病毒學國考總複習

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Virion Structure: Naked Capsid

Component
- Protein

Properties*
- Is environmentally **stable** to the following:
  - Temperature
  - Acid
  - Proteases
  - Detergents
  - Drying
- Is released from cell by **lysis**

Consequences*
- Can be spread easily (on fomites, from hand to hand, by dust, by small droplets)
- Can dry out and retain infectivity
- Can survive the adverse conditions of the gut (**fecal-oral** route transmission)
- Can be resistant to detergents and poor sewage treatment
- Antibody may be sufficient for immunoprotection

* Exception exist

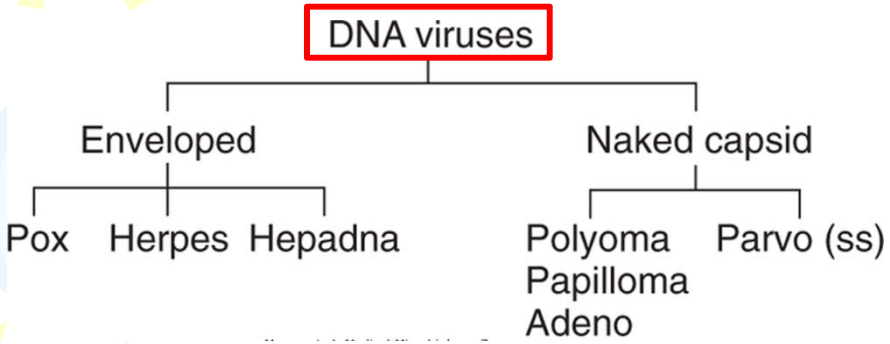
Virion Structure: Envelope

Components
- Membrane
- Lipids
- Proteins
- Glycoproteins

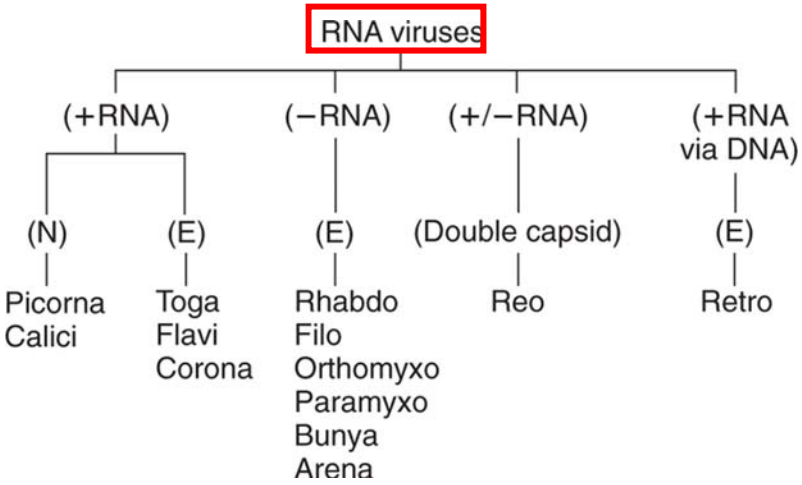
Properties*
- Is environmentally **labile**—disrupted by the following:
  - Acid
  - Detergents
  - Drying
  - Heat
- Modifies cell membrane during replication
- Is released by budding and cell lysis

Consequences*
- Must stay wet
- Cannot survive the gastrointestinal tract
- Spreads in large droplets, secretions, organ transplants, and blood transfusions
- Does not need to kill the cell to spread
- May need antibody and cell-mediated immune response for protection and control
- Elicits hypersensitivity and inflammation to cause immunopathogenesis.

Families of DNA and RNA Viruses



DNA viruses: 7 families



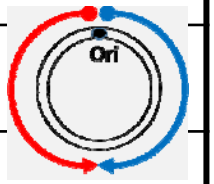
RNA viruses: at least 13 families

Properties of DNA Viruses

- DNA is **not** transient or labile.
- Many DNA viruses establish **persistent infections** (e.g., latent, immortalizing).
- DNA genomes reside in the **nucleus** (except for poxviruses).
- Most DNA viruses use the cell's **DNA-dependent Pol II and other enzymes to make mRNA**, but may encode their own transcriptional activators to regulate their gene expression. (but, poxvirus…..)
- Viral gene transcription is **temporally regulated**.
- **Early genes** encode DNA-binding proteins and enzymes.
- **Late genes** encode structural and other proteins.
- DNA polymerases require a primer to replicate the viral genome.
- The larger DNA viruses encode means to promote efficient replication of their genome.

Properties of RNA Viruses

- RNA is **labile** and transient.
- (+)-RNA viruses *vs*. (-)-RNA viruses: what is the difference?
- **(+) RNA can be used directly for protein translation**; (-) RNA cannot. So, **naked (+) RNA is infectious** and naked (-) RNA is not.
- Most RNA viruses replicate in the **cytoplasm**. (except for bornavirus and Influenza virus)
- Cells cannot replicate RNA. RNA viruses must encode an **RNA-dependent RNA polymerase (RdRP),** which are prone to mutation → **quasispecies of viruses**.
- **RNA viruses, except (+) RNA genome, must carry polymerases.**
- **All (–) RNA viruses are enveloped.**

	Parvo	Polyoma
Virion structure	Icosahedral capsid, naked capsid	Icosahedral capsid, naked capsid
Genome	Linear, ssDNA, ~5 kb 	Circular, dsDNA, ~5.3 kb DNA with minichromosome 
Replication	1. ITR as primer, strand displacement 2. Cellular DNA polymerase + Rep proteins for replication and transcription 3. Must replicate in mitotically active cells: prefer erythroid precursor cells	1. Bidirectional from Ori. 2. Ts: early (T and t antigens) and late (VP1, VP2, and VP3) 3. Cellular DNA Pol + LTAg for DNA replication, and Pol II for RNA Ts 4. LTAg inactivates pRb and p53
Lytic and/or Latency (site)	**Lysis** by nuclear and cytoplasmic membrane degeneration	Permissive cells→ **cell death** Non-permissive cells→ **transformation** latent in kidney and lungs
Pathogenesis	**B19 virus causes biphasic diseases:** 1. Early infection phase, viremia: flu-like symptoms 2. Late infection phase, Immune-mediated: • adults: rash and arthralgia • children: erythema infectiosum (fifth disease) • fetus: anemia-related disease and death (hydrops fetalis) • Chronic hemolytic patients: life threatening aplastic crisis (再生不良性貧血)	**JC and BK viruses**: Ubiquitous infection in humans, rare diseases, unless in **immunosuppressed** patients: **JC**: CNS → PML, JCV partially transform astrocytes and kills oligodendrocytes, causing demyelination. **BK**: urinary tract → hemorrhagic cystitis (出血性膀胱炎)
Transmission	Respiratory and oral secretions	Respiratory transmission or oral route → viremia to kidney or lung
viruses	**B19, Bocavirus** (acute respiratory disease), **AAV** (dependovirus, no disease)	**BK, JC viruses**, Merkel cell virus, SV40, polyoma
Others	Rash is due to immune complexes. B19 infection in utero causes spontaneous abortion	Virus is ubiquitous and infections are asymptomatic.

	Papilloma	Adenovirus
Virion structure	Icosahedral capsid, naked capsid	Icosadeltahedral capsid with fibers, naked capsid
Genome	Circular, dsDNA, ~8 kb DNA with minichromosome	Linear dsDNA, ~35 kb 
Replication	1. Bidirectional from Ori. 2. Ts all in one direction 3. Ts: early (E1-E7) and late (L1 and L2) 4. E7 inactivates pRb; E6 inactivates p53 to promote cell growth	1.pTP (protein) as primer 2.Virus-encoded DNA polymerases 3.Strand-displacement mechanism 4.E1A inactivates pRb; E1B inactivates p53 to promote cell growth
Lytic and/or Latency (site)	The infectious cycle follows differentiation of epithelial cells: Persist in the basal layer and then produce virus in terminally differentiated keratinocytes	Lytic in mucoepithelial cells Latent in lymphoid tissues
Pathogenesis	**Cutaneous HPV**: skin warts **Mucosal HPV**: benign head and neck tumors, anogenital warts: **HPV6, 11**: Laryngeal papilloma, anogenital warts, condyloma acuminatum (尖形濕疣) **HPV16, HPV18**: cervical cancer	Diseases are determined by tissue tropisms of specific groups or serotypes, diseases : • Acute respiratory disease • Pharyngitis • Conjunctivitis • Hemorrhagic cystitis • gastroenteritis
Transmission	Close contact (direct or **sexual**)	Aerosol, close contact, fecal-oral
viruses	HPV, many serotypes	Adenoviruses, many serotypes
Others	• Viral replication is determined by cell differentiation states. • Vaccines are available for HPV 6, 11, and/or 16, 18. • Pap smear: koilocytes	Can be used as vectors for gene therapy. Ad virus transforms rodent cells, but not human cells.

	Human Herpesviruses			
	HSV (HHV-1, -2)	**VZV (HHV-3)**	**EBV (HHV-4)**	**CMV (HHV-5)**
Virion / Genome/ replication	• HSV-1, HSV-2, Enveloped, Icosadeltahedral capsid ds linear DNA • early: bidirectional, late: rolling circle • encodes its own polymerase and scavenging enzymes	• Same as HSV	• Same as HSV	• Same as HSV
Types	α	α	γ	β
Lytic in __cells	**Lytic**: fibroblast, epithelial cells	**Lytic**: fibroblast, activated T, epithelial cells, epidermal cells	**Lytic:** activated B cells, epithelial cells	**Lytic**: epithelial cells, fibroblast, granulocyte..
Latent sites	**Latent**: **neuron cells**	**Latent**: **neuron cells**	**Latent**: **memory B cells**	**Latent**: **myeloid cells, monocytes, lymphocytes**, ..
Pathogenesis	Labial and genital lesions, e.g., cold sore, pharyngitis, encephalitis, keratoconjunctivitis whitlow …	• Varicellar (chickenpox) in children • Zoster (shingles) in adults	• Infectious mononucleosis (hetrophile Ab-positive), pharyngitis, • Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma	• Most: asymptomatic • Congenital defects, mononucleosis (heterophile Ab-negative) • Opportunistic under immunosuppression
Transmission	Orally and sexually, close contact viruses in saliva, vaginal secretions, lesion fluid	Respiratory droplet, inhalation, close contact	Saliva, close contact	Orally, sexually, blood transfusion, tissue transplantation, in utero, at birth, by nursing
Others	**Cowdry type A** inclusion body, **syncytia** Anti-viral drugs available	Vaccine and anti-viral drugs are available	Atypical lymphocytes **(Downey cells)**	Large cell and **owl's eye inclusion body** Anti-viral drugs available

	Human Herpesviruses	
	HHV6/7	**HHV8**
Virion / Genome/ replication	• Same as HSV	• Same as HSV
Types	β	γ
Latent sites	**Latent: T cells and monocytes**	**Latent: B cells**
Pathogenesis	Exanthem subitum (roseola infantum) (玫瑰疹)	• Kaposi's sarcoma associated with AIDS • Primary effusion lymphoma (a rare B lymphoma)
Transmission	Saliva The salivary gland is an in vivo reservoir for HHV-6	Blood and sexual transmission
Others	Lymphotropic (same as CMV) Rapid onset of high fever	

	Poxvirus
Viron structure	Enveloped, internal core (dumbbell) and lateral bodies
Genome	Linear, dsDNA with closed hairpin ends, no free 3' and 5' ends
DNA replication	1.self-priming **2.Replication in the cytoplasm** 3.Virus-encoded DNA-dependent DNA and RNA polymerases, capping and polyadenylation enzymes 4.mRNAs do not contain introns
Lytic or latent	Cell lysis or exocytosis
Pathogenesis	• Smallpox virus: lytic, only infect humans, vesicle appears all at once, bioterror agent • Molluscum contagiosum: wart-like growth, only infect humans • Vaccinia: lytic viruses, zoonotic
Transmission	Smallpox: aerosols and direct contact All other poxviruses: contact
viruses	Variola, vaccinia, molluscum contagiosum
Others	The largest DNA virus in human Virus is completely eradicated by vaccine

	Picorna	Corona	Noro (Calici)
Virion structure	Naked capsid, (+) RNA	Enveloped, (+) RNA	Naked capsid, (+) RNA
Genome	VPg protein at 5' end, IRES at 5'-UTR, and poly-A at 3' end	Cap at 5 end and poly-A at 3' end, the largest RNA virus	VPg protein at 5' end and poly-A at 3' end,
Protein synthesis	1 polyprotein, IRES-dependent translation	Early proteins and late proteins	Early proteins and late proteins
RNA replication /transcription	(+) RNA → (-) RNA → (+) RNA Encodes RdRP	(+) RNA → (-) RNA → subgenomic RNAs and (+) RNA	(+) RNA → (-) RNA → subgenomic RNA and (+) RNA
Pathogenesis	**Tissue tropic:** Polio: encephalitis, paralysis Coxackie A: hand-foot-mouth, herpangina, meningitis Coxackie B (A, echo): myocarditis (心肌炎), pericarditis (心包炎), pleurodynia (肌肋痛) EV71: rash, HFMD, meningitis (腦膜炎), encephalitis HAV: hepatitis	CoV: Common cold (2nd) SARS-CoV: pneumonia, diarrhea (bat → palm civets → human) MERS-CoV: pneumonia, renal failure (? → dromedary →human)	Diarrhea, nausea and vomit, and abdominal cramps
Transmission	Fecal-oral or Respiratory (rhinovirus)	Respiratory or Fecal-oral	Fecal-oral
viruses	Poliovirus, enterovirus, rhinovirus (1st common cold, >33°C cannot grow)	CoV: cannot grow >33°C SARS-CoV: replicate at 37°C MERS-CoV: replicate at 37°C	Norwalk-like viruses Caliciviruses Astroviruses
Others	• Virus is the pathologic effect • OPV (live) vs. IPV (killed) vaccines • **Rarely cause enteric diseases**	• Detergent resistant due to glycoprotein corona	

	Toga	Flavi
Virion structure	Enveloped, (+) RNA	Enveloped, (+) RNA
Genome	Cap at 5' end of RNA	HCV contains IRES at 5' end, others contain Cap
Protein synthesis	Early / Late proteins	One polyprotein
RNA replication /transcription	(+) RNA → (-) RNA → subgenomic RNA and (+) RNA	(+) RNA → (-) RNA → (+) RNA
Pathogenesis	• **Arboviruses** (WEE, EEE, VEE): encephalitis • Sindbis, Semliki Forest: subclinical • Chikungunya: fever, arthritis, arthralgia • Rubella (not arbovirus): German measles, rash, swollen glands (lymphadenopathy). Immune complexes most likely cause the rash and arthralgia.	• **Arboviurses** • Encephalitis viruses: St. Louis, West Nile, JEV • Hemorrhagic diseases: Yellow fever virus: jaundice, hepatitis, black vomit Dengue virus: hemorrhagic fever, breakbone fever, dengue shock syndrome • HCV (not arbovirus): chronic hepatitis
Transmission	Arthropod vector (*Aedes* and *Culex* mosquitoes), reservoir in birds or small animals. Viruses spread in blood to neurons and brain. Rubella virus: respiratory spread HCV: blood and sexual transmission	
viruses	Sindbis virus, semliki Forest, WEE, EEE, VEE, Chikungunya, and Rubella	Yellow Fever, JEV, dengue virus, Dengue virus, ZIKV, and HCV
Others	Rubella: congenital diseases. Vaccine is available.	ZIKV: congenital diseases (microcephaly) Non-neutralizing Ab promotes dengue infection (ADE: Ab-dependent enhancement). Four serotypes.

	Rhabdo	Filo	Borna	Paramyxo
Virion	Enveloped, (-) RNA	Enveloped, (-) RNA	Enveloped, (-) RNA	Enveloped, (-) RNA
segment	Non-segmented	Non-segmented	Non-segmented	Non-segmented
Replication cycle	(-) RNA → mRNA → (-) RNA replication and transcription	(-) RNA → mRNA → (-) RNA replication and transcription	(-) RNA → mRNA → (-) RNA replication and transcription	(-) RNA → mRNA → (-) RNA replication and transcription
Pathogenesis	• Rabies virus: encephalitis and neuron degenerate. • Negri body in infected cells	• Widespread hemorrhage (internal bleeding, liver damage, organ dysfunction) high mortality rate • Virus replicates efficiently in EC, monocytes, DC, macrophages	• neuropsychiatric disease, such as schizophrenia (精神分裂症), bipolar disorder (躁鬱症), depression (憂鬱), and autism (自閉症).	• Measles virus: rubeola (麻疹), high fever and CCC+P (咳嗽，鼻炎，結膜炎，畏光), otitis (耳炎), croup (哮吼), bronchopneumonia, encephalitis (e.g., SSPE) • Parainfluenza: mild cold, or lower RT disease (25%), or croup (2-3%) • Mumps virus: parotitis (腮腺炎), orchitis (睪丸炎) • Respiratory syncytia virus (RSV): highly fatal acute respiratory tract infection in infants and young children
Transmission	Zoonosis: animal bite aerosol (bat)	contact with blood, secretions, organs or **bodily fluids**	?? Olfactory route ?? Hematogenous transmission	Aerosol: respiratory Subacute sclerosing panencephalitis (SSPE) occurs several years after measles.
viruses	VSV, Rabies virus	Ebola virus, Marburg virus	Borna disease virus	Measles, parainfluenza, mumps, RSV, Hendra, Nipah, new castle disease virus
Others	• Hydrophobia • Post-exposure prophylaxis is possible.	Handle in BSL4	Replication in the nucleus	• Induce syncytia • Mucous Koplik spots for measles • Measles and mump virus: life-long immunity • Paramyxovirus (parainfluenza and mumps): HN, used for HA assay • Pneumovirus (RSV): G, will not agglutinate erythrocytes • MMR vaccines: measles, mumps, rubella

	Orthomyxo	Bunya	Arena
Virion	Enveloped, (-) RNA	Enveloped, (-) RNA	Enveloped, (-) RNA
segment	8	3	2
Replication cycle	(-) RNA → 10 mRNA → (-) RNA replication and transcription in the nucleus	(-) RNA → mRNA → (-) RNA replication and transcription	(-) RNA → mRNA → (-) RNA replication and transcription
Pathogenesis	• Flu symptoms: due to virologic and immunopathologic effects • Pneumonia by influenza or secondary bacterial infection	• Encephalitis viruses: **arbovirus** • Hantavirus (not arbovirus): pulmonary syndrome	• LCMV: meningitis • Lassa fever virus: hemorrhagic fever
Transmission	• Aerosol • Annual epidemics due to mutations (drift) • Pandemics due to reassortment of genome segments between human and animal viruses (shift)	• Encephalitis viruses: insects • Hantavirus: inhalation of aerosol from rodent urines or feces	• inhalation of aerosol from rodent urines or feces • LCMV: worldwide • Lassa fever: Africa
viruses	Influenza A, B (no reassortment), C (no human disease)	Bunyavirus, Hantavirus	LCMV, Lassa
Others	• Have 2 spliced RNAs, cap is stolen from host in the nucleus • HA and NA can elicit protective Ab • H5N1 and H7N9 are avian influenza viruses, but occasionally infect human, high mortality rates • Human influenza virus uses (SAα2,6Gal) receptor; Avian influenza virus uses (SAα2,3Gal) receptor • Live attenuated or killed vaccines: two flu A and one flu B • Neuraminidase inhibitors: Tamiflu, Relenza (release) • M2 inhibitors: amantadine, rimantadine (uncoating)	• Ambisense translation in some viruses • cap is stolen from host in the cytoplasm • Hantavirus is not an arbovirus	• Ambisense translation • Two circle RNA segments • Viruses persist in specific rodents

	Reovirus	Retrovirus	Prion
Virion	Double capsid, dsRNA	Enveloped, diploid (+)RNA	Infectious protein aggregates, PrP^{Sc}
segment	10-12	diploid	
Replication cycle	±RNA → 10-12 mRNA → packaged, and (-)RNAs are synthesized and transcribed in the capsid	(+)RNA→reverse transcription→cDNA→proviral DNA→mRNA and genomic DNA→assembly Simple retroviruses have three genes: gag. Pol, and env Complex retroviruses (HIV, HTLV): gag, pol, env and accessory genes	Prion binds to normal PrP, alter their conformation, and build fibrils in the brain
Pathogenesis	• Rotavirus: serious diarrhea in young children • Colorado tick fever: arbovirus, DV-like disease	• HIV: AIDS (when CD4 T cells drop below 200/μL) • HTLV (long latency) and many other animal viruses (short latency): tumors	• Spongiform encephalopathy CJD, Kuru, GSS disease, FFI
Transmission	• Rotavirus: fecal-oral	Blood and sexual	Surgical device, injection, food, genetics …
viruses	Rotavirus, reovirus	HIV, HTLV, and many animal retroviruses carrying oncogenes	
Others	• ISVP (infectious subviral particle) facilitates infection • dsRNA remains in the core • Reassortment is possible • NSP4 is a toxin-like molecule causing diarrhea, dehydration	• Virions carry RT, integrase, protease enzymes • Cause syncytia • HIV: CD4 is the receptor • CCR5 (M-tropic, macrophage and memory T) and CXCR4 (T-tropic, naïve T) as co-receptors • Tat/Tax transactivate viral gene expression • Rev/Rex facilitates the transport of unspliced and singly spliced mRNA to the cytoplasm • Nef: essential for AIDS • Other accessory molecules: modulate cellular antiviral activities • Treatment: HAART, nucleoside analogs, protease inhibitor	• Resistant to protease, heat and UV radiation • No immune response, no inflammation • No means of prevention or control

Feature	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Virus structure	Picornavirus; capsid, RNA	Hepadnavirus; envelope, DNA	Flavivirus; envelope, RNA	Viroidlike; envelope is from HBV, circular RNA	Hepevirus; capsid, RNA Calici-like virus
Transmission	Fecal-oral	blood, sexual	blood, sexual	blood, sexual	Fecal-oral
Onset	Abrupt	Insidious	Insidious	Abrupt	Abrupt
Severity	Mild	Occasionally severe; <10% chronicity in immune-competent adults	Usually subclinical; 70% chronicity	*Coinfection* with HBV occasionally severe; *superinfection* with HBV often severe	Normal patients, mild; pregnant women, severe
Mortality pregnant	<0.5%	1%-2%	~4%	High to very high	Normal patients, 1%-2%; pregnant women, 20%
Chronicity/ carrier state	No	Yes	Yes	Yes	No
Other diseases	None	Primary hepatocellular carcinoma, cirrhosis	Primary hepatocellular carcinoma, cirrhosis	Cirrhosis, fulminant hepatitis	None
Laboratory diagnosis	Symptoms and anti-HAV IgM	Symptoms and serum levels of HBsAg, HBeAg, and anti-HBc IgM Recovered: anti-HBs (+)	Symptoms and anti-HCV ELISA	Anti-HDV ELISA	-
Treatment or vaccine	Inactivated vaccine, hygiene	rHBsAg vaccine: anti-HBs(+) but anti-HBc(-)	Anti-viral drugs, no vaccine	Immunization for HBV	

HBV infection	Viral antigens or DNA	Anti-viral antibodies
Acute infection	eAg (+), sAg (+), DNA (+)	Anti-HBc IgM
Chronic infection	eAg (+) → Anti-HBe (+) sAg (+), DNA (+)	
Recovered	-	Anti-HBc, anti-HBe, **anti-HBs**
vaccinated	-	**Anti-HBs**

HCV infection	RNA	Antiviral antibody
Chronic infection	RT-qPCR	ELISA for antiviral Ab

HDV infection	RNA	HDV infection
Chronic infection	RT-qPCR	ELISA for delta antigen

Viruses-induced Diseases

1. Oral and respiratory tract infections:

oral: stomatitis (HSV), herpangina, Hand-foot-and-mouth (Coxsackie A virus)

respiratory	common cold	pharyngitis	laryngitis, croup, tonsillitis, bronchitis	bronchiolitis	pneumonia
Etiologic agent	• Rhinovirus* • Coronavirus* • Influenza • Parainfleunza • Respiratory syncytial virus (RSV) • Metapneumovirus • Adenovirus • Enterovirus	• HSV • EBV • Adenovirus* • Coxsackie A virus* (herpangina, Hand-foot-and-mouth) and other enteroviruses	• Parainfluenza virus 1* • Parainfluenza virus 2* • Influenza • Adenovirus • EBV	• RSV* (infants) • Parainfluenza 3* (infants and children) • Metapneumovirus • Parainfluenza 1 and 2	• RSV* (infants) • Parainfluenza* (infants) • Influenza virus* • Adenovirus • Metapneumovirus • VZV (primary infection of adults or immunocompromised hosts)

2. Gastrointestinal tract infections

gastroenteritis, diarrhea, vomiting

Gastrointestinal viruses
Infants Rotavirus*, Adenovirus 40, 41, **infants, children, and adults:** Norwalk virus*, Calicivirus, Astrovirus, Rotavirus A and B, Reovirus

* Most common causal agent

3. Exanthems and hemorrhagic fevers

maculopapular, nodules, vesicular, hemorrhagic fever

Conditions	Etiologic agent
Rash	
Rubeola	Measles virus
German measles	Rubella virus
Roseola infantum	Human herpesvirus 6
Erythema infectiosum	Human parvovirus B19
Boston exanthema	Echovirus 16
Infectious mononucleosis	EBV
	Also caused by enterovirus, DV, and other flaviviruses.
Vesicles	
Oral or genital herpes	Herpes simplex virus
Chickenpox/shingles	Varicella-zoster virus
Hand-foot-and-mouth disease, herpangina	Coxsackie A virus*
Papilloma, etc.	
Warts	Papillomavirus*
Molluscum	Molluscum contagiosum

Hemorrhagic fever
Yellow fever virus
Dengue virus
Ebola virus
Lassa fever
Hantavirus

4. Hematologic diseases

mononucleosis (EBV or CMV),
adult T-cell leukemia (HTLV),
AIDS (HIV)

*most common cause

5. Infections of the organs and tissues

Organs and diseases

Liver (hepatitis)
• Hepatitis A*, B*, C*, G, D, and E viruses
• Yellow fever virus
• Epstein-Barr virus
• Hepatitis in the neonate or immunocompromised person:
  • Cytomegalovirus
  • Herpes simplex virus
  • Varicella-zoster virus
  • Rubella virus (congenital rubella syndrome)
Heart (myocarditis)
• Coxsackie B virus*
Kidney
• Cytomegalovirus
Muscle
• Coxsackie B virus (pleurodynia)
Glands
• Cytomegalovirus
• Mumps virus
Eye (conjunctivitis, keratoconjuctivitis)
• Herpes simplex virus
• Adenovirus*
• Measles virus
• Rubella virus
• Enterovirus 70
• Coxsackie A24 virus

6. Central nervous system infections

Central Nervous System Infection

Meningitis
• Enteroviruses
  Echoviruses
  Coxsackie virus*
  Poliovirus
• Herpes simplex virus 2
• Adenovirus
• Mumps virus
• Lymphocytic choriomeningitis virus
• Arboencephalitis viruses
 	
Paralysis
• Poliovirus
• Enteroviruses 70 and 71
• Coxsackie A7 virus
 	
Encephalitis
• Herpes simplex virus 1*
• Varicella-zoster virus
• Arboencephalitis viruses*
• Rabies virus
• Coxsackie A and B viruses
• Polioviruses

Transmission Routes

Transmitted through blood

- Hepatitis B, C, G, D
- Human immunodeficiency virus
- Human T-cell lymphotrophic virus 1
- Cytomegalovirus
- Epstein-Barr virus
- West Nile encephalitis virus

Sexually Transmitted

- Human papillomavirus 6, 11, 42
- Human papillomavirus 16 and 18 (associated with human cervical carcinoma)
- Herpes simplex virus (predominantly HSV-2)
- Cytomegalovirus
- Hepatitis B, C, and D viruses
- Human immunodeficiency virus
- Human T-cell lymphotrophic virus 1

Arboviruses and Zoonosis

Virus	Family	Reservoir/Vector
Eastern equine encephalitis	Toga	Birds/Aedes mosquito
Western equine encephalitis	Toga	Birds/Culex mosquito
West Nile encephalitis	Flavi	Birds/Culex mosquito
St. Louis encephalitis	Flavi	Birds/Culex mosquito
California encephalitis	Bunya	Small mammals/Aedes mosquito
La Crosse encephalitis	Bunya	Small mammals/Aedes mosquito
Yellow fever	Flavi	Birds/Aedes
Dengue	Flavi	Mosquito
Colorado tick fever	Reo	Tick
Lymphocytic choriomeningitis	Arena	Small mammals
Lassa fever	Arena	Rats
Sin Nombre virus	Hanta	Deer mice
Ebola	Filo	unknown
Rabies	Rhabdo	Bats, foxes, raccoons, etc.

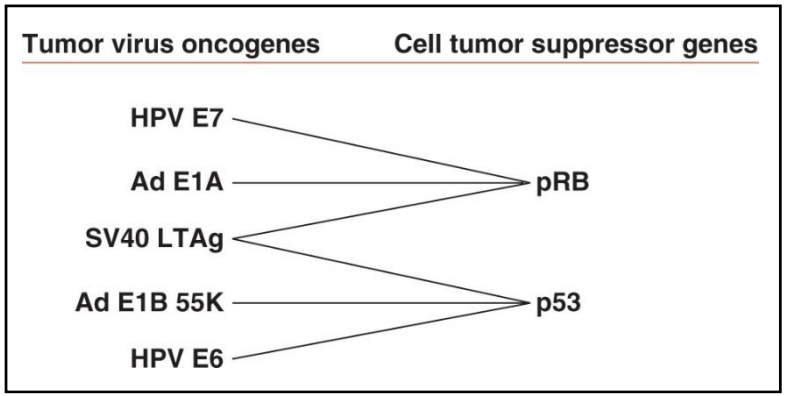
Chronic and Oncogenic Infection

Chronic infections (occur when the immune system has difficulty resolving the infection):

- latent infection: The DNA viruses (except parvovirus and poxvirus)
- chronic, productive infection: HBV, HDV, HCV, HDV, and retroviruses (CMV and some herpesviruses)

Transformations:

- **EBV:** Burkitt's lymphoma, Hodgkin's lymphoma, nasopharyngeal carcinoma
- **HTLV**: Adult T-cell Lymphocytic Leukemia (ATLL)
- **Papillomavirus**: Cervical carcinoma
- **HBV/HCV**: hepatocellular carcinoma
- **HHV-8**: Kaposi's sarcoma



Prenatal, Neonatal and perinatal Infection

- **Rubella, CMV, and ZIKV** are examples of **teratogenic viruses** that can cause congenital infection and severe **congenital abnormalities**.
- **HSV** acquired during passage at birth can result in **life-threatening disseminated disease**.
- **HIV** acquired in utero or mother's milk initiates a **chronic infection**.
- **B19** acquired in utero can cause **spontaneous abortion**.

Examples of Targets for Antiviral Drugs

Replication step or target	Agent	Targeted virus
Attachment	Peptide analogue of attachment protein Neutralizing antibodies Heparan and dextran sulfate	HIV (CCR5 co-receptor antagonist) Most viruses HIV, HSV
Penetration and uncoating	Amantadine, Rimantadine (against influenza M2 protein)	Infleuenza A virus
Protein synthesis	Interferon	HCVs, papillomavirus
DNA replication (viral polymerase)	Nucleoside analogues, e.g., acyclovir, AZT	Herpesviruses, HBV, poxviruses, etc
Nucleoside biosynthesis	Ribavirin	RSV, Lassa fever virus, HCV
Nucleoside scavenging enzyme	Nucleoside analogues	HSV, VZV
Glycoprotein processing	-	HIV
Assembly (protease)	Hydrophobic substrate analogues e.g., HAART for HIV	HIV, HCV
Assembly (neuraminidase)	Oseltamivir (Tamiflu), zanamivir (Relenza)	Influenza A, B virus

1. Drugs preventing attachment and entry of virions

- **Pleconaril** blocks many picornaviruses
- **Enfuvirtide** binds to HIV-1 virion, block gp41 conformational change
- **Maraviroc** binds to cellular HIV-1 co-receptor, **CCR5**
- **Amantadine and Rimantadine** block **M2** ion channels and inhibits uncoating of influenza virus

2. Replication inhibitors: nucleoside analogues: prevent chain elongation or induce inactivating mutation

- **Acyclovir** is selectively phosphorylated by herpesvirus thymidine kinases. The acyclovir triphosphate is preferentially incorporated by HSV and VZV DNA polymerase.
- **Azidothymidine (AZT)**-triphosphate is a more potent inhibitor of HIV reverse transcriptase than of human DNA polymerase.
- **Ribavirin** induces inactivating mutation in RNA viral genomes.

3. Protease inhibitors

- **HCV and HIV protease inhibitors**
- **Cocktail therapy for HIV: HAART** (highly active antiretroviral treatment) include protease inhibitor, AZT and a second non-nucleoside RT inhibitor.

4. Immunomodulators

- **IFN-α, pegylated IFN-α**: HBV, HCV, HSV

5. Rational design of neuraminidase inhibitors

- **Zanamivir (Relenza)** and **oseltamivir (Tamiflu)** are designed to mimic sialic acid in order to fit in the active site of **neuraminidase**

Major types of antiviral vaccines

- **Live wild-type viruses**
  - Simple and effective
  - Viruses may replicate poorly in non-natural host but share **immunogenic** determinants with related target viruses

- **Live attenuated viruses**

  Serial passage and in vitro cultivation of viruses reduces their pathogenicity

- **Inactivated viruses**

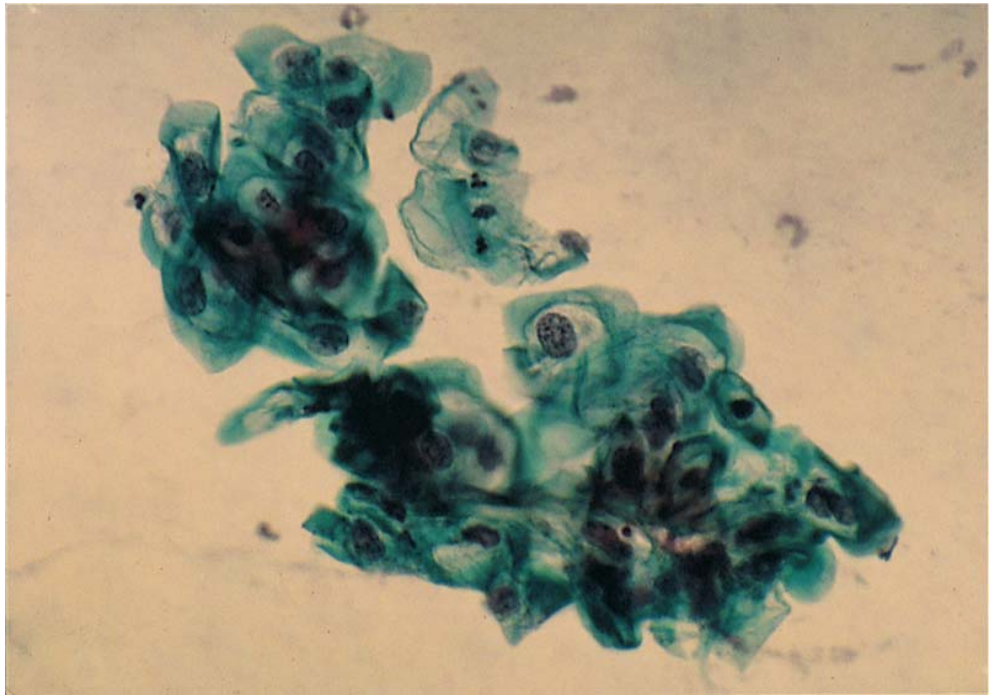
  Virus is grown, purified, and subjected to inactivation by treatment with chemicals or high temperatures

- **Subunit vaccines**

  Consists of purified viral proteins that are immunogenic

Live wild-type viruses	Vaccinia (cowpox)[a]
Live attenuated viruses	Adenovirus[b]
	Influenza A (cold adapted)
	Measles
	Mumps
	Polio (Sabin)
	Rotavirus (human-recombinant)
	Rubella (german measles)
	Varicella (chickenpox)
	Yellow fever
Whole inactivated viruses	Hepatitis A
	Influenza A
	Influenza B
	Polio (Salk)
	Rabies
	Tick-borne encephalitis
Subunit vaccine	Hepatitis B surface antigen
Virus-like particles	Human papillomavirus
Chimeric virus	Rotavirus (human-bovine)

[a] *Smallpox eradicated (supply of vaccine tenuous).*
[b] *Military use only.*

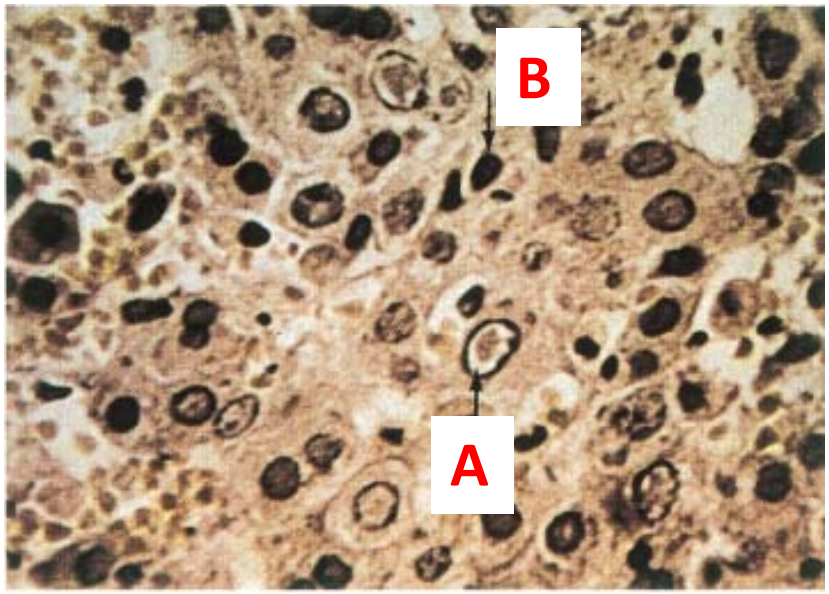


Perinuclear cytoplasmic vacuolization **(Koilocytes),** characteristic of human papillomavirus infection:

Squamous epithelial cells with clear halos around shrunken nuclei

- Characteristic histologic changes: **Inclusion bodies** in the nucleus or cytoplasm, margination of chromatin

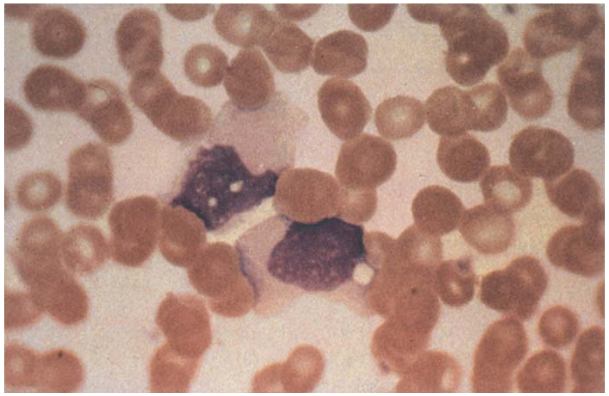
- **Syncytia**: Multinucleated giant cells caused by virus-induced cell-cell fusion



A: acidophilic Cowdry type A intranuclear inclusion body

B: smaller condensed nucleus (pyknotic) caused by HSV infection.

Downey cells



Cytomegalic cells

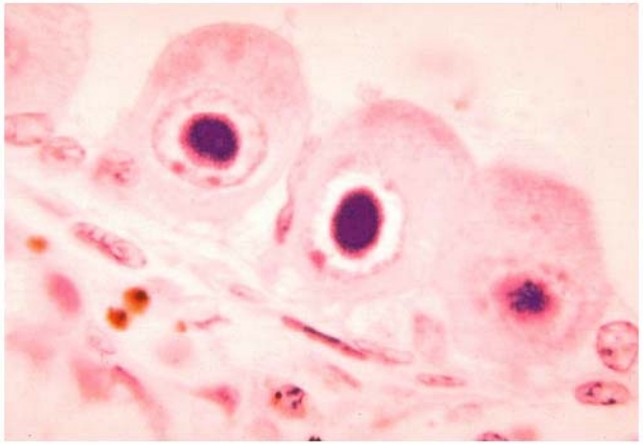


FIGURE 43-17 Cytomegalovirus-infected cell with basophilic nuclear inclusion body.

Enlarged cells : dense, central, "**owl's eye**", basophilic intranuclear inclusion body

Functions of human retroviral accessory proteins

Gene	virus	Function
Tax	HTLV	Transactivation of viral and cellular genes
Tat	HIV-1	Transactivation of viral gene
Rex	HTLV	Regulation of RNA splicing and promotion of export to cytoplasm
Rev	HIV-1	Regulation of RNA splicing and promotion of export to cytoplasm
Nef	HIV-1	Decreases cell surface CD4; facilitates T cell activation, **progression to AIDS (essential)**
Vif	HIV-1	Virus infectivity, promotion of assembly, blocks a cellular antiviral protein (APOBEC-3G) to prevent it from hypermutating the cDNA
Vpu	HIV-1	Facilitates virion assembly and release by degrading a cellular antiviral protein (tetherin), induces degradation of CD4
Vpr	HIV-1	Transport of cDNA to nucleus, arrest cell growth at G2 phase, which is optimal for HIV replication