesviridae</i>	(3 Subfamilies) < history >
Subfamily: <i>Alphaherpesvirinae</i>	(5 Genera) < history >
Genus: <i>Iltovirus</i>	(2 Species) < history >
Genus: <i>Mardivirus</i>	(5 Species) < history >
Genus: <i>Scutavirus</i>	(1 Species) < history >
Genus: <i>Simplexvirus</i>	(11 Species) < history >
Genus: Unassigned	(1 Species) < history >
Genus: <i>Varicellovirus</i>	(17 Species) < history >
Subfamily: <i>Betaherpesvirinae</i>	(4 Genera) < history >
Genus: <i>Cytomegalovirus</i>	(8 Species) < history >
Genus: <i>Muromegalovirus</i>	(3 Species) < history >
Genus: <i>Proboscivirus</i>	(1 Species) < history >
Genus: <i>Roseolovirus</i>	(3 Species) < history >
Genus: Unassigned	(3 Species) < history >
Subfamily: <i>Gammapesvirinae</i>	(4 Genera) < history >
Genus: <i>Lymphocryptovirus</i>	(8 Species) < history >
Genus: <i>Macavirus</i>	(9 Species) < history >
Genus: <i>Percavirus</i>	(3 Species) < history >
Genus: <i>Rhadinovirus</i>	(9 Species) < history >
Genus: Unassigned	(3 Species) < history >
Genus: Unassigned	(1 Species) < history >
Family: <i>Malacoherpesviridae</i>	(2 Genera) < history >

Peixes e anfíbios

Mamíferos, aves e répteis

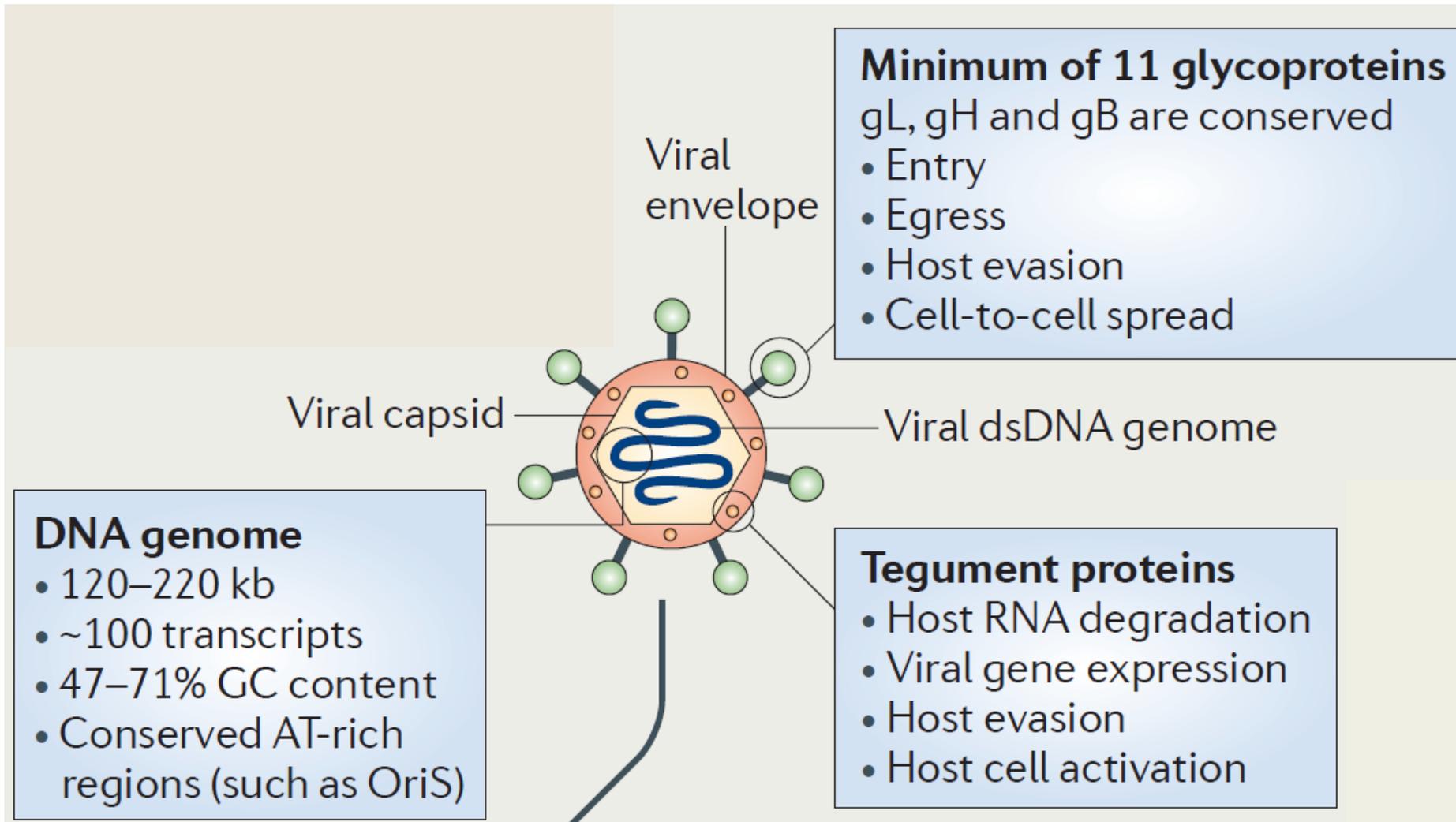
Bivalves

HERPESVÍRUS



Herpesvírus

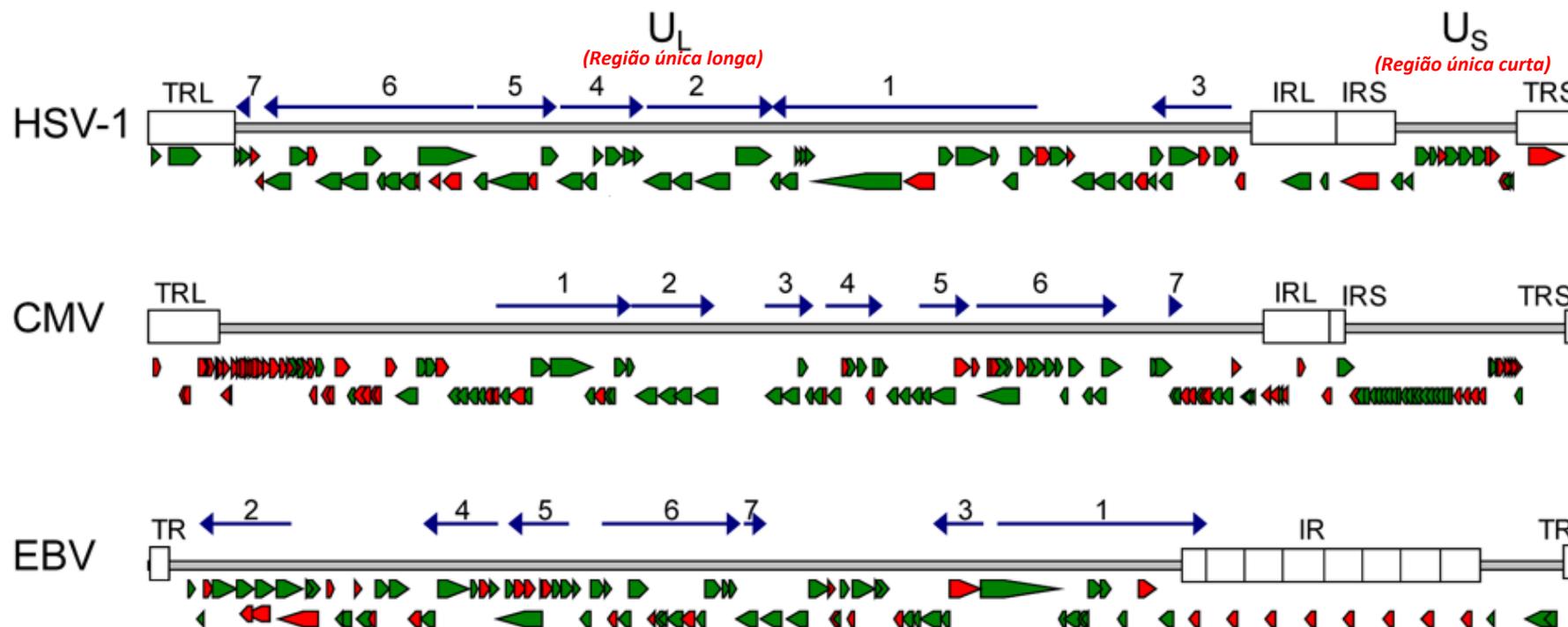
HERPESVÍRUS



HERPESVÍRUS

■ Organização do genoma

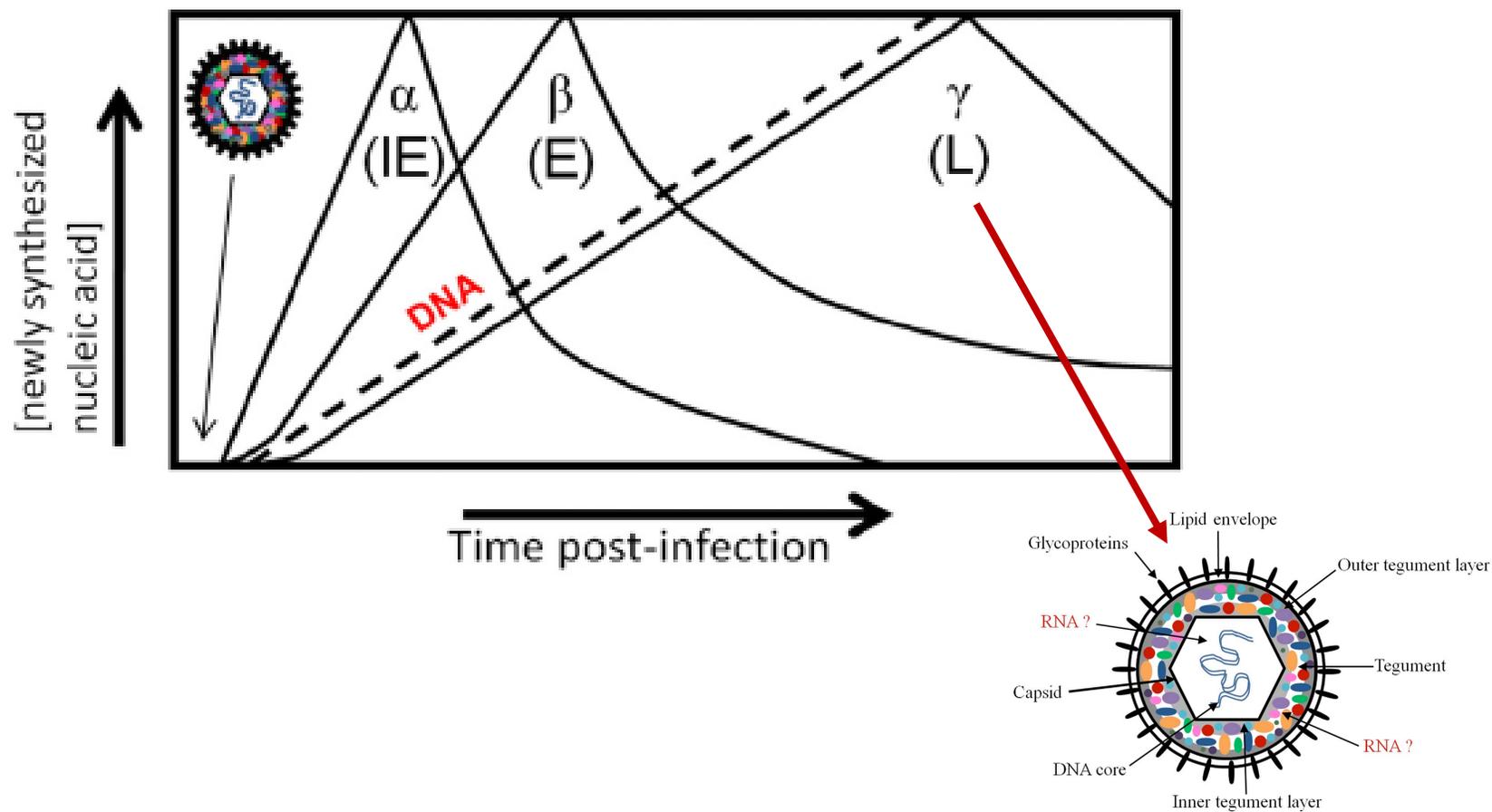
- Genoma formado por fragmento curtos e longos, orientados em “qualquer” direção, gerando 4 isômeros
- Sete blocos de genes conservados.



HERPESVÍRUS

■ Ciclo viral

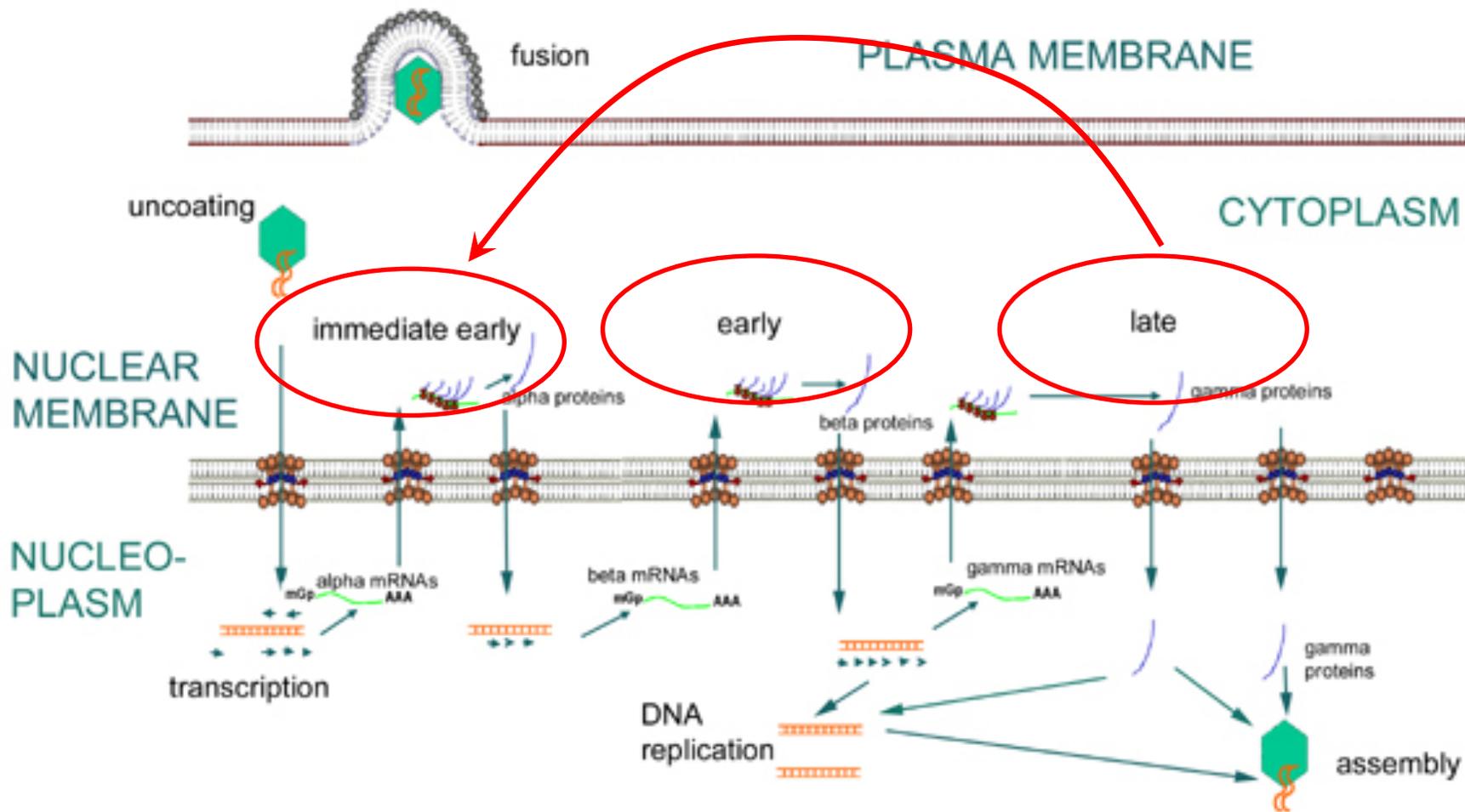
- Expressão dos genes precoces imediatos, precoces e tardios



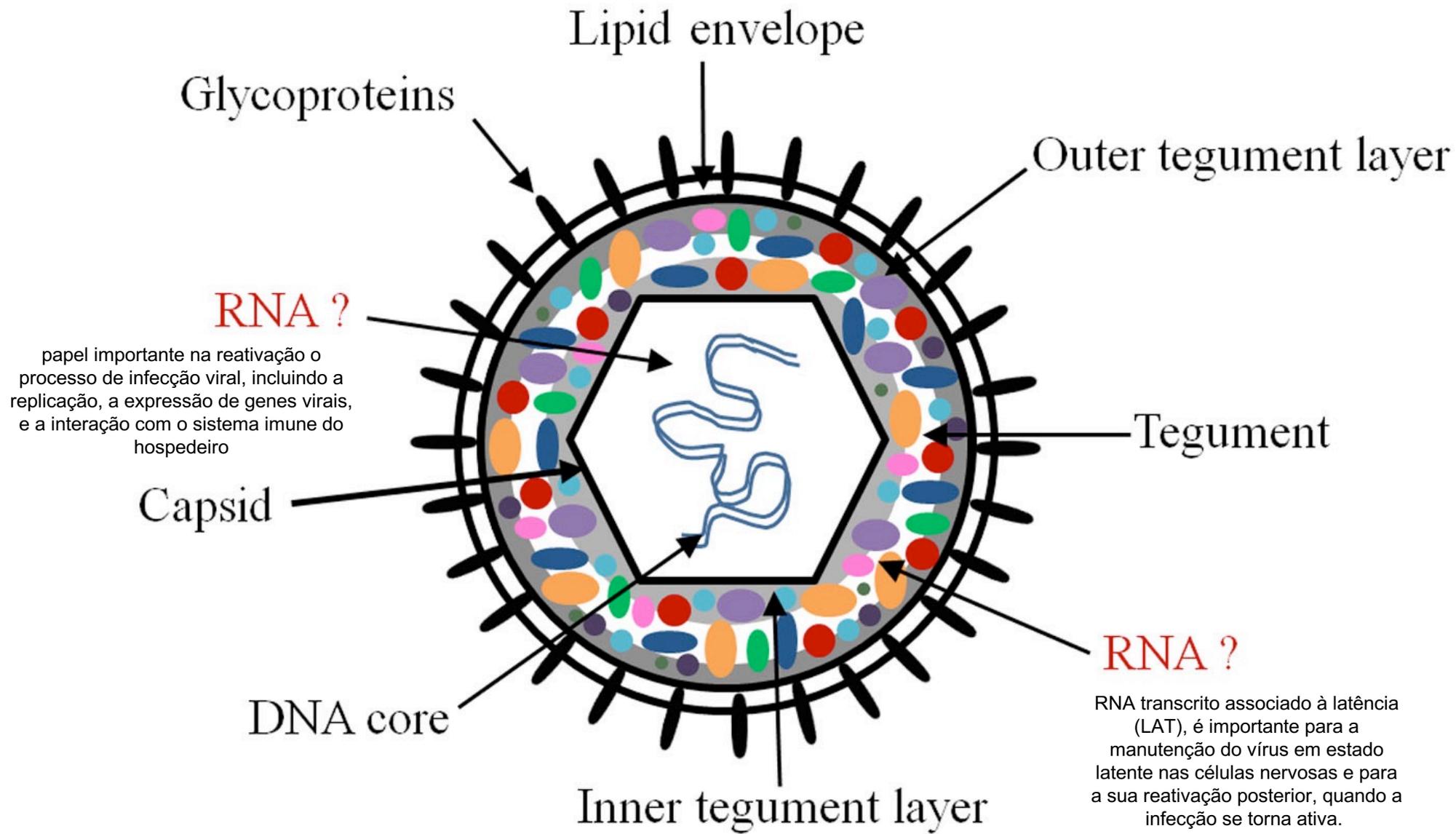
HERPESVÍRUS

■ Ciclo viral

- Expressão dos genes precoces imediatos, precoces e tardios



HERPESVÍRUS

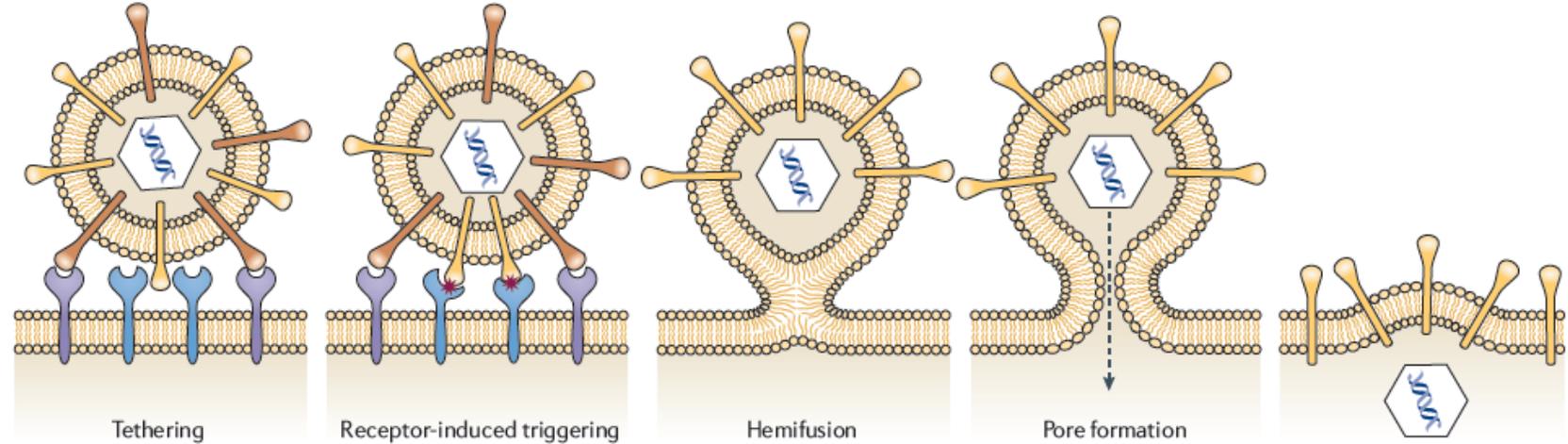


HERPESVÍRUS

REPLICAÇÃO: ADSORÇÃO E ENTRADA

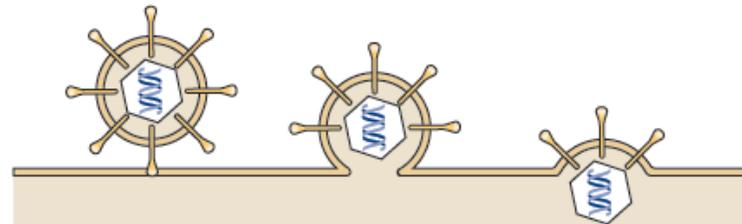
a

Binding to the host cell

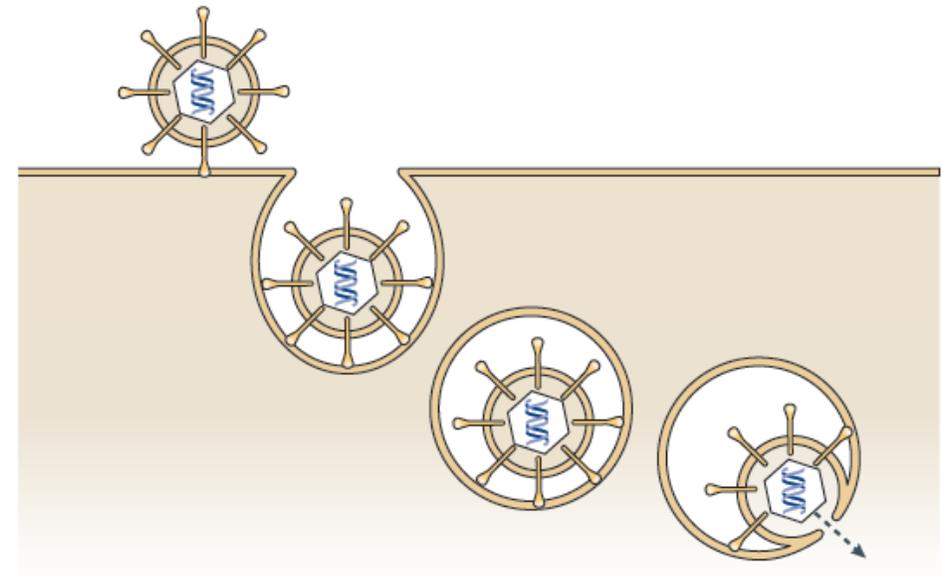


b

Fusion with the plasma membrane

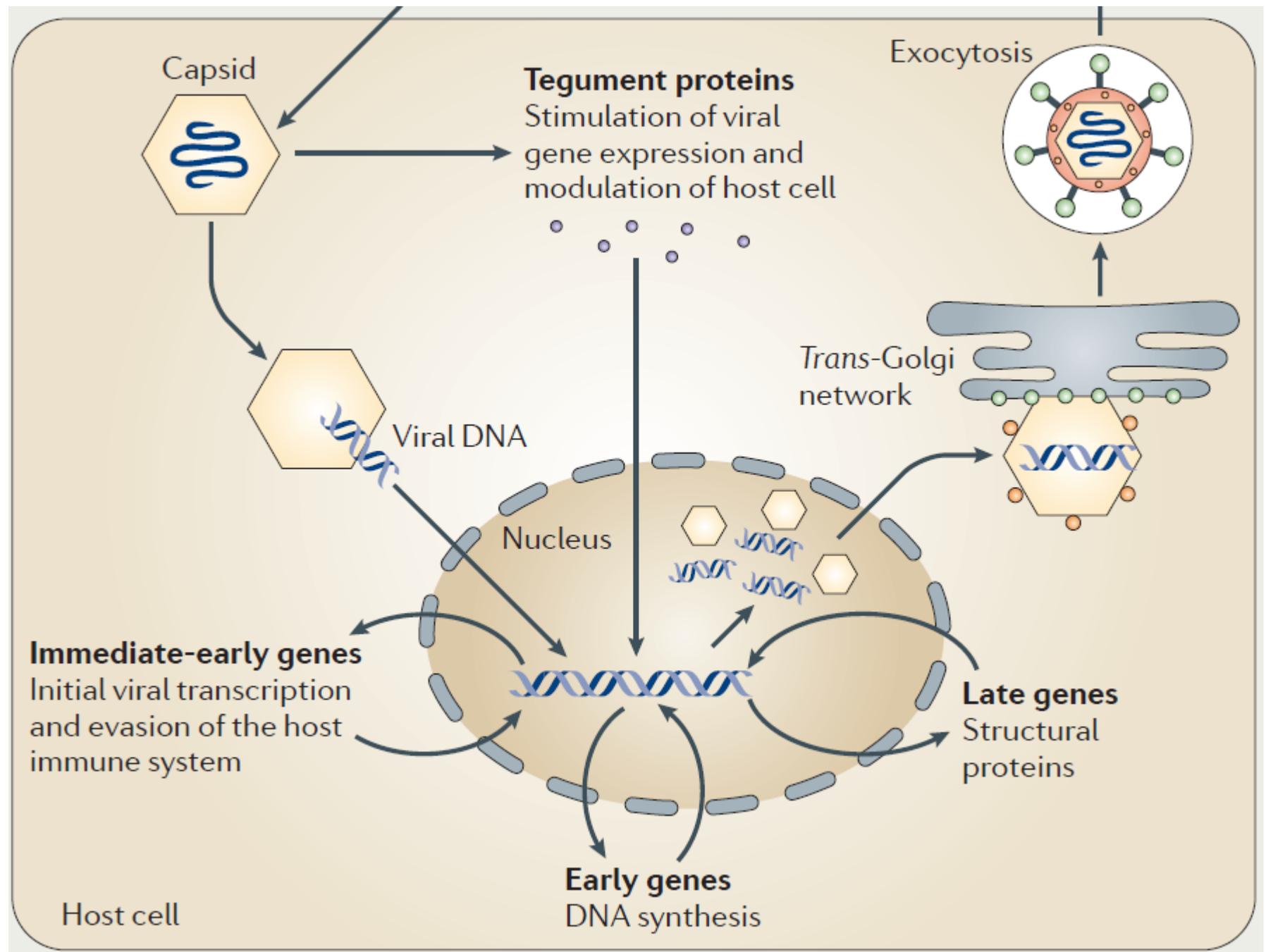


Fusion with the endocytic membrane



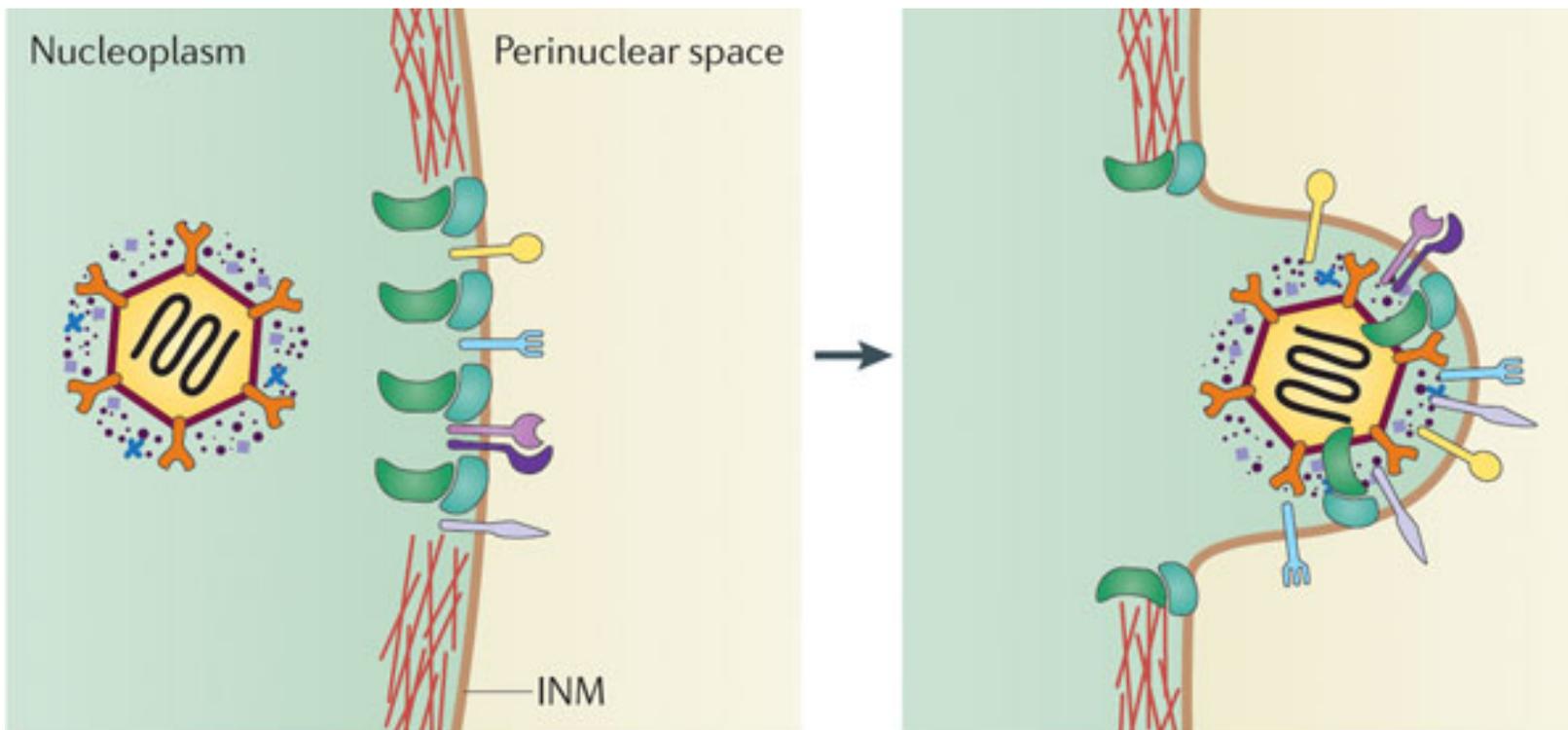
Herpes simplex virus (HSVs) e Epstein–Barr virus (EBV) podem entrar por fusão da membrana celular ou membrana endocítica e envelope

- DNA dupla fita: codifica pelo menos 100 transcritos
- Capsídeo icosaédrico: 162 capsômeros, incluindo quatro subunidades de proteínas
- Tegumento, uma camada amorfa de proteínas que é liberada na célula hospedeira após a infecção
- Envelope de bicamada de membrana lipídica, que é derivado da rede trans-Golgi da célula produtora
- Glicoproteínas (pelo menos 11) que estão incorporadas na bicamada lipídica.



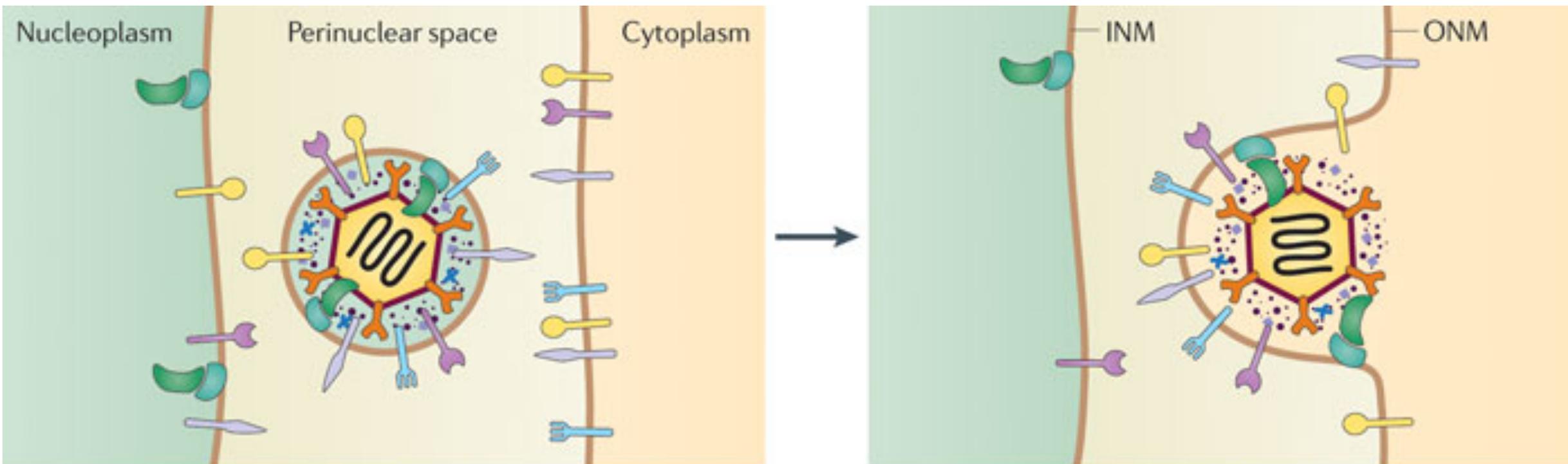
HERPESVÍRUS

REPLICAÇÃO: MONTAGEM E ADQUISIÇÃO DO ENVELOPE



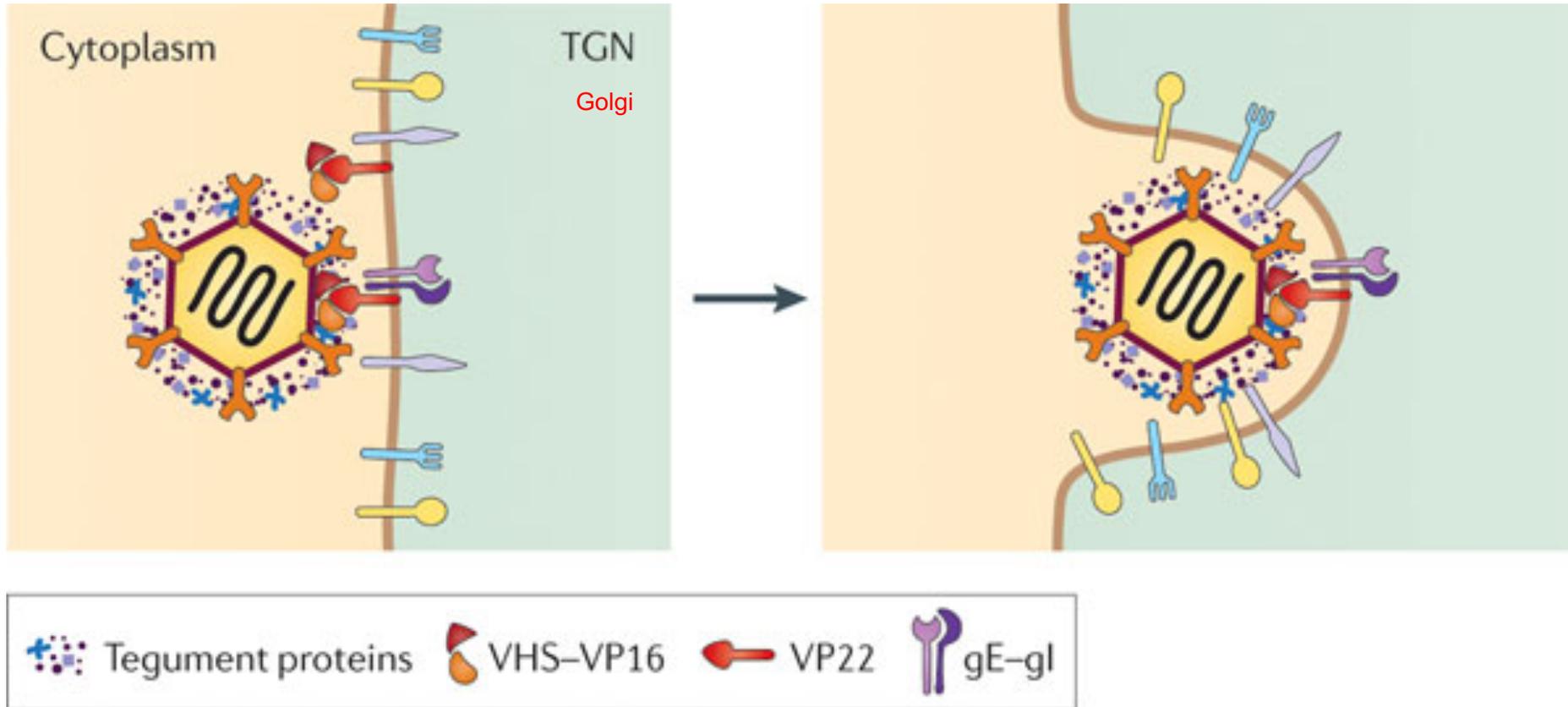
HERPESVÍRUS

REPLICAÇÃO: MONTAGEM E ADQUISIÇÃO DO ENVELOPE

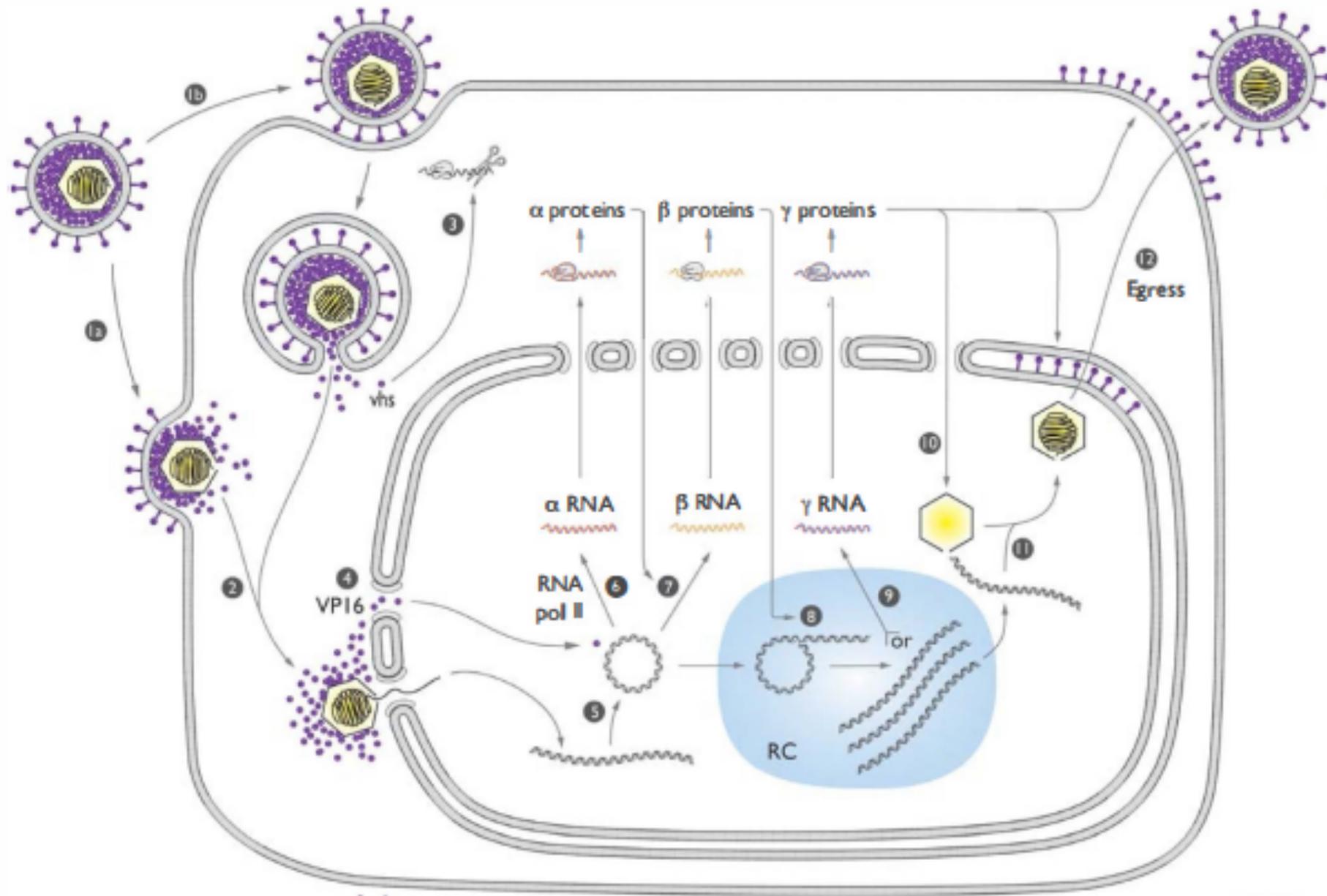


HERPESVÍRUS

REPLICAÇÃO: MONTAGEM E ADQUISIÇÃO DO ENVELOPE



REPLICAÇÃO: VISÃO GERAL



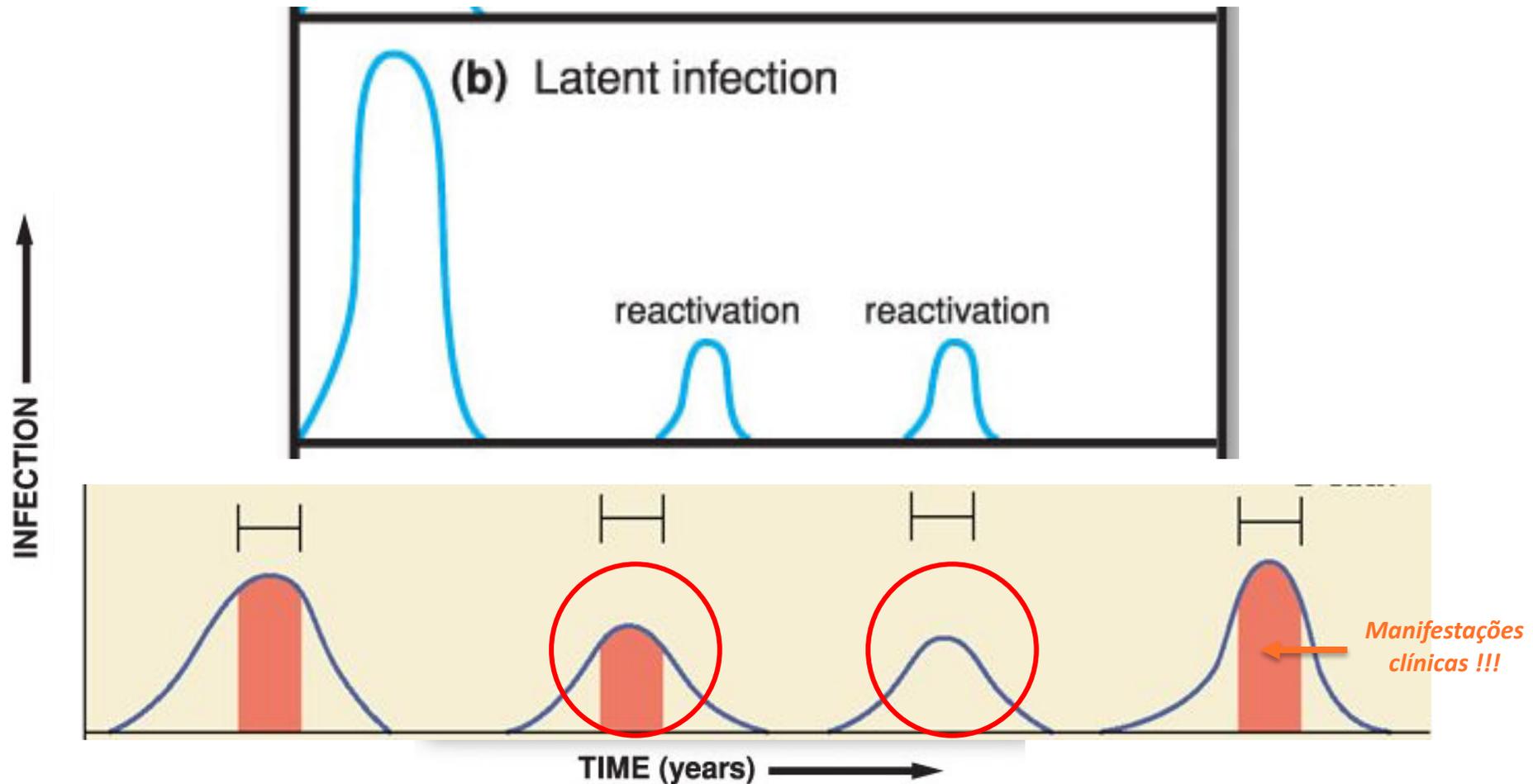
FAMÍLIA HERPESVIDAE

- 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 (pode haver manifestação subclínica)

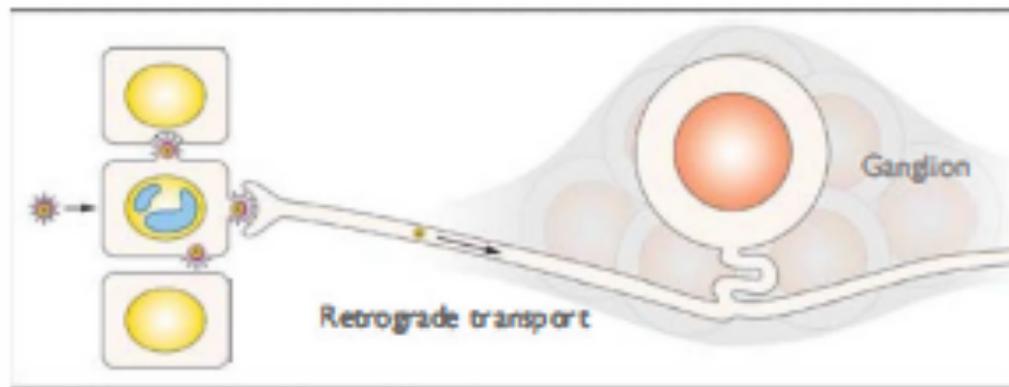
HERPESVÍRUS

INFECÇÃO LATENTE

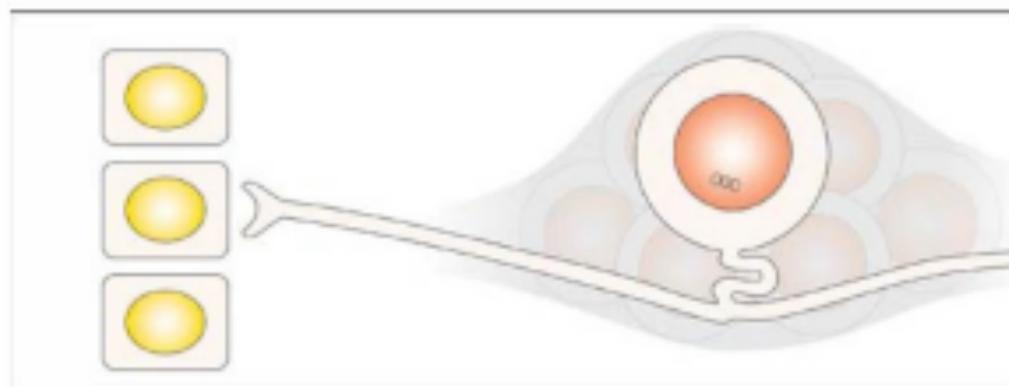
Latência - Estado transcricional e traducional único do vírus. O ciclo produtivo não funciona mas pode ser ativado a qualquer momento.



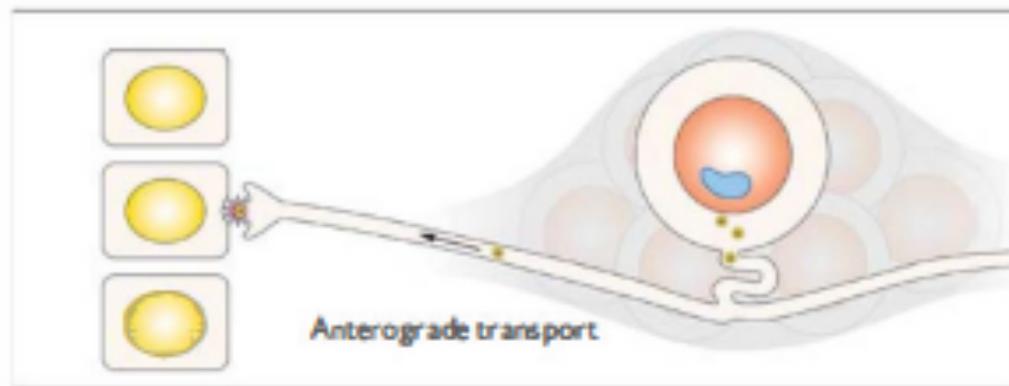
INFEÇÃO LATENTE e REATIVAÇÃO DO HSV



A Primary Infection and Establishment



B Latent Infection



C Reactivation and Recurrent Infection

Initiation of infection

Receptor binding
Membrane fusion at plasma membrane or after endocytosis
Management of intrinsic responses by tegument proteins
Transport of nucleocapsid and tegument-associated IE-activators to nucleus
Injection of viral genome through nuclear pores into nucleus
Genome chromatinization and initial interactions with transcriptional machinery

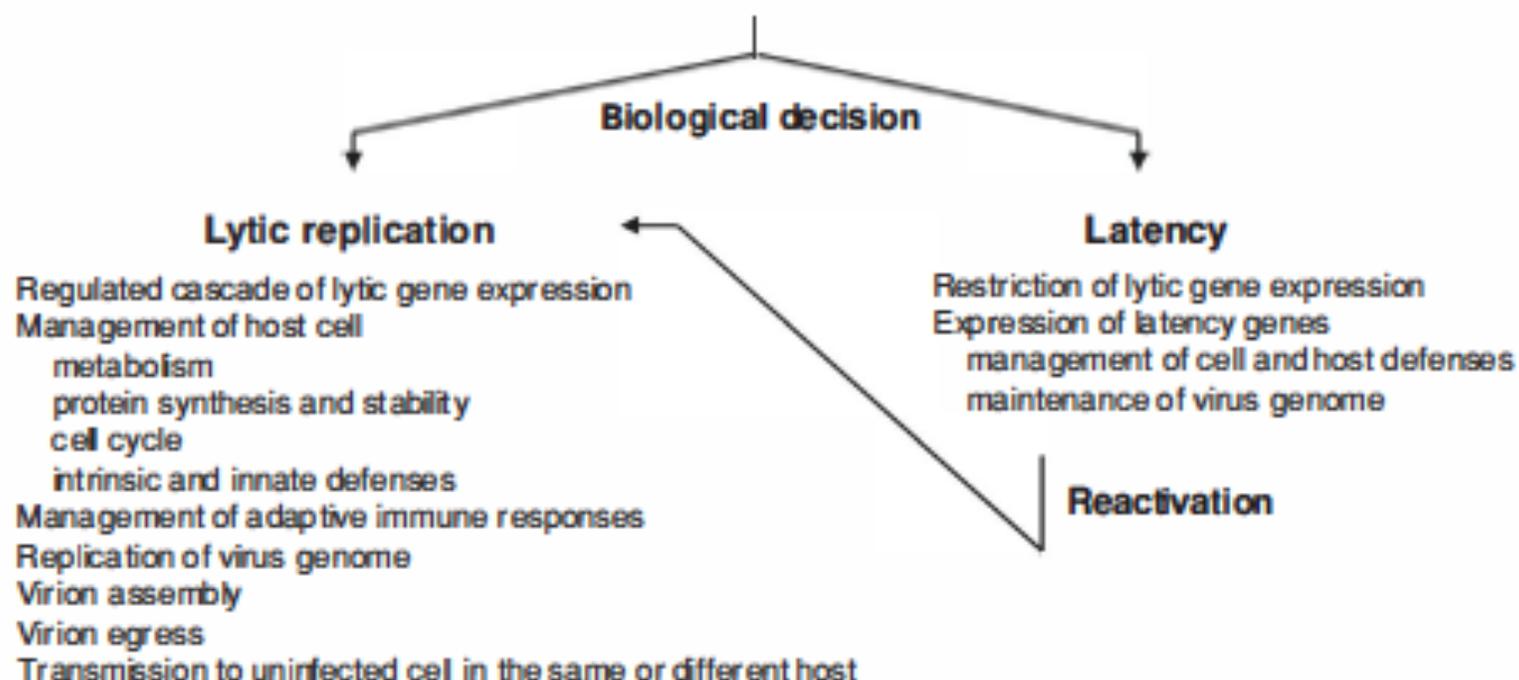
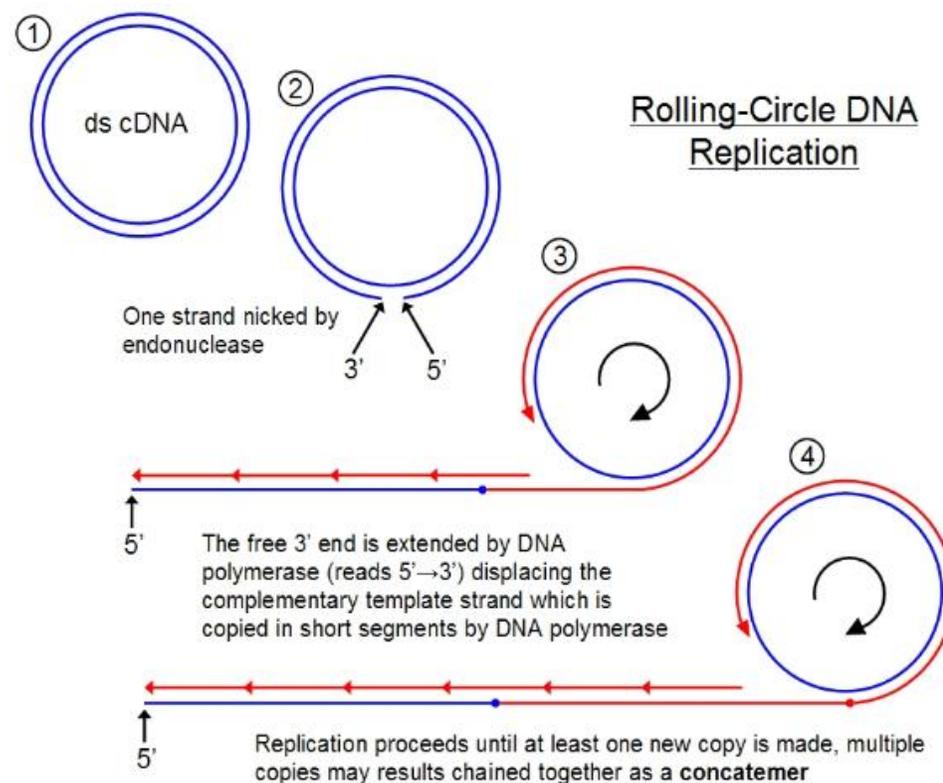


FIGURE 59.7. Herpesvirus biological cycle.

HERPESVÍRUS

REPLICAÇÃO DO GENOMA

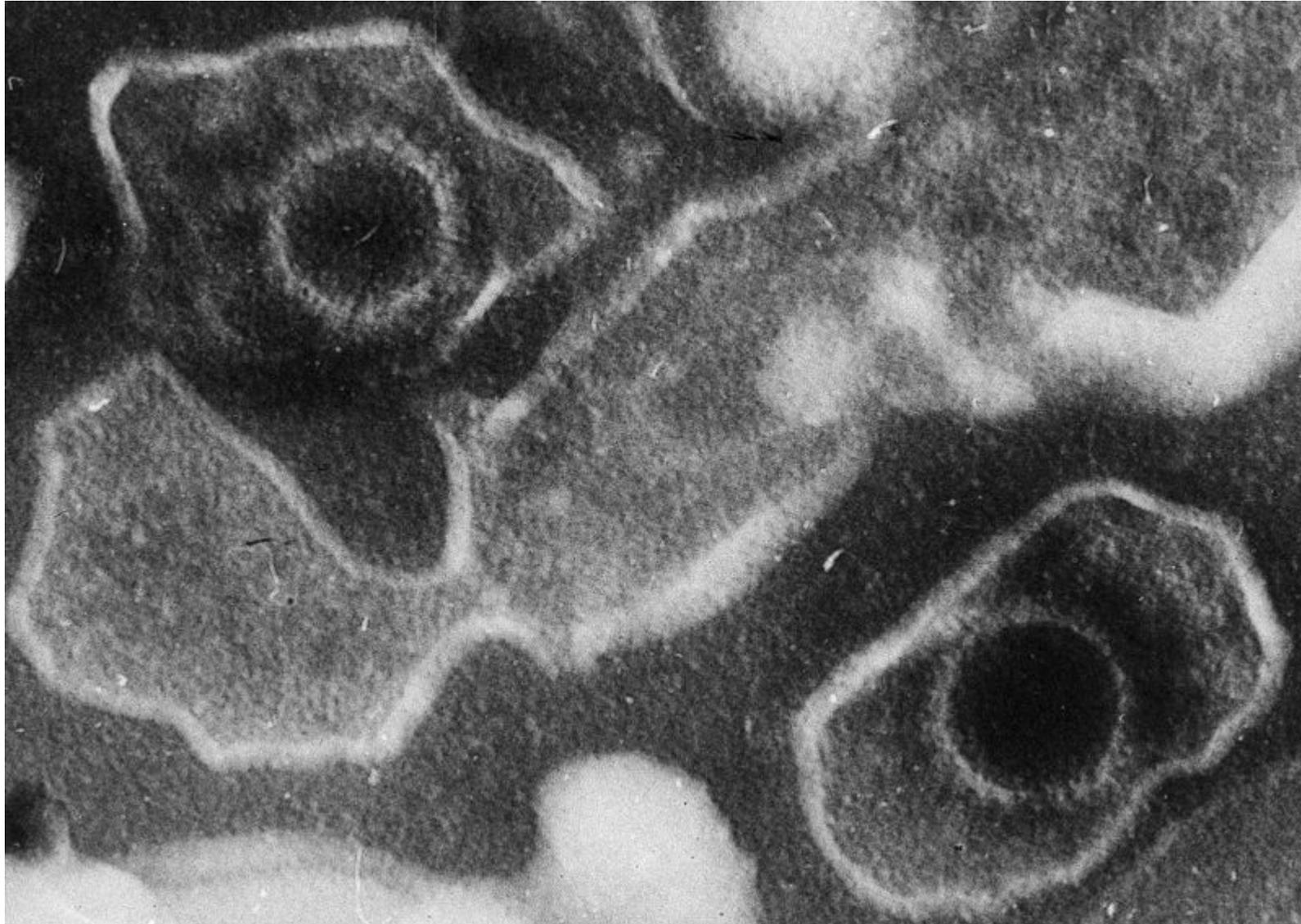
- A replicação acontece pelo mecanismo de “rolling circle” formando repetições em tandem.
- Finalmente estes repetidos são clivados.



Vírus Epstein-Barr (Herpesvírus 4)

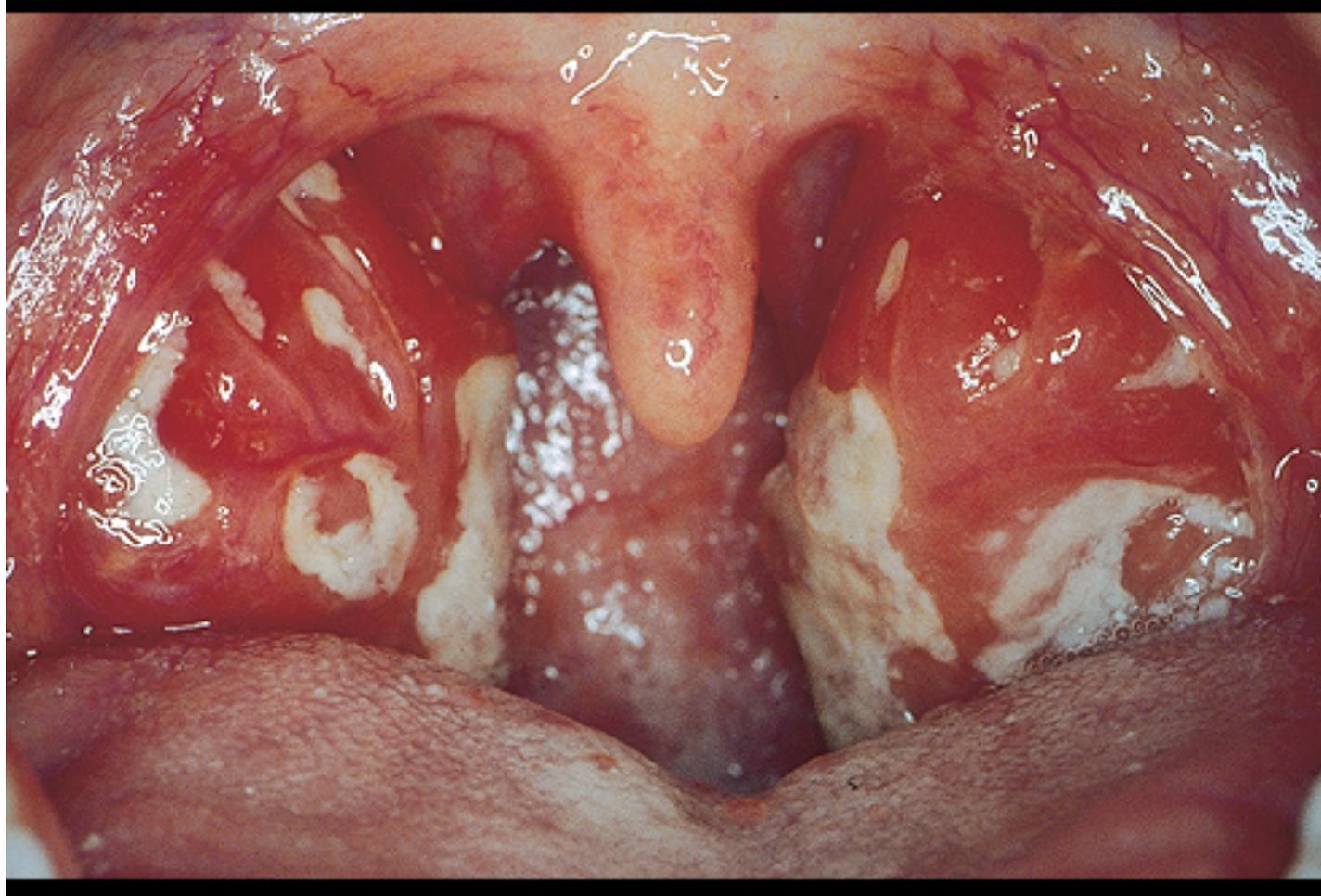
(mononucleose infecciosa)

Vírus Epstein-Barr (EBV)



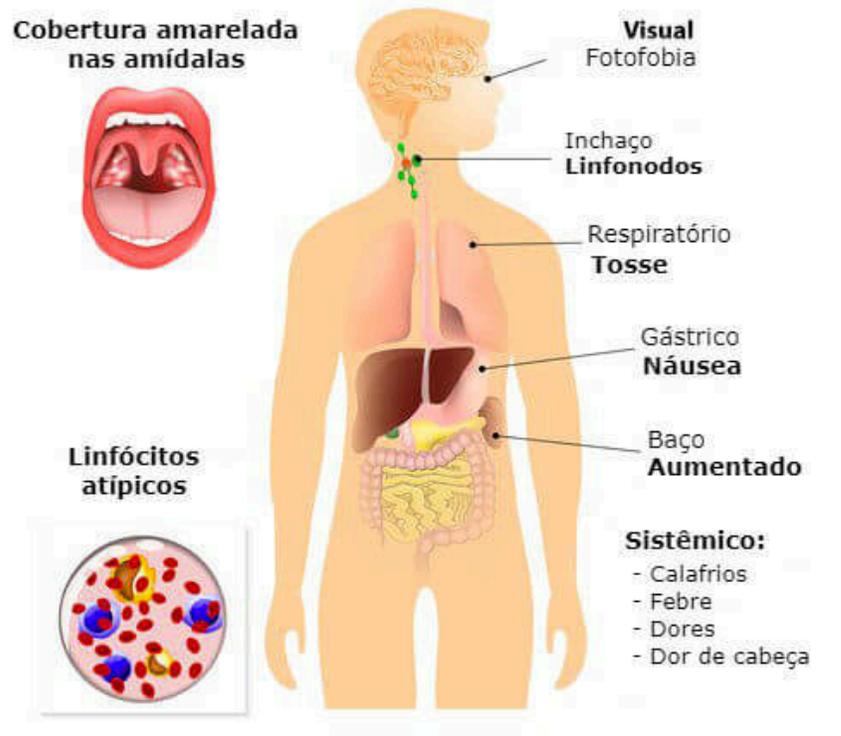
Vírus Epstein-Barr (EBV)

- Mononucleose



- Faringite e adenopatias...

Mononucleose

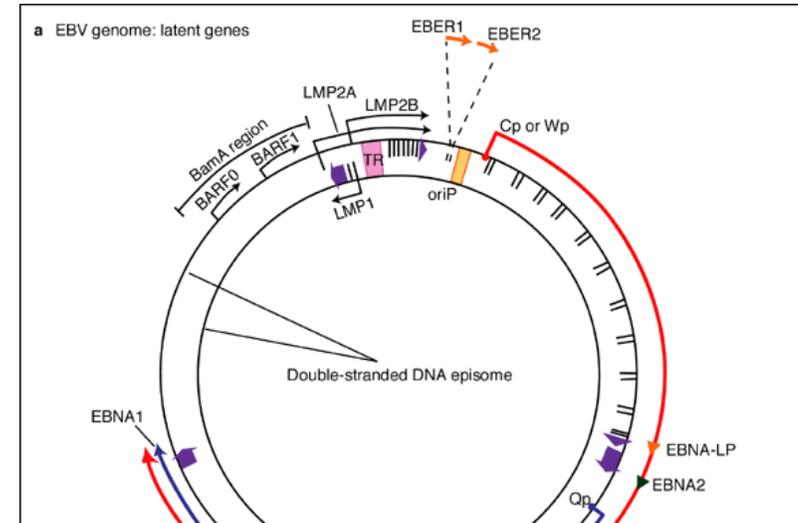
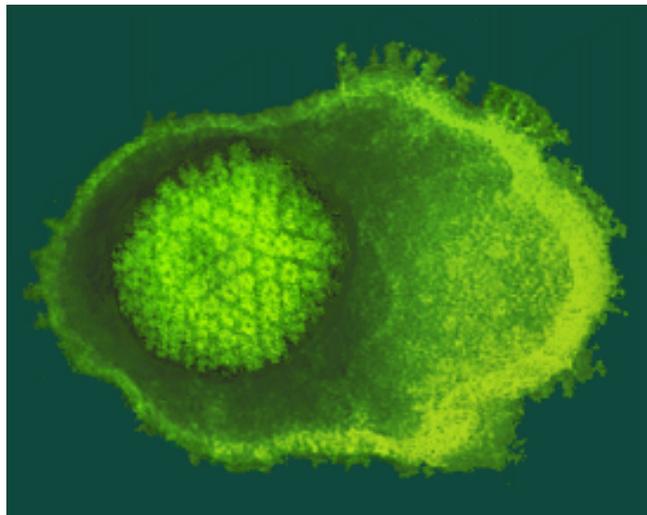


A mononucleose infecciosa é causada pelo vírus Epstein-Barr (herpes-vírus humano tipo 4) e caracteriza-se por fadiga, febre, faringite e linfadenopatia. A fadiga pode persistir durante semanas ou meses. Complicações graves, incluindo obstrução das vias respiratórias, ruptura esplênica e síndromes neurológicas, ocorrem de maneira ocasional.

Vírus Epstein-Barr (EBV)

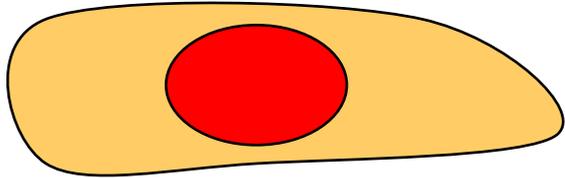
Receptor: CD21 (linfócitos B e células epiteliais da naso- e orofaringe)

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

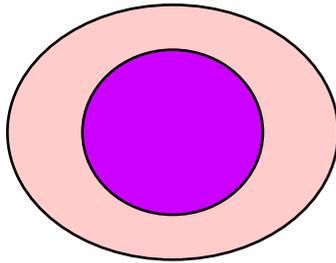


- Etiologicamente associado com:
- Mononucleose
- Linfoma de Burkitt,
- Doença de Hodgkin
- Carcinoma naso-faríngeo

Vírus Epstein-Barr (EBV)



As células epiteliais permitem o ciclo lítico completo.



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.

HERPESVÍRUS

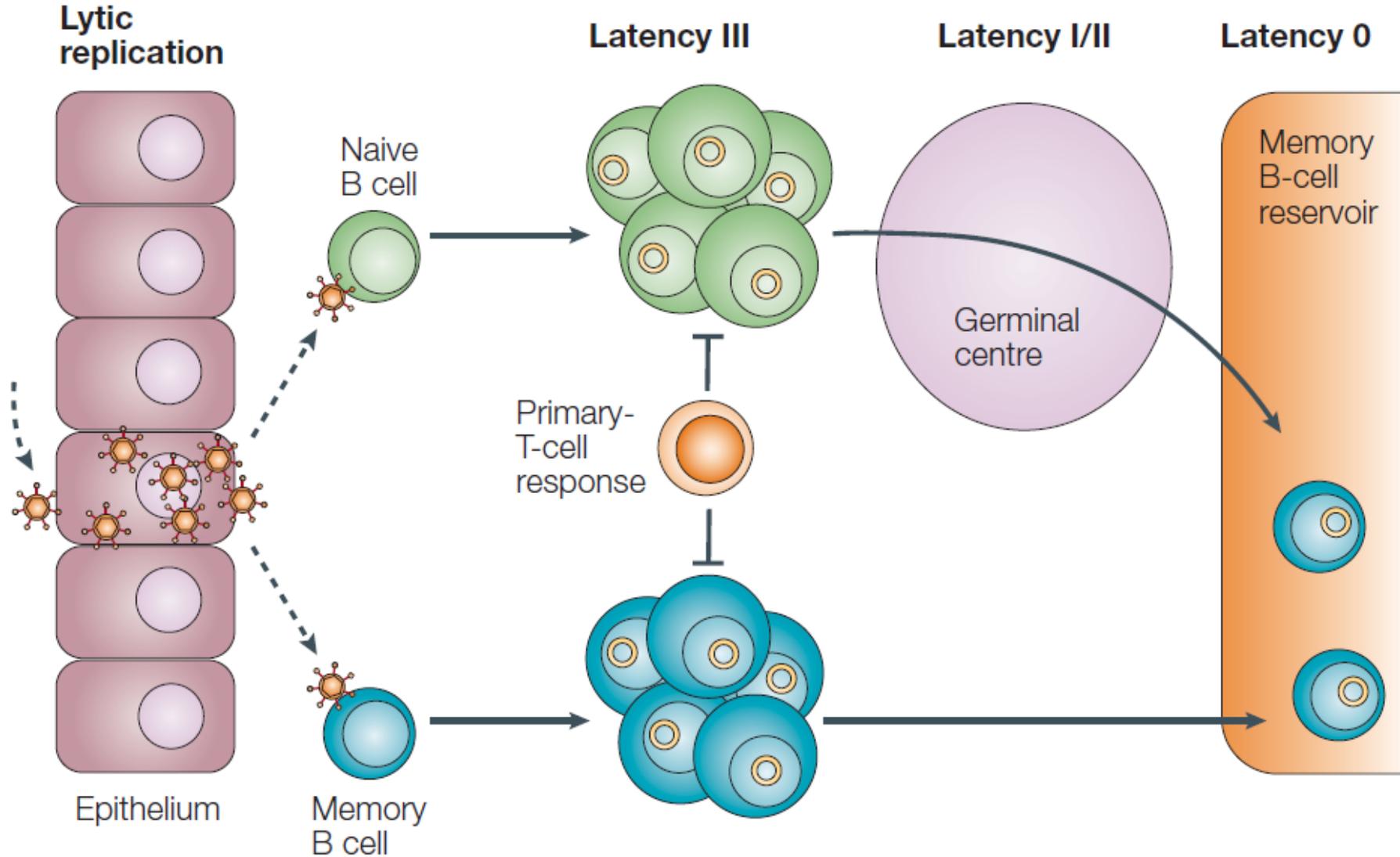
Table 1 | **Human herpesviruses**

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.

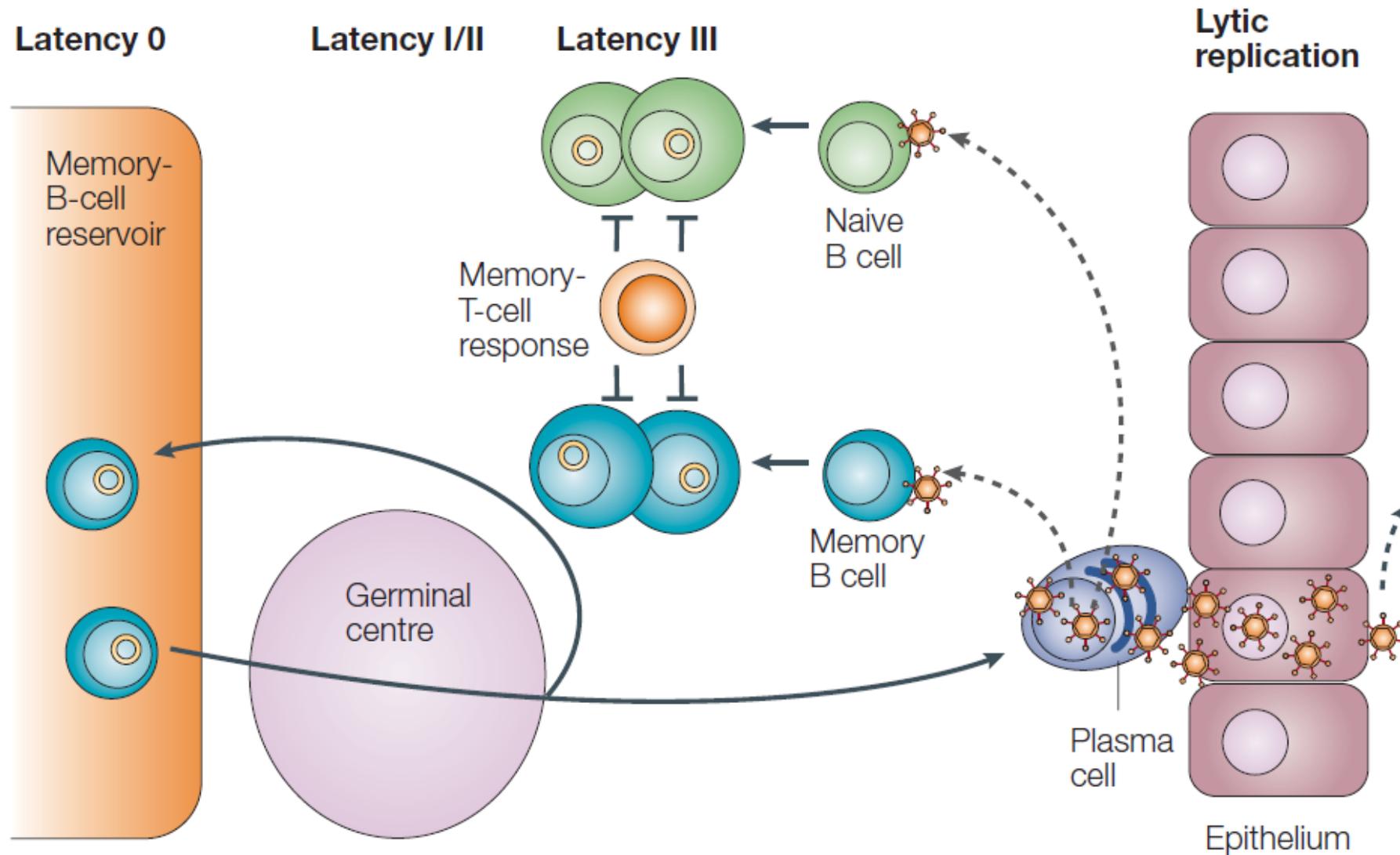
Virus Epstein-Barr (EBV)

a Primary infection

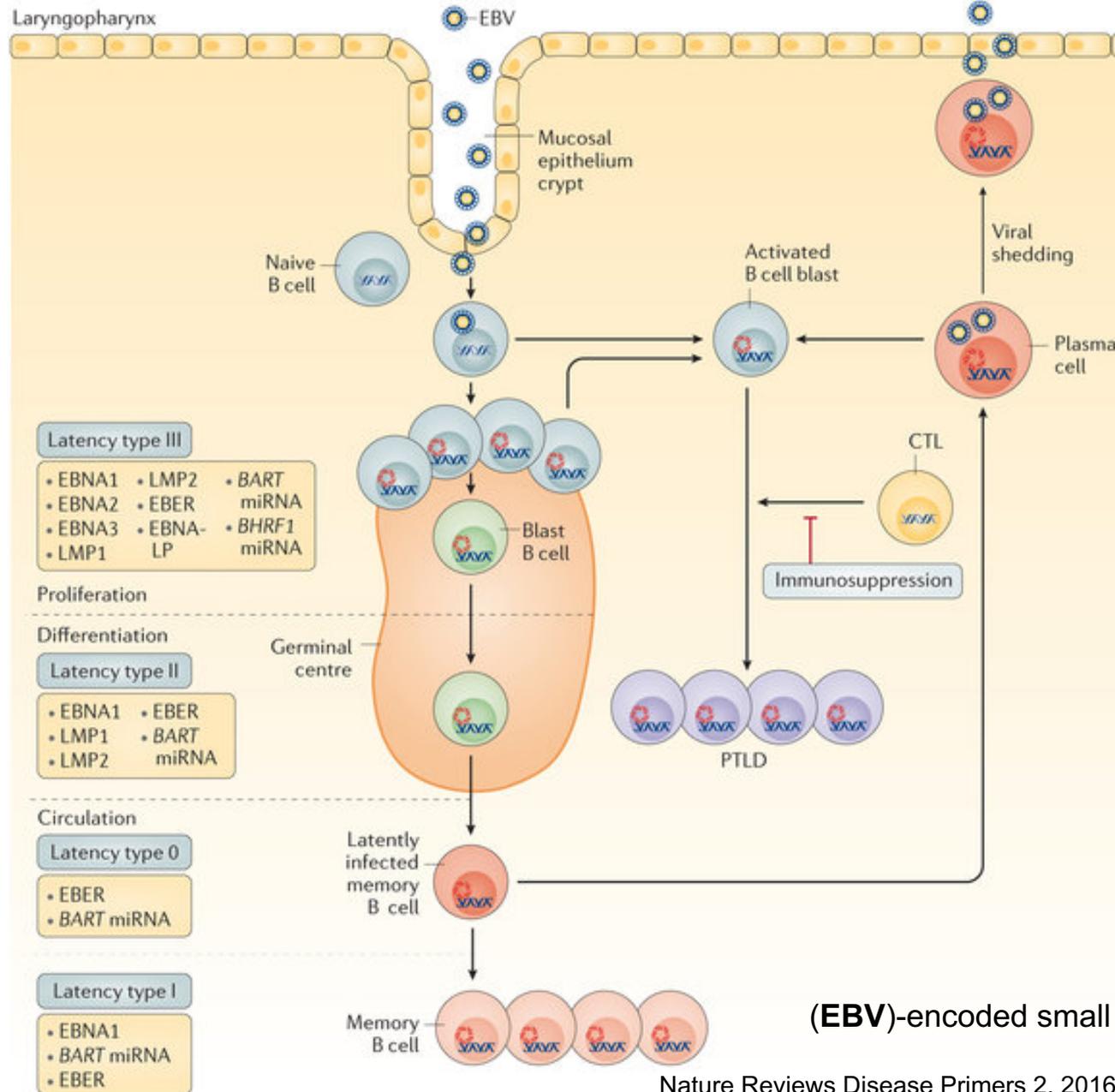


Virus Epstein-Barr (EBV)

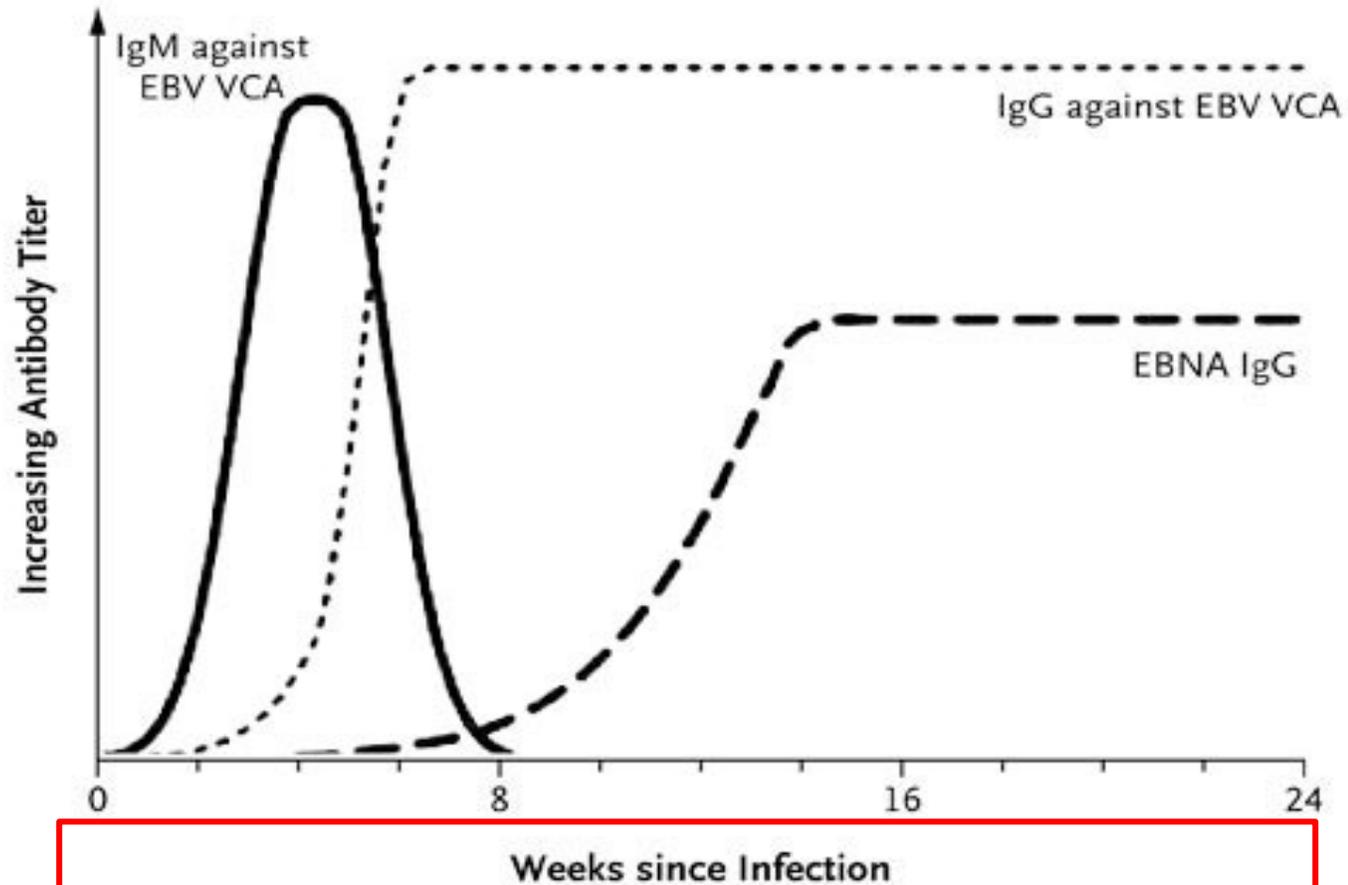
b Persistent infection



Virus Epstein-Barr (EBV)



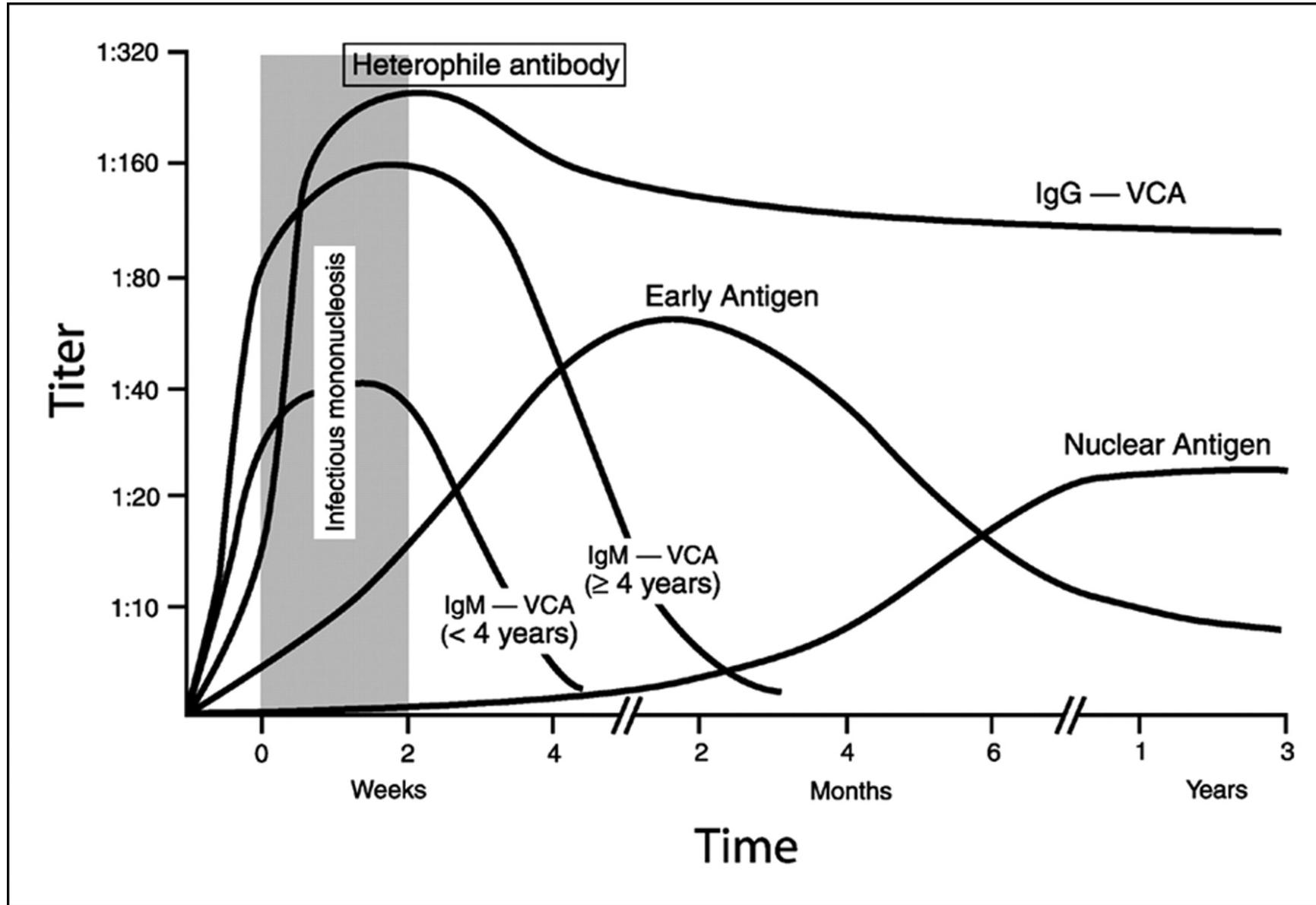
DIAGNÓSTICO



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

DIAGNÓSTICO

O diagnóstico é clínico ou feito por testes de anticorpos heterófilos.



Laboratory Testing

Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a gamma herpes virus that occurs only in humans. Laboratory testing can help distinguish whether someone is susceptible to EBV infection or has a recent or past infection.

Healthcare providers can test for antibodies to the following EBV-associated antigens:

- **Viral capsid antigen (VCA)**

- Anti-VCA IgM appears early in EBV infection and usually disappears within four to six weeks.
- Anti-VCA IgG appears in the acute phase of EBV infection, peaks at two to four weeks after onset, declines slightly then persists for the rest of a person's life.

- **Early antigen (EA)**

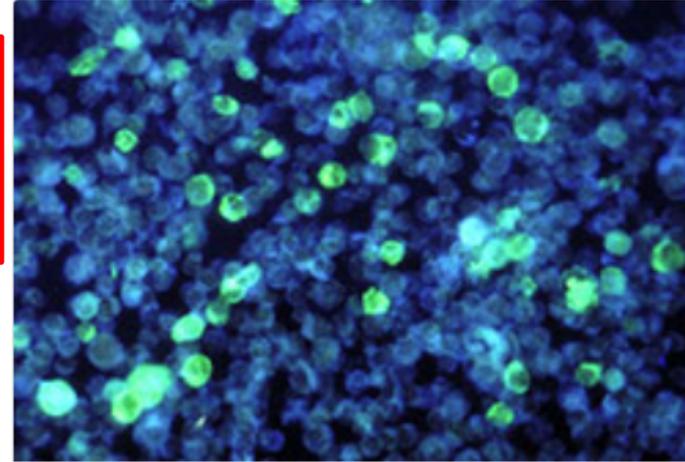
Anti-EA IgG appears in the acute phase of illness and generally falls to undetectable levels after three to six months. In many people, detection of antibody to EA is a sign of active infection. However, 20% of healthy people may have antibodies against EA for years.

- **EBV nuclear antigen (EBNA)**

Antibody to EBNA, determined by the standard immunofluorescent test, is not seen in the acute phase of EBV infection but slowly appears two to four months after onset of symptoms and persists for the rest of a person's life. Other EBNA enzyme immunoassays may report false positive results.

- **Monospot test**

The Monospot test is not recommended for general use. The antibodies detected by Monospot can be caused by conditions other than infectious mononucleosis. Moreover, studies have shown that the Monospot produces both false positive and false negative results. For example, the heterophile antibodies detected by Monospot are often not present in children with infectious mononucleosis. At best, the Monospot test may indicate that a person has a typical case of infectious mononucleosis, but does not confirm the presence of EBV infection.



This photomicrograph depicts leukemia cells that contain Epstein-Barr virus using an FA staining technique.

“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

O tratamento é de suporte.

Vírus Epstein-Barr (EBV)

Linfoma de Burkitt



Vírus Epstein-Barr (EBV)

Leucoplasia pilosa



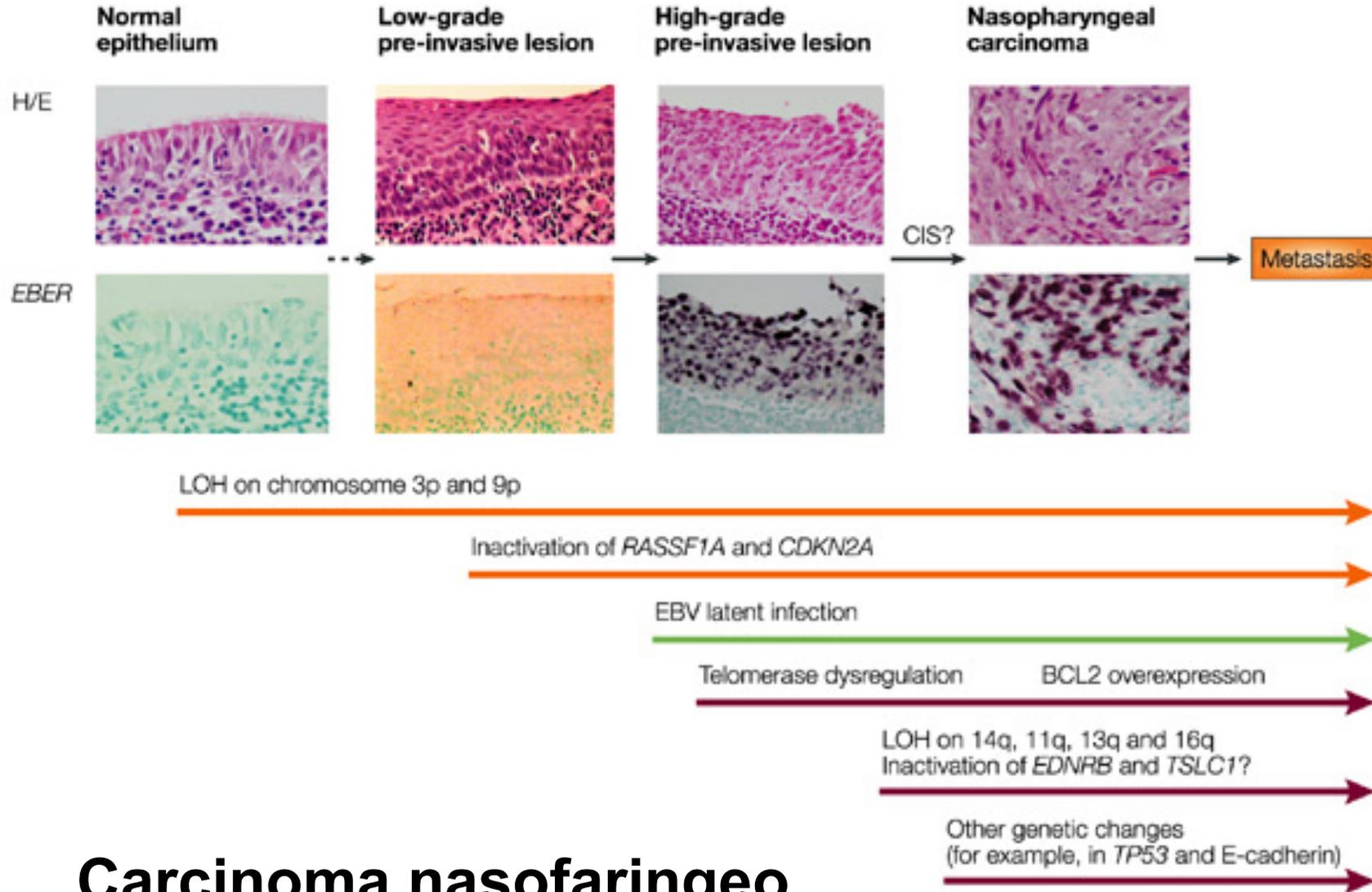
Vírus Epstein-Barr (EBV)

Carcinoma nasofaríngeo

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

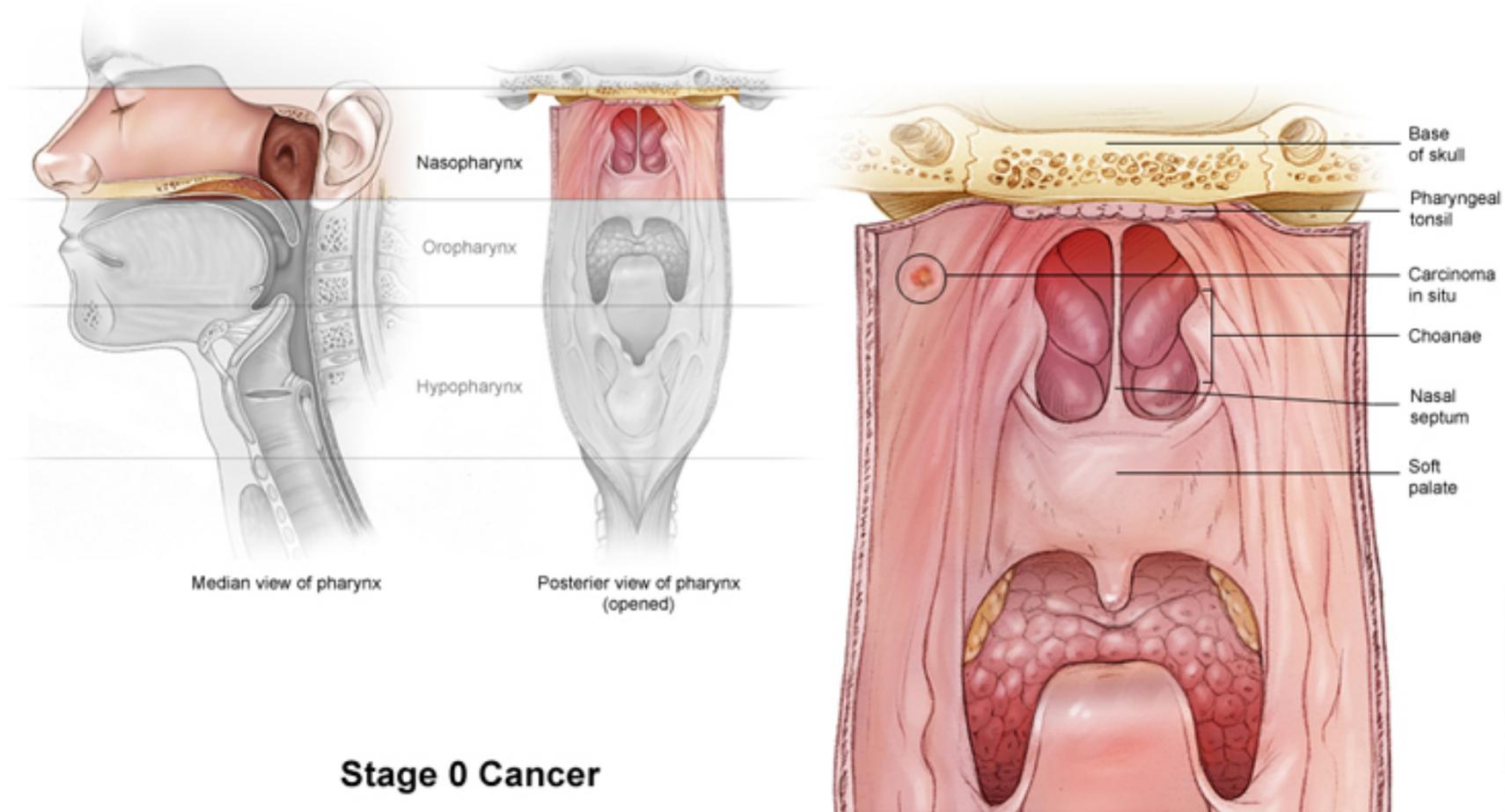
Virus Epstein-Barr (EBV)



Carcinoma nasofaringeo

Virus Epstein-Barr (EBV)

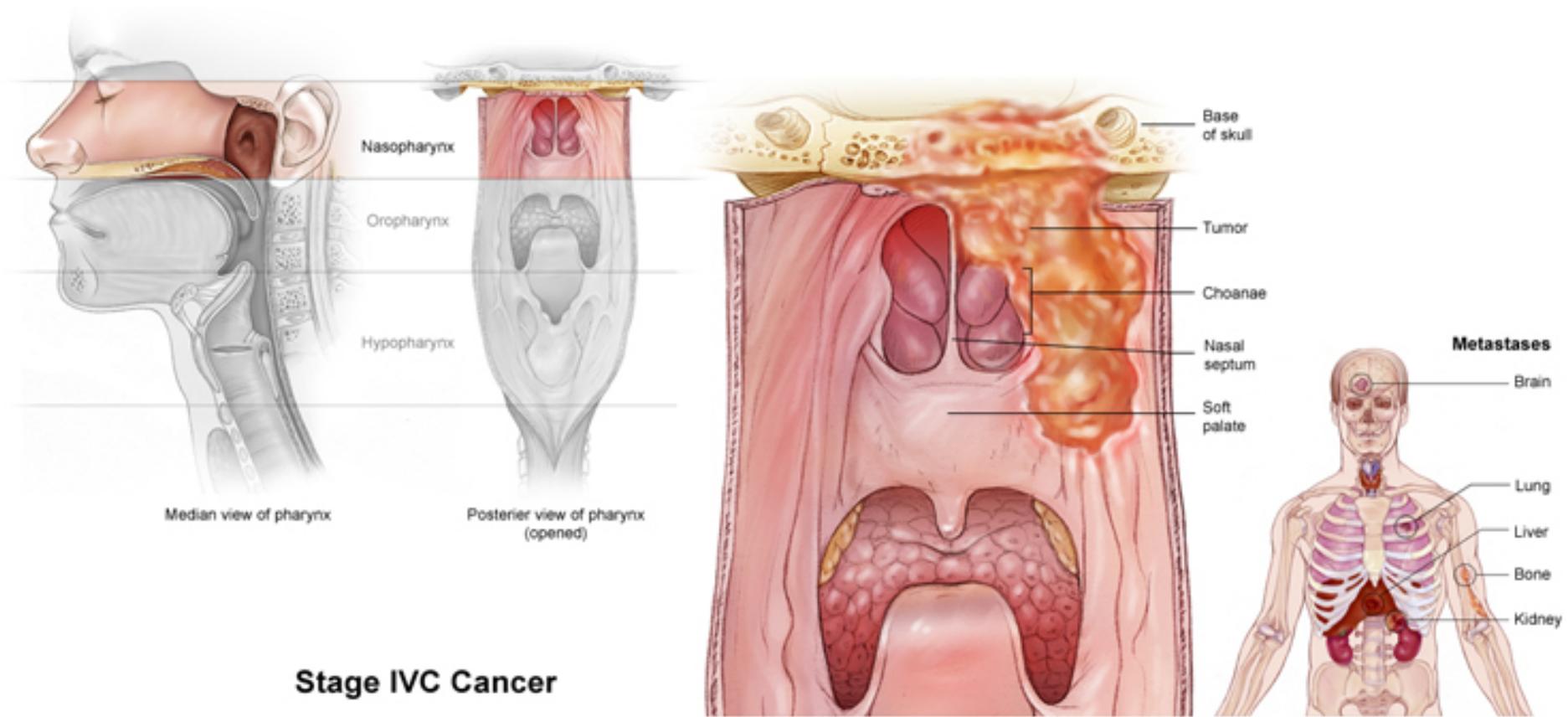
Carcinoma nasofaringeo



Stage 0 Cancer

Virus Epstein-Barr (EBV)

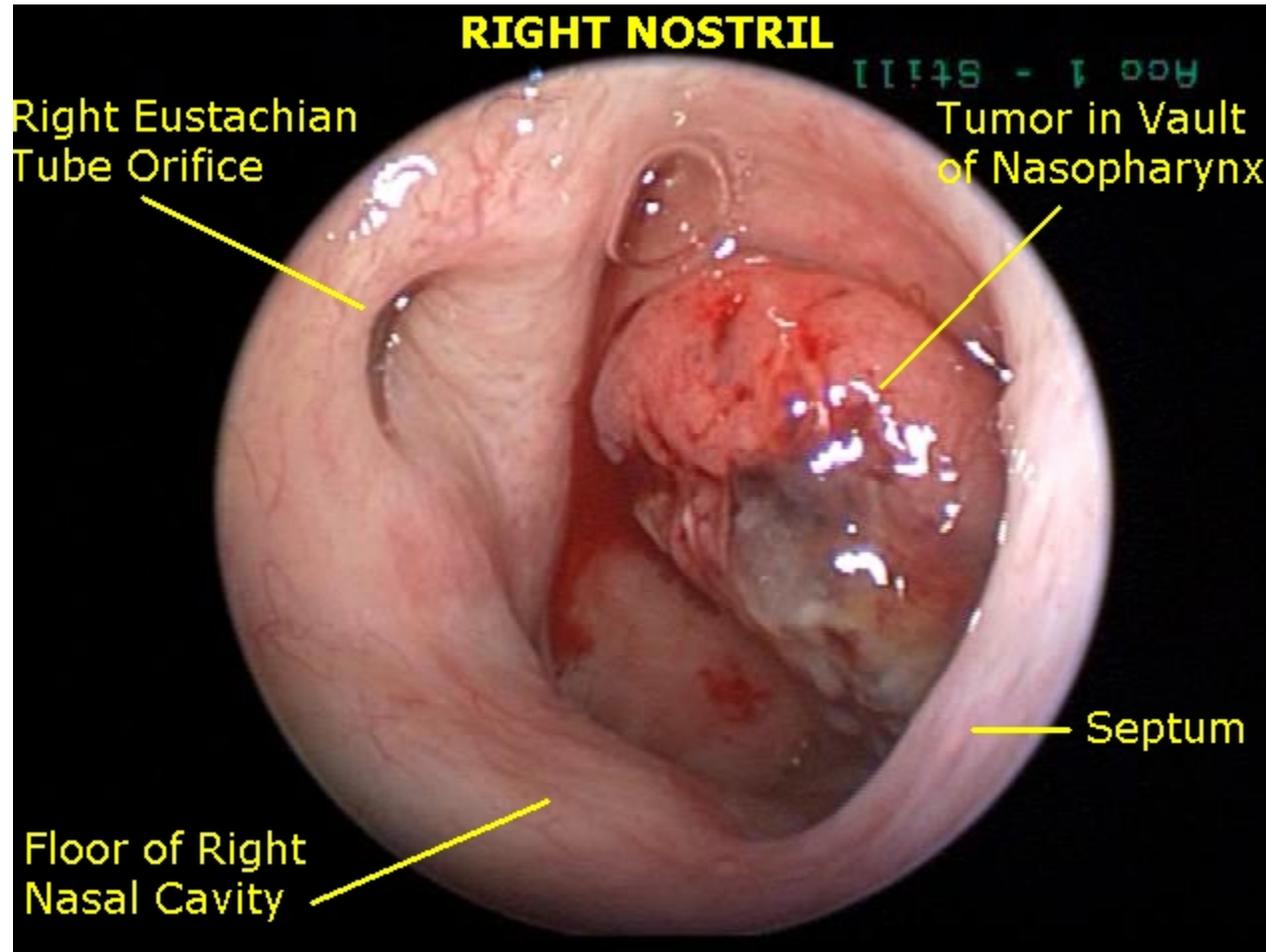
Carcinoma nasofaringeo



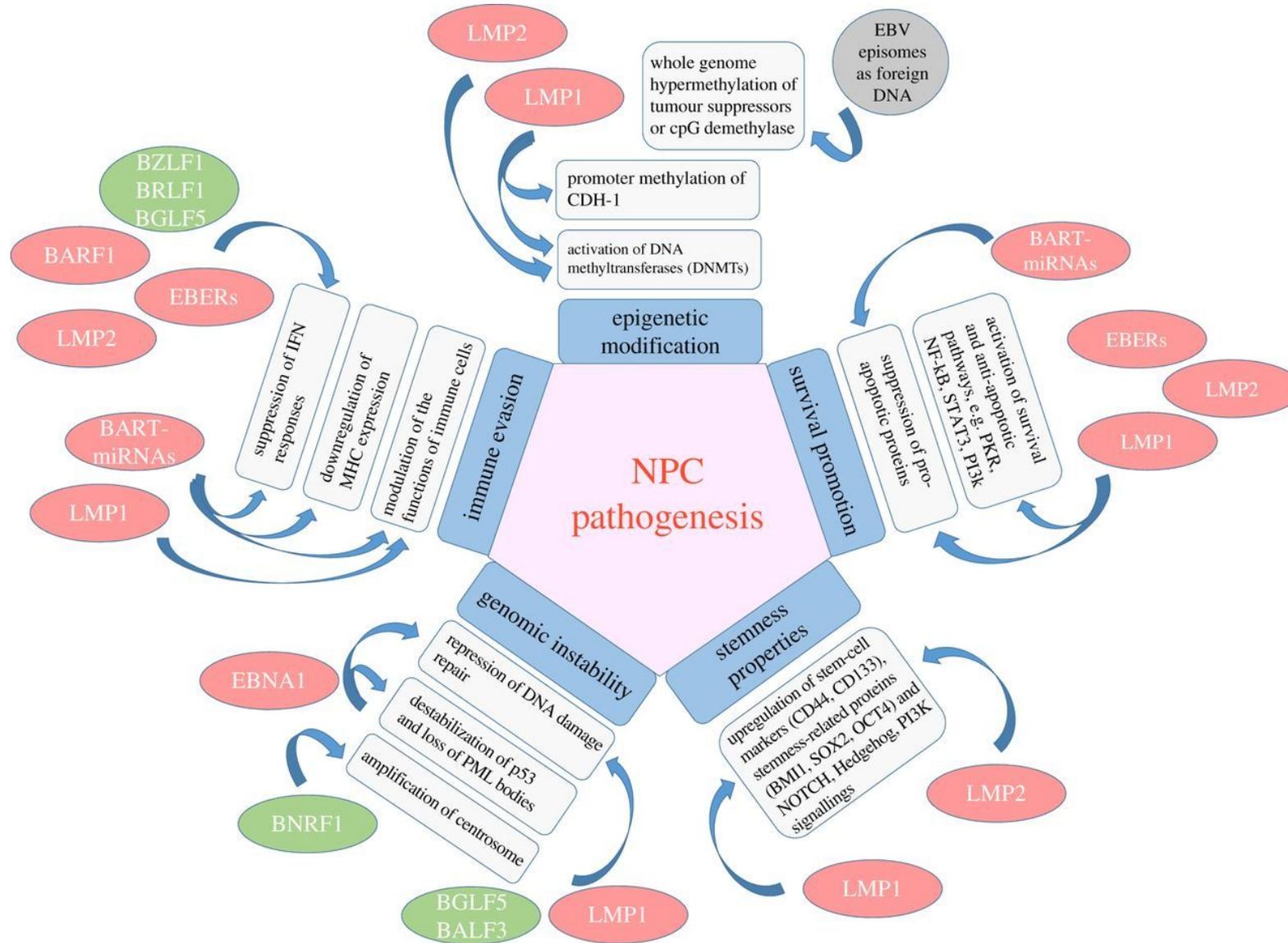
Stage IVC Cancer

Virus Epstein-Barr (EBV)

Carcinoma nasofaringeo



EBV: Carcinoma nasofaringeo



PRENATAL: TORCHS

TOXOPLASMOSE

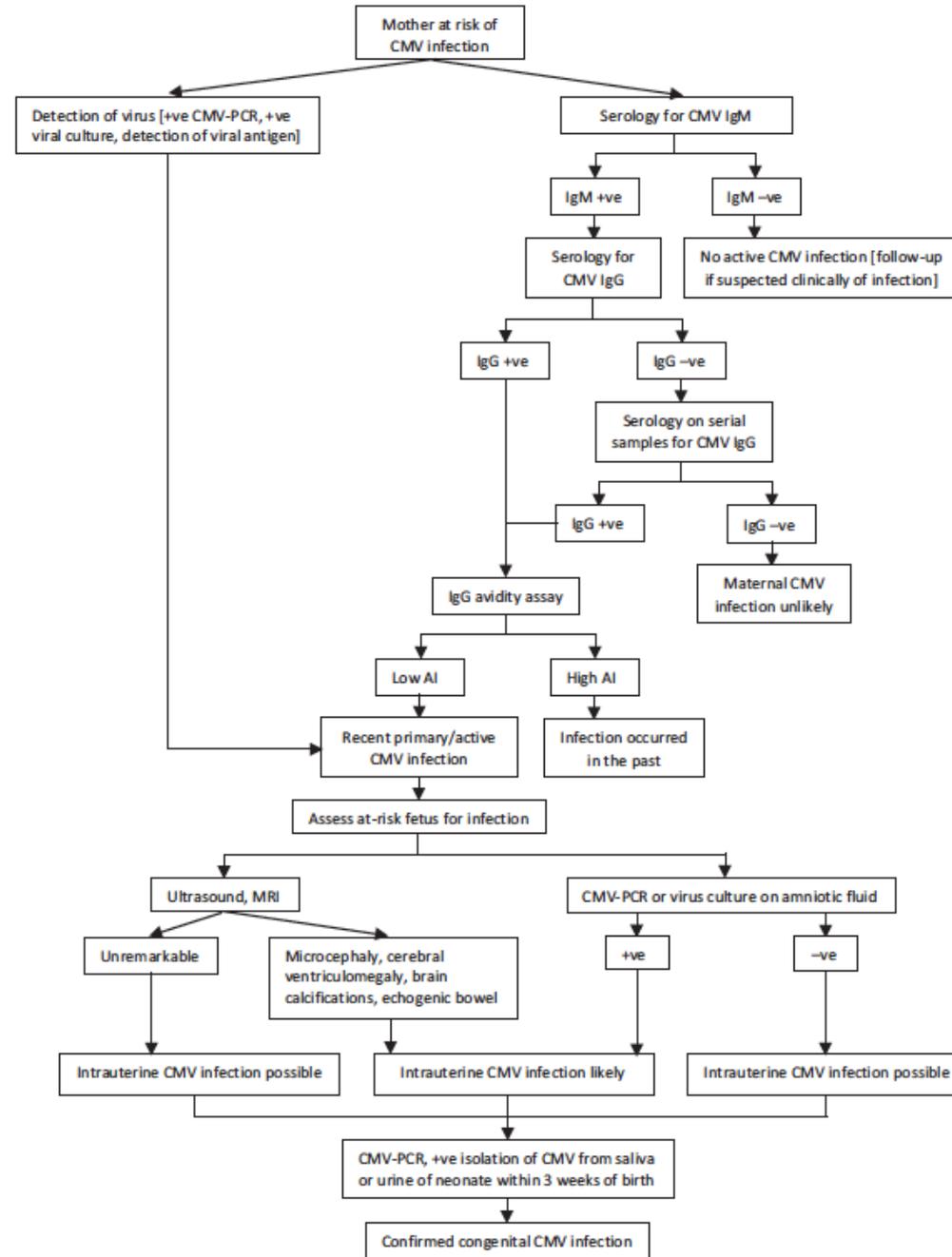
RUBÉOLA

CMV

HSV, HIV

SÍFILIS

- **PODEM INFECTAR O FETO**
- **OUTROS VIRUS PODEM INFECTAR E CAUSAR A MORTE DA MAE E DO FETO (EBOLA, INFLUENZA, LASSA FEVER)**



CITOMEGALOVIRUS (CMV)

- Herpesviridae, DNA, icosaédrico, envelopado
- Transmissão secreções nasofaringeais, urina, saliva, semem, secreções vaginiais e cervicais, leite, tecidos ou sangue
- Soroprevalência aumenta com a idade, área geográfica e classe social
- Infecta 60% de mulheres até a adolescência em países desenvolvidos e 90% em subdesenvolvidos

CITOMEGALOVIRUS na gestação

- Infecção primária ocorre em 1 a 4%
- Reativação de Infecção em 10% de mulheres soropositivas
- Infecção materna manifesta-se como febre leve, fadiga, mialgia, renite, faringite e dor de cabeça
- Ac principal fator contra infecção congênita, por isso mais comum em países desenvolvidos

CITOMEGALOVIRUS na gestação

- Transmissão vertical: ocorre em casos de infecção primária
- CMV é o vírus causador de infecção congênita mais comum (0,2 a 2,5%)
- Afeta nervos cranianos, surdez, SNC
- Quanto mais avançada a gestação menos grave a doença no feto
- Gestação avançada inversamente proporcional a gravidade da doença
- Hepatoesplenomegalia no feto

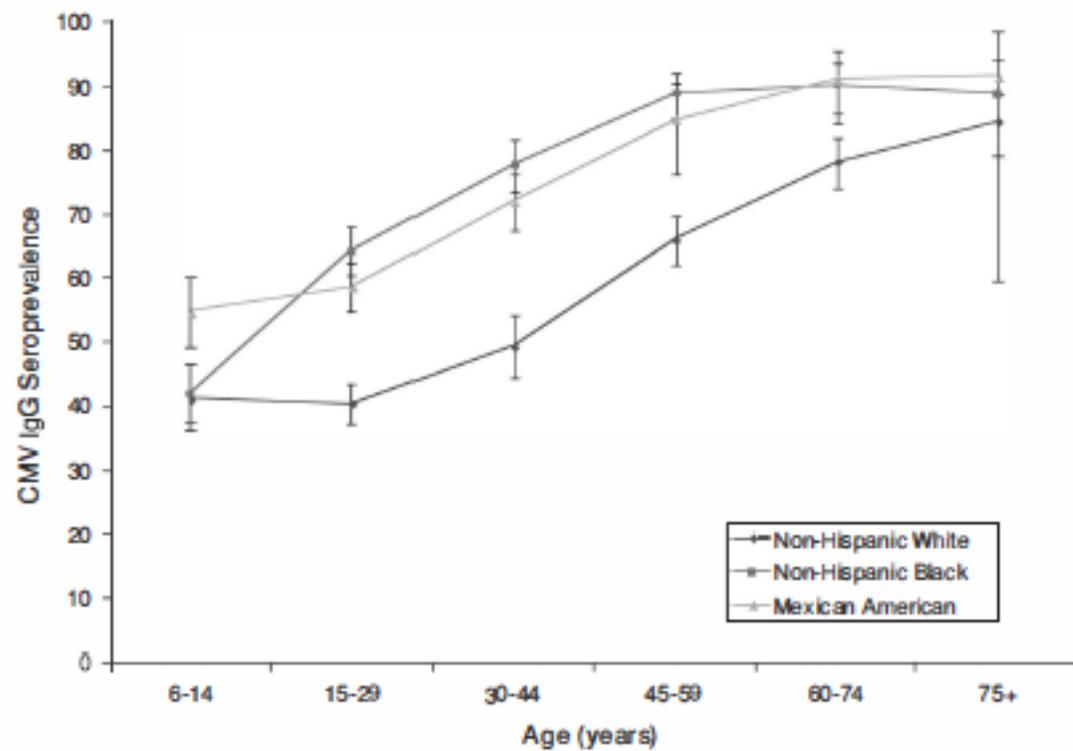


FIGURE 62.4. CMV seroprevalence in the United States by age and race. (Reprinted from Staras SA, Dollard SC, Radford KW, et al. Seroprevalence of cytomegalovirus infection in the United States, 1988–1994. *Clin Infect Dis.* 2006;43(9):1143–1151, with permission from Oxford University Press.)

HERPES SIMPLEX VIRUS (HSV)

- HSV-1 e HSV-2
- Herpesviridae, DNA, icosaédrico, envelopado
- 90% infecções são inaparentes (seis meses)
- Estomatite herpética (HSV1)
- Vulvovaginite herpética (HSV2)
- HSV-2 mais comum transmitido em mulheres (1:5 mulheres e 1:9 homens)
- Transmissão através das mucosas: HSV1-ganglio trigêmeo-latente, HSV2-ganglio lombosacral-latente
- Soroprevalência na população: 72% USA



www.mdsaude.com



EPIDEMIOLOGIA DOS HERPESVIRUS



HIV Total: 33.3 million
HSV 2 Total: 536 million

FIGURE 60.19. Numbers of cases of herpes simplex virus 2 infection in 2003 (*red*)⁶⁷⁸ and persons living with human immunodeficiency virus in 2009 (*black*) (UNAIDS) globally. (Copyright David Knipe.)

TABLE 60.4 Drugs for Herpes Simplex Virus

Infection	Drugs	Adult dosage ^a	
Oral	<i>Topical</i>		
	Acyclovir Ointment	5% cream 5×/d × 4 d	
	Docosanol	10% cream 5×/d until healing	
	Penciclovir	1% cream applied q2h while awake × 4	
	<i>Oral</i>		
	Acyclovir	400 mg PO 5×/d while awake × 4	
	Famciclovir	400 mg PO bid × 7 d	
	Valacyclovir	2 g PO q12h × 1 d	
Genital	First episode	Acyclovir	400 mg PO tid or 200 mg PO 5×/d × 7–10 d ^b
		Famciclovir	250 mg PO tid × 7–10 d
		Valacyclovir	1 g PO bid × 7–10 d
	Episodic treatment of recurrences	Acyclovir	800 mg tid or 400 mg PO tid × 3–5 d
		Famciclovir	125 mg PO bid × 5 d
		Valacyclovir	500 mg PO bid × 3 d
	Suppression of recurrences	Acyclovir	400 mg PO bid
		Famciclovir	250 mg PO bid
		Valacyclovir	500 mg or 1 g PO 1×/d
Mucocutaneous (immunocompromised)	Acyclovir	5 mg/kg IV q8h × 7–14 d or 400 mg PO 5×/d × 7–10 d	
	Famciclovir	500 mg bid × 7–10 d	
	Valacyclovir	500 mg or 1 g bid × 7–10 d	
Encephalitis	Acyclovir	10–15 mg/kg IV q8h × 14–21 d	
Neonatal	Acyclovir	20 mg/kg IV q8h × 14–21 d	
Keratoconjunctivitis	Trifluridine	1% solution 1 drop q2h (max 9 drops/d)	
Acyclovir resistant (severe infection, immunocompromised)	Foscarnet	40 mg/kg IV q8h × 14–21 d	

^aDosage adjustment may be required for renal insufficiency.

^bFor severe initial genital herpes, IV acyclovir (5–10 mg/kg q8h for 5–7 d) can be used.

Note: Generic and trade names of drugs are as follows: acyclovir (Zovirax), docosanol (Abreva), penciclovir topical (Denavir), famciclovir (Famvir), valacyclovir (Valtrex), trifluridine (Viroptic), and foscarnet (Foscavir).

HERPES SIMPLEX VIRUS na gestação

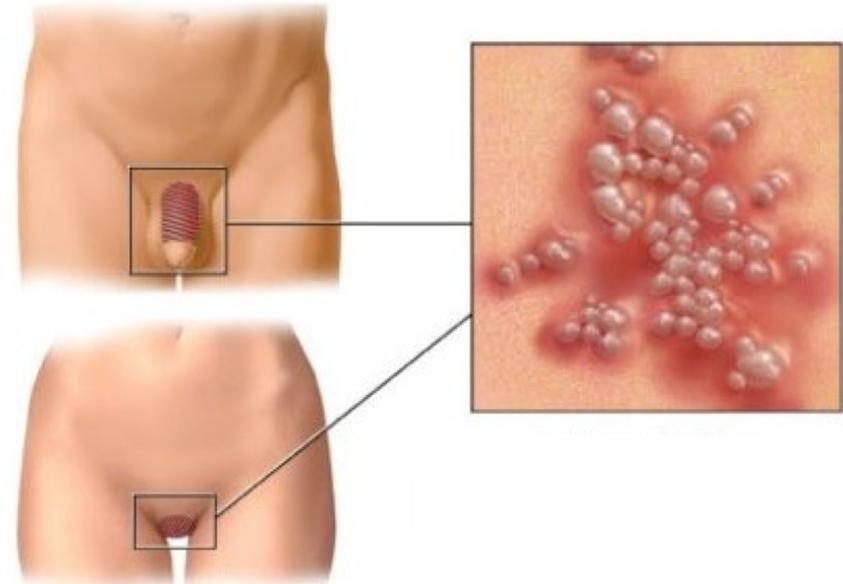
- Transmissão pelo canal de parto: herpes neonatal (80-90% dos casos)
- Transmissão Transplacentária (mais rara)
 - 1) branda: ocorre em cerca de 40% dos casos, lesões na pele região ocular e bucal
 - 2) Encefalite: 15% de óbito
 - 3) Infecção disseminada: lesões necrotizantes no fígado, pulmão, adrenais, coagulação intravascular (60% de óbito)

HERPES SIMPLEX VIRUS na gestação

- Aborto espontâneo
- IUGR
- Parto prematuro
- Infecção congênita
- Infecção neonatal

X

- Manejo da infecção com antivirais
- **CESAREANA EM CASOS DE LESÕES APARENTES**



HERPES SIMPLEX VIRUS na gestação

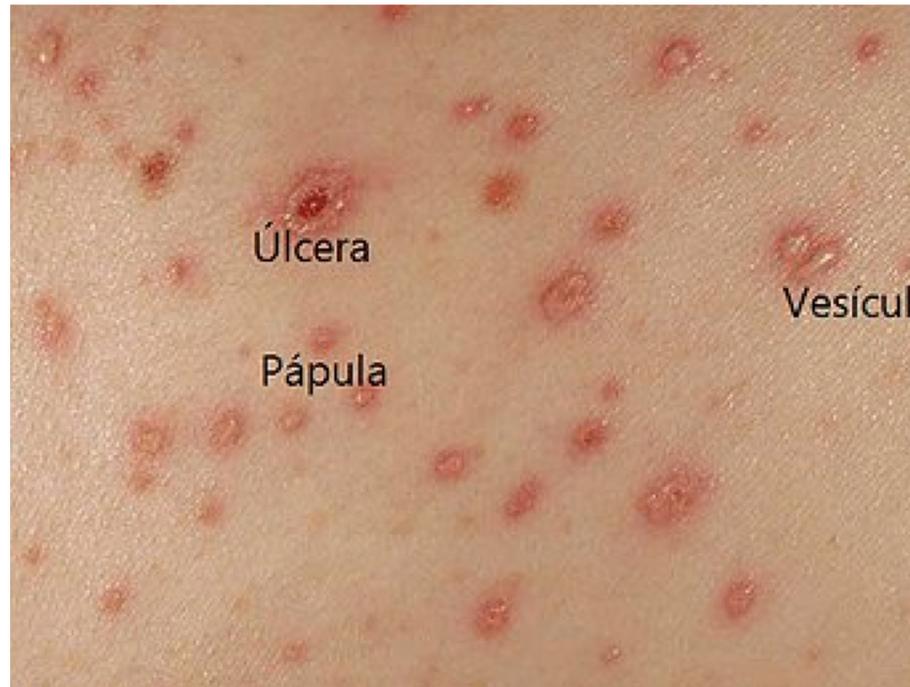
- Presença de anticorpos diminui o risco de infecção
- Infecção primária no 2º/3º trimestre tem 30 a 50% chances de passar ao feto
- Infecção primária no 1º trimestre tem 1% chances de passar ao feto

HERPES SIMPLEX NEONATAL

- Localizada na pele, olhos e boca (SEM- skin, eye, mouth)
- Localizada no SNC com ou sem SEM, neonato apresenta deficits neurológicos, cegueira, convulsões e deficit cognitivo
- Disseminada (80% mortalidade)

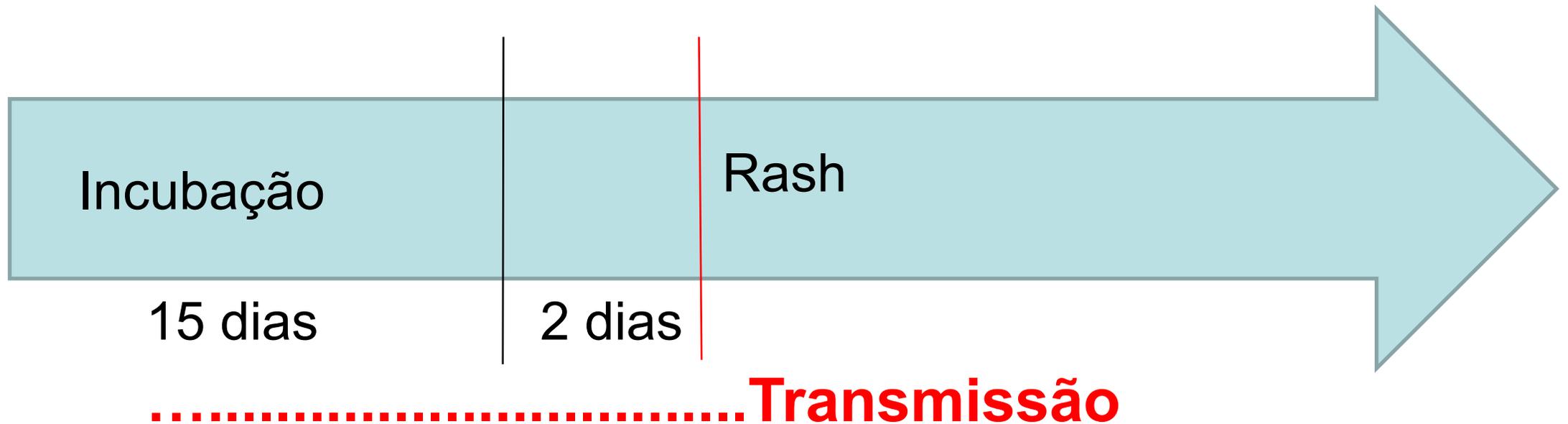
VIRUS VARICELA ZOOSTER (VVZ)

- Varicela (catapora)
- Herpesviridae, DNA, icosaédrico, envelopado



VIRUS VARICELA ZOOSTER

- Transmitido por perdigotos inalados
- Altamente contagiosos
- Ocorre principalmente na infância



VIRUS VARICELA ZOOSTER na **Gestação**

- Incidência de 0.7/1.000
- Associado a alta taxa de mortalidade da mãe e do bebe
- Pneumonia por varicella durante a gestação (10 a 20% tem)= 40%
desfecho em morte
- Vacina, maioria das mulheres é imunizada antes de engravidar

VIRUS VARICELA ZOOSTER na Gestação

- Síndrome congênita: resulta na reativação do vírus intra útero e primária no feto
- hipoplasia dos membros, microcefalia, hidrocefalia, catarata, IUGR e retardo mental
- Risco de 0,4-2% de passar para o feto e causar síndrome congênita nas primeiras 20 semanas de gestação

VIRUS HERPEX ZOOSTER (VHZ)

- Herpes Zoster: adulto (cobreiro)
- Herpesviridae, DNA, icosaédrico, envelopado



VIRUS HERPEX ZOOSTER na gestação

- Incidência: 1/10.000
- Risco congênito é ínfimo, pois mãe tem anticorpos que previnem a passagem do vírus pela placenta
- Infecção neonatal pode ocorrer em 10 a 20% dos neonatos se as mães ficarem doentes 5 a 2 dias antes do parto
- Bebês ficam doentes 5-10 dias após o parto, e a mortalidade é de 30%

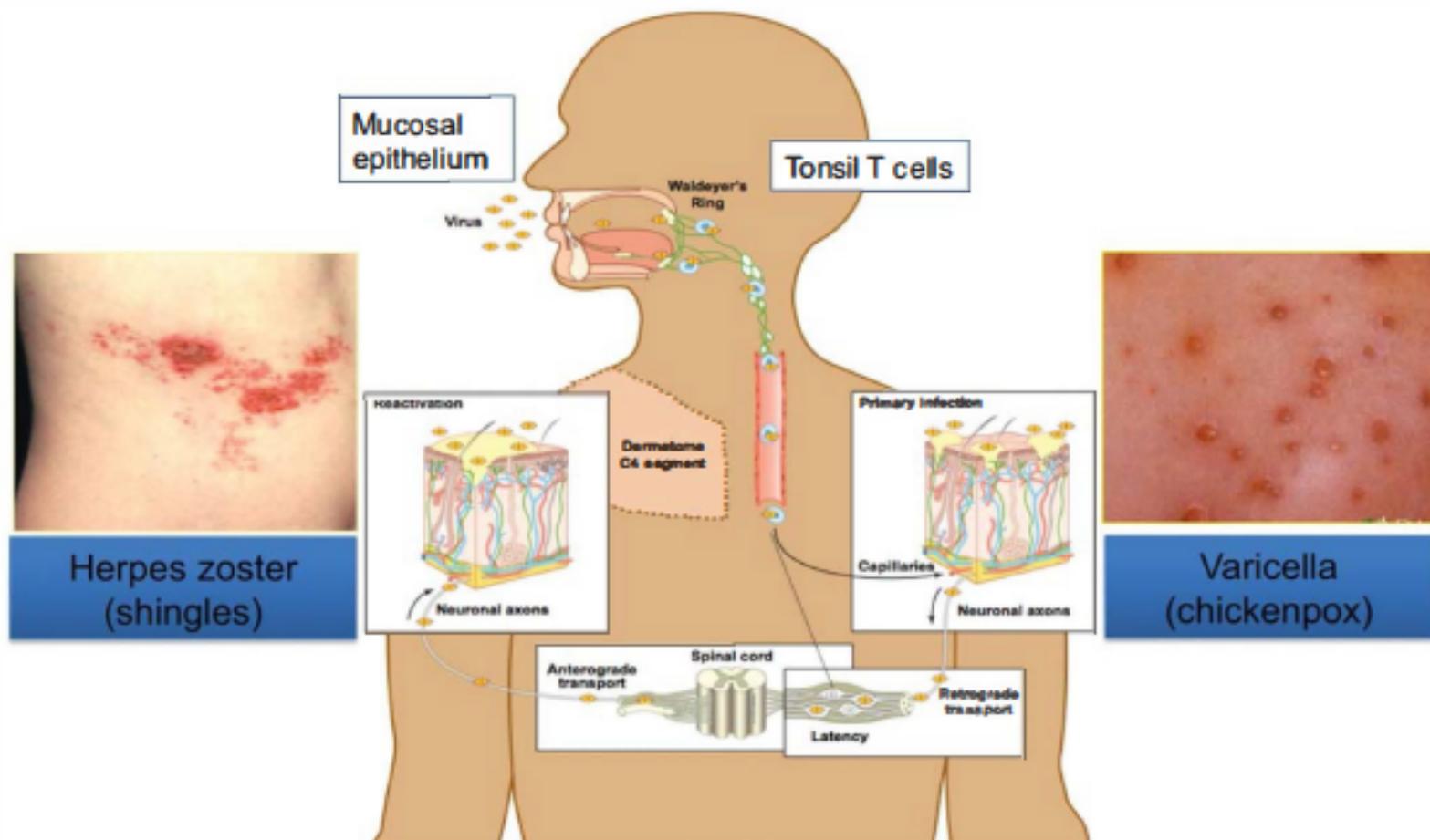


FIGURE 63.1. Model of the pathogenesis of varicella-zoster virus (VZV) infection. Primary VZV infection is acquired by inoculation of mucosal epithelial cells of the upper respiratory tract. Replication at the site of entry allows VZV transfer into tonsils and other local lymphoid tissues, where T cells become infected. Infection of dendritic cells in the mucosal epithelium may support virus transfer to regional lymph nodes. VZV-infected T cells transport the virus to skin sites of replication via a cell-associated viremia. After a 10- to 21-day interval, skin infection produces the vesicular rash associated with varicella (chickenpox). In the course of primary infection, VZ virions gain access to the sensory nerve cell body by retrograde axonal transport or via T cell viremia to establish latent infection within neurons of the sensory ganglia. Episodes of reactivation, during which VZV gains access to skin via anterograde axonal transport, can cause symptoms of zoster (shingles).

Neurologic and Ocular Complications of VZV Reactivation

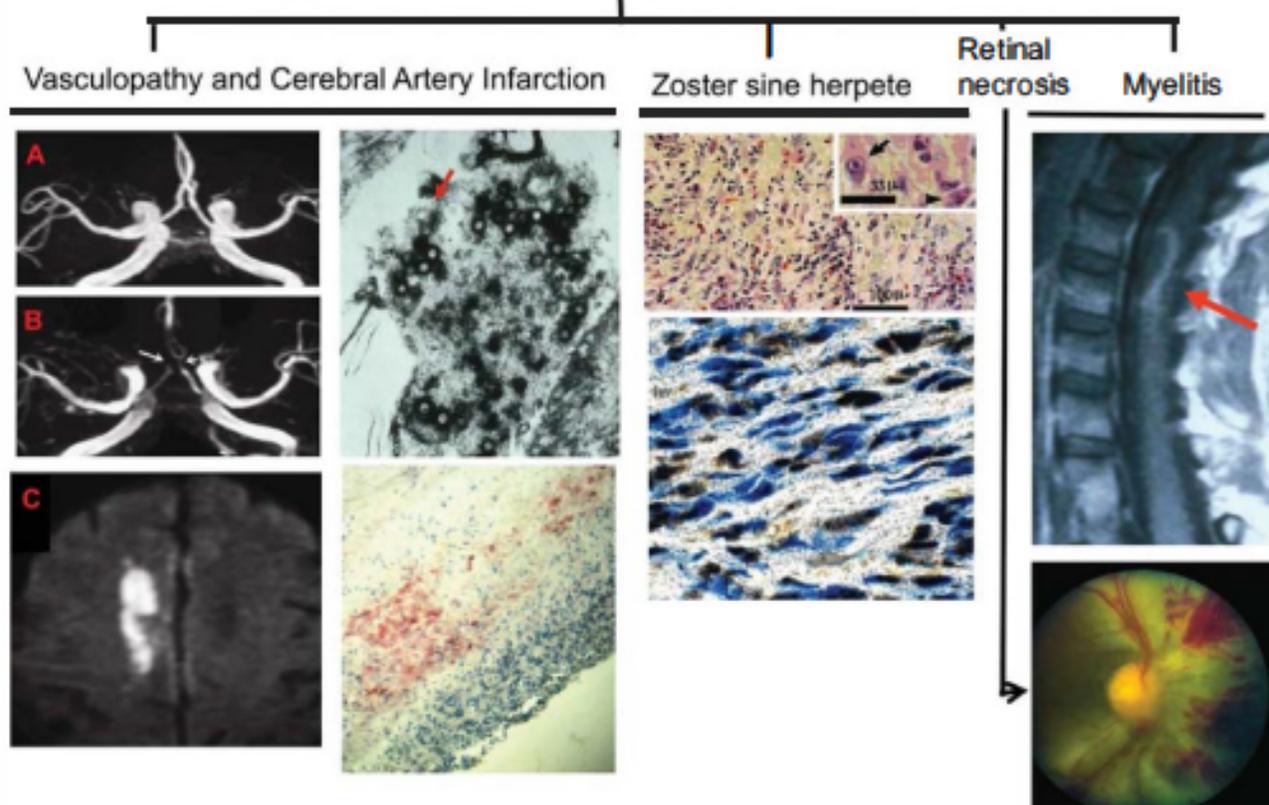


FIGURE 63.16. Neurologic and ocular complications of varicella-zoster virus reactivation. **A:** VZV-induced vasculopathy and infarction. Three-dimensional time-of-flight magnetic resonance angiography of the Circle of Willis 5 months before infarction shows normal anterior cerebral arteries (**a**), while the same analysis at the time of infarction (**b**) shows marked narrowing of anterior cerebral arteries, with a new flow gap at the junction of A1 and A2 segments of the right anterior cerebral artery, indicating occlusion on the right (*long arrow*) and marked stenosis on the left (*short arrow*). (**c**) Diffusion-weighted image (B value 1,000) shows restricted diffusion in the right anterior cerebral artery territory, indicating acute infarction. *Upper right:* Multiple herpes virions within a cerebral artery. *Lower right:* VZV antigen (*red*) in the media of a cerebral artery of a patient with VZV vasculopathy. **B:** Ganglionitis and intranuclear inclusions in zoster sine herpette. H&E staining of the trigeminal ganglion (*upper panel*) shows widespread chronic inflammation with fibrosis and loss of neurons. Cells in some foci contain Cowdry type A intranuclear inclusions (*arrow, inset*) indicative of virus infection; the inflammatory cells are mainly lymphocytes, with some plasma cells (*arrowhead, inset*). Immunohistochemical staining of the same ganglion (*lower panel*) with mouse monoclonal antibody against VZV IE63 indicates VZV antigen (*brown staining*) in multiple cells throughout the ganglion. Adjacent sections stained with antibody against HSV or with normal rabbit serum were negative (not shown). **C:** Fundus photograph of a patient with VZV vasculopathy and progressive outer retinal necrosis. Note the diffuse retinal hemorrhages and whitening, with macular involvement. **D:** MRI abnormality in a patient with VZV myelitis; note the longitudinal, serpiginous enhancing lesion.

Report

Virus exposure and neurodegenerative disease risk across national biobanks

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Table 2. Discovery (FinnGen) and replication (UKB) results for replicated viral/NDD pairs

NDD	Virus_description	Cohort	HR/OR	CI_min	CI_max	p	N	p_FDR
AD	viral encephalitis, not elsewhere classified/unspecified*	FinnGen	30.72	11.84	79.68	1.89E-12	24	1.26E-11
AD	viral encephalitis, not elsewhere classified/unspecified*	UKB	22.06	5.47	88.94	1.37E-05	3	5.47E-05
AD	viral and other specified intestinal infections	FinnGen	3.03	1.73	5.32	1.08E-04	122	3.58E-04
AD	viral and other specified intestinal infections	UKB	3.09	1.93	4.96	2.63E-06	19	1.32E-05
AD	influenza and pneumonia*	FinnGen	4.11	3.38	4.99	4.01E-46	2,141	8.03E-45
AD	influenza and pneumonia*	UKB	2.60	2.25	2.99	5.47E-40	231	1.09E-38
AD	meningitis*	FinnGen	2.81	1.39	5.67	3.95E-03	33	7.47E-03
AD	meningitis*	UKB	62.20	18.35	210.78	3.29E-11	6	2.20E-10
ALS	influenza and pneumonia*	FinnGen	1.81	1.35	2.43	7.09E-05	53	7.09E-05
ALS	influenza and pneumonia*	UKB	7.91	6.02	10.40	1.08E-49	76	5.38E-49
DEM	viral encephalitis, not elsewhere classified/unspecified*	FinnGen	6.56	1.60	26.97	9.05E-03	48	2.17E-02
DEM	viral encephalitis, not elsewhere classified/unspecified*	UKB	40.12	12.09	133.14	1.61E-09	5	5.07E-09
DEM	other viral diseases, not elsewhere classified*	FinnGen	2.01	1.20	3.36	7.98E-03	144	2.17E-02
DEM	other viral diseases, not elsewhere classified*	UKB	3.24	2.19	4.81	5.02E-09	27	1.38E-08
DEM	viral warts	FinnGen	3.70	2.23	6.14	3.83E-07	74	3.07E-06
DEM	viral warts	UKB	2.38	1.29	4.39	5.31E-03	11	7.30E-03
DEM	all influenza*	FinnGen	5.07	3.06	8.41	3.04E-10	348	3.65E-09
DEM	all influenza*	UKB	4.56	2.56	8.13	2.55E-07	13	5.10E-07
DEM	influenza and pneumonia*	FinnGen	2.87	2.40	3.43	6.78E-31	3,174	1.63E-29
DEM	influenza and pneumonia*	UKB	6.12	5.48	6.85	1.63E-222	439	3.59E-221
DEM	viral pneumonia*	FinnGen	3.48	2.00	6.04	1.01E-05	104	6.04E-05
DEM	viral pneumonia*	UKB	4.44	1.90	10.36	5.59E-04	6	8.78E-04
MS	herpesviral [herpes simplex] infections*	FinnGen	1.91	1.14	3.22	1.45E-02	19	2.60E-02
MS	herpesviral [herpes simplex] infections*	UKB	4.95	1.28	19.12	2.03E-02	3	4.05E-02
MS	varicella-zoster virus (zoster [herpes zoster])*	FinnGen	2.12	1.09	4.12	2.66E-02	11	3.98E-02
MS	varicella-zoster virus (zoster [herpes zoster])*	UKB	3.76	1.18	12.00	2.54E-02	5	4.57E-02
PD	viral hepatitis*	FinnGen	2.88	1.37	6.05	5.13E-03	14	1.37E-02
PD	viral hepatitis*	UKB	2.20	1.06	4.55	3.43E-02	8	4.66E-02
PD	viral infections characterized by skin and mucous membrane lesions	FinnGen	1.58	1.18	2.13	2.44E-03	77	1.37E-02
PD	viral infections characterized by skin and mucous membrane lesions	UKB	2.46	1.70	3.56	1.88E-06	31	5.10E-06
PD	all influenza (not pneumonia)*	FinnGen	2.01	1.23	3.31	5.71E-03	36	1.37E-02
PD	all influenza (not pneumonia)*	UKB	3.69	2.06	6.59	1.05E-05	13	2.49E-05
PD	all influenza*	FinnGen	1.84	1.20	2.83	5.48E-03	51	1.37E-02
PD	all influenza*	UKB	4.31	2.50	7.43	1.55E-07	15	4.91E-07
PD	influenza and pneumonia*	FinnGen	1.72	1.48	1.99	1.27E-12	418	1.52E-11
PD	influenza and pneumonia*	UKB	2.98	2.62	3.38	1.34E-63	294	1.27E-62
VAS	viral and other specified intestinal infections	FinnGen	2.79	1.59	4.89	3.61E-04	45	5.06E-04
VAS	viral and other specified intestinal infections	UKB	5.26	2.31	11.95	7.37E-05	6	1.37E-04
VAS	varicella-zoster virus (zoster [herpes zoster])*	FinnGen	2.33	1.25	4.36	7.77E-03	33	9.07E-03
VAS	varicella-zoster virus (zoster [herpes zoster])*	UKB	6.22	2.27	17.00	3.71E-04	4	6.03E-04
VAS	all influenza*	FinnGen	2.96	1.66	5.27	2.36E-04	71	4.13E-04
VAS	all influenza*	UKB	4.99	1.57	15.83	6.39E-03	3	6.92E-03
VAS	influenza and pneumonia*	FinnGen	4.62	3.81	5.59	1.73E-55	708	1.21E-54
VAS	influenza and pneumonia*	UKB	6.79	5.40	8.53	9.63E-61	103	1.25E-59

Discovery (FinnGen, reporting hazard ratios) and replication (UKB, reporting odds ratios) analyses showing the 22 replicated associations between virus exposures and neurodegenerative diseases. In this table N reflects the overlapping count of samples with both virus and neurodegenerative disease exposures. The final column for each phase denotes the FDR corrected p value. Meningitis includes both viral and bacterial codes.

*Denotes potentially neurotropic virus coding derived from EMR. As a note, "influenza and pneumonia" is a super-set of "all influenza."