



VIROLOGY LIVE

WITH VINCENT RACANIELLO

Persistent Infections

Lecture 17
Virology Live
Fall 2021

Paralyze resistance with persistence

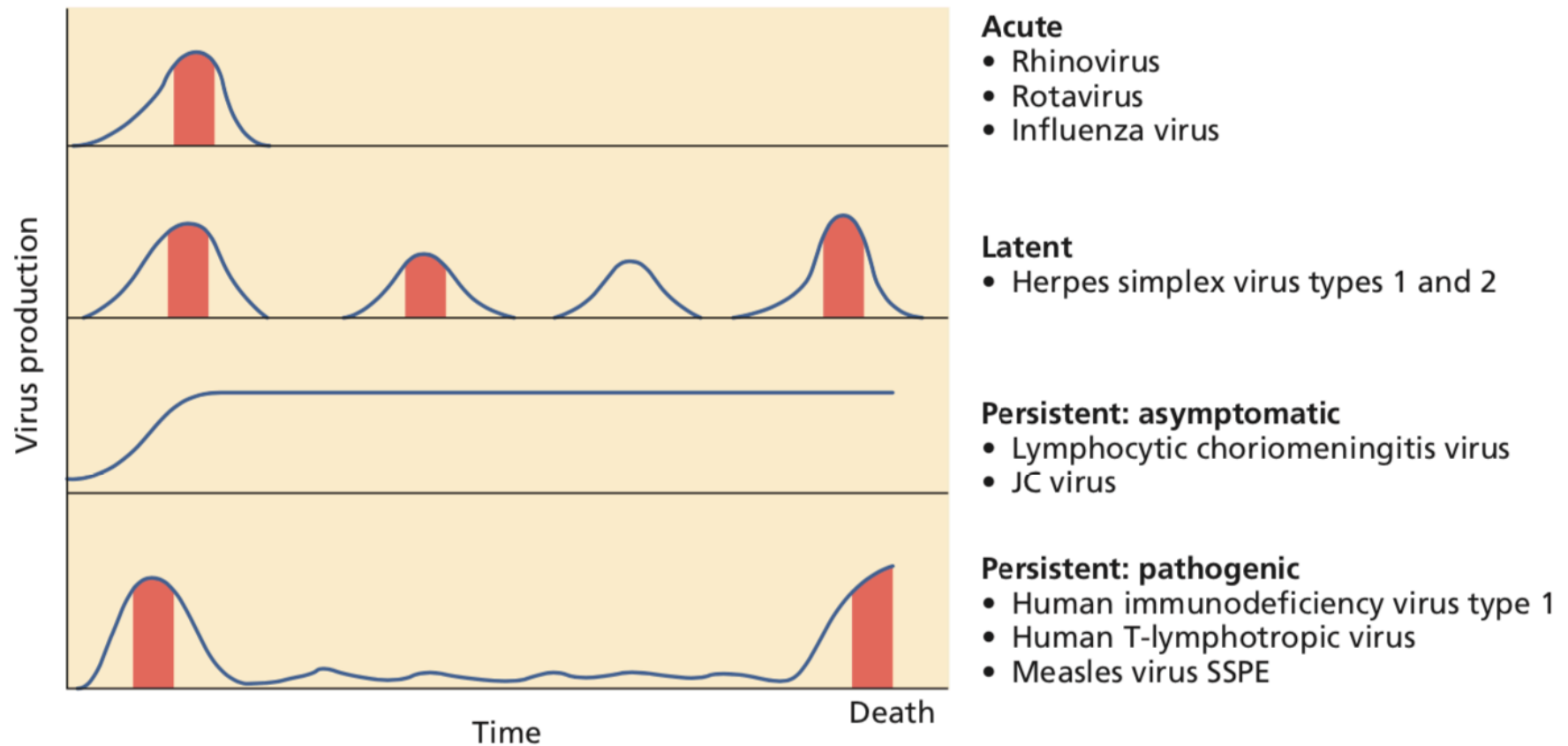
–WOODY HAYES

Acute vs persistent infections

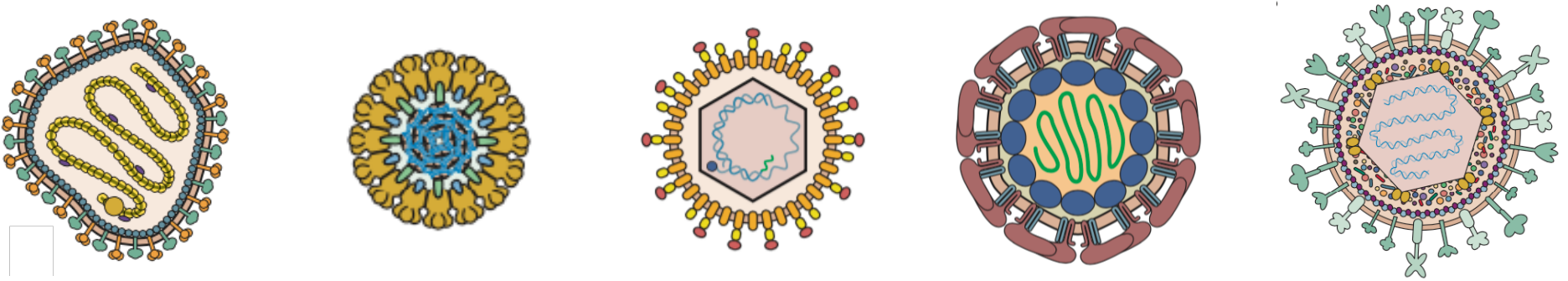


- Acute infection - rapid and self-limiting
- Persistent infection - long term, life of host
- Stable, characteristic for each virus
- Most persistent infections probably begin as an acute infection

General patterns of infection

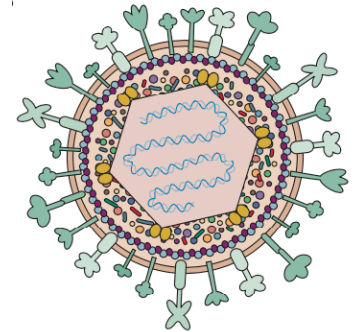
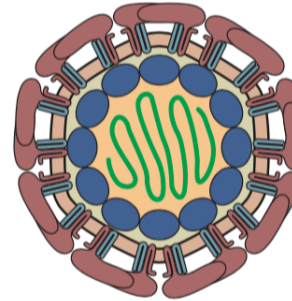
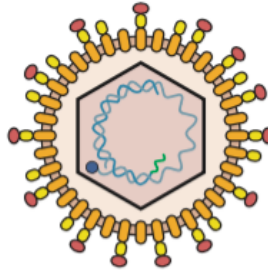
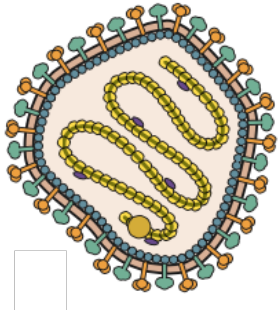


Persistent infections



- Occur when primary infection is not cleared by immune response
- Virus particles, protein, genomes continue to be produced
- Viral genomes may remain after proteins are not detected

Persistent infections



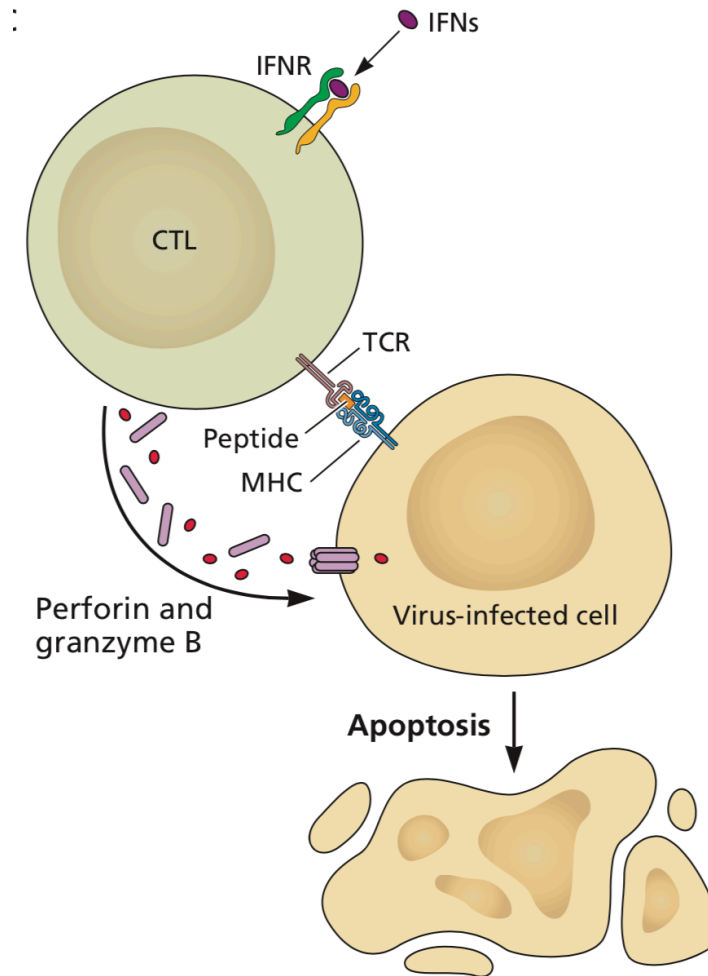
- No single mechanism
- When cytopathic effects are absent and host defenses are reduced, persistent infection is likely
- Viral immune modulation

Persistent human infections

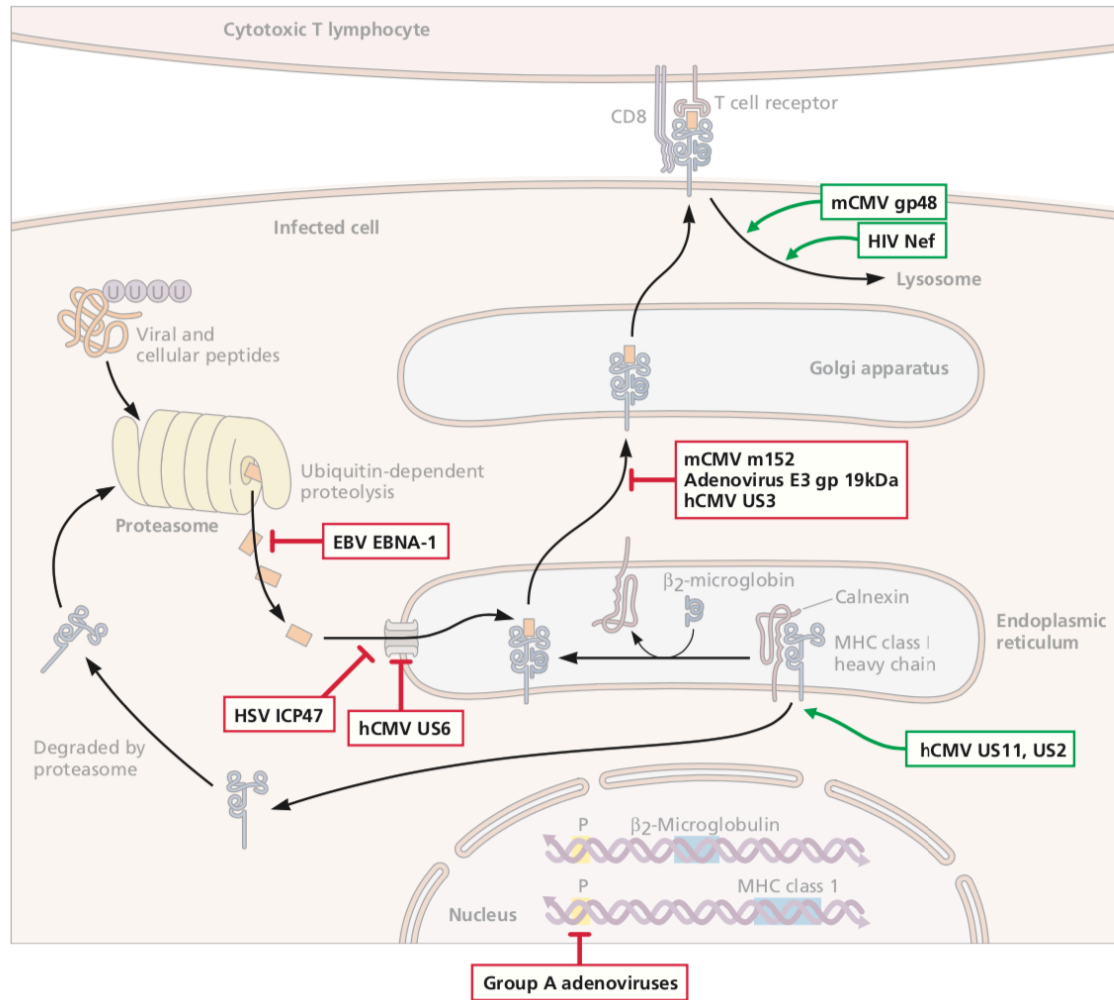
Virus	Site(s) of persistence	Consequence(s)
Adenovirus	Adenoids, tonsils, lymphocytes	None known
* Epstein-Barr virus	B cells, nasopharyngeal epithelia	Burkitt's lymphoma, Hodgkin's disease
* Human cytomegalovirus	Kidneys, salivary gland, lymphocytes, ^a macrophages, ^a stem cells, ^a stromal cells ^a	Pneumonia, retinitis
* Hepatitis B virus	Liver, lymphocytes	Cirrhosis, hepatocellular carcinoma
* Hepatitis C virus	Liver	Cirrhosis, hepatocellular carcinoma
Human immunodeficiency virus	CD4 ⁺ T cells, macrophages, microglia	AIDS
* Herpes simplex virus types 1 and 2	Sensory and autonomic ganglia	Cold sore, genital herpes
Human T lymphotropic virus types 1 and 2	T cells	Leukemia, brain infections
Papillomavirus	Skin, epithelial cells	Papillomas, carcinomas
* Polyomavirus BK	Kidneys	Hemorrhagic cystitis
* Polyomavirus JC	Kidneys, central nervous system	Progressive multifocal leukoencephalopathy
* Measles virus	Central nervous system	Subacute sclerosing panencephalitis, measles inclusion body encephalitis
Rubella virus	Central nervous system	Progressive rubella panencephalitis
* Varicella-zoster virus	Sensory ganglia	Zoster (shingles), postherpetic neuralgia

^aProposed but not certain.

The cytotoxic T lymphocyte response

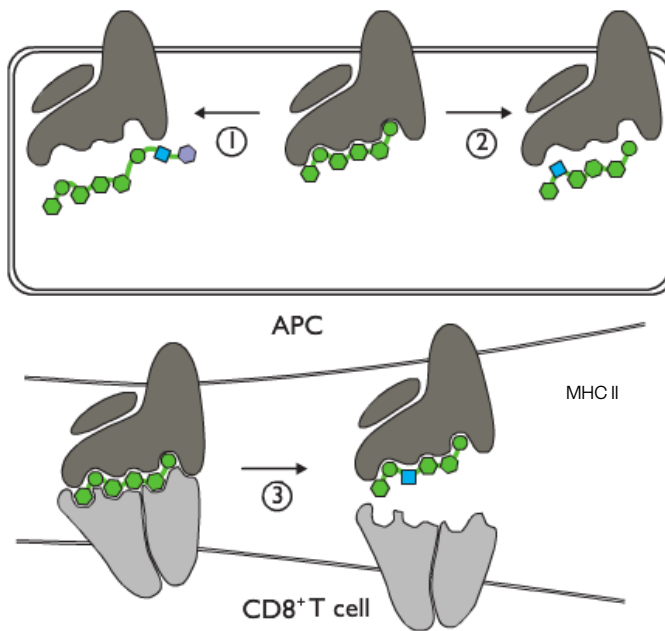


Modulation of MHC I system

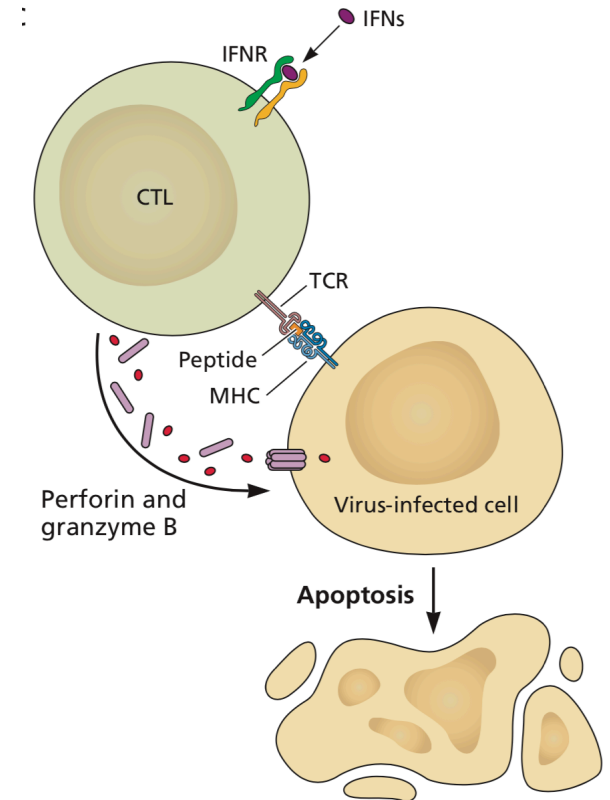


CTL escape mutants

- Herpes simplex virus
- Hepatitis C virus

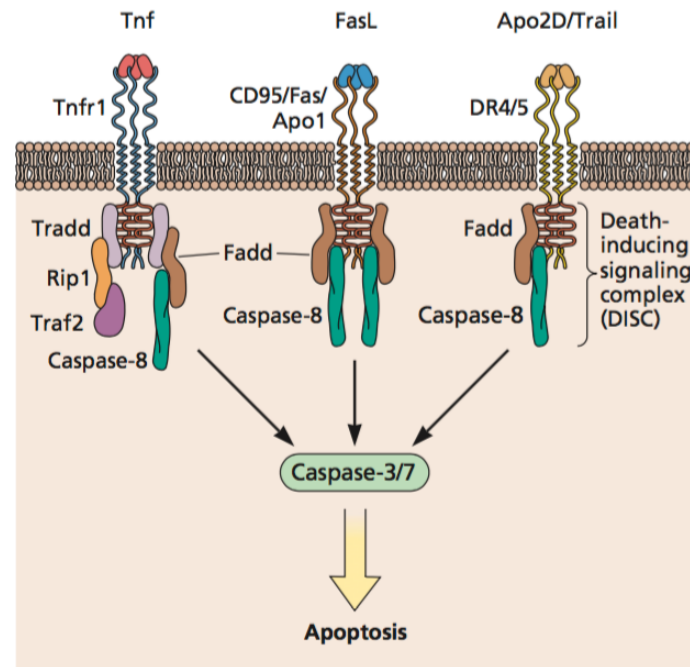
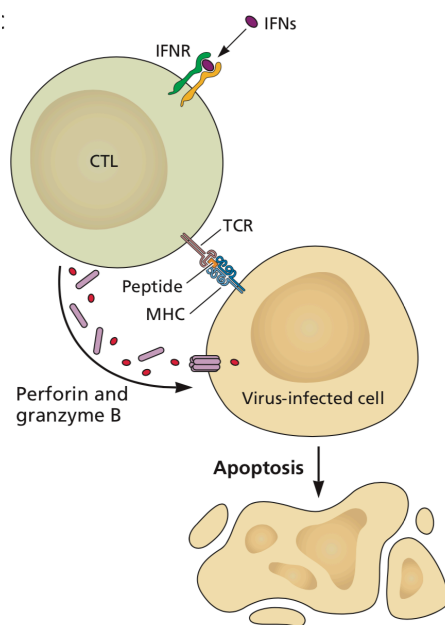


Changes may also affect proteasomal processing



Killing activated T cells

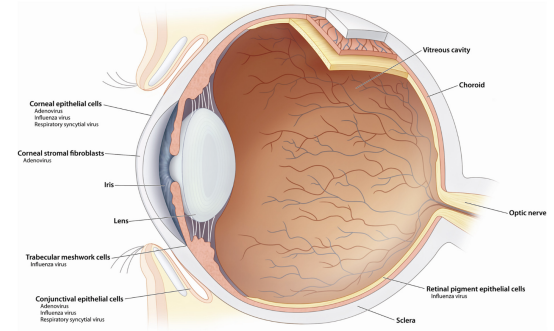
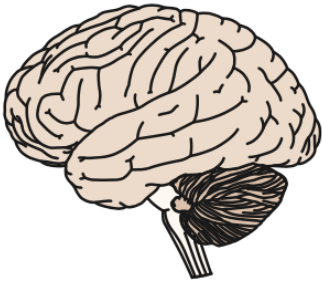
- When CTL engages an infected cell, the CTL may die instead of the target
- An example of viral defense
- A normal cell process to limit immunopathology



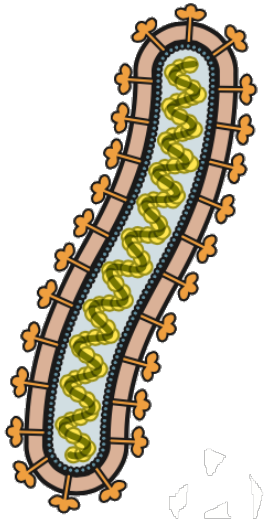
HIV, CMV induce FasL on infected cell surface

CTL

Reduced immune surveillance



- Cells and organs differ in degrees of immune defense
- CNS, vitreous humor of eye, skin, are devoid of initiators and effectors of immune response (eye, high FasL)
- Could be damaged by fluid accumulation, swelling, and ionic imbalances of inflammation
- Persistent infections of these tissues are common



BRIEF REPORT

Persistence of Ebola Virus in Ocular Fluid during Convalescence

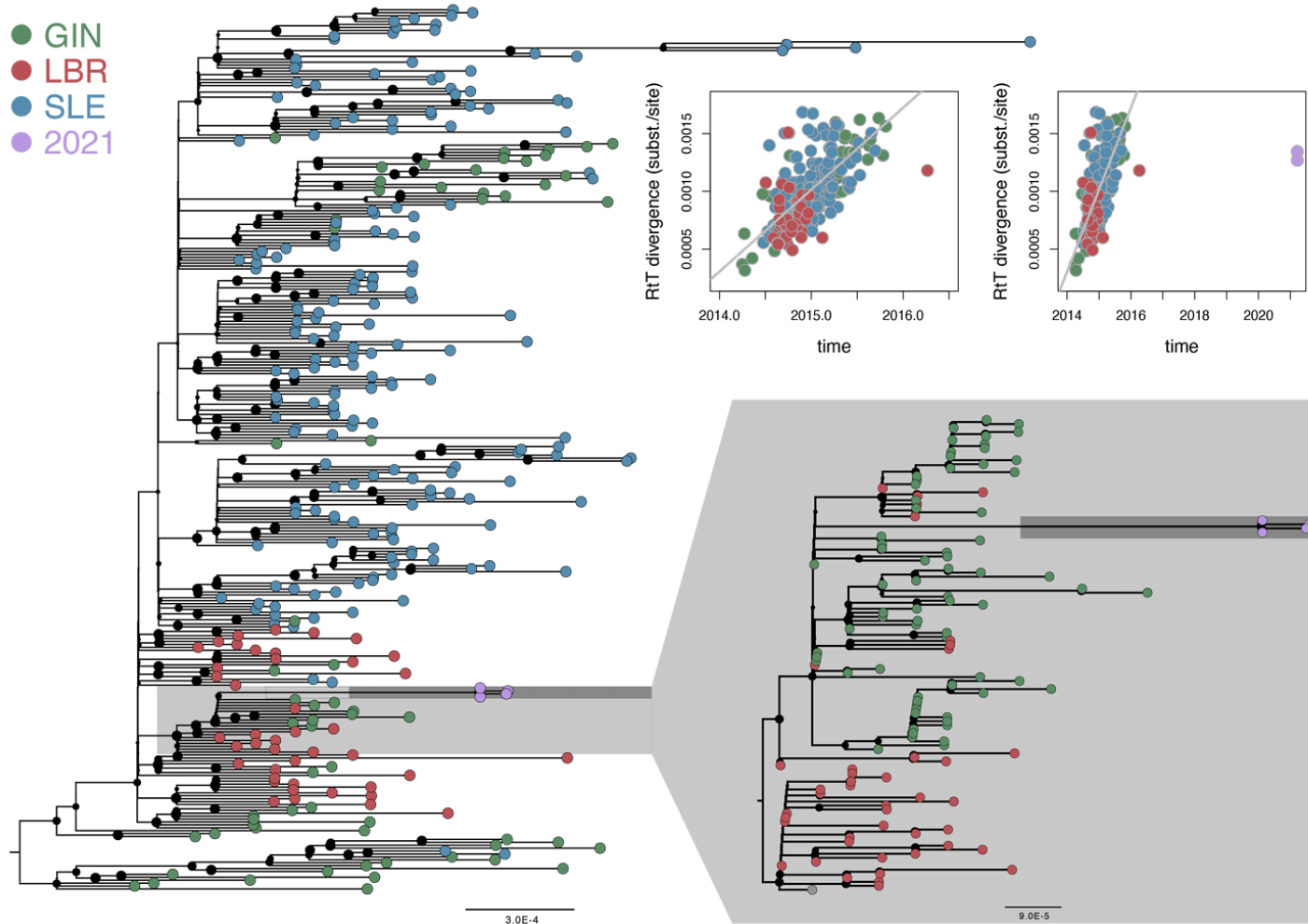
Jay B. Varkey, M.D., Jessica G. Shantha, M.D., Ian Crozier, M.D.,
Colleen S. Kraft, M.D., G. Marshall Lyon, M.D., Aneesh K. Mehta, M.D.,
Gokul Kumar, M.D., Justine R. Smith, M.B., B.S., Ph.D.,
Markus H. Kainulainen, Ph.D., Shannon Whitmer, Ph.D., Ute Ströher, Ph.D.,
Timothy M. Uyeki, M.D., M.P.H., M.P.P., Bruce S. Ribner, M.D., M.P.H.,
and Steven Yeh, M.D.

SUMMARY

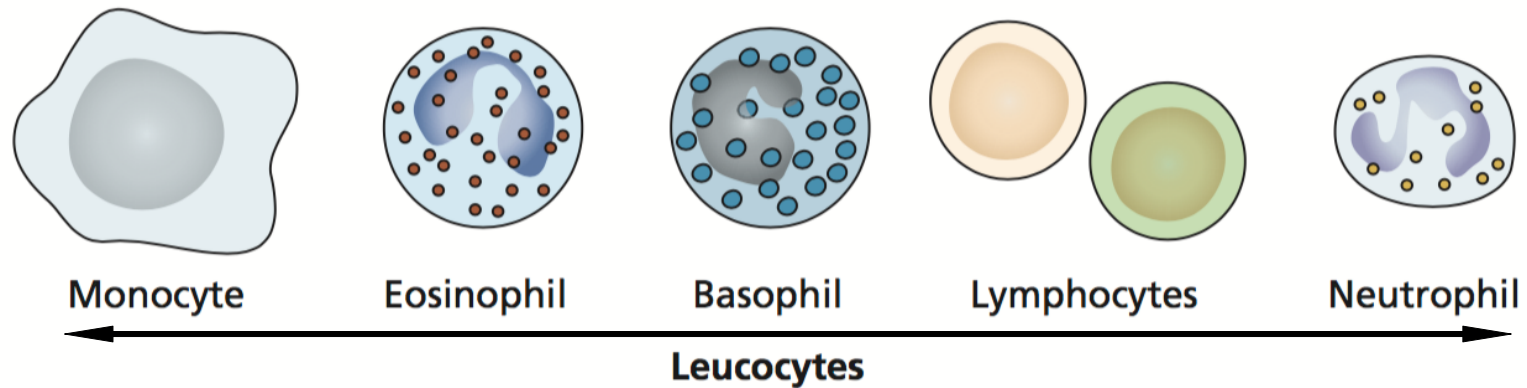
Among the survivors of Ebola virus disease (EVD), complications that include uveitis can develop during convalescence, although the incidence and pathogenesis of EVD-associated uveitis are unknown. We describe a patient who recovered from EVD and was subsequently found to have severe unilateral uveitis during convalescence. Viable *Zaire ebolavirus* (EBOV) was detected in aqueous humor 14 weeks after the onset of EVD and 9 weeks after the clearance of viremia.

Also: flare-up in 2021 in Guinea originating from a survivor with virus persistence in seminal fluid for more than 500 days

Ebolavirus genomes from Guinea 2021 outbreak



Infection of immune cells



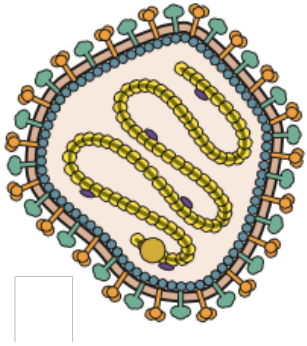
- Many viruses infect cells of the immune system
- Measles virus infection of APCs
- HIV-1 infection of CD4 T cells, monocytes, macrophages, dendritic cells

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Which of the following are features of persistent infections?

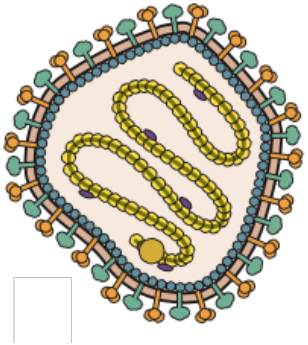
- A. They last the lifetime of the host
- B. Viral immune modulation is involved
- C. Immune cells may be infected
- D. They may occur in areas of reduced immune surveillance
- E. All of the above



Measles virus

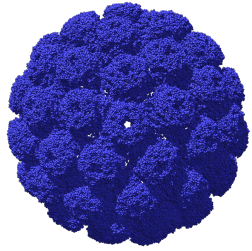


- *Paramyxoviridae*
- One of most contagious human viruses
- 207 000 deaths globally in 2019 - preventable
- Lifelong immunity after infection
- A classic acute virus infection

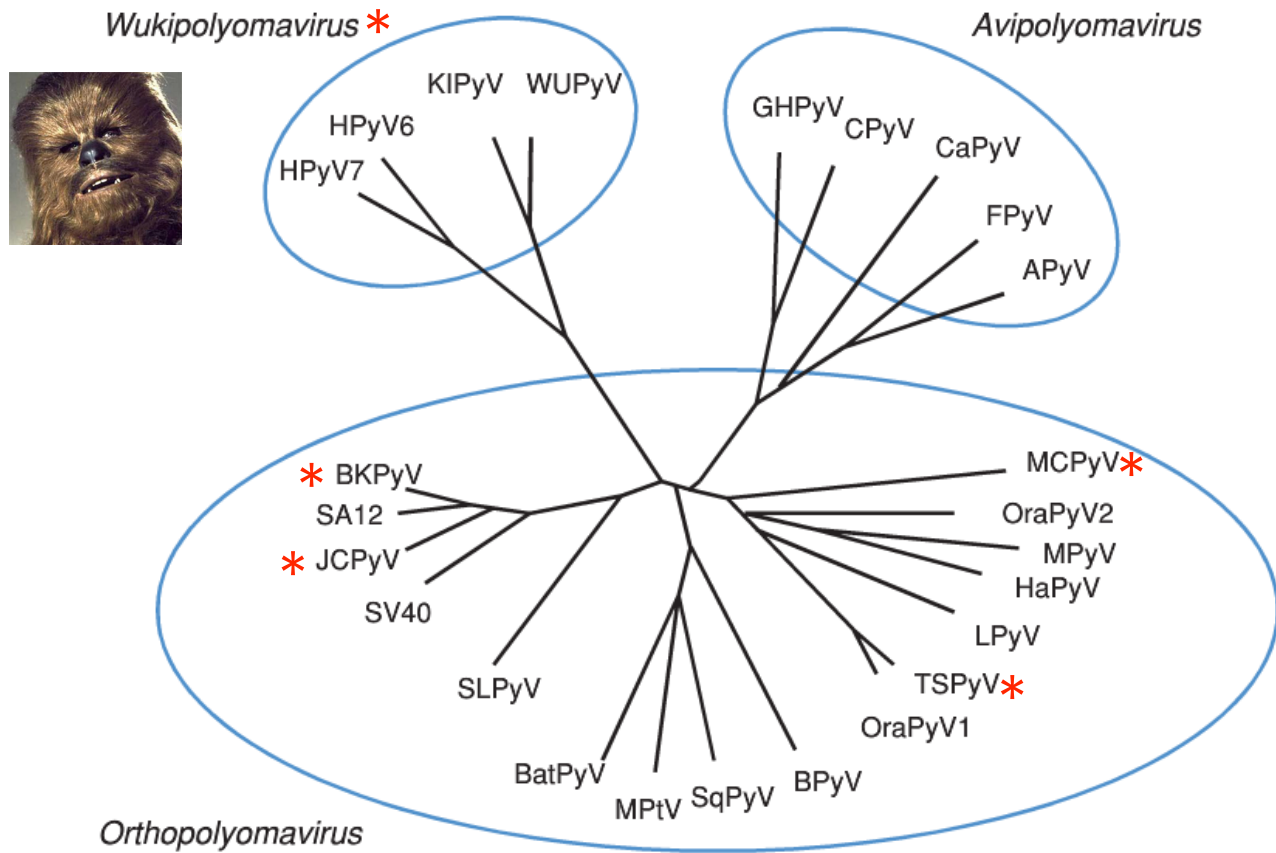


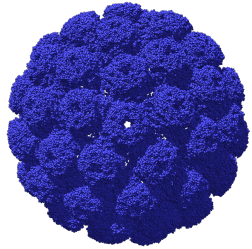
SSPE

- Subacute sclerosing panencephalitis, a progressive, degenerative encephalitis
- After measles, 1/million contract SSPE
- 6-8 yr incubation
- Viral nucleoprotein particles detected in brain, but no infectious virus produced
- Genomes spread between synaptically connected neurons



Polyomavirus

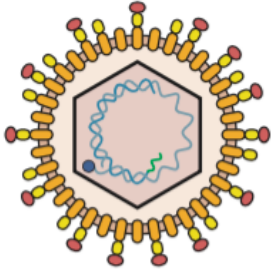




Polyomavirus persistence

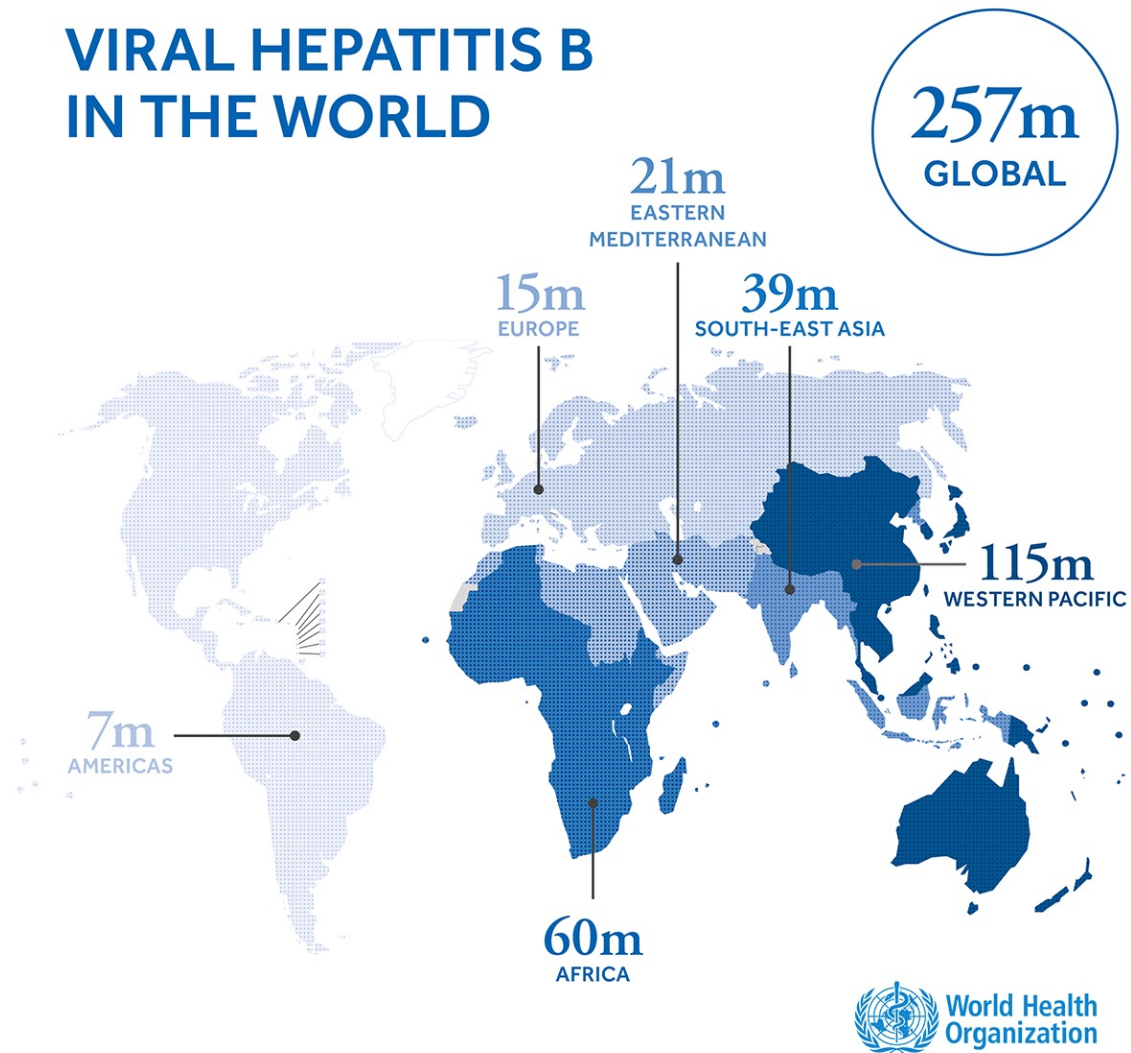
- Infected for life, high seropositivity in human populations
- Variety of organs - kidney, intestine, respiratory tract
- 100,000 particles/ml in urine
- Unknown mechanisms of persistence
- Progressive Multifocal Leukoencephalopathy (PML)
- TWiV #250 - Wookie viruses microbe.tv/twiv/twiv-250-wookie-viruses/

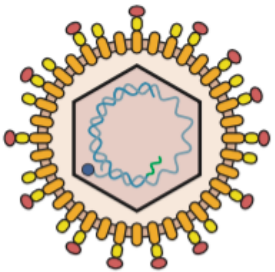
Hepatitis B virus



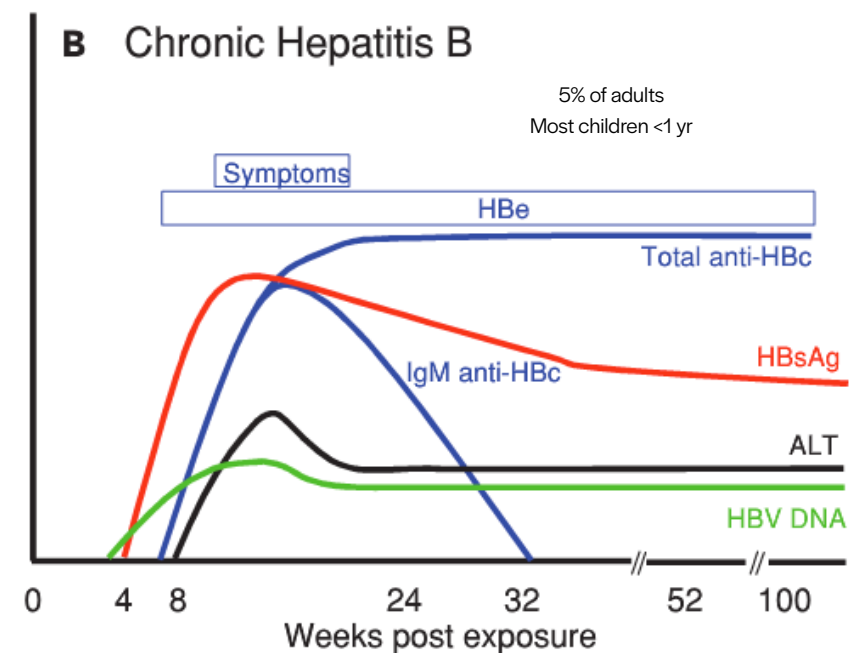
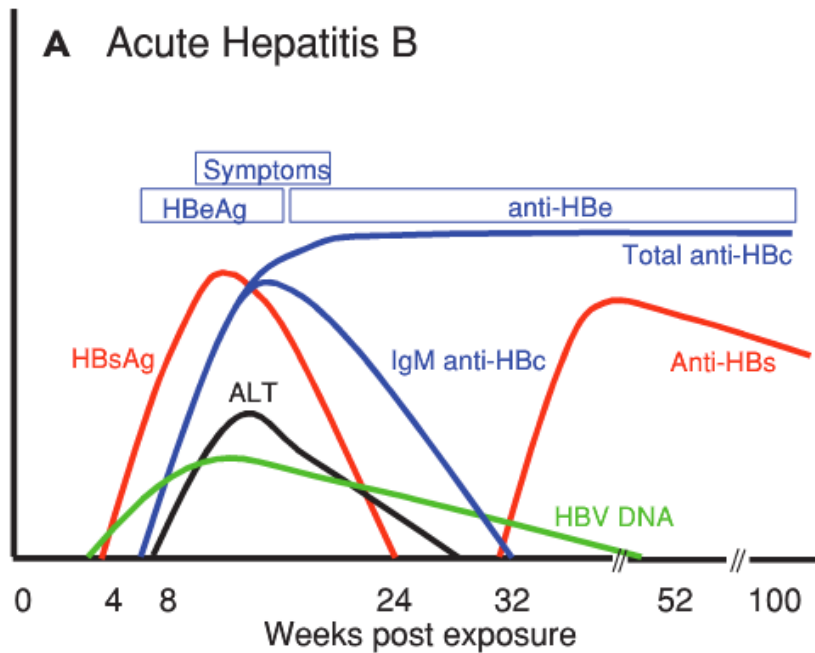
- Transmitted by exposure to blood (childbirth, transfusion, sex, drug use, tattooing, nosocomial)
- Main target is hepatocyte
- 95% of adults, 5-10% newborns resolve acute infection

VIRAL HEPATITIS B IN THE WORLD

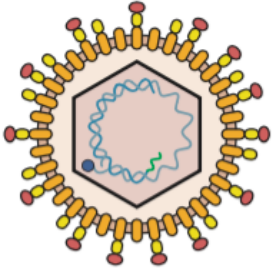




Hepatitis B virus pathogenesis



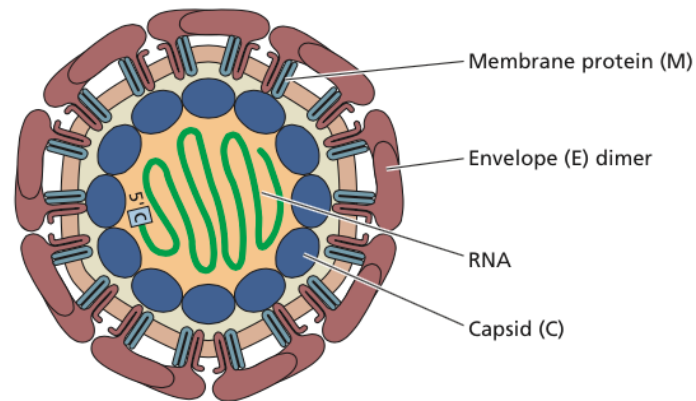
ALT = alanine transaminase



Chronic HBV

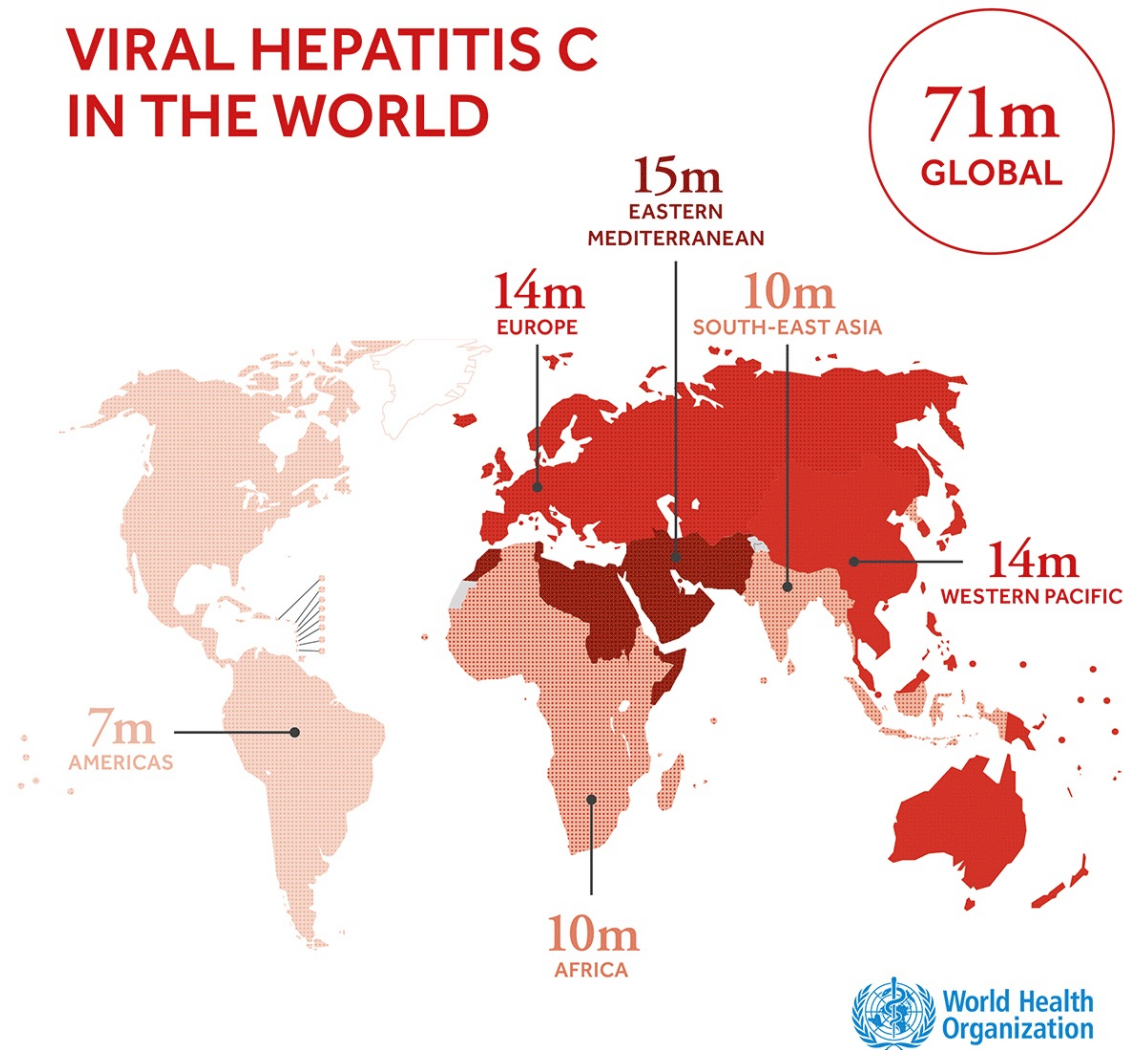
- Virus is not cytopathic (!) for hepatocytes
- CTL kill infected hepatocytes
- T cell exhaustion may lead to T cell dysfunction (persistence)
- During chronic infection, fibrosis leads to cirrhosis, liver failure
- Hepatocellular carcinoma develops after 20-30 yr of chronic (often asymptomatic) infection

Hepatitis C virus

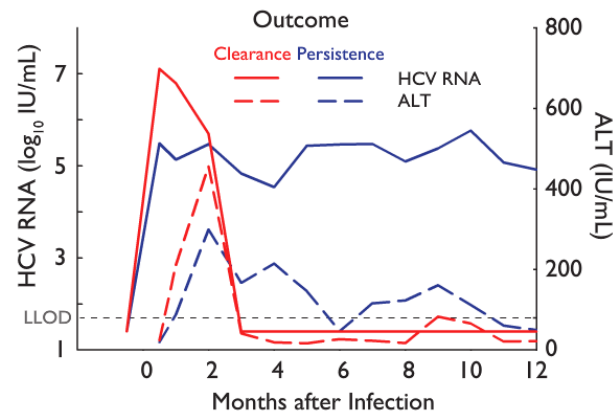
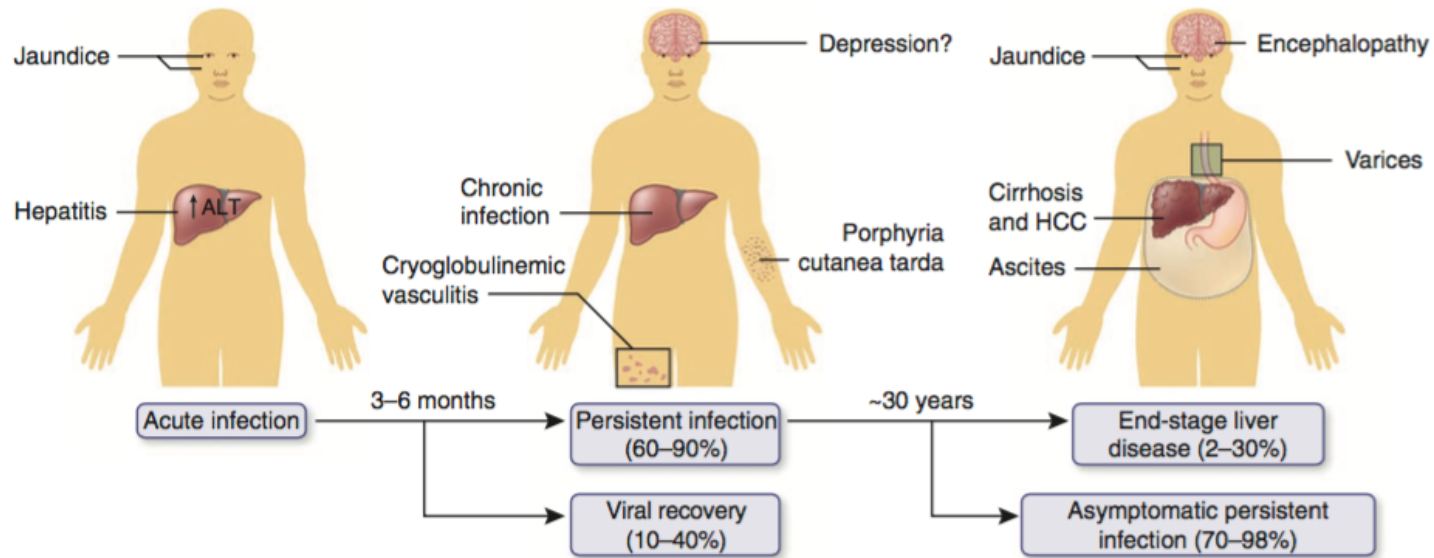


- + strand RNA virus, *Flaviviridae*
- Transmitted by exposure to contaminated blood (sex, drug use, tattooing, during birth)
- 71 million infected globally

VIRAL HEPATITIS C IN THE WORLD

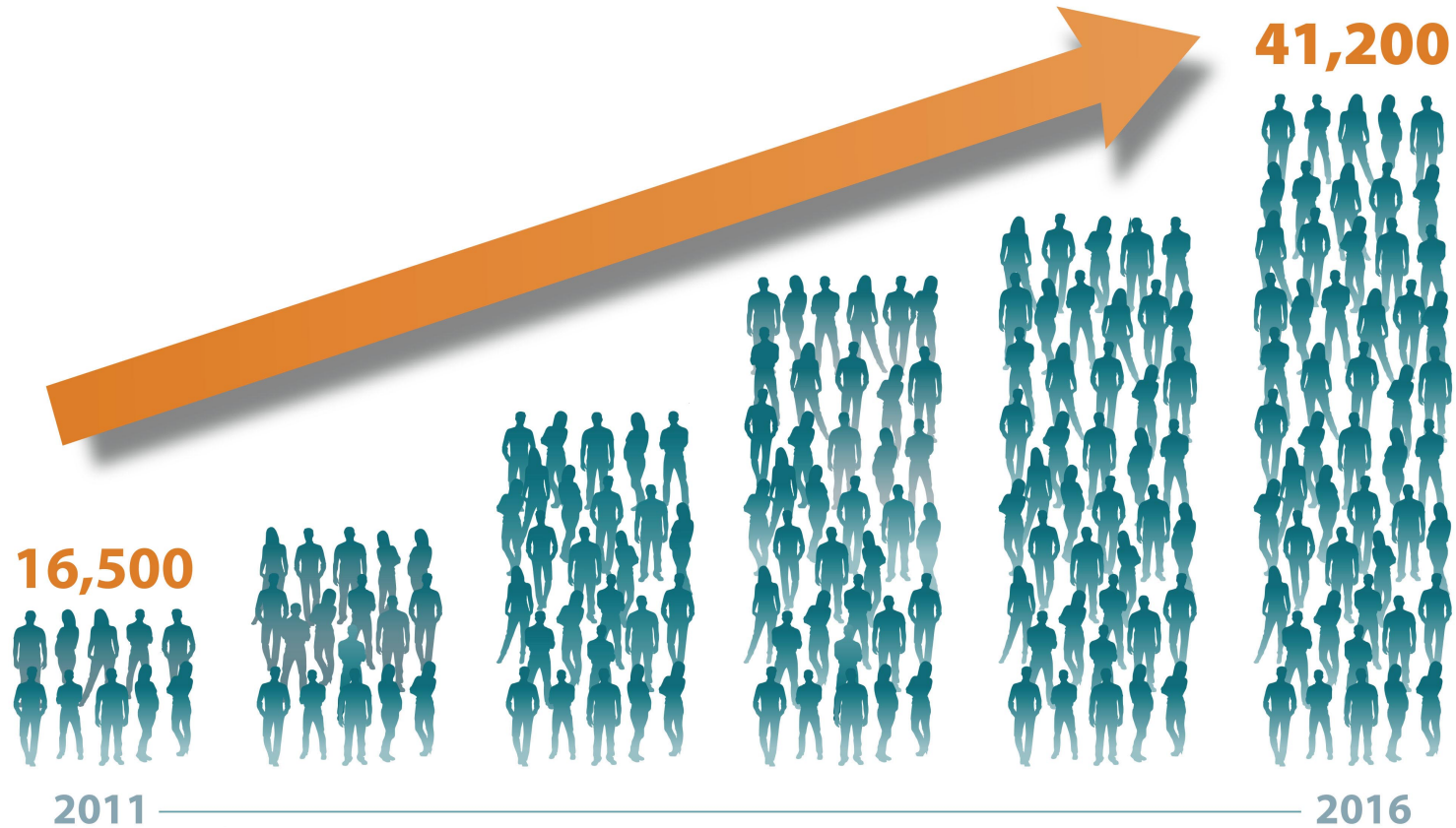


HCV



*Persistence via
multiple immune
modulation
mechanisms*

Opioid crisis has led to increase in HCV infections in US

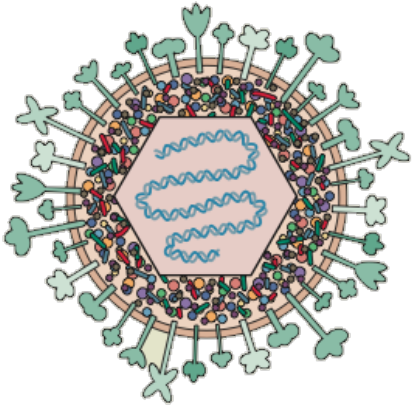


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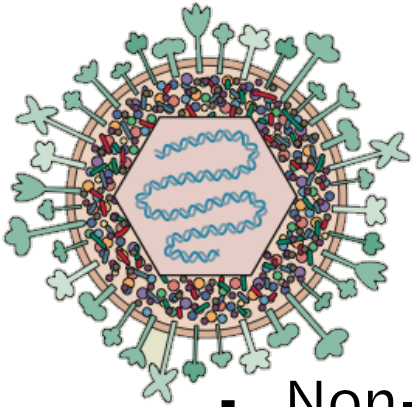
Which are shared features of persistent infections with polyomavirus, HBV, and HCV?

- A. Genomes are present but not expressed
- B. Liver damage
- C. Kidney damage
- D. Virus particles are produced
- E. All of the above



Latent infections - general properties

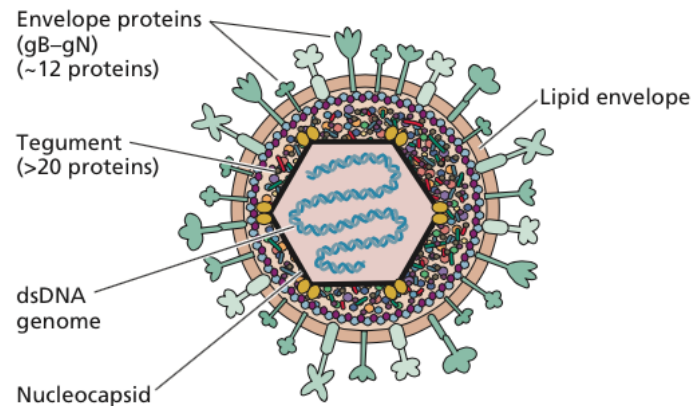
- Viral gene products that promote productive replication are not made or found in low concentrations
- Cells harboring the latent viral genome are poorly recognized by the immune system
- Viral genome persists intact so that productive infection can be initiated to *spread infection* to new hosts



State of the genome

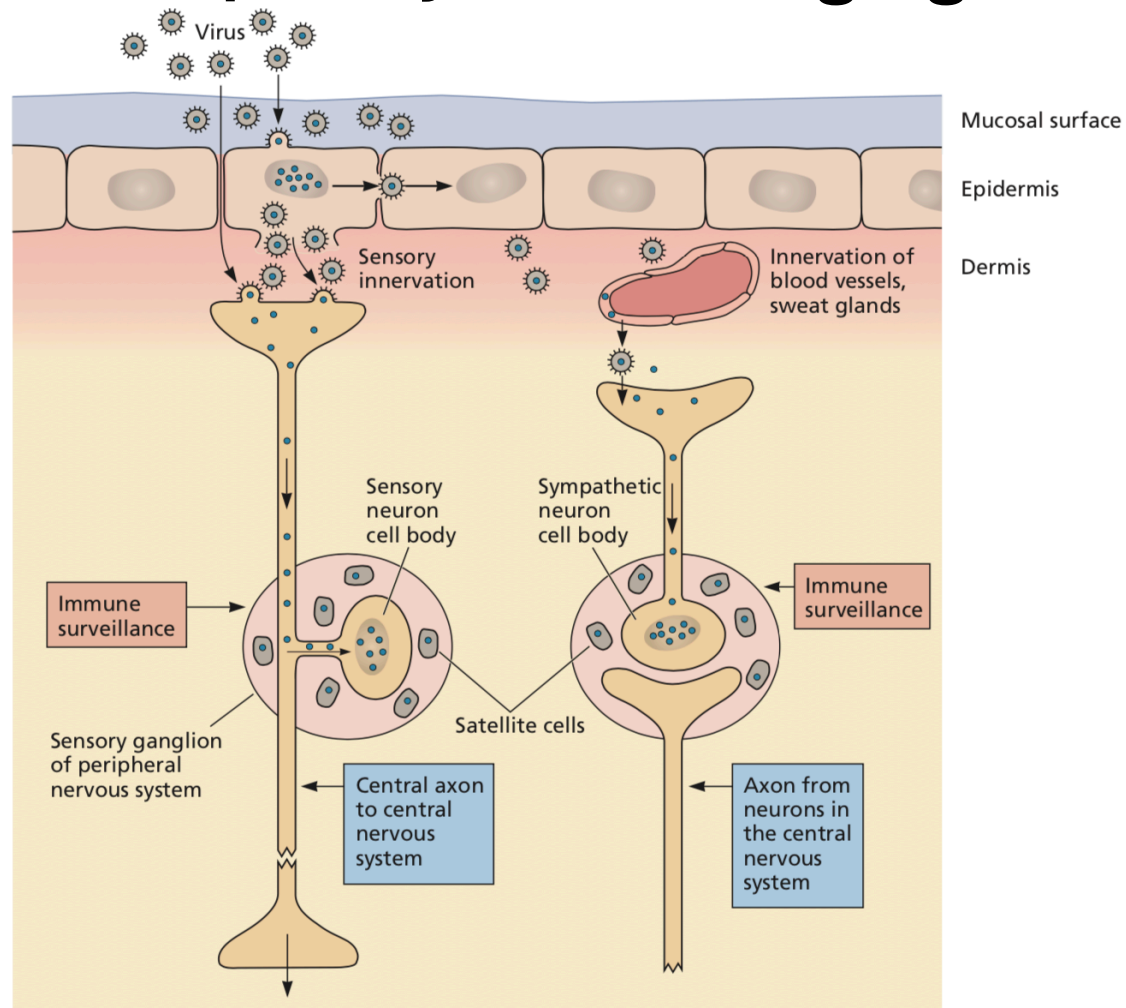
- Non-replicating DNA in a non-dividing cell
 - HSV, VZV in neurons
- Autonomous self-replicating DNA in dividing cell
 - EBV, CMV, HPV, HBV, KSHV
- Integrated into host chromosome, replicates with host
 - HHV6

Herpes simplex virus infections



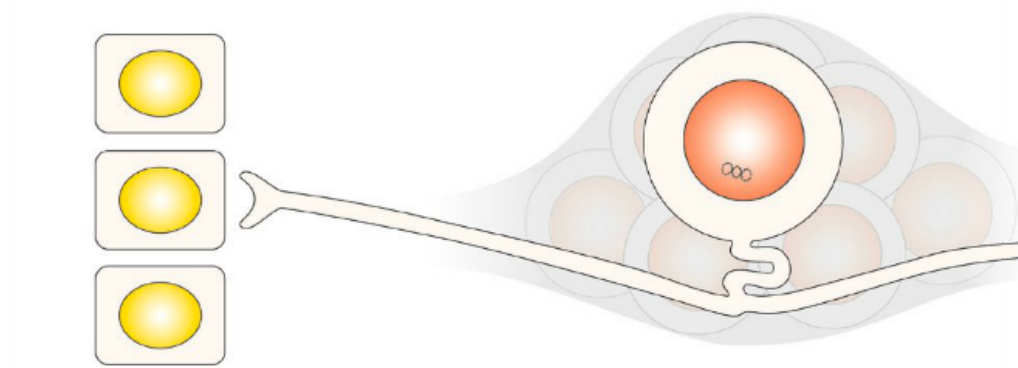
- US >80% seropositive with genomes in PNS
- Millions carry latent viral genomes in nervous system without symptoms
- 40 million experience recurrent herpes disease
- HSV-1, HSV-2
- A well-adapted pathogen

HSV primary infection of ganglia



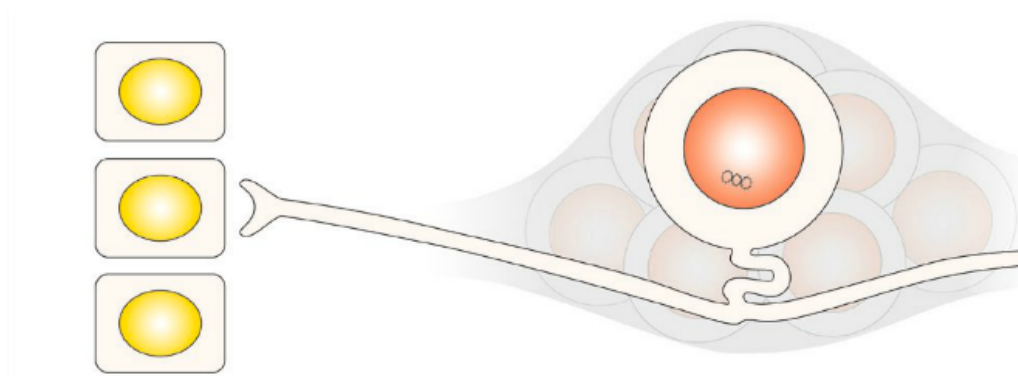
- Often infected in utero or during birth (80% of babies)
- Incubation 2-12 days
- Primary infection usually inapparent, but can result in combinations of fever, sore throat, ulcerative and vesicular lesions, gingivostomatitis, edema, swollen lymph nodes, anorexia, malaise

Post-infection events in neurons



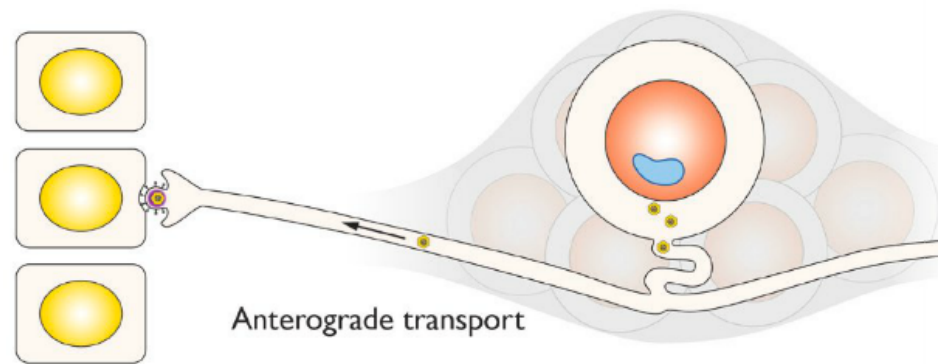
- Viral genome silenced, coated with nucleosomes
- Multiple copies of episomal viral DNA remain in nucleus
- No further replication needed to persist - neurons do not divide
- Herpes is forever - drugs and vaccines cannot cure a latent infection

Latency associated transcript

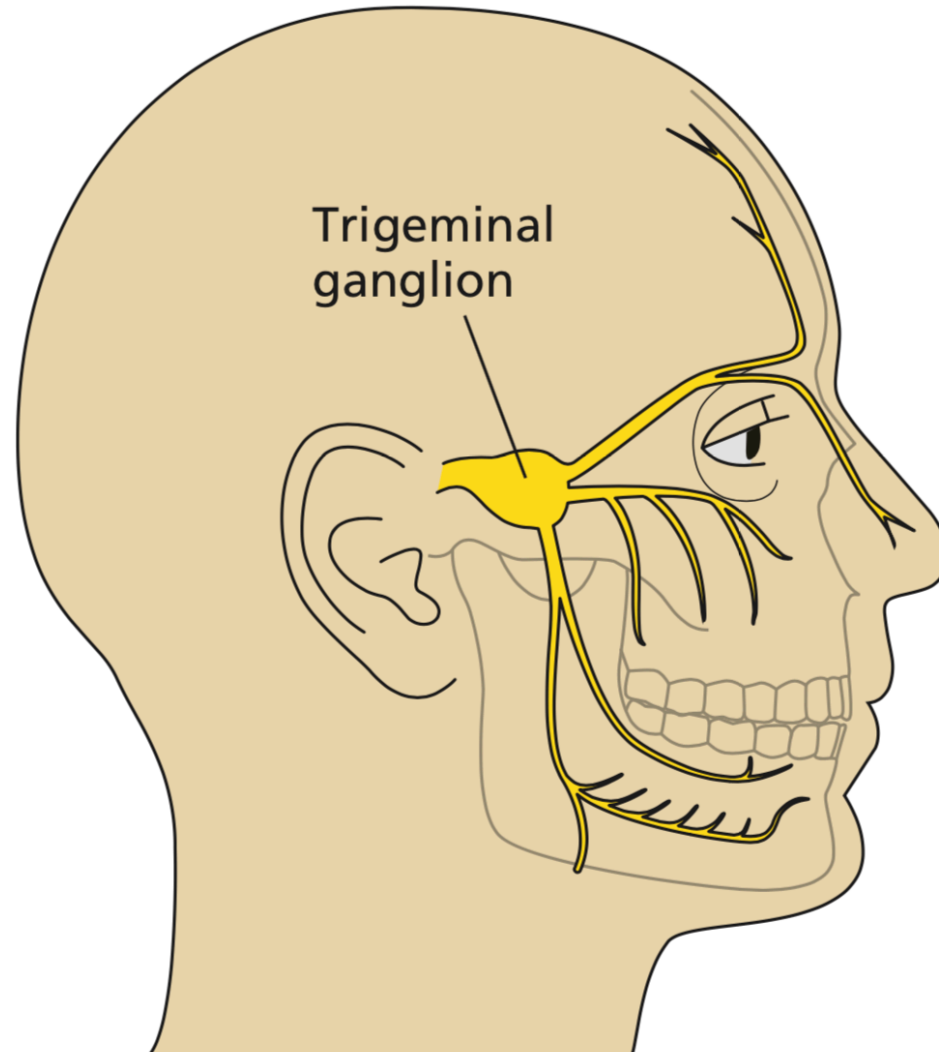


- Only LATs, miRNAs made in latently infected neurons
- No proteins translated from LATs
- RNA silencing to maintain viral genome in latent state
- Host contribution

Reactivation

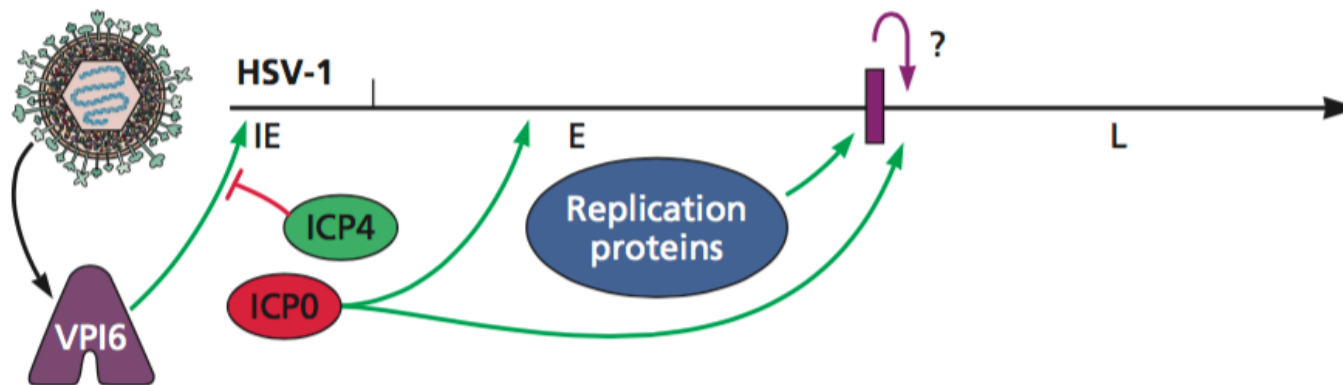


- Small number of neurons in ganglion reactivate
- Virions appear in mucosal tissue innervated by latently infected ganglia, blisters ensue (not always)
- This is how infection is transmitted (intimate contact)
- Immune response is too slow (viral antagonism) to prevent shedding
- Some reactivate every 2-3 weeks; others never

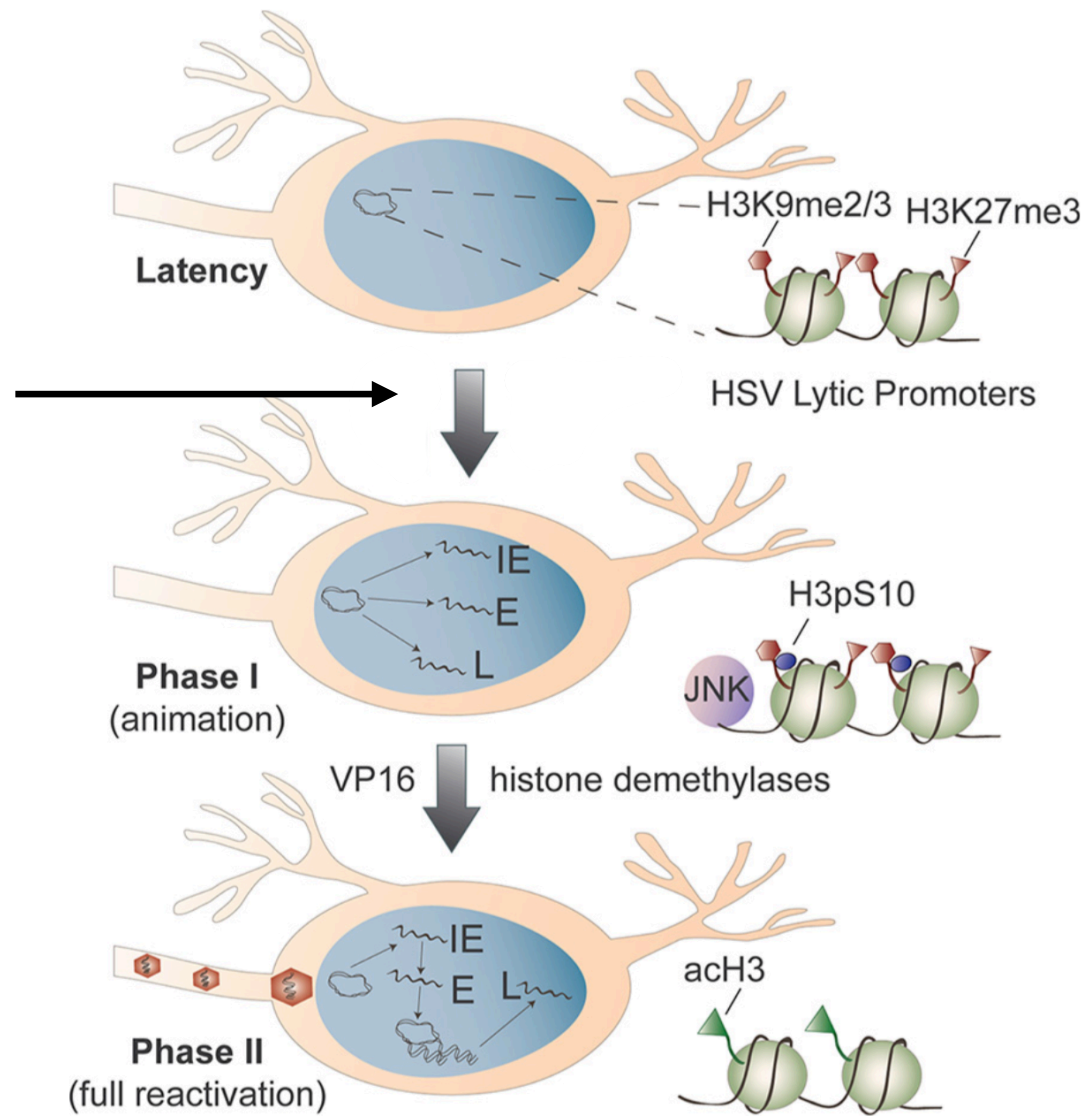


Reactivation

- Sunburn (UV), physical or emotional stress, nerve damage, hormonal imbalance, steroids
- Stimulate production of viral proteins needed to activate viral transcription program



Neuronal stress Kinase activation

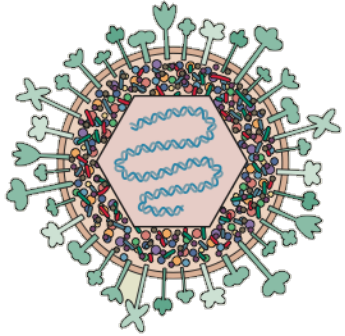


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Persistence of herpes simplex virus in nerve ganglia requires which of the following?

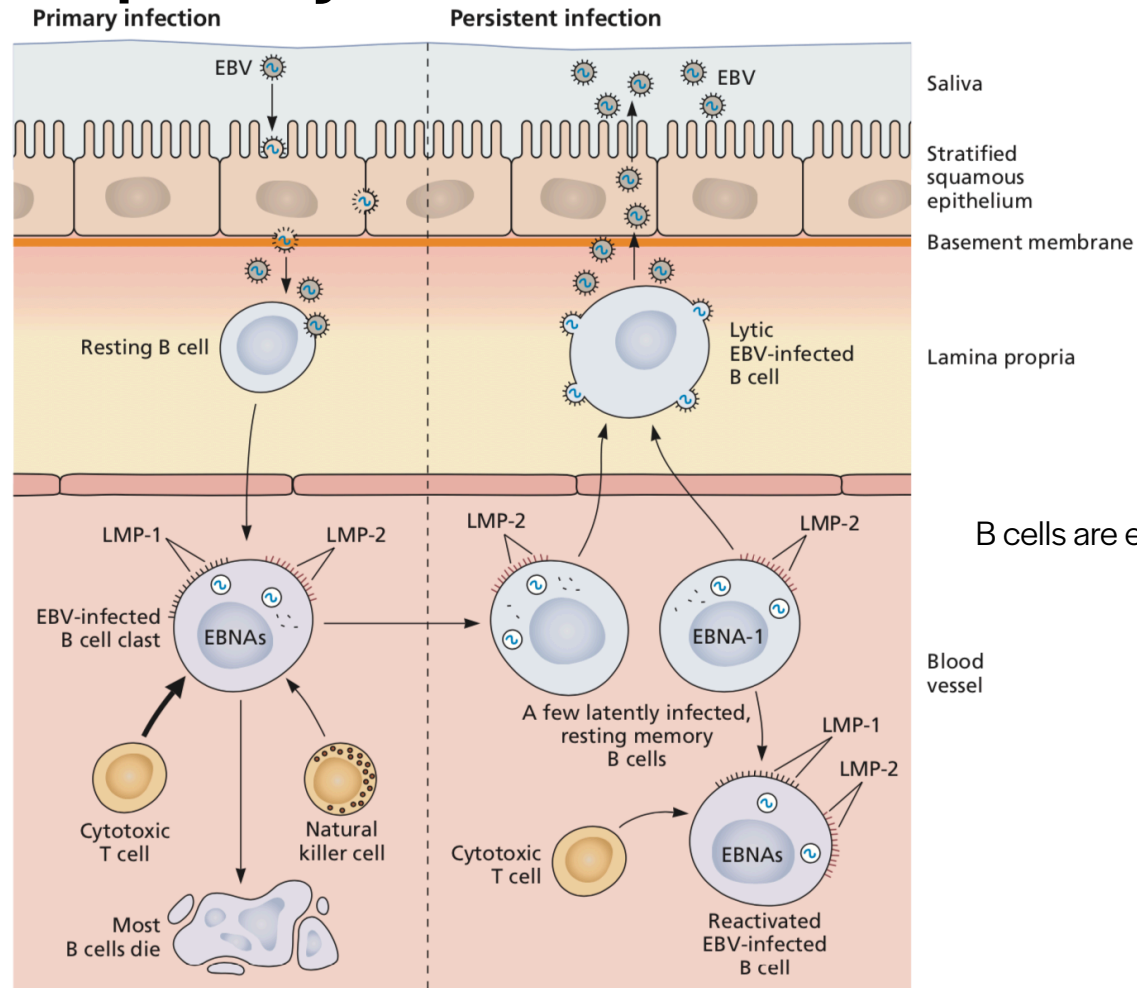
- A. Continuous episomal DNA replication
- B. Low level production of virus particles
- C. Silencing of all gene expression except LAT and miRNA
- D. UV light, stress, or steroids
- E. All of the above



Epstein-Barr virus

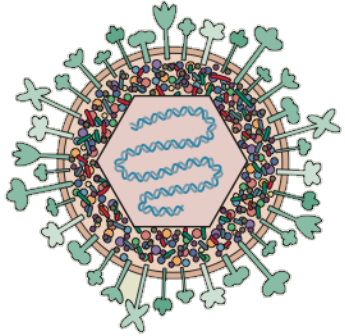
- 95% of US adults are seropositive and carry EBV genome
- Genome resides in B lymphocytes
- Most are infected at an early age, are asymptomatic
- Causal agent of:
 - Infectious mononucleosis
 - Human cancers (Hodgkins lymphoma, nasopharyngeal carcinoma, Burkitt's lymphoma)

EBV primary and latent infection



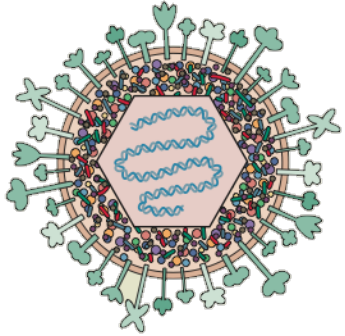
B cells are essential for EBV latency

Infectious mononucleosis

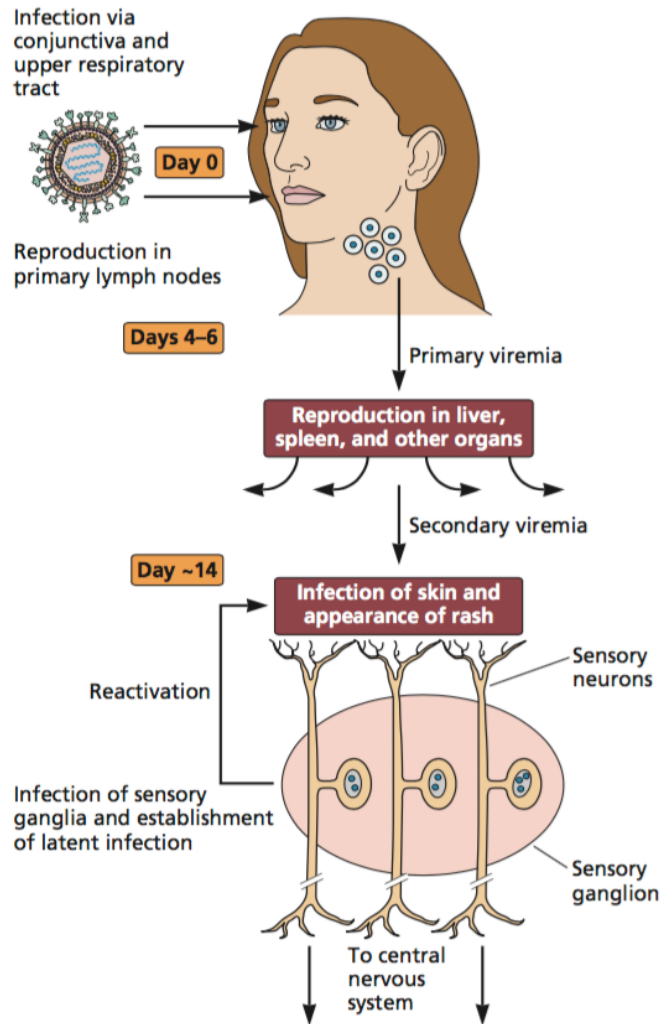


EBV latency

- Viral DNA is self-replicating episome, associates with nucleosomes in B cells
- Produces limited repertoire of viral genes
- B cells home to bone marrow and lymphoid organs
- Not killed by CTLs or antibody unless reactivation occurs (modulation of MHC)



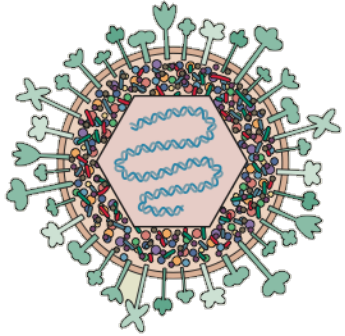
Varicella-zoster virus (VZV)



Varicella (chickenpox)

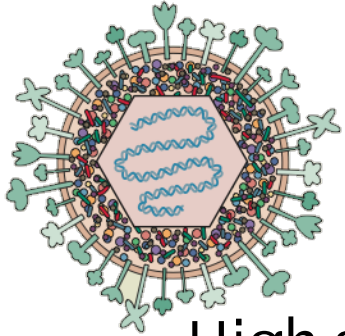


Herpes zoster (shingles)



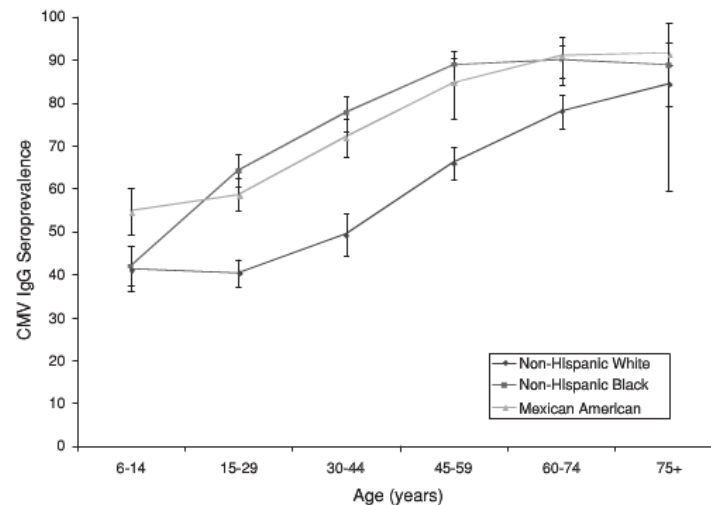
VZV

- 99% adults infected pre-vaccine, 30% develop zoster, 2/3 >50 years of age
- Latency: Episomal viral DNA, 2-9 genomes in 1-7% of neurons (non-replicating)
- Viral gene expression is restricted, IE, E, L genes
- Factors that trigger reactivation from neurons are unknown



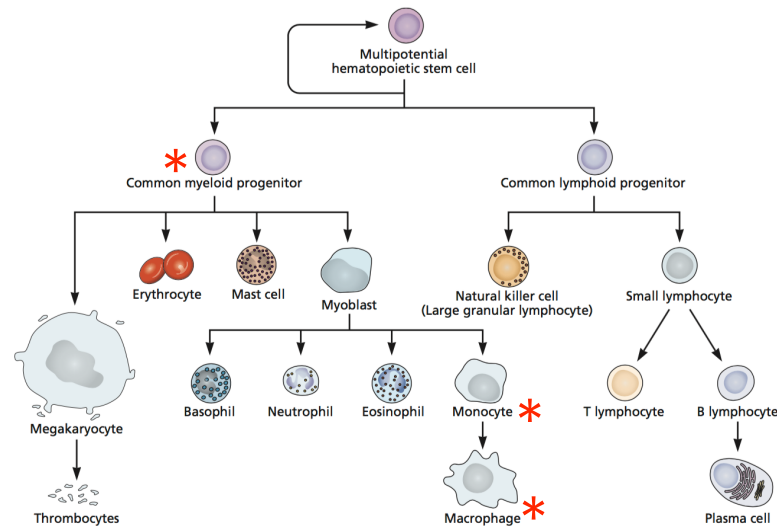
Cytomegalovirus (HCMV)

- High seroprevalence (50-99%) globally
- Transmitted by respiratory routes (virus in saliva), urine, sex
- Replicates in peripheral blood leukocytes, endothelial cells



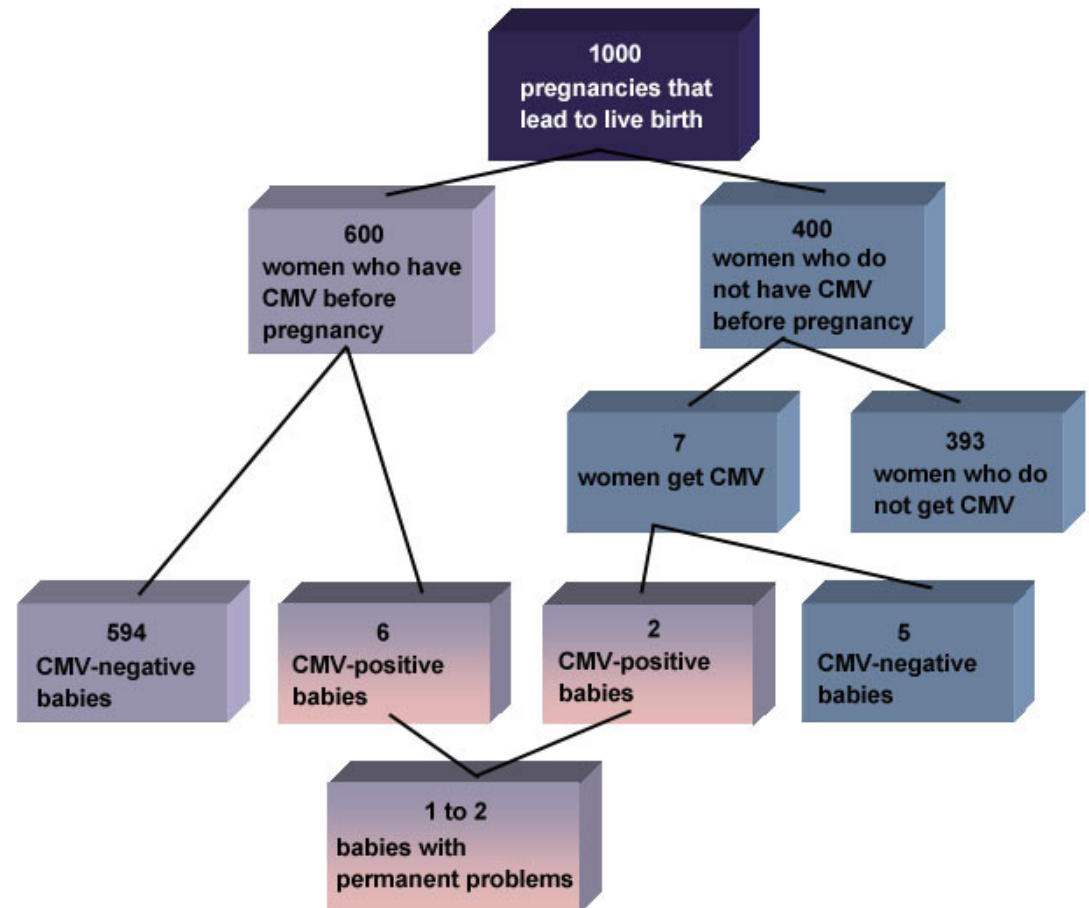
HCMV

- Primary infection in immunocompetent host usually asymptomatic or febrile, mono-like illness
- Persistent shedding of virus in saliva and urine for months to years
- Resolved by cellular immune response, but latently infected myeloid cells remain in bone marrow (precursors of monocytes, macrophages, dendritic cells)



HCMV

- Major problem in organ transplantation
- Virus crosses placenta, can cause severe multi-organ congenital defects, death

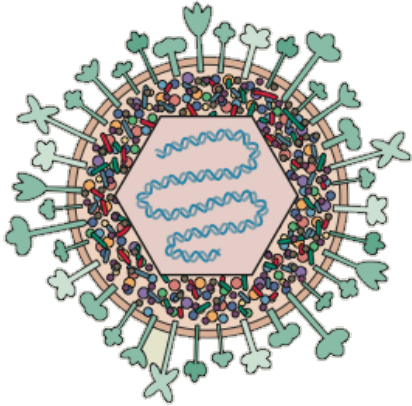


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What do persistent infections with EBV, VZV, and CMV have in common?

- A. B cells are essential for latent infection
- B. May cause congenital birth defects
- C. Viral DNA persists as an episome
- D. The factors governing reactivation are well known
- E. All of the above

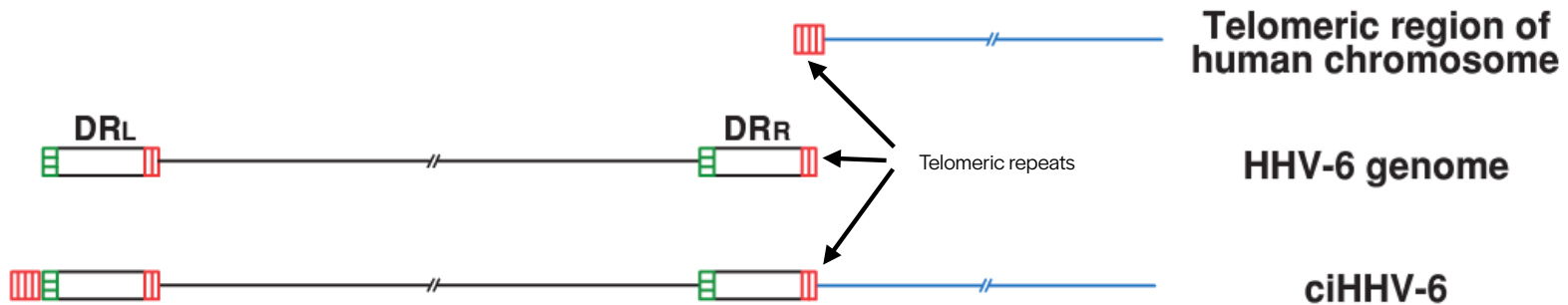


HHV-6, HHV-7



- Agents of exanthem subitum, mild childhood rash (sixth disease)
- >85% of adults have antibody to both viruses
- Horizontal infection through respiratory secretions, parent to child
- Infect lymphoid, endothelial, liver, CNS, salivary cells
- Latency: HHV-6 monocytes, macrophages, CD34+ progenitors; HHV-7 CD4+ lymphocytes

HHV-6 integration

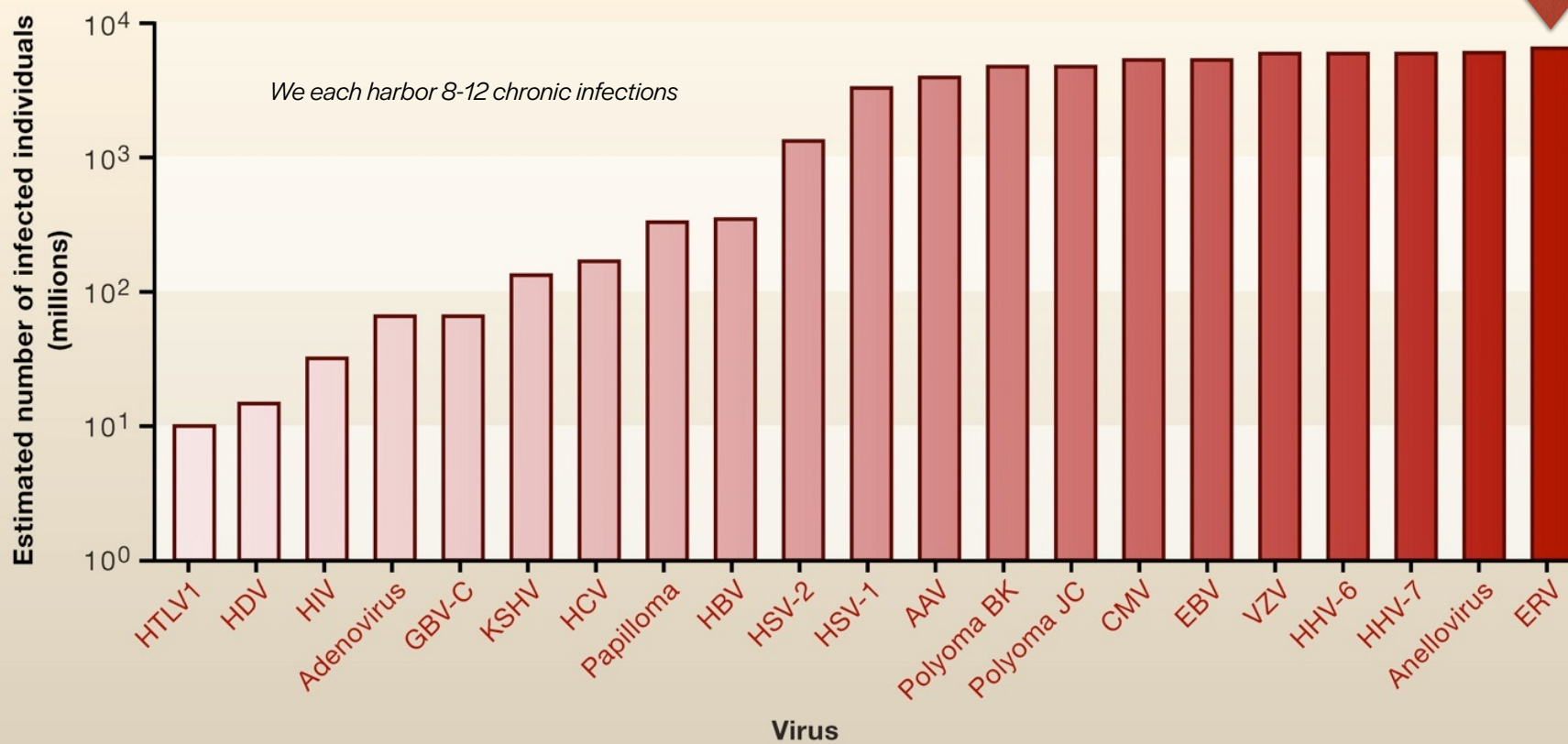


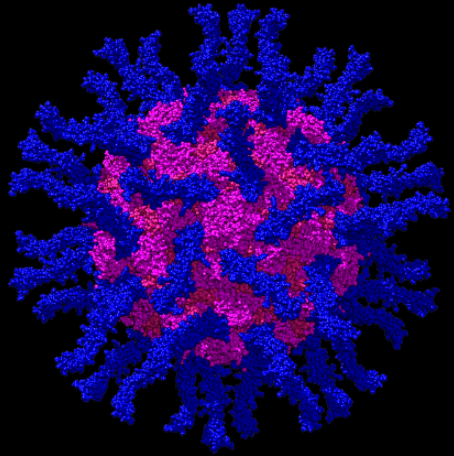
- In some cell types viral DNA integrates into telomeres
- About 1% of transmission acquires HHV-6 via germline
- Plausible strategy for latency and transmission

Everyone



Estimated burden of chronic viral infection in humans





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Next time: Transformation and oncogenesis