VIRUSES

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Viroids and Plasmids

- Viroids replicate in a host and are transmitted via insects or pollen.
- Their RNA is circular. They create RNA once in the cell through rolling circle amplification.
- Within the cell polymerases make long concatemers of single stranded RNA. The cell then processes these concatemers by cutting them into pieces and re-circularizing them.
- Viroids don't code for any peptides.
- Down regulate host mRNAs that share short (19-25bp) sequence homology of the viroid. This is process known as RNA interference

Viroids and Plasmids

- Viroids often have Ribozyme activity that helps to chop the concatemers into 256bp pieces for further circularization.
- Ribozymes are RNAs that fold into molecules that behave like catalytic enzymes.
- Obelisks contain circular RNA.
- Obelisks are rod-shaped, usually under 1200bp BUT they contain short open reading frames and sometimes ribozymes.
- Plasmids contain circular DNA.
- Replicate in bacterial microbiome

Viroids and Plasmids

- Viruses code for proteins.
- They are not necessarily circular, nor short or rod-shaped hairpins.
- Viruses usually have an encoded polymerase (RdRp) to help with the replication.

Viruses

- The interaction of surface virus proteins with specific surface receptor proteins on cell surfaces determines both species and organ specificity of the virus.
- Infectious nucleic acid can enter and replicate within cells that the intact virion cannot.
- If the genome has the same base sequence as the mRNA, it is referred to as positive polarity.
- All viruses require virus specific mRNA to synthesize virus specific proteins.
- With the exception of Herpes viruses, all enveloped viruses acquire their envelope by budding through the external cell membrane.

Main viral portals of entry

Respiratory Tract	Influenza virus, Rhinovirus, Respiratory syncytial virus, Epstein-Barr virus, Varicella-Zoser virus, Herpes virus 1, Cytomegalovirus, Measles virus, Mumps virus, Rubella virus, Hantavirus, Adenovirus
Gastrointestinal Tract	Hepatitis A virus, Poliovirus, rotavirus
Skin	Rabies virus, Yellow fever virus, Dengue virus, Human papilloma virus
Genital Tract	Human papilloma virus, Hepatitis B virus, Herpes virus 2, Human immunodeficiency virus
Blood	Hepatitis B, C, D viruses, Human T-cell lymphotropic virus, Human immunodeficiency virus, Cytomegalovirus

Virus families

Structure	Viruses
DNA enveloped viruses	Herpes viruses (Herpes 1-8, Epstein-Barr virus, Cytomegalovirus), Hepatitis B virus, Smallpox virus
DNA nucleocapsid viruses	Adenovirus, papilloma virus, Parvovirus B19
RNA enveloped viruses	Influenza virus, parainfluenza virus, respiratory syncytial virus, measles virus, mumps virus, rubella virus, rabies virus, Human Immunodeficiency Virus, Human T-cell Lymphotorpic virus, Hepatis C virus
RNA nucleocapsid viruses	Pico or Enteroviruses (poliovirus, coxsackie virus, echovirus, Hepatitis A virus), rhinovirus, rotavirus, Norwalk virus

Both DNA and RNA viruses

- Retroviruses are RNA viruses that use a DNA intermediate to replicate their genomes.
- Retroviruses are RNA viruses with two identical sense-strand genomes and associated reverse transcriptase and integrase enzymes.
- Retroviruses differ from all other viruses in that they reverse transcribe themselves into partially duplicated double-strand DNA copies and then routinely integrate into the host genome as part of their persistence and replication strategies
- Hepatitis B virus (HBV) is a DNA virus that uses an RNA intermediate to replicate its genome.

Latent of persistent infection

- HBV, HCV, rabies virus, measles virus, HIV, HTLV, HPV, HHVs, and MCV may cause latent or persistent infection.
- 20% of human neoplasias

DNA virus families

Virus family	Envelope	Capsid Symmetry	Nucleic Acid	Medically important virus
Parvovirus	No	Icosahedral	Single stranded, linear	Parvovirus B19
Papillomavirus Polyomavirus	No	Icosahedral	Double stranded, circular, supercoiled	HPV JC
Adenovirus	No	Icosahedral	Double stranded, linear	Adenovirus
Hepdnavirus	Yes	Icosahedral	Double stranded, incomplete circular	Hepatitis B virus
Herpes virus	Yes	Icosahedral	Double stranded, linear	Herpes virus 1-8, Epstein-Barr virus, Cytomegalovirus
Pox virus	Yes	Acquired by Golgi wrapping	Double stranded, linear	Smallpox virus, vaccinia virus, Monkeypox virus

DNA viruses

- All DNA viruses encode their own DNA polymerase that replicates the genome.
- All replicate in the cell nucleus apart from the Pox viruses which replicate in the cytoplasm.
- Parvovirus single stranded DNA is converted to double stranded DNA by host cell polymerase.
- As with Papilloma virus, mRNA is synthesized by host cell RNA polymerase in the nucleus.
- Preferentially infects erythroblasts.
- Hepatitis B virus uses a virion encoded RNA-dependent DNA polymerase to synthesize its progeny DNA with full-length mRNA as a template.

DNA viruses

- The genome of Parvovirus, Papilloma virus, Adenovirus and Herpes virus is infectious.
- Pox virus genome is not infectious.
- The Hepatitis B genome is not infectious.
- Herpes viruses acquire their envelope by budding through the nuclear membrane.
- Matrix protein mediates the interaction of the nucleocapsid with the envelope.
- HPV 16, 18 (cervical cancer); 6,11 (anogenital and laryngeal papillomas); 1,4 (plantar warts)

Herpes simplex virus

- α-group viruses infect epithelial cells and produce latent infection in neurons (HSV-1, HSV-2, VZV)
- Lymphotropic β-group viruses (CMV, HHV6, HHV7)
- γ-group viruses produce latent infection principally in lymphoid tissues (EBV, HHV8)
- Latency only viral RNA transcripts (LATS) synthesized may be micro (mi)RNAs that confer resistance to apoptosis.
- Inhibit MHC class I recognition pathway
- Produce receptors for the Fc domain of immunoglobulin and inhibit complement

Herpes simplex virus

- HSV micro-RNA appears to silence expression of the key neurovirulence factor infected-cell protein ICP34.5 and to bind in an antisense configuration to the immediate-early protein ICP0 messenger RNA to prevent expression
- Infected cells contain large eosinophilic intranculear inclusions (Cowdry type A) that consist of virions with the stained host chromatin pushed to the periphery of the nucleus.
- Inclusion bearing multinucleated syncytia also produced as a result of cell fusion.

Herpes simplex virus

- HSV-1
- Often asymptomatic.
- Illness begins with abrupt onset of fever, anorexia.
- Lasts 2-3 weeks with virus shedding beginning 7-10 days post-infection.
- 12 to 96 days after constitutional symptoms mouth becomes sore.
- Gingivitis.
- No deep pharyngitis.

Herpes simplex virus

- Pathognomomic for HSV-1 oral infections are vesicles that become ulcers found on the tongue, inner surface of the lips and the buccal and sublingual mucosa.
- Major cause of corneal blindness, sporadic encephalitis.

Herpes simplex virus

- HSV-2.
- Vesicles appear on the glans penis or the penile shaft.
- Usually average 6-10 lesions
- Extragenital lesions may also occur on the thigh, buttocks, and perineum.
- Constitutional symptoms include fever, dysuria, localized inguinal adenopathy, malaise, stiff neck, headache and photophobia.
- Painful bilateral inguinal and pelvic lymphadenopathy

Herpes simplex virus

- HSV-2
- Primary genital infections in females.
- May be asymptomatic
- 2-7 days after sexual contact (incubation period)
- Herpetic lesions may develop on cervix.
- Vesicles rupture quickly, leaving shallow tender ulcers covered with a yellowish-gray exudate and surrounded by a red area.
- Cervix continues to shed virus for weeks.
- Severe pain, dysuria, and profuse watery discharge
- Painful bilateral inguinal and pelvic lymphadenopathy

Herpes simplex virus

- HSV-2 increases risk of infection with HIV-1
- HSV-2 reactivation is associated with a localized persistent inflammatory response consisting of high concentrations of CCR5-enriched CD4+ T cells as well as inflammatory dendritic cells in the submucosa of the genital skin.
- These cells can support HIV infection and replication

Herpes simplex virus

- HSV will lodge in trigeminal ganglia if primary oral infection
- HSV will lodge in sacral ganglia if primary genital infection
- May reach meninges
- Infection of the autonomic ganglia plays an important role in both activation and reactivation

Herpes simplex virus

- Encephalitis.
- Acquired in neonates during passage through the birth canal (50-70% HSV-2).
- Mortality rate approaches 65%
- No orbitofrontal or temporal lobe localization in neonates as in adults as virus not yet in trigeminal ganglion.
- Encephalitis in adults is complication of disseminated viremia.
- 95% HSV-1 (perhaps more than one strain)
- 10-20% of sporadic viral encephalitis
- Herpetic lesions may be found elsewhere.

Herpes simplex virus

- Herpetic Whitlow is a primary herpetic infection of the fingers.
- Tissue disruption is severe and intense local pain is always present.
- HSV keratitis presents as an acute onset of pain, blurred vision, chemosis, conjunctivitis, and characteristic dendritic lesions of the cornea.
- An HSV-1 epitope that is autoreactive with T cell–targeting corneal antigens has been postulated to be a factor in this infection.
- Major cause of corneal blindness in the US

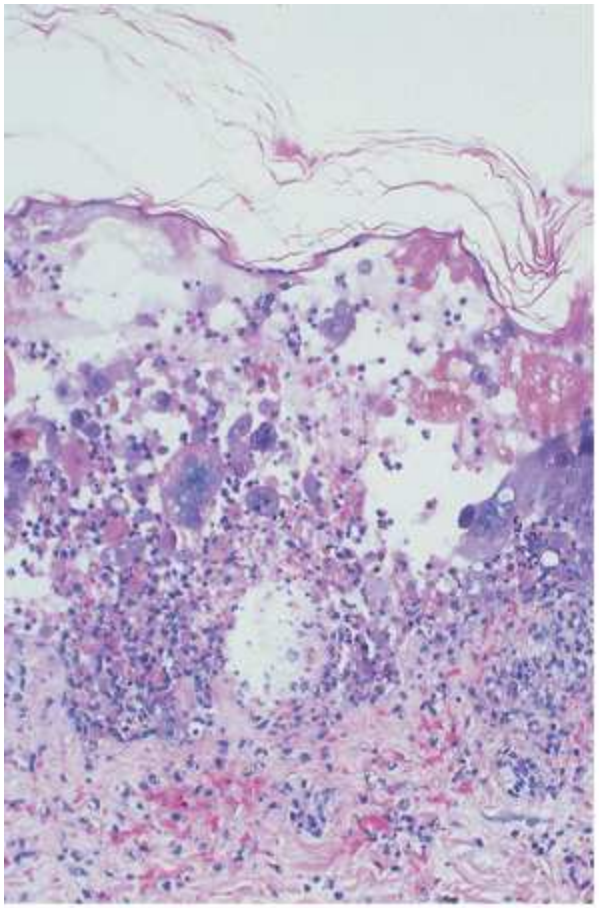
Herpes simplex virus

- Chorioretinitis, usually a manifestation of disseminated HSV infection, may occur in neonates or in patients with HIV infection.
- Both HSV and VZV may cause necrotizing retinitis

Herpes simplex virus

- First episode of genital herpes treated with valacyclovir.
- If recurrent, may use suppressive therapy with famciclovir.
- Treat sexual partner.
- Condom use.
- May be transmitted to infant in birth canal.
- Active infection may be a reason for C-section.
- Oral infections often controlled with acyclovir.
- Preventive measures include daily ingestion of active lactobacillus culture.

Herpes virus infection



The epidermis shows marked ballooning degeneration, cytolysis, and intraepidermal vesiculation. Perivascular lymphocytic infiltrate. Acantholytic and multinucleated epidermal giant cells are a clue to herpetic infection.

Fig. 6-7 Accessed 07/16/2010

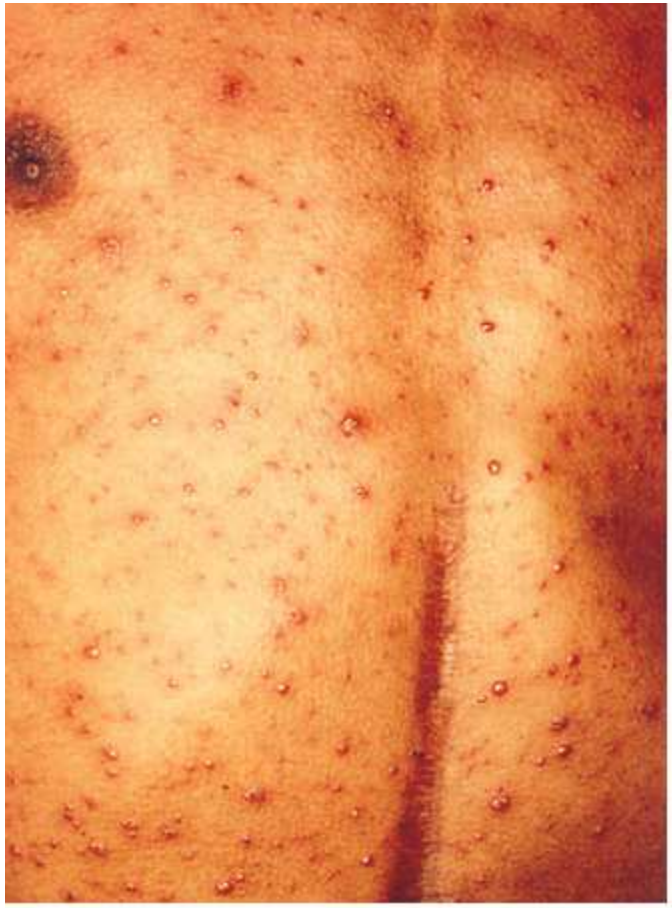
Herpes varicella-zoster virus

- Chickenpox (primary infection)
- 2 week incubation period
- Prodrome of low fever and malaise.
- Maculopapular lesions begin on and around the scalp, spreading to the trunk and after a few days to the extremities.
- Rash progresses from maculopapules to vesicles, to crusting scabs.
- New lesions continue to develop in groups over about 4 days.
- All three lesion types may be found simultaneously.
- May have systemic disease.

Herpes varicella-zoster virus

- The most common extracutaneous site of involvement in children is the CNS.
- Acute cerebellar ataxia and meningeal inflammation
- Appears 21 days after onset of the rash and rarely develops in the pre-eruptive phase.
- Benign complication requiring no therapy
- Varicella pneumonia develops more often in adults (up to 20% of cases) than in children and is particularly severe in pregnant women.
- Onset 3–5 days into the illness
- Resolution follows skin rash improvement

Chickenpox



Numerous varicella lesions at various stages of evolution: vesicles on an erythematous base, umbilical vesicles, and crusts.

(Courtesy of R. Hartman; with permission.)

Fig. 173-1 Accessed 07/01/2010

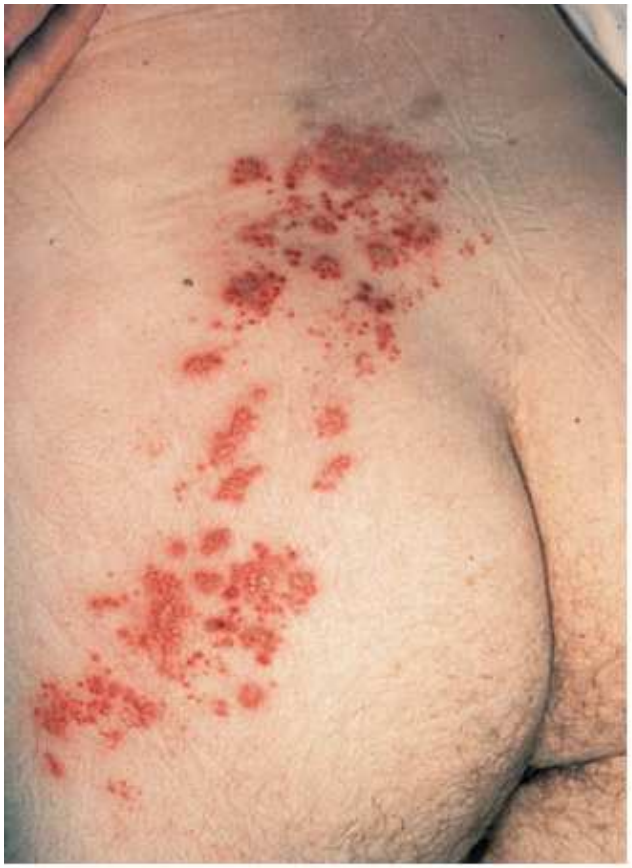
Herpes varicella-zoster virus

- Shingles.
- Due to reactivation of latent virus from ganglia.
- Vaccination reduces probability of reactivation by more than 50%.
- Occurs at any age.
- Occurrence of Zoster correlates with a decrease in virus-specific T-cells in the individual.
- Dermatome distribution.
- Usually T3-L3
- Responds to famciclovir.

Herpes varicella-zoster virus

- Virus is shed in the vesicular fluid of skin lesions of Zoster.
- Much less contagious than chickenpox.
- No respiratory component.
- If transmitted to susceptible host, that patient will develop chickenpox, not shingles.

Herpes zoster infection (Shingles)



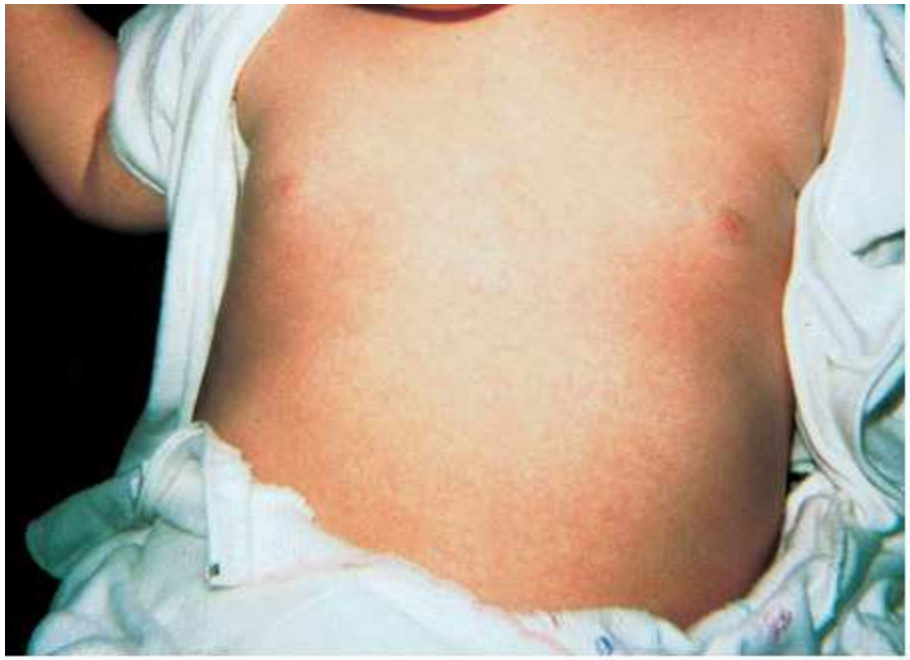
Hemorrhagic vesicles and pustules on an erythematous base grouped in a dermatomal distribution. Dermatome distribution. Pain often precedes eruption. Reactivation of vaccinia virus dormant in neuron soma.

Fig. 173-3 Accessed 07/16/2010

Human Herpes virus

- HHV-6
- Transmitted by respiratory droplets.
- Fever and diarrhea
- Minority develop a rash (exanthem subitum, roseola infanticum).
- 10-20% of febrile seizures
- Replicates in T and B cells.
- HHV-7
- Found in some CD4+ cells in cases presenting as roseola.

Exanthem subitum



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

Exanthem subitum occurs most commonly in young children. A diffuse maculopapular exanthem follows resolution of fever.

HHV-6

(Photo courtesy of Stephen E. Gellis, MD; with permission.)

Fig. e5-5Accessed 07/01/2010

Kaposi's sarcoma

- HHV-8
- Encodes a G protein-coupled receptor (vGPCR) that may induce transformation of endothelial cells by activating NFk-B and by production of a homologue of IL-6 as well as a homologue of MIP-1
- IL-6 has angiogenic and mitogenic effects
- Chemotactic recruitment of endogenous cytokine producing cells to amplify the response

Kaposi's sarcoma

- HHV-8 is related to γ-herpesvirus family (lymphotropic).
- HHV-8 induces genetic reprogramming of both vascular and lymphatic cells so that they more closely resemble each other as opposed to their corresponding uninfected phenotypes.
- May cause primary effusion lymphoma or multicentric Castleman disease (B-cell disorders).

Kaposi's sarcoma

- LANA-1, a latent nuclear antigen of HHV-8, targets the RB gene.
- HHV-8 encodes cyclin K, which inhibits the transcription of oncostatin M, a protein with growth-suppressive effects that prevent tumorigenesis .
- Viral interferon regulatory factor induces cellular transformation and prevents apoptosis mediated by p53 tumor suppressor, thereby facilitating uncontrolled cellular proliferation.
- Viral IL-6 also blocks host production of IFN-α.

Kaposi's sarcoma

- Improvement if underlying HIV infection treated.
- Patients are treated more aggressively if generalized organ involvement or confluence of lesions leads to compromise of limb function.
- Localized radiotherapy has been employed.
- Chemotherapy agents traditionally employed are bleomycin and doxorubicin.
- Systemic hyperthermia leads to tumor regression

Kaposi's sarcoma

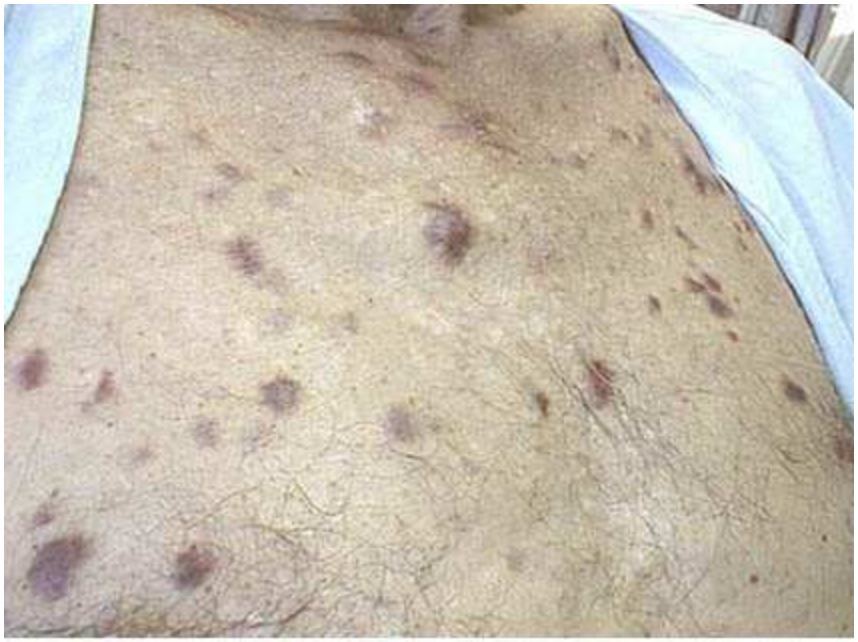


Fig. Ch. 6 Accessed 07/16/2010

Epstein-Barr virus

- Primary target cell for EBV is the B-cell.
- Envelope glycoprotein 350/220 binds to CD21 (CR2, the C3d receptor) or CD35.
- Potent B-cell mitogen.
- Leads to production of heterophile antibodies.
- Memory B cell is the reservoir

Epstein-Barr virus

- Secondary target cell for EBV is the epithelial cell within the oropharynx
- Especially the parotid glands
- Envelope glycoprotein 350/220 binds to α5/β1 integrin, but not efficiently.
- HLA II serves as a co-receptor for EBV entry into B cells.
- EBV expresses MHC I homologues that bind NK inhibitor receptors.
- Target MHC II complexes for degradation.
    - Immunosuppressive.

Epstein-Barr virus

- LMP-1 allows the B-cell blast to become a resting memory cell.
- As it also possesses T-cell epitopes and induces expression of adherins, infected B-cells may be found in clusters with infected T-cells, evading surveillance.
- LMP-1 also induces early protein BHRF-1 (a homologue of BCL-2) and engages TNFR, immortalizing the cell.
- Late protein BCRF-1 is a homologue of IL-10.

Epstein-Barr virus

- LMP-2 is disrupted by linearization of the genome.
- Oncogenic.
- EBNA-2 activates CD23 (allowing naïve B cells to enter germinal centers, be infected, and emerge) as well as upregulates EBV genes.
- It is essential for immortalization of the B-cell.
- Viral DNA maybe incorporated into cell genome but cannot complete the replication cycle as viral genes essential for replication are interrupted during integration of viral DNA (abortive infection).

Epstein-Barr virus

- Viral DNA circularizes in host cell genome as DNA episome and replicates in S-phase.
- EBNA-1 is essential to persistence of the genome (latent infection).
- Cells that become persistently infected and express LMP-2 lead to destruction of the host cell (lytic infection).
- LMP-2 serves as a substrate for SRC tyrosine kinases
- LMP-2 also possesses T-cell epitopes.

Epstein-Barr virus

- Virus shed in saliva throughout life span of host.
- May see hairy leukoplakia in the immunocompromised host.
- EBV-1 more common in the US

Infectious mononucleosis

- Infections in infants and young children either are asymptomatic or present as mild pharyngitis with or without tonsillitis.
- Meningitis and encephalitis may be only symptoms (often antibody negative)
- May develop tonsillar or adenoidal enlargement
- 75% of infections in adolescents present as IM
- Pharyngitis, bilateral anterior cervical lymphadenopathy, undulant fever, fatigue
- May show axillary, inguinal adenopathy.
- Splenomegaly.
- 0.5% may rupture spontaneously.

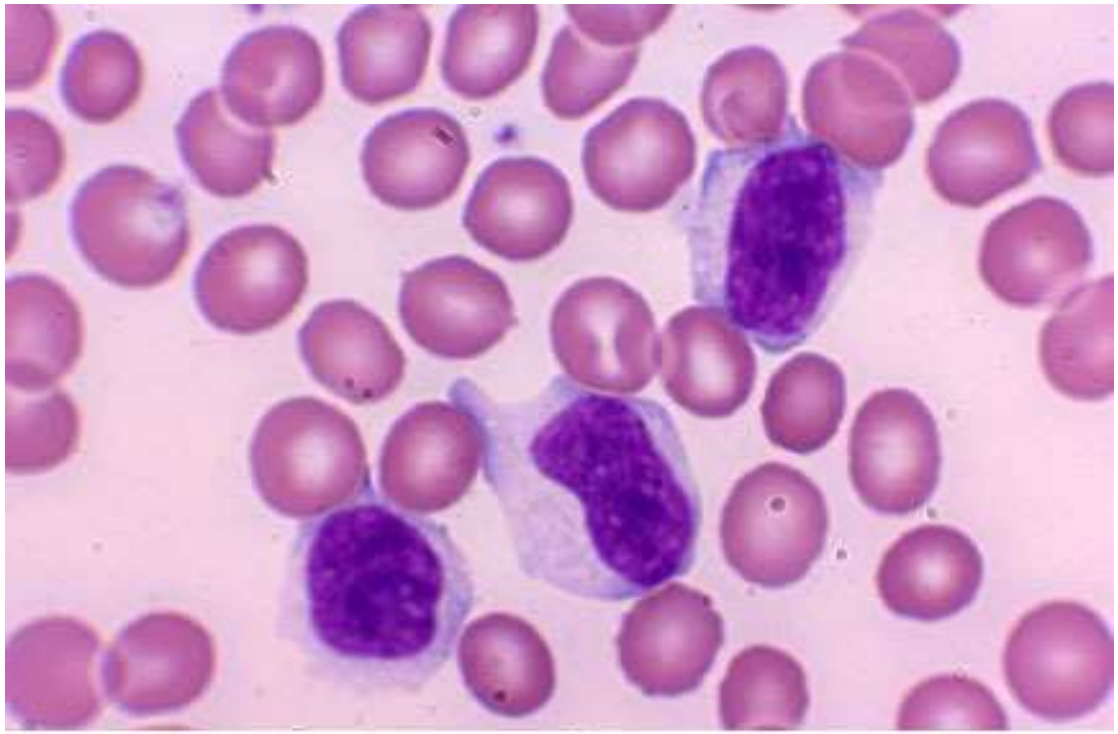
Infectious mononucleosis

- IM in the elderly often presents with nonspecific symptoms, including prolonged fever, fatigue, myalgia, and malaise.
- Pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytes are relatively rare in elderly patients

Infectious mononucleosis

- Morbilliform rash in 5-10%.
- All who receive ampicillin will express a rash.
- This is not an allergic reaction.
- Atypical (T, NK) lymphocytes.
- Express CD8, CD16 markers.
- 2% will have Coombs positive hemolytic anemia
- Cold agglutinins

Atypical lymphocytes



Source: Lichtman MA, Shafer MS, Felgar RE, Wang N:
Lichtman's Atlas of Hematology: http://www.accessmedicine.com

Cytoplasmic periphery conforms to red cell outlines. Nuclear shape not a strict circle but elongated or irregular.

Fig. II.G.9
Accessed 02/01/2010

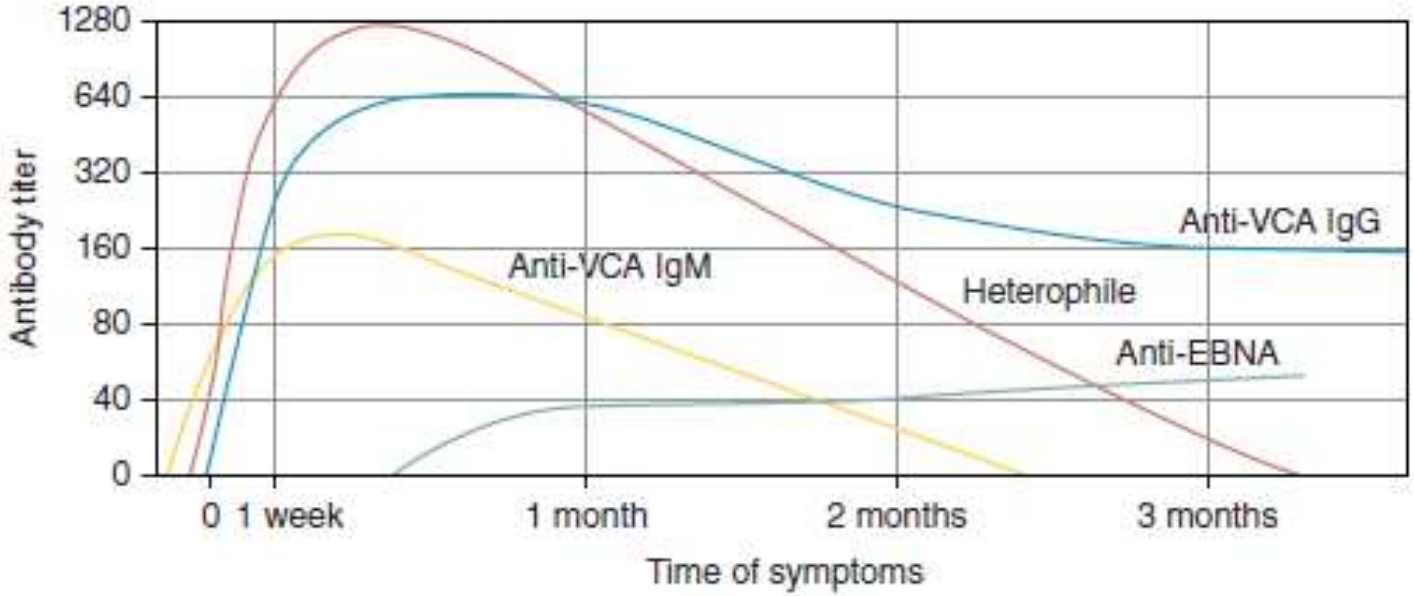


FIGURE 189-4 Pattern of Epstein-Barr virus (EBV) serology during acute infection. EBNA, Epstein-Barr nuclear antigen; VCA, viral capsid antigen. *(From JI Cohen, in NS Young et al [eds]: Clinical Hematology. Philadelphia, Mosby, 2006.)*

TABLE 189-2 Differential Diagnosis of Infectious Mononucleosis

ETIOLOGY	SIGN OR SYMPTOM				DIFFERENCES FROM EBV MONONUCLEOSIS
	FEVER	ADENOPATHY	SORE THROAT	ATYPICAL LYMPHOCYTES	
EBV infection	+	+	+	+	—
CMV infection	+	±	±	+	Older age at presentation, longer duration of fever
HIV infection	+	+	+	±	Diffuse rash, oral/genital ulcers, aseptic meningitis
Toxoplasmosis	+	+	±	±	Less splenomegaly, exposure to cats or raw meat
HHV-6 infection	+	+	+	+	Older age at presentation
Streptococcal pharyngitis	+	+	+	–	No splenomegaly, less fatigue
Viral hepatitis	+	±	–	±	Higher aminotransferase levels
Rubella	+	+	±	±	Maculopapular rash, no splenomegaly
Lymphoma	+	+	+	+	Fixed, nontender lymph nodes
Drugs[a]	+	+	–	±	Occurs at any age

[a]Most commonly phenytoin, carbamazepine, sulfonamides, or minocycline.

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpesvirus.

Epstein-Barr virus

- A causative agent of Multiple Sclerosis.
- Chronic, active EBV disease is a systemic lymphoproliferative disorder characterized by fever, lymphadenopathy, and splenomegaly developing after primary virus infection in patients with known immunodeficiency.
- May present as an aggressive T-cell, NK cell or B-cell disorder
- Principally affecting those of Asian origin.
- EBV receptor acquired by synaptic transfer from B cells

Epstein-Barr virus

- Excessive macrophage activation and hemophagocytosis may occur.
- Elevated IFN-γ and TNF-α noted.
- Fatal complication.

Burkitt lymphoma

- Highly aggressive lymphoma
- Found principally in children (40-50% of lymphomas).
- Tumors usually form near jaw.
- EBV DNA found in genome.
- EBNA 2 drives DNA replication.

Burkitt lymphoma

- African version restricted to parts of Africa and Papua New Guinea.
- Likely co-carcinogen is malaria infection.
- Non-African version has t(8,14).
- C-MYC gene locates near immunoglobulin heavy chain gene, and is activated.
- Progression free survival 92% at 2 years following therapy with cyclophosphamide, vincristine, doxorubicin, high dose methotrexate/ifosfamide, etoposide, and high dose cytosine arabinoside.

Nasopharyngeal carcinoma

- Tumors originate from the nasopharyngeal epithelium.
- Tumors are aggressive and metastasize to regional lymph nodes, particularly the cervical lymph node.
- Found in males between the ages of 20-50 years.
- Chinese with ancestry tracing back to the southern provinces of China have very high susceptibility rates.
- EBV DNA found in genome.
- EBNA2 drives DNA replication.

Cytomegalovirus

- Primary infections of pregnant women in first two trimesters place the fetus at greatest risk.
- Congenital CMV infection is the most common viral cause of birth defects.
- Major cause of congenital hearing loss and mental retardation.
- Pregnant women who have recurrent CMV infection will transmit infection to fetus.
- These infants do not suffer serve consequences.
- High level of transmission among toddlers in day care centers.

Cytomegalovirus

- Adults are commonly infected through sexual contact.
- At least one-third of women seen in STD clinics shed CMV; 40% of men shed CMV in semen.
- Patients who have received organ transplants will frequently develop CMV infections.
- In clinically immunosuppressed patients, source of the virus may be endogenous (reactivation) or exogenous (blood transfusion, organ transplants).
- Often fatal.
- Inclusion body surrounded by clear halo noted in nucleus of infected cells.

Cytomegalovirus

- Clinical manifestations include low birth weight, jaundice, petechiae, and hepatosplenomegaly.
- Severe symptoms are deafness, chronic liver damage, tooth defects, inguinal hernia, ventricular and arterial septal defects, cleft palate, and microcephaly.
- Most common manifestation of infection in immunocompetent hosts beyond the neonatal period is an infectious mononucleosis-like illness with fever, lymphadenopathy, mild hepatitis.

Cytomegalovirus

- Immunocompromised patients who develop interstitial pneumonia should be suspected of having CMV pneumonitis.
- Chorioretinitis occurs primarily in congenital infections, immunosuppressed patients.
- Cotton wool spots noted.
- Produces homologues of TNF-receptor, IL-10, and MHC class I molecules
- Induce ligands for activating receptors on NK cells as a well as induce MHC class I-like proteins that engage NK inhibitory receptors

Viral hepatitis

Virus	Structure	Incubation period	Chronic hepatitis
Hepatitis A (Fecal-oral transmission)	Icosahedral capsid ssRNA	2-6 weeks	None
Hepatitis B (Body fluid transmission)	Icosahedral capsid ssRNA	4-26 weeks	5-10% Up to 1% as carriers
Hepatitis C (Body fluid transmission)	Icosahedral capsid ssRNA	2-26 weeks	>50% As many as 10% as carriers

HAV

- HAV shed in stool 2-3 weeks before and 1 week after onset of jaundice.
- IgM-anti-HAV appears in blood at onset of symptoms.
- Fecal shedding of virus ceases as IgM titer rises.
- IgM declines after several months.
- IgG-anti-HAV persists and is thought to confer lifelong immunity.

HBV

- Neonatal vaccination highly effective.
- HBV remains in the blood up to and during active episodes of acute and chronic hepatitis.
- HBV is also present in all body fluids with the exception of stool.
- No transplacental transmission.
- Virus not present in colostrum.
- Half the adult population infected with HBV do not show icterus (jaundice).
- Transaminases normalize within 4 months if infection resolves.

HBV

- Vaccination may also provide post-exposure propylaxis.
- Entecavir and Tenofovir are nucleoside/nucleotide analogs with significant antiviral activity.
- Preferred for treatment of those physicians engaged in invasive procedures. R
- Rapid decline in HBV levels to below threshold levels (1,000IU/ml) following initiation of therapy.
- Low incidence of drug resistance.
- Interferon-α or pegylated interferon-a for chronic hepatitis are also employed.

HBV

- The “Dane” particle, the HBV virion, is spherical, measures 42nm, and consists of an outer surface envelope enclosing a 28nm core.
- There is a nucleocapsid core protein (HBcAg) and a longer polypeptide transcript with a precore and core region (HBeAg).
- The precore region directs the HBeAg polypeptide toward secretion into blood.
- HBcAg remains in hepatocytes for assembly into complete virions.

HBV

- Non-infective surface protein, HBsAg.
- The envelope glycoprotein may consist of pre-S1, pre-S2, and S antigen (large); pre-S2 and S (middle); S (small).
- DNA polymerase exhibiting reverse transcriptase activity.
- Genomic replication occurs via an intermediate RNA template.

HBV

- HBx acts as a transcriptional transactivator of the viral genes and is necessary for replication.
- In the proliferative phase, the virus is present in hepatocytes and HBcAg and HBsAg are expressed. CD8+ cytotoxic lymphocytes are activated to control the infection.
- For infected hepatocytes not destroyed by the immune system, viral DNA may be incorporated in the host genome, the integrative phase.

HBV

- HBsAg appears before onset of symptoms, peaks during overt disease, and is generally undetectable after 3-6 months.
- HBeAg, HBV-DNA, and DNA polymerase appear in the serum soon after HBsAg.
- They indicate active viral replication.
- IgM-anti-HBc appears shortly before onset of symptoms, concurrent with rise in ALT/AST. After months, it is replaced with IgG-anti-HBV.

HBV

- Anti-HBe is detectable shortly after the disappearance of HBeAg, implying that the acute infection has peaked.
- Anti-HBs is detectable some time after the disappearance of HBsAg.
- It may confer lifelong immunity.
- Prolonged replication poses risk for development of cirrhosis and hepatocellular carcinoma.

HCV

- Most common blood-borne infection in the US
- CD 81 receptor.
- Icterus is rare.
- Acute infection generally undetected clinically.
- 70% of infected individuals have viral RNA in the serum.
- The rise in viral RNA levels parallels the rise in ALT/AST.
- IgM-anti-HCV detected in 50-70% of patients with symptomatic acute hepatitis, emerging in the rest within 3-6 weeks.
- Should be confirmed with recombinant immunoblot assay.

HCV

- IgG-anti-HCV does not confer immunity.
- 5’ end of genome encodes a highly conserved nucleocapsid protein followed by two envelope proteins.
- The second envelope protein (E2) gene sequence contains two hypervariable regions.
- Towards the 3’ end are six less conserved non-structural proteins that contribute cis-acting functions essential for viral replication.

HCV

- The protein p7 functions as an ion channel.
- Virus inherently unstable (RNA polymerase, NS5B, not highly conserved).
- HCV circulates as a population of divergent but closely related variants (quasispecies).
- Enables viral strains to evade neutralizing antibodies as well as interferon mediated cellular antiviral response that limit infection.
- Leads to recrudescent disease.
- 80% will have chronic hepatitis.
- Presently 6 genotypes identified.

HCV

- Progression is common.
- 20% will have cirrhosis.
- Alcohol accelerates progression.
- Genotype 1b poses higher risk for development of hepatocellular carcinoma.
- If no viral clearing after 3 months, ribavirin and pegylated interferon-α may be instituted.
- Those patients with reversible fibrosis experience longer survivals.
- No correlation between transaminase levels and degree of hepatic injury.

HCV

- Do not treat those with normal ALT values, those with advanced cirrhosis, pregnant women, or active users of alcohol or drugs of abuse.
- 28% of HCV+ patients have Monoclonal B-cell Lymphocytosis

HDV

- Dependent on HBV for its life cycle.
- HDV is a replication defective circular single stranded RNA virus that infects only when encapsulated by HBsAg. Host RNA polymerase, principally, Pol II, directs RNA synthesis.
- The only protein produced by the virus is a polypeptide encircled by HBsAg, the delta antigen (HDAg).
- May represent co-infection or superinfection.
- Prevent with Hepatitis B vaccination.

HDV

- Common in Africa, Mediterranean basin, Pacific islands.
- Suppresses HBV replication.
- Types I, III associated with fulminant hepatitis.
- 80% progress to chronic hepatitis.
- Alcohol, marijuana, transfusions aggravate.
- 43% of cirrhotic patients harbor cancer.
- AFP may be elevated.

HEV

- Zoonosis
- Enterically transmitted; water borne
- 20% mortality rate in pregnant women
- Hepesvirus (RNA)
- HEV Ag identified in cytoplasm of hepatocytes during active infection

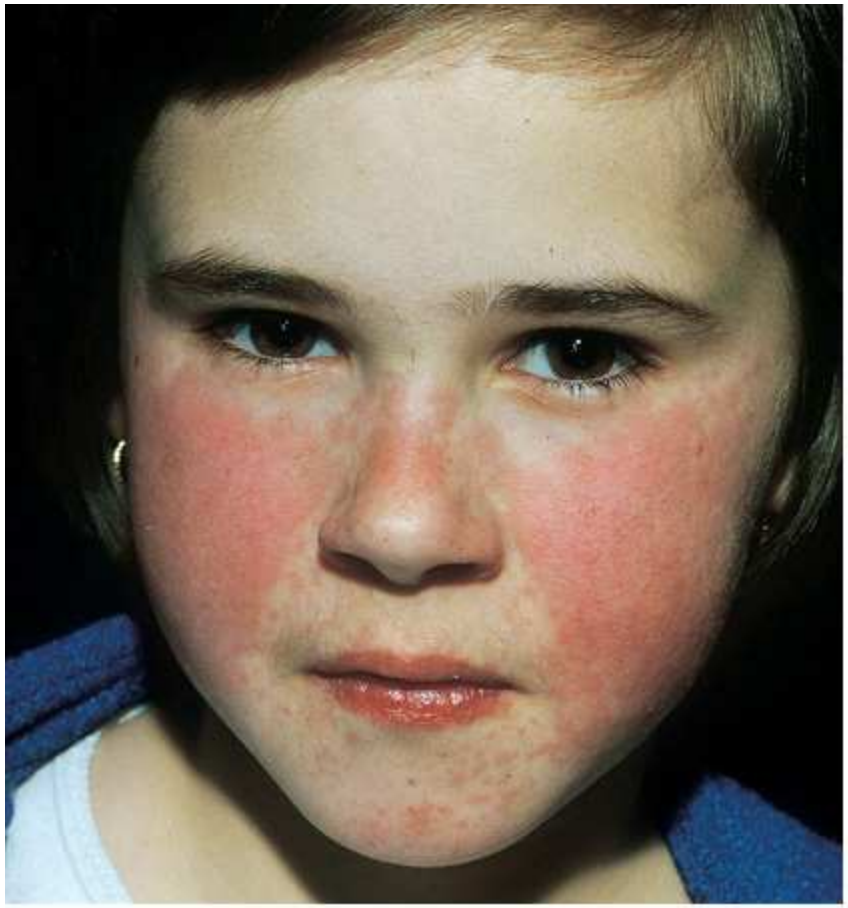
HGV

- Flavavirus.
- Originally thought to be related to HCV
- Reproduces in mononuclear cells, not liver.
- Induces HIV inhibitory cytokines but does not block vertical transmission.

Parvovirus

- Prodrome of fever, possibly sore throat, malaise, and myalgia in children.
- A rash (erythema infectiosum) that presents initially on the cheeks (as if slapped) and that spreads to the extremities is typical of the infection. (Fifth disease)
- Relapse is common.
- In adults the presentation is polyarthralgia (particularly in adolescents and adult women) or arthritis (hands, wrists, knees and ankles).

Fifth disease



A

Hot cheeks followed some days later by a prominent rash as if “slapped”. Lace-like pink rash over limbs, then to trunk. Parvovirus B19 infection.

Fig. 27-24A Accessed 07/16/2010

Parvovirus

- Vasculitis may be seen.
- Parvovirus B19 transmitted by droplets.
- Targets erythroid precursors.
- Binds to P antigen (globoside).
- Depletes red cell precursors.
- May see transient aplastic crisis
- Parvovirus crosses the placenta.
- May result in erythroblastosis fetalis, severe fetal anemia.
- May precipitate aplastic crisis in patients with sickle cell disease.

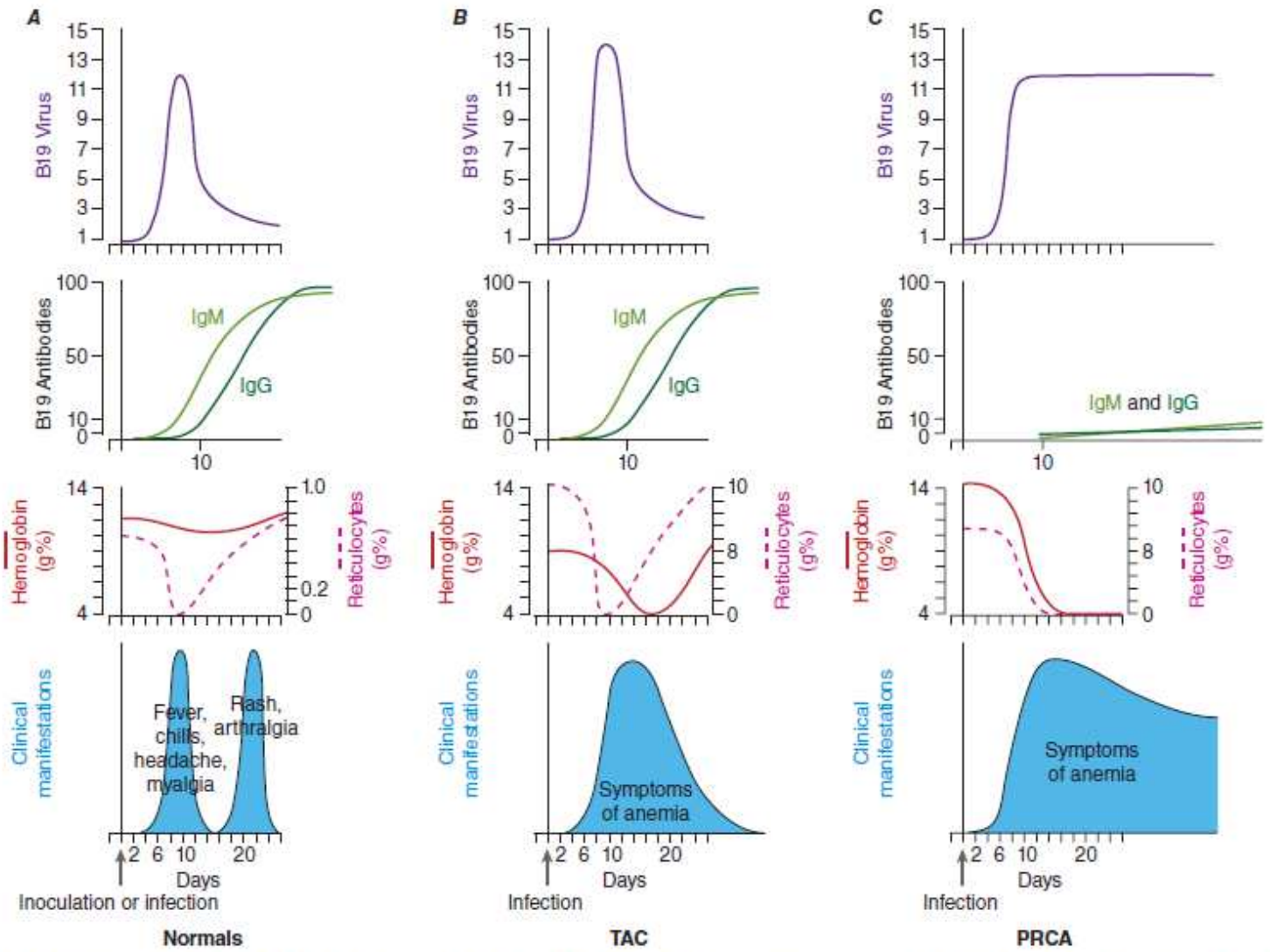


FIGURE 192-1 Schematic of the time course of parvovirus B19 infection in (***A***) normals (erythema infectiosum), (***B***) transient aplastic crisis (TAC), and (***C***) chronic anemia/pure red-cell aplasia (PRCA). *(Reprinted with permission from NS Young, KE Brown: N Engl J Med 350:586, 2004. © 2004 Massachusetts Medical Society. All rights reserved.)*

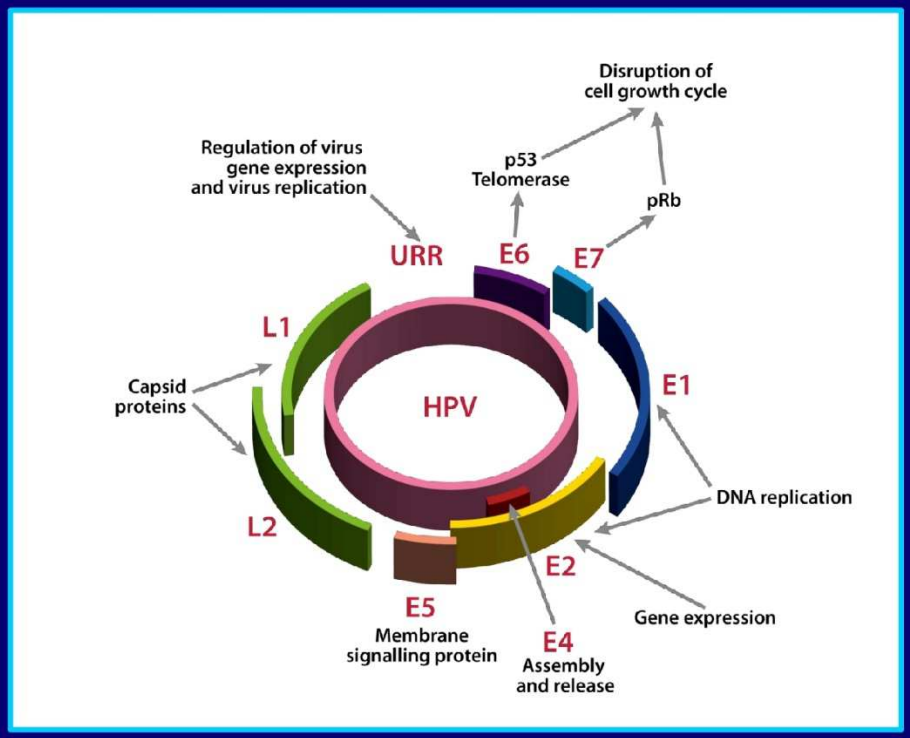
Human papillomavirus

- Human papilloma viruses 1 and 4 are the most common causes of verrucae.
- Appearance of verruca depends upon which viral strain infects and the site of infection.
- Regress over time.
- Papillomas of oropharynx, larynx are commonly cuased by HPV-6, HPV-11.
- Anogenital warts (condylomata accuminata) are generally caused by HPV-6 or HPV-11.
- Present as papules but may have cauliflower appearance.

Human papillomavirus

- The virus does not have an envelope.
- E6, E7 proteins inactivate p53 and Rb genes (upregulate cyclin E) respectively as well as induce centrosome duplication. E6 also upregulates telomerase.
- Perinuclear halo noted in cervical cells on Pap smear.
- May be reported as atypical cells of unknown significance.
- DNA probe for HPV

Human Papillomavirus



Human papillomavirus

- Cryotherapy (liquid nitrogen or cryoprobe)
- Podophyllin (not to be used with anal warts) or topical 5-FU for non-mucosal lesions
- External genitalia warts and perianal warts respond to Imiquimod.
- Imiquimod activates the body's immune response through the toll-like receptor.
- Imiquimod disrupts cytokine activity and simultaneously attacks the body's mucus membrane tissues.
- Imiquimod does not prevent the emergence of new warts.

Condyloma lata

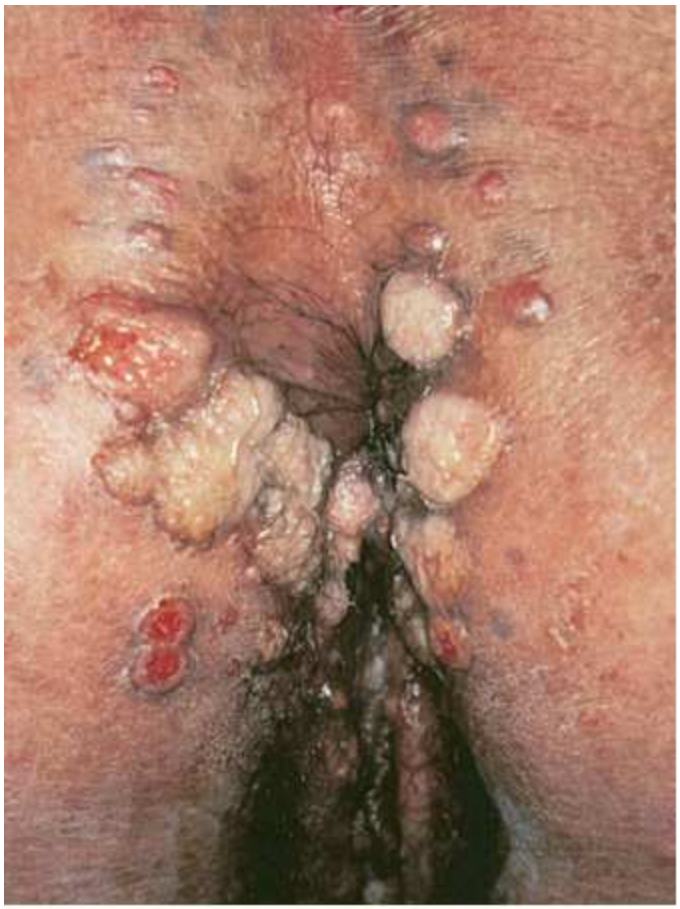


Fig. e5-20 Accessed 07/01/2010

HPV oncogenesis

- Cervical dysplasia and neoplasia are associated with HPV-16 and HPV-18.
- The replication of DNA viruses is dependent on the replication machinery of the host cells.
- The viral genome is incorporated into the cell genome.
- The viral DNA is interrupted almost always within the E1/E2 open reading frame of the viral genome.
- Because the E2 region of the viral DNA normally represses the transcription of the E6 and E7 early viral genes, its interruption causes over-expression of the E6 and E7 proteins.

HPV oncogenesis

- E6 binds to p53 and E7 binds to RB, inducing the degradation of these proteins.
- E7 can also interfere with p53 transcriptional activity and inactivate p21.
- E6 and E7 act together to immortalize cell. Clonal proliferation.

Molluscum contagiosum

- Spread by direct contact.
- Swimming pools (children)
- Sexual contact (adults)
- Lesions nodular to verrucoid, flesh colored, with umbilicated centers.
- Present in clusters.
- Not on palms or soles
- 2-8 week incubation.
- Cytoplasmic inclusions in epithelial cells
- MCV-1 most prevalent strain (of four)
- MCV-2 generally sexually transmitted

Adenovirus

- Pharyngitis (with pink eye) mimics strep throat.
- Acute respiratory tract disease with fever, cough, pharyngitis, cervical adenitis is seen in those living at close quarters.
- Colds, laryngitis, croup, bronchiolitis, pertussis-like syndrome and viral pneumonia are also seen.
- Conjunctivitis and epidemic keratoconjunctivitis
- Diarrhea (Serotypes 40, 41)
- Acute hemorrhagic cystitis (hematuria in young boys)
- Genital and skin infections.

Oncogenesis

- Adenovirus is not known to be oncogenic in humans.
- However, adenovirus encodes for oncogenes that down-regulate mRNA synthesis.
- Tumor antigens from the E1A region bind to the gene product of the RB gene
- Those of E1B bind to the gene product of p53
- One of the protein products of E1B also blocks the function of TNF.
- The E3 transcription unit gp19 K can block expression of MHC I antigens (evading cytotoxic lymphocytes) and block the actions of TNF, fas, and TRAIL, leading to cell immortalization.

Polyoma virus

- Merkel cell carcinoma associated with polyoma virus
- Immunosuppression and dysregulation as risk factors
- CLL, HIV, transplantation
- Large T antigen mutated
- Virus noninfectious, thus preventing autoactivation of integrated virus replication
- Terminates in neoplasia, not cell death

RNA virus families

Virus	Envelope	Capsid Symmetry	Nucleic Acid	Medically Important Virus
Picovirus (enterovirus)	No	Icosahedral	Single stranded, linear, non-segmented, positive polarity	Poliovirus, Rhinovirus, Hepatitis A virus, Coxsackie
Calcivirus	No	Icosahedral	Single stranded, linear, non-segmented, positive polarity	Norwalk virus, Hepatitis E virus
Reovirus	No	Icosahedral	Double stranded, linear, 10 segments	Rotavirus
Flavivirus (mosquito vector)	Yes	Icosahedral	Single stranded, linear, non-segmented, positive polarity	Yellow fever (Aedes), Dengue virus (Aedes), West Nile fever virus (Culex), Hepatitis C virus

RNA virus families

Virus	Envelope	Capsid Symmetry	Nucleic Acid	Medically Important Virus
Togavirus	Yes	Icosahedral	Single stranded, linear, non-segmented, positive polarity	Rubella virus, Eastern and Western Equine
Retrovirus	Yes	Icosahedral	Single stranded, linear, diploid, non-segmented, positive polarity	Human immunodeficiency virus, Human T-cell leukemia virus
Orthomyxo virus	Yes	Helical	Single stranded, linear, 8 segments, negative polarity	Influenza virus
Paramyxo virus	Yes	Helical	Single stranded, linear, non-segmented, positive polarity	Measles virus, Mumps virus, Respiratory Syncytial virus

RNA virus families

Virus	Envelope	Capsid Symmetry	Nucleic Acid	Medically Important Virus
Rhabdovirus	Yes	Helical	Single stranded, linear, non-segmented, negative polarity	Rabies virus
Filovirus	Yes	Helical	Single stranded, linear, non-segmented, negative polarity	Ebola virus, Marburg virus
Coronavirus	Yes	Helical	Single stranded, linear, non-segmented, positive polarity	Coronavirus (SARS)
Arenavirus	Yes	Helical	Single stranded, circular, 2 segments with cohesive ends, negative polarity	Lymphocytic choriomeningitis virus, Lassa fever

RNA virus families

Virus	Envelope	Capsid Symmetry	Nucleic Acid	Medically Important Virus
Bunyavirus	**Yes**	**Helical**	**Single stranded, circular, 3 segments with cohesive ends, negative polarity**	**California encephalitis virus, Hanta virus**
Deltavirus	**Yes**	**Spherical**	**Single stranded, circular, closed circle, negative polarity**	**Hepatitis D virus**

RNA viruses

- All RNA viruses replicate in the cytoplasm.
- 3’ sequences of both positive and negative strand RNAs contribute cis-acting functions essential for viral replication.
- Retroviruses, Influenza virus, and Hepatitis D virus require an intra-nuclear step.
- Picornavirus and Flavivirus synthesize a precursor polypetide formed from translation of the entire genome which are then cleaved in the cytoplasm by a virus encoded protease.

RNA viruses

- Coronavirus synthesizes more than one precursor polypeptide from translation of the entire genome.
- Togavirus does so from translation of sub-genomic mRNAs
- Single stranded, non-segmented, positive polarity RNA containing viruses do not have their own polymerase.
- The source of mRNA is its own genome.
- The genome is infectious.

RNA viruses

- Retroviruses contain an RNA-dependent DNA polymerase
- mRNA is transcribed from DNA intermediate.
- The genome RNA is not infectious
- However, the DNA intermediate is infectious.

RNA viruses

- All other RNA viruses carry their own RNA-dependent RNA polymerase.
- Their genomes are not infectious.
- Those viruses with segmented genomes do not produce precursor polypeptides as each segment encodes a specific functional polypeptide.
- Retrovirus gag and pol genes are translated into precursor polypeptides.
- Cleavage occurs in the budding virion.

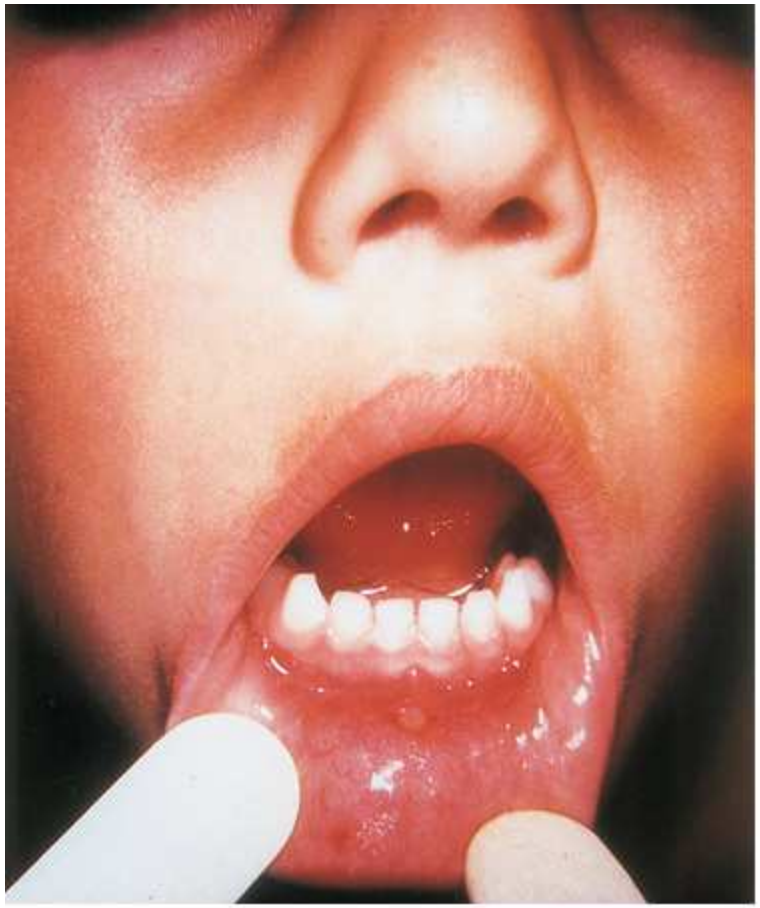
RNA viruses

- Virtually all viruses cause cytopathic effect in culture (not rubella).
- Respiratory syncytial virus reproduces more rapidly at temperatures cooler than body temperature, accounting for its survival in nasal passages.
- Influenza, para-influenza virus, and respiratory syncytial viruses adsorb red cells.
- Hemagglutin is binding site.
- Respiratory syncytial virus and measles virus produce giant cells in tissue.
- Influenza virus downregulates toll-like receptors, leading to a “paralysis” of the immune system.

Picovirus

- Coxsackie A
- Herpangina
- Fever, sore throat, pain on swallowing, anorexia, vomiting.
- Classic finding is vesicular ulcerated lesions around soft palate and uvula.
- Hand-Foot and Mouth Disease
- Coxsackie A16 (also caused by Enterovirus 71)
- Vesicular lesions on hand, feet, mouth and tongue. Mild fever subsides in a few days.

Hand-foot-and-mouth syndrome



(Courtesy of Stephen E. Gellis, MD; with permission.)

Fig. 184-1 Accessed 07/01/2010

Coxsackie B

- Myocarditis
- Febrile illness with sudden and unexplained onset of heart failure (cyanosis, tachycardia, cardiomegaly, and hepatomegaly). Often fatal.
- May see involvement of other organs at autopsy (brain, liver).
- Acute, benign pericarditis affects young adults; may be seen in older adults, symptoms of MI.

Coxsacke B

- Pleurodyna (Devil's grip)
- Sudden onset of fever, unilateral low thoracic pain, abdominal pain and vomiting.
- Resolves within 4 days; relapse may occur.
- Diabetes mellitus
- Coxsackie B identified in many children with onset of diabetes mellitus.
- Islet cell inflammation?

Polio virus

- Spherical, unencapsulated
- Three major strains
- Uses human CD155 to gain entry into cells
- 1% of patients have CNS invasion; replicate in motor neurons

Calcivirus

- Compromise function of intestinal brush border. Gastroenteritis.
- Fecal oral spread.
- Diarrhea and nausea. 24-48 hour incubation.
- 10% of all gastroenteritides
- 60% of all non- bacterial gastroenteritides.

West Nile virus

- Mosquito borne.
- Transferred as well in blood and breast milk.
- 3-14 day incubation.
- Replicates in dendritic cells of skin.
- Generally subclinical
- Mild fever, headache, myalgia common.
- Occasionally a rash on the trunk and lymphadenopathy.
- Several day duration.

West Nile virus

- Severe encephalitis or meningitis ten times higher for patients 50-59 years; 43 times higher for those over 80 years
- Encephalitis characterized by high fever, neck stiffness, stupor, disorientation, coma, tremor, seizure, muscle weakness and paralysis.
- Lasts several weeks.
- Temporal lobes and brain stem principally involved.
- Loss of CCR5 function associated with lethality.

Viral hemorrhagic fevers

- RNA enveloped viruses:
- Arenavirus (Lassa fever)
- Filovirus (Ebola)
- Flavivirus (dengue, yellow fever)
- Bunyavirus (Sin nombre)
- Disease manifestations related to activation of immune response.

Flavivirus

- Dengue
- Bite of Aedes mosquito
- High fever, retro-orbital pain, severe headache, severe muscle and joint pain, nausea and vomiting.
- Generalized maculopapular rash that diminishes as fever subsides
- 6-7 day duration.
- May see rash and skin hemorrhage, gingival bleeding, nasal bleeding, GI bleeding, hematuria. Associated with low platelet count and leaky capillaries. Shock may result.

Flavivirus

- Zika
- Associated with microcephaly in infants of mothers infected in pregnancy (crosses placenta).
- Virus in testes 120 days post infection
- Usually follows Aedes mosquito bite
- May be transmitted through male sexual contact
- Acute presentation with low grade fever and myalgia
- Descending maculopapular rash, often pruritic
- No lymphadenopathy

Bunyavirus

- Hantavirus
- Sin nombre
- Fever, myalgia, fatigue onset 1-3 weeks
- Shed by deer mouse
- Recruitment of leukocytes into the pulmonary microvascular circulation with resulting endothelial damage.
- Hemorrhagic tissue destruction and lethal pulmonary complications result.
- May also present with abdominal pain

Orthomyxovirus

- Inhaled virus is deposited on the mucous membrane lining the respiratory tract.
- Infects the ciliated columnar epithelial cells.
- Hemagglutinin binds to sialic acid receptors
- Virus is phagocytized.
- pH drops to 5.5 in endosome as M2 protein acts as ion channel in virus envelope
- Essential for virus uncoating from M1 protein.
- Nucleocapsids are released into cytoplasm.
- Incubation period varies from 1-4 days.

Orthomyxovirus

- Characterized by abrupt onset of fever (102-104°F) with headache, severe retro-orbital pain, myalgia, sore throat, and non-productive cough.
- There is no coryza associated with influenza infection.
- Croup caused by parainfluenza virus.
- Stridor characteristic.

Orthomyxovirus

- Symptoms last about 1 week.
- At the 4th day of illness, respiratory symptoms predominate (pharyngitis, laryngitis, and tracheobronchitis).
- Cough and malaise may last 1-2 weeks after other symptoms have disappeared.
- There is no viremia and the infection is confined to the respiratory tract.
- Cell damage initiates an acute inflammatory response.
- Systemic symptoms are due to release of the inflammatory mediators (TNF-α).

Paramyxovirus

- Mumps is an acute, benign, parotitis.
- Two surface glycoproteins:
- One has hemaglglutinin and neruamidase activity
- The second has cell fusion and lytic activity.
- Replicates preferentially in activated T-cells.
- Lytic infection.
- Localized in ductal epithelial cells in salivary glands.
- Virus spreads through the blood to testes, ovary, pancreas, thyroid, and (in half the patients) brain.
- Lifelong immunity.

Paramyxovirus

- Rubeola (Measles)
- Incubation period of 7-10 days.
- Begins with high fever (102-104F).
- Cough, conjunctivitis and coryza.
- Photophobia.
- Hemagglutinin attachment to CD46, inactivates C3 convertase, and signaling lymphocytic activation molecule (SLAM), blocking T-cell activation.
- CD46 expressed on all nucleated cells; SLAM, only on lymphocytes.

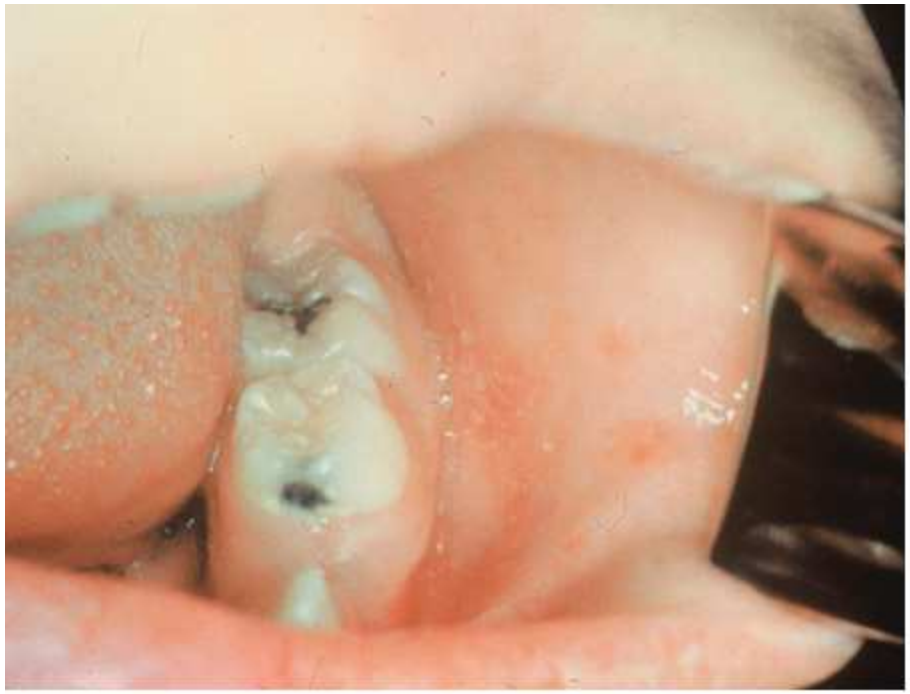
Measles

- Small white spots with a red halo (Koplik spots) appear after 2 days.
- Most commonly found on buccal mucosa but may be seen on other mucosal surfaces.
- Within 12-24 hrs after the appearance of Koplik spots, fever rises and the maculopapular exanthem of measles begins below the ears and spreads all over the body.
- Fever breaks.

Measles

- Warthin-Finkeldey cells are multinucleate giant cells with eosinophilic nuclear and cytoplasmic inclusion bodies.
- Pathognomonic for measles.
- Found in hyperplastic lymph nodes, lung, and sputum.

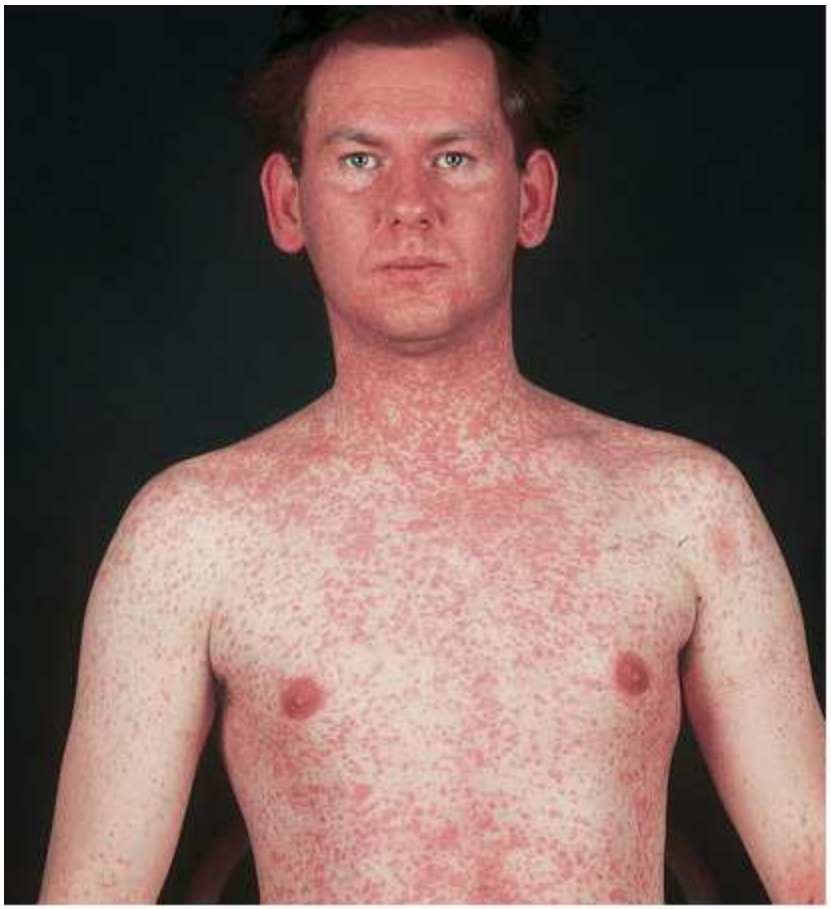
Koplik’s spots



Koplik's spots manifest as white or bluish lesions with an erythematous halo on the buccal mucosa. Usually occur in the first 2 days of measles symptoms and may briefly overlap the measles exanthem. The presence of the erythematous halo differentiates Koplik's spots from Fordyce's spots (ectopic sebaceous glands), which occur in the mouths of healthy individuals.

(Source: CDC. Photo selected by Kenneth M. Kaye, MD.) Fig. 185-1 Accessed 07/01/2010

Measles



Coryza precedes several days before eruption.
Koplik spots present in oral mucosa 48 hours before rash.
Discrete erythematous lesions on face and below eyes, become confluent on the face and neck over 2–3 days as the rash spreads downward to the trunk and arms, where lesions remain discrete. No pruritis.

Fig. 27-22 Accessed 07/16/2010

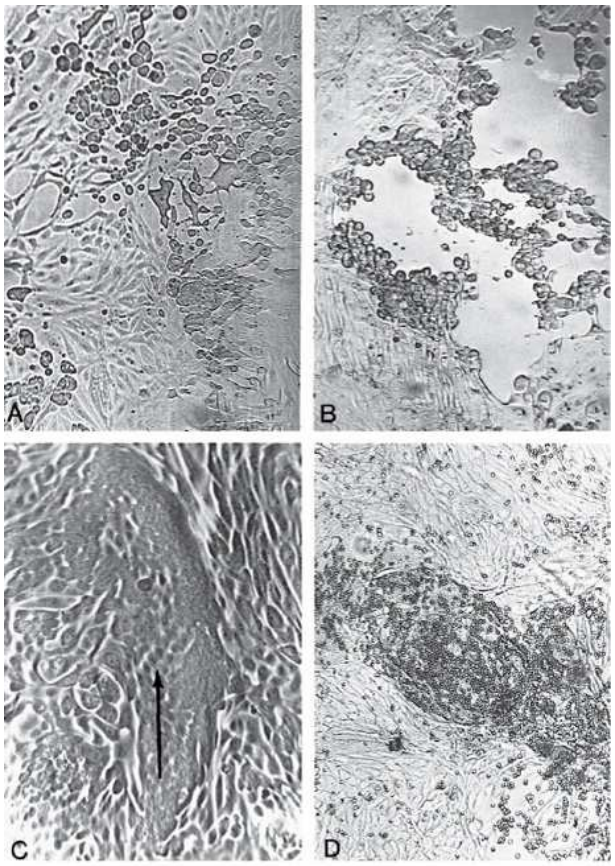
Measles

- Complications include pneumonia.
- May lead to secondary bacterial or viral infection.
- 60% of deaths by measles is due to pneumonia
- Atypical Measles occurs in people who have been vaccinated by inactivated (occasionally live) and have insufficient protection.
- Illness begins abruptly and is more intense than primary measles.

Subacute sclerosing panencephalitis (SSPE)

- Rare, late neurological sequelae of measles. Occurs months to years after clinical measles.
- Defective measles virus in brain acts as slow virus. Virus can replicate and spread from cell to cell but is not released.
- Changes in behavior, muscle jerks, blindness may result. May present as Multiple Sclerosis.
- High levels of measles antibody in blood and CSF.

Virus identification



(Courtesy of I Jack; reproduced from White DO, Fenner FJ: *Medical Virology,* 3rd ed. Academic Press, 1986.) Fig. 29-7 Accessed 07/01/2010

A: Enterovirus—rapid rounding of cells progressing to complete cell destruction. B: Herpesvirus—focal areas of swollen rounded cells. C: Paramyxovirus—focal areas of fused cells (syncytia). D: Hemadsorption. Erythrocytes adhere to those cells in the monolayer that are infected by a virus that causes a hemagglutinin to be incorporated into the plasma membrane. Many enveloped viruses that mature by budding from cytoplasmic membranes produce hemadsorption.

Respiratory syncytial virus

- RSV infections can range from the common cold to pneumonia.
- Usually involve the upper respiratory tract with prominent rhinorrhea.
- ICAM-1 is receptor.
- Some cases can progress to the lower respiratory tract and cause bronchiolitis.
- Because of inflammation at the level of the bronchiole, there is air trapping and decreased ventilation.

Respiratory syncytial virus

- Low grade fever, tachypnea, tachycardia and expiratory wheezes.
- Giant cells found in lungs.
- Fusion protein as virulence factor.
- Usually self-limited however, can be fatal in infants.
- Vaccine attempts abandoned as vaccinated infants later challenged with RSV became quite ill; many died (Antibody Dependent Enhancement)
- Ribavarin therapy

Influenza virus

- Affects the epithelium diffusely
- May result necrotizing bronchitis and/or bronchiolitis and diffuse alveolar damage.
- Histologic features are epithelial necrosis of the airways with submucosal chronic inflammation.
- Adenovirus has its greatest effect in the terminal bronchioles
- May produce necrotizing bronchiolitis and result in a necrotizing bronchopneumonia with diffuse alveolar damage similar to that seen in severe Herpes simplex infection

Influenza

- Acute onset
- High fever
- Non-productive cough.
- Chest x-ray may demonstrate unilateral or patchy bilateral areas of consolidation but no lobar change
- Nodular opacities
- Flattened diaphragms
- Hyperlucency at apices.
- Pleural effusion common.
- May require CT for further characterization

Influenza

- Clinically indistinguishable from Influenza
- Parainfluenza
- Respiratory syncytial virus
- Eosinophilia
- Otitis media
- Human metapneumovirus (paramyxovirus)
- Children and elderly
- Rapid influenza tests in patients with fever and cough combined with a history of acute onset have a high likelihood of being positive (LR+, 4.7; LR- 0.06).

Influenza virus

- Virus propagated in birds, but may pass to pigs and horses
- Influenza A
- The Hemagglutinin (HA) and Neuraminidase (NA) proteins of influenza viruses are the major sites for antibody recognition on the virus.
- To help the virus evade antibody detection, the RNA segments that encode HA and NA are able to mutate so that their functions are kept intact but they are less well recognized by antibodies. (Antigenic drift)

Influenza virus

- Because the RNA genomes of influenza viruses are segmented they can undergo reassortment if two different influenza viruses infect the same cell. (Antigenic shift)
- One strain predominates in epidemics
- H5N1 associated with pandemic of 2009
- Occurs from December to May in the Northern Hemisphere
- B and C strains cause mild disease
- Children

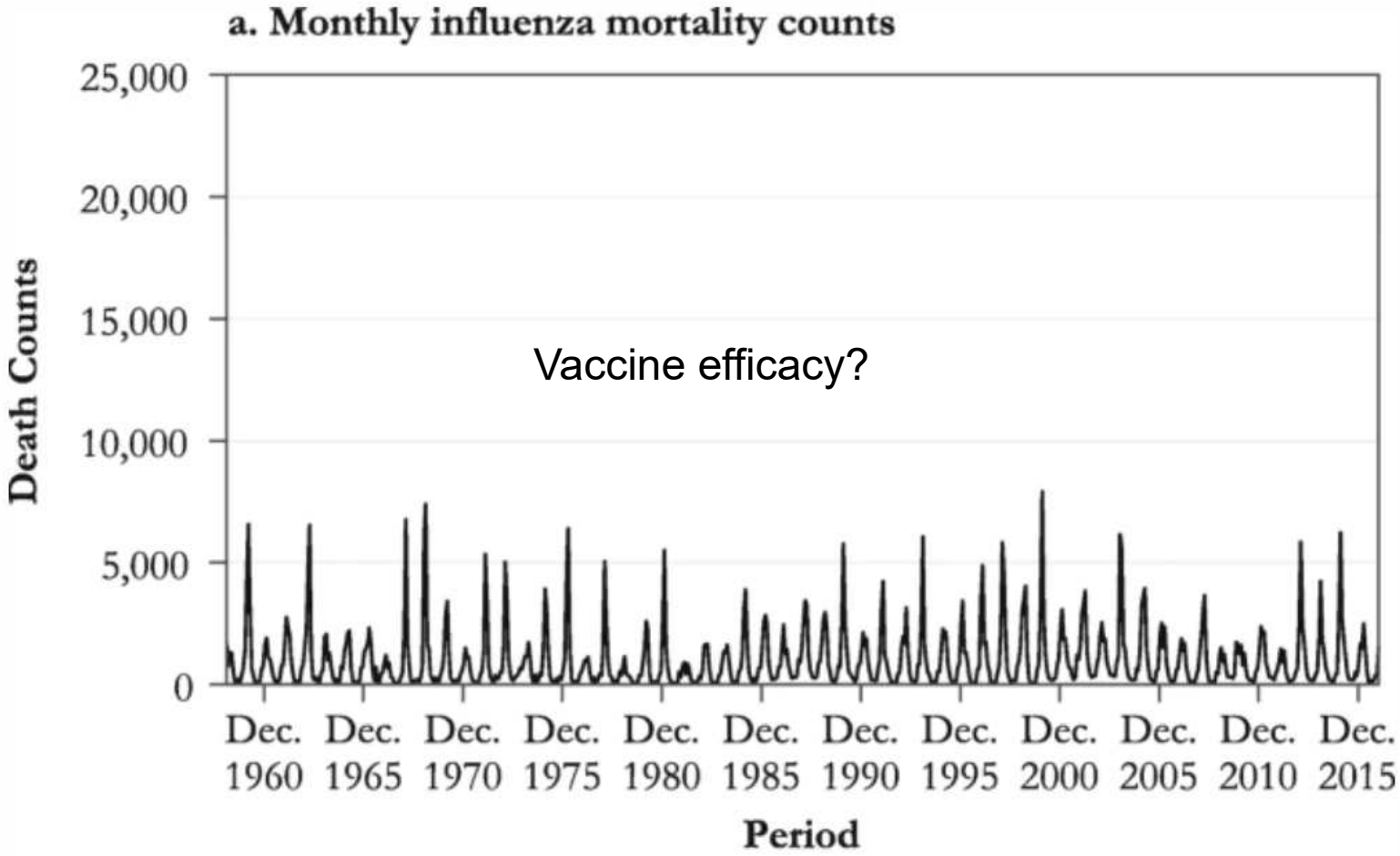
Influenza virus

- Because the RNA genomes of influenza viruses are segmented they can undergo reassortment if two different influenza viruses infect the same cell. (Antigenic shift)
- One strain predominates in epidemics
- H5N1 associated with pandemic of 2009
- Occurs from December to May in the Northern Hemisphere
- B and C strains cause mild disease
- Children

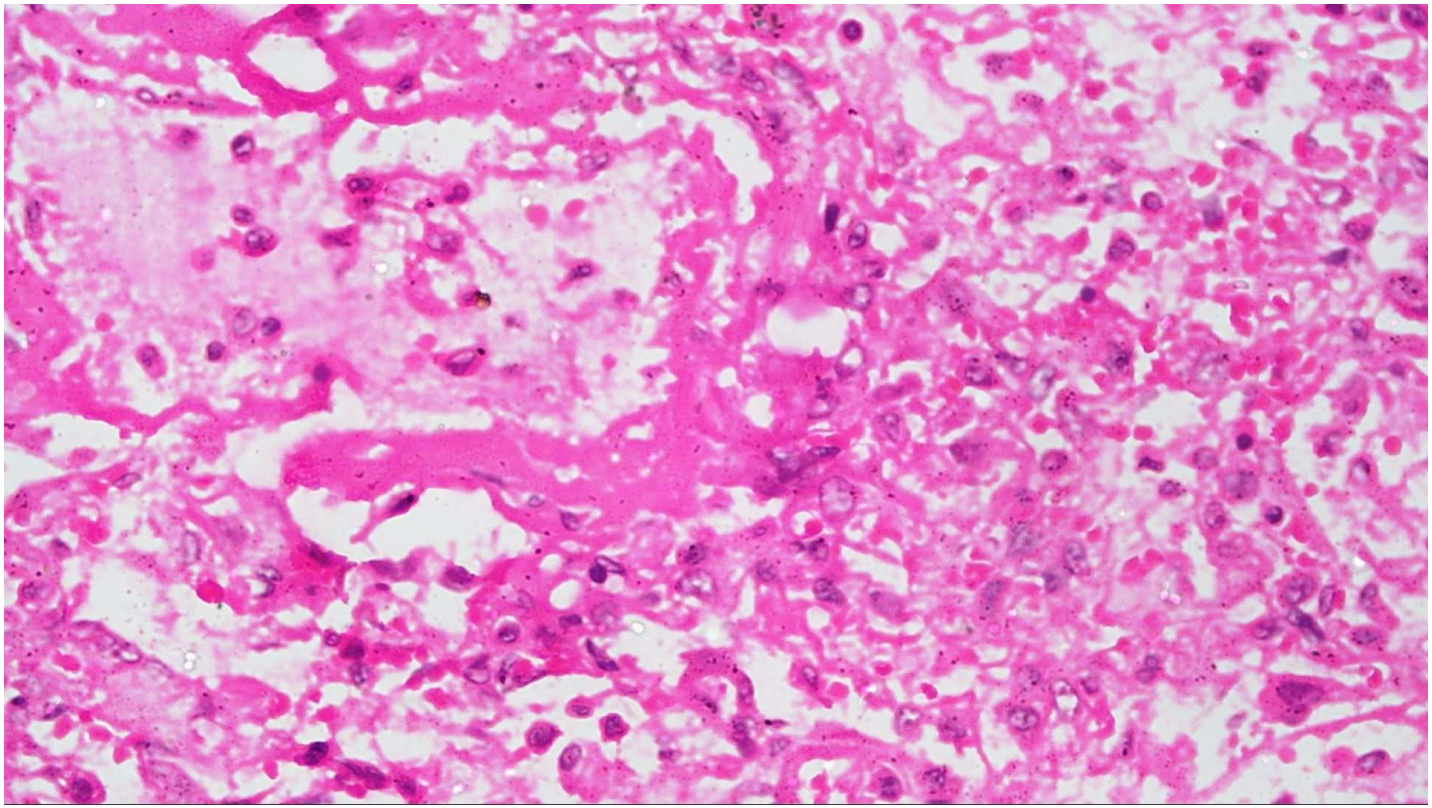
Influenza virus

- Swine influenza strains
- H1N1, H1N2, H3N1, H3N2
- H1N1 outbreak in 2009

Fig. 3


a. Monthly influenza mortality counts
Death Counts
25,000
20,000
15,000
10,000
5,000
0
Vaccine efficacy?
Dec. 1960
Dec. 1965
Dec. 1970
Dec. 1975
Dec. 1980
Dec. 1985
Dec. 1990
Dec. 1995
Dec. 2000
Dec. 2005
Dec. 2010
Dec. 2015
Period

Influenza pneumonia



Diffuse alveolar damage with hyaline membrane formation.

http://www.pathologyoutlines.com/topic/lungnontumorinfluenza.html Accessed 12/10/2019

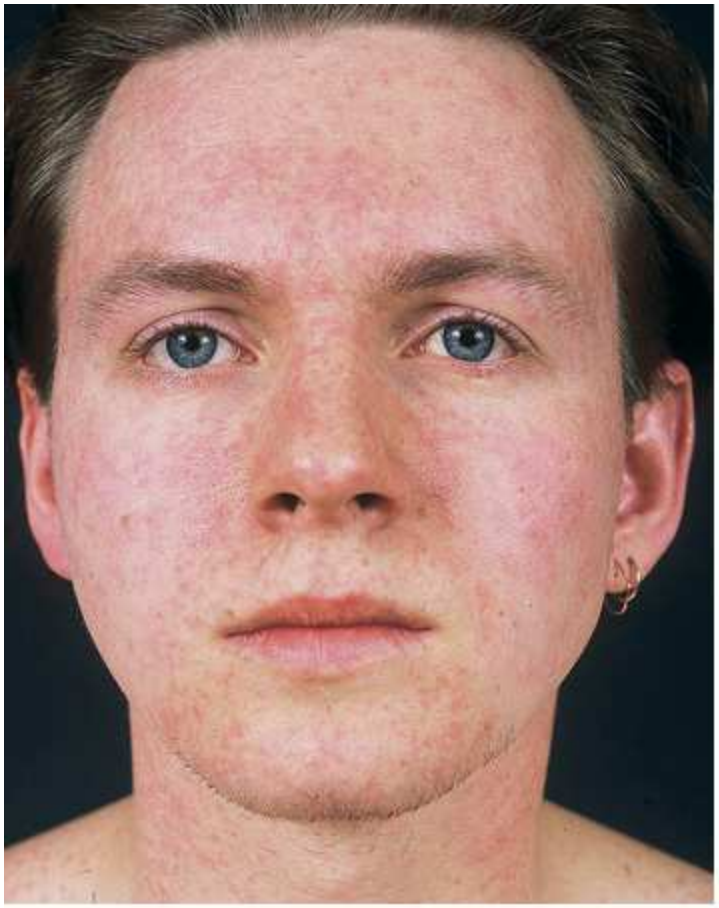
Rotavirus

- Rotavirus major cause of viral gastroenteritis in infants and young children
- Infects mature villus tip cells of small intestine.
- Young replacement cells cannot absorb as efficiently.

Rubella

- Rash as first sign of illness in children
- In older children and adults, 1-5 day prodomal syndrome of low grade fever, malaise, and upper respiratory system
- 5% may have no rash
- Posterior auricular or occipital adenopathy at second week
- Thombocytopenia and encephalitis uncommon

Rubella



Coryza precedes rash.
Posterior auricular lymphadenopathy.
An erythematous exanthem spreads from the hairline downward and clears as it spreads.
May itch. Shed in flakes.

Fig. 27-21 Accessed 07/16/2010

Congenital rubella syndrome

- Hearing impairment common
- 10% with cataracts, hearing impairment, and heart defects
- First trimester infection
- Thrombocytopenia with purpura/petechiae

Cornavirus

- Coronaviruses are the most common viruses associated with cold symptoms
- SARS and MERS (coronavirus)
- β-coronaviruses
- Presents 2-10 days after infection
- Fever and chills with dry cough
- Malaise
- Myalgias

Coronavirus

- Virus confined to pneumocytes
- Spike protein attacks ACE2 receptor (SARS)
- Spike protein attacks CD26 (MERS)
- Viral origin from bats to wild masked palm civets (China); from bats to camels (Middle East).
- Epidemiology differs, however
- Hydrochloroquine and invermectin as effective antimicrobial agents if used less than 5 days after onset of symptoms
- Pneumonia is secondary to ARDS (acute respiratory distress syndrome)

SARS-Covid-19

- Covid 19
- Product of gain-of-function research
- SARS backbone with spike protein modified with introduction of furan ring that permits its cleavage in human cells, facilitating attack on ACE2 receptor
- ACE2 receptor is found in blood vessels as well as in pneumocytes
- The spike protein alone is sufficient to cause such damage; the virus is only a “vector”
- Vascular damage and cytokine storm (SIRS) explains disease manifestations and progression to ARDS

Cornavirus

- Cytokine storm (SIRS) may lead to respiratory insufficiency, multi-organ failure, and encephalitis.
- Vaccine attempts abandoned as laboratory test animals later challenged with virus became quite ill; many died (Antibody Dependent Enhancement)
- The spike protein is toxic

Mechanism

- Spike protein binds to ACE2
- ACE2 is found in every part of the body that
- interfaces with the circulatory system
- Vascular endothelial cells and pericytes, brain astrocytes, renal tubules and podocytes, pancreatic islet cells, bile duct and intestinal epithelial cells, and the seminiferous ducts of the testis, as well as the lungs

Mechanism

- The spike protein undergoes a conformational change
- S1 trimers flip up and extend, locking onto ACE2 bound to the surface of a cell. ACE2 is suppressed, leading to diminished degradation of bradykinin.
- TMPRSS2, or transmembrane protease serine 2, cuts off the heads of the Spike, exposing the S2 stalk-shaped subunit inside.

Mechanism

- The remainder of the Spike protein undergoes a conformational change that causes it to unfold, embedding itself in the cell membrane. Then, it folds back upon itself, pulling the viral membrane and the cell membrane together. The two membranes fuse, with the virus's proteins migrating out onto the surface of the cell.
- The nucleocapsid enters the cell, disgorging its genetic material and beginning the viral replication process, hijacking the cell's own structures to produce more virus.
- May lead to formation of syncytia

Mechanism

- The envelope protein, a viroporin, act as a calcium ion channel, introducing calcium into infected cells.
- Hypocalcemia marked in persons deficient in Vitamin D
- The natural interferon response is suppressed, resulting in delayed inflammation.
- The N protein can also directly activate the NLRP3 inflammasome. Also, it suppresses the Nrf2 antioxidant pathway.

Mechanism

- Bradykinin upregulates cAMP, cGMP, COX, and Phospholipase C activity.
- Results in prostaglandin release and vastly increased intracellular calcium signaling
- Promotes highly aggressive reactive oxygen species (ROS) release and ATP depletion.
- NADPH oxidase releases superoxide into the extracellular space. Superoxide radicals react with nitric oxide to form peroxynitrite.

Mechanism

- Peroxynitrite reacts with the tetrahydrobiopterin cofactor needed by endothelial nitric oxide synthase (NOS), causing nitric oxide synthase to synthesize more superoxide instead.
- Continues in a positive feedback loop until nitric oxide bioavailability in the circulatory system is depleted.
- Endothelial nitrogen oxide species (NOS) is antiviral against SARS-like coronaviruses as it blocks palmitoylation of the spike protein
- Viral replication is not impeded as endothelial NOS is depleted

Mechanism

- Cells of the innate immune system engulf invaders and attack them with superperoxide dismutase and myeloperoxidase
- Neutrophils also eject these enzymes into the extracellular space (neutrophil extracellular trap formation)
- Iron is removed from heme
- Red cells lose oxygen carrying capacity
- Unliganded iron, hydrogen peroxide, and superoxide in the bloodstream undergo the Haber-Weiss and Fenton reactions, producing extremely reactive hydroxyl radicals that oxidize fats and DNA

Mechanism

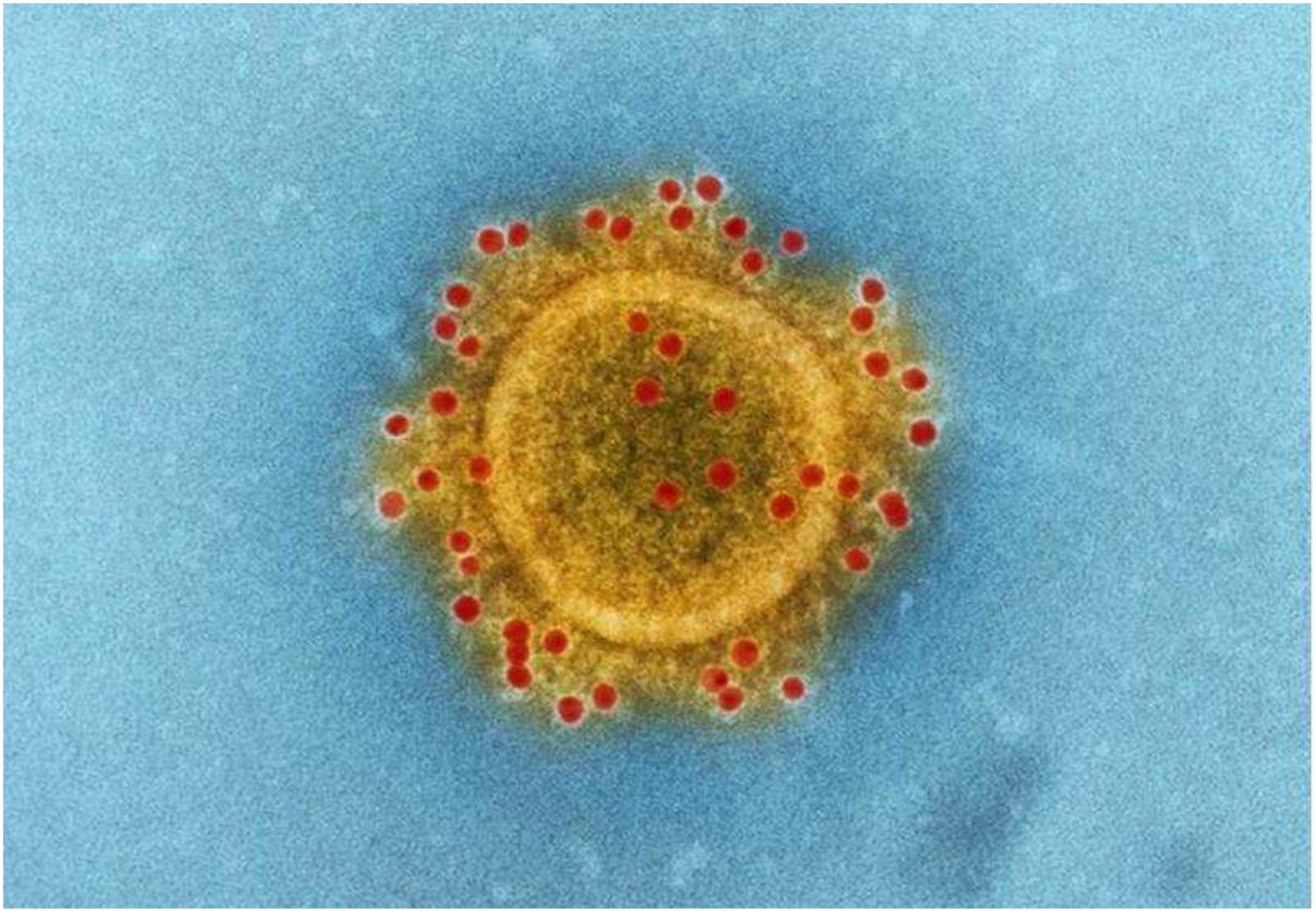
- COVID-19's pathology is dominated by extreme oxidative stress and neutrophil respiratory burst
- The end-stage of COVID-19 is severe lipid peroxidation
- Oxidized lipid epitopes drive autoimmune response
- The spike protein does not only bind to ACE2. It is suspected to have regions that bind to basigin, integrins, neuropilin-1, and bacterial lipopolysaccharides as well.
- The Spike S1 receptor binding domain may bind to heparin-binding proteins and promote amyloid aggregation (prion like).

Mechanism

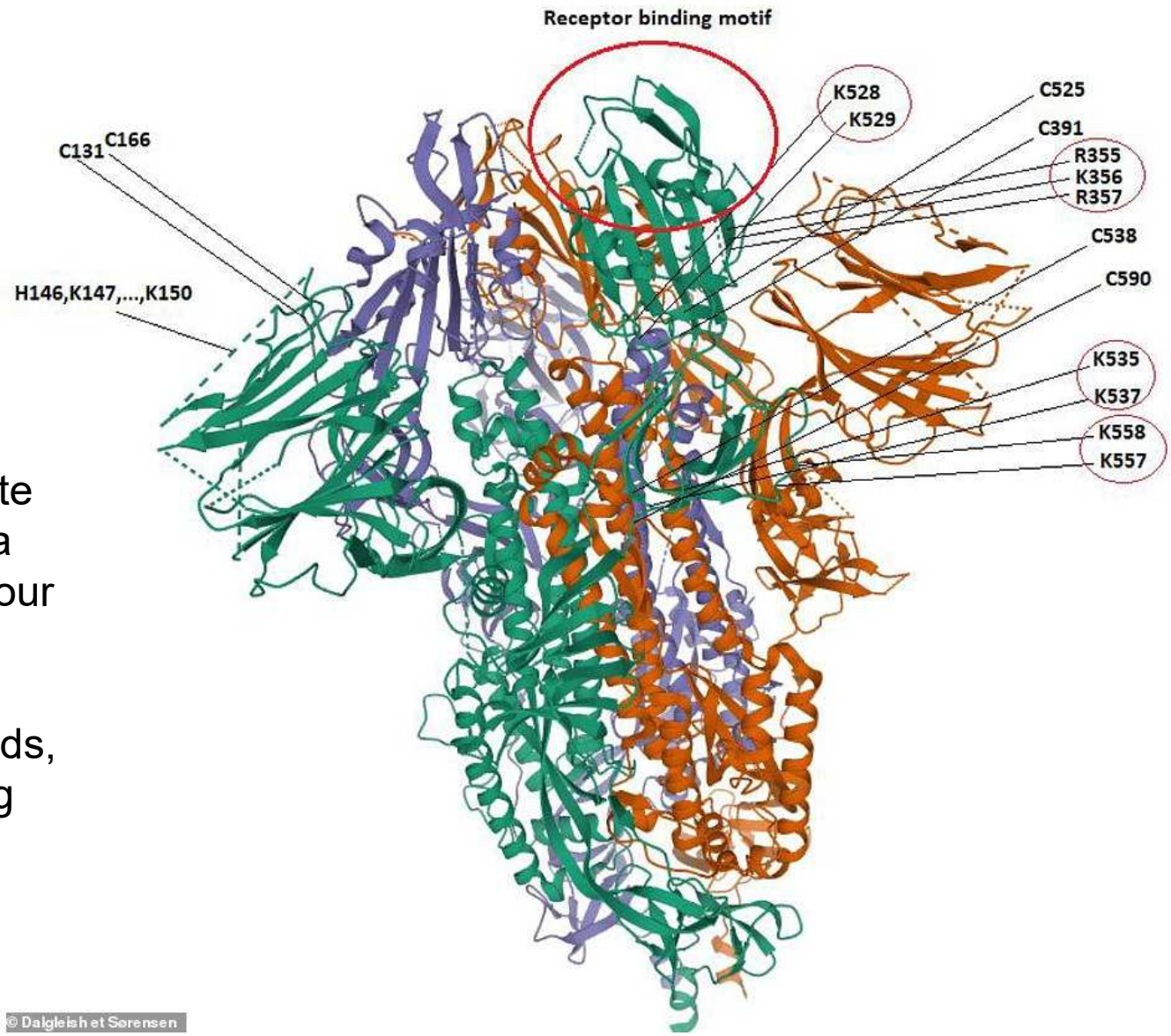
- Locally generated antibodies against the spike protein on the SARS-CoV-2 virus expressed upon human alveolar epithelium ignites the terminal complement cascade, specifically the C5-convertase.
- This in turn promotes the assembly of proteins derivative of the C5, C6, C7, and C8 pathways to construct the membrane attack complex (MAC).

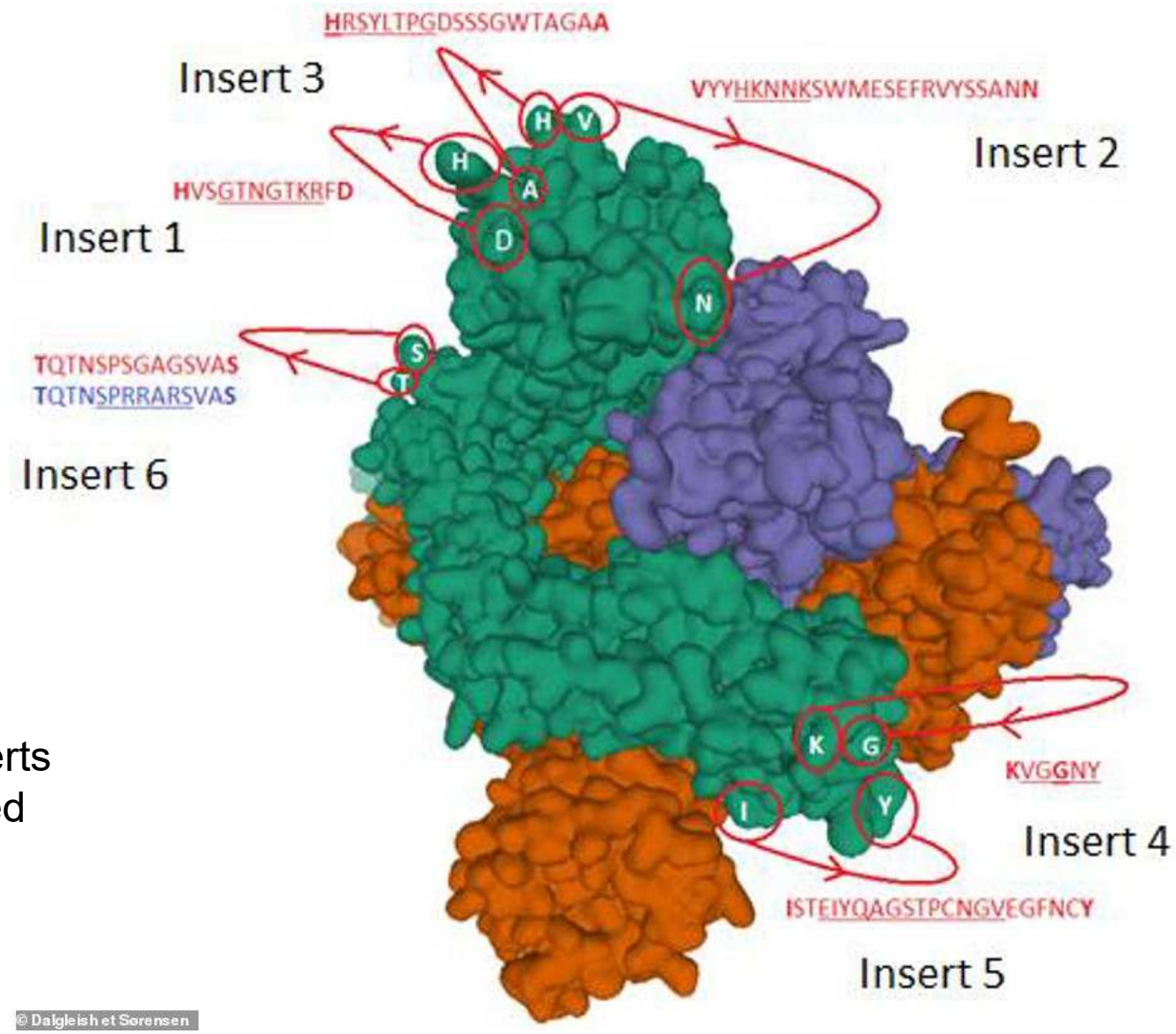
Mechanism

- The MAC architecture includes a centrally localized channel which facilitates the passage of the terminal complement protein C9 from the opening orientation directly toward the alveolar space.
- Upon reaching the terminus of the MAC adhered to the epithelial surface, C9 then penetrates the alveolar cell membrane, inflicting an irreversible breach in the integrity of the cell's barrier.
- Complement dependent cytotoxicity
- Additionally, spike protein leads to impairment of immunoglobulin rearrangement as well as to T cell destruction.



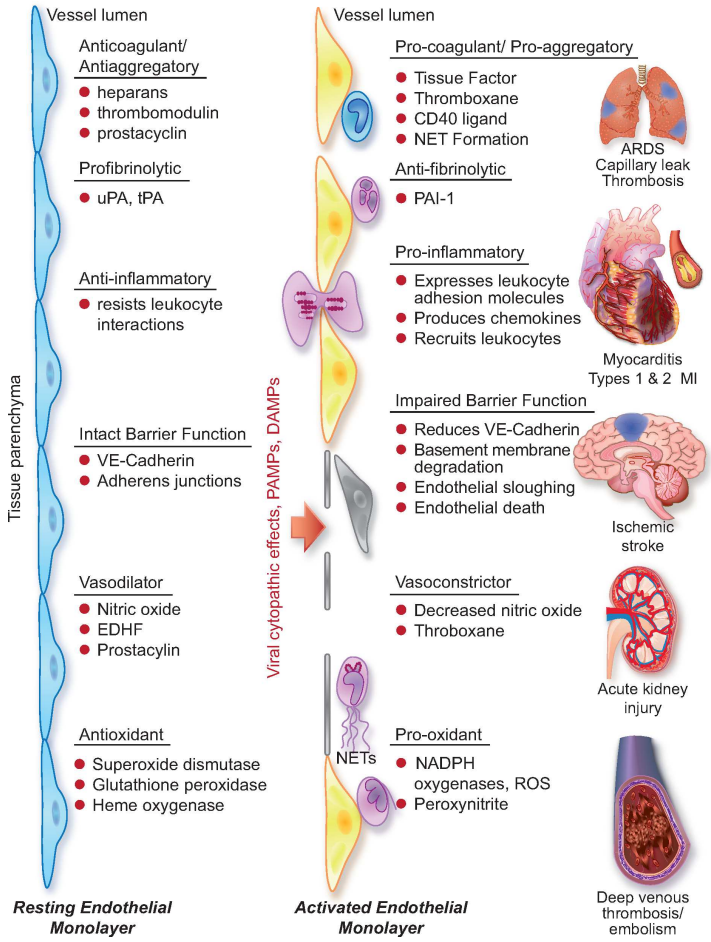
Receptor binding site contains a string of four positively charged amino acids, enhancing infectivity.





Six inserts identified

Figure 1 The left side of the diagram depicts a resting endothelial monolayer with the endothelial cells of squamous ...



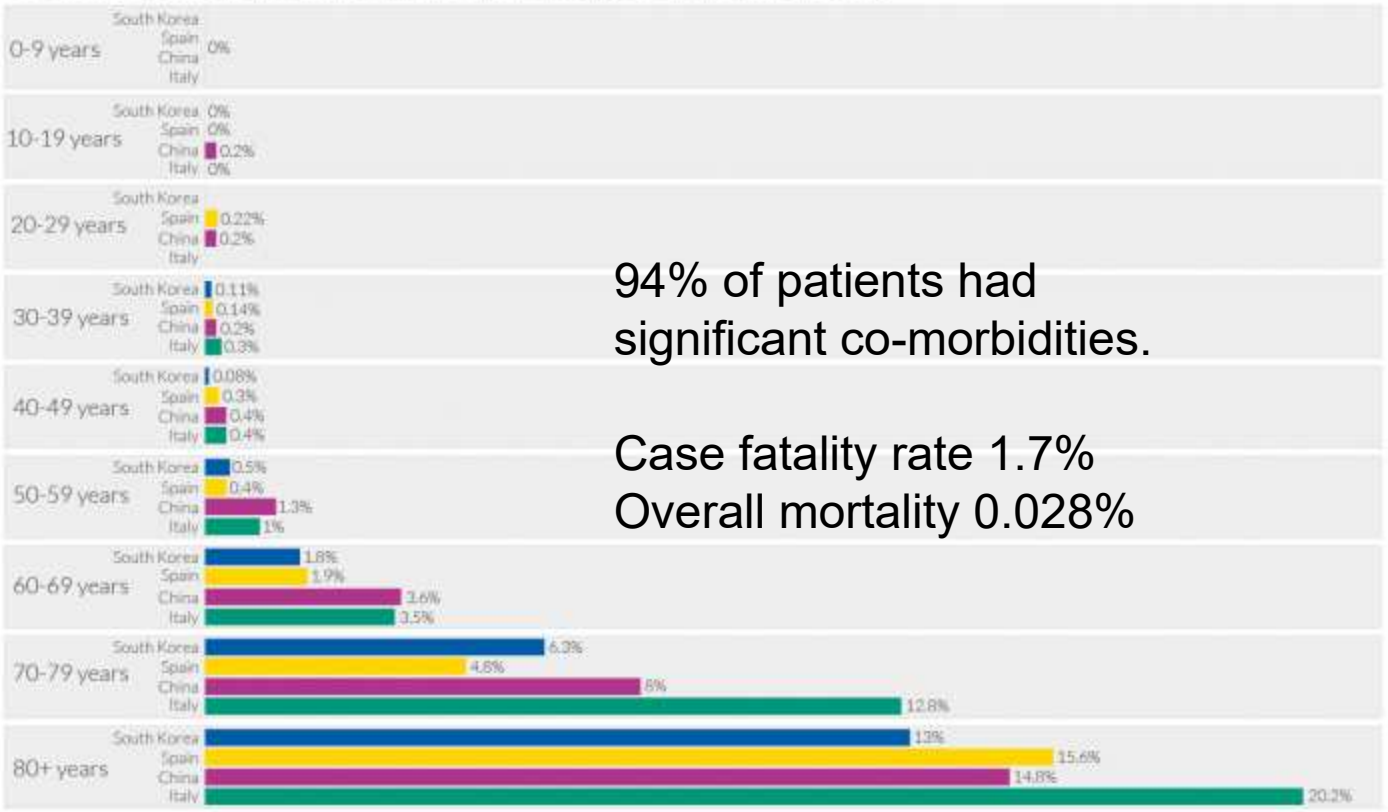
Eur Heart J, Volume 41, Issue 32, 21 August 2020, Pages 3038–3044, https://doi.org/10.1093/eurheartj/ehaa623

Coronavirus: case fatality rates by age

Our World in Data

Case fatality rate (CFR) is calculated by dividing the total number of confirmed deaths due to COVID-19 by the number of confirmed cases.

Two of the main limitations to keep in mind when interpreting the CFR:
(1) many cases within the population are unconfirmed due to a lack of testing.
(2) some individuals who are infected will eventually die from the disease, but are still alive at time of recording.



94% of patients had significant co-morbidities.

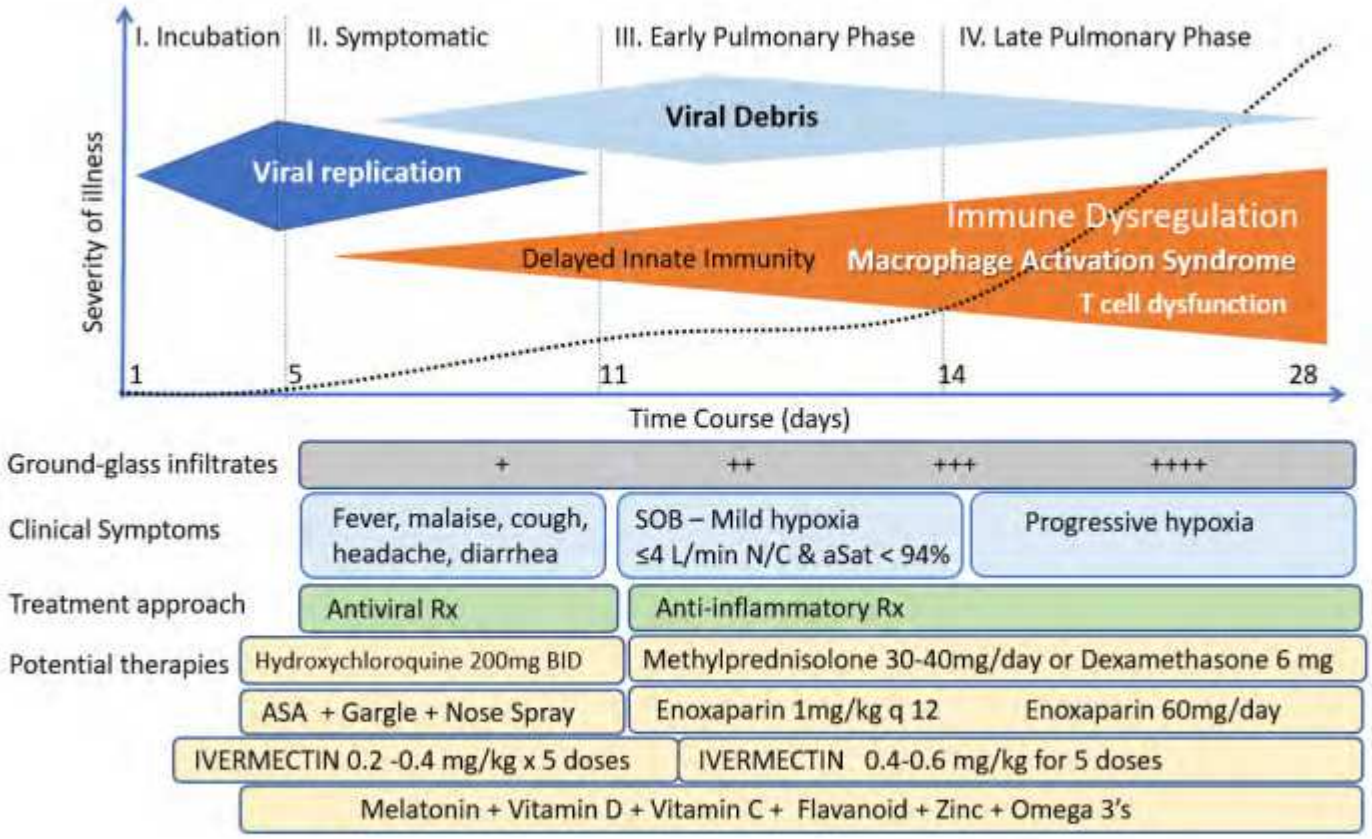
Case fatality rate 1.7%
Overall mortality 0.028%

Note: Case fatality rates are based on confirmed cases and deaths from COVID-19 as of: 17th February (China); 24th March (Spain); 24th March (South Korea); 17th March (Italy).

Data sources: Chinese Center for Disease Control and Prevention (CDC); Spanish Ministry of Health; Korea Centers for Disease Control and Prevention (KCDC); Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA.

OurWorldinData.org – Research and data to make progress against the world's largest problems.

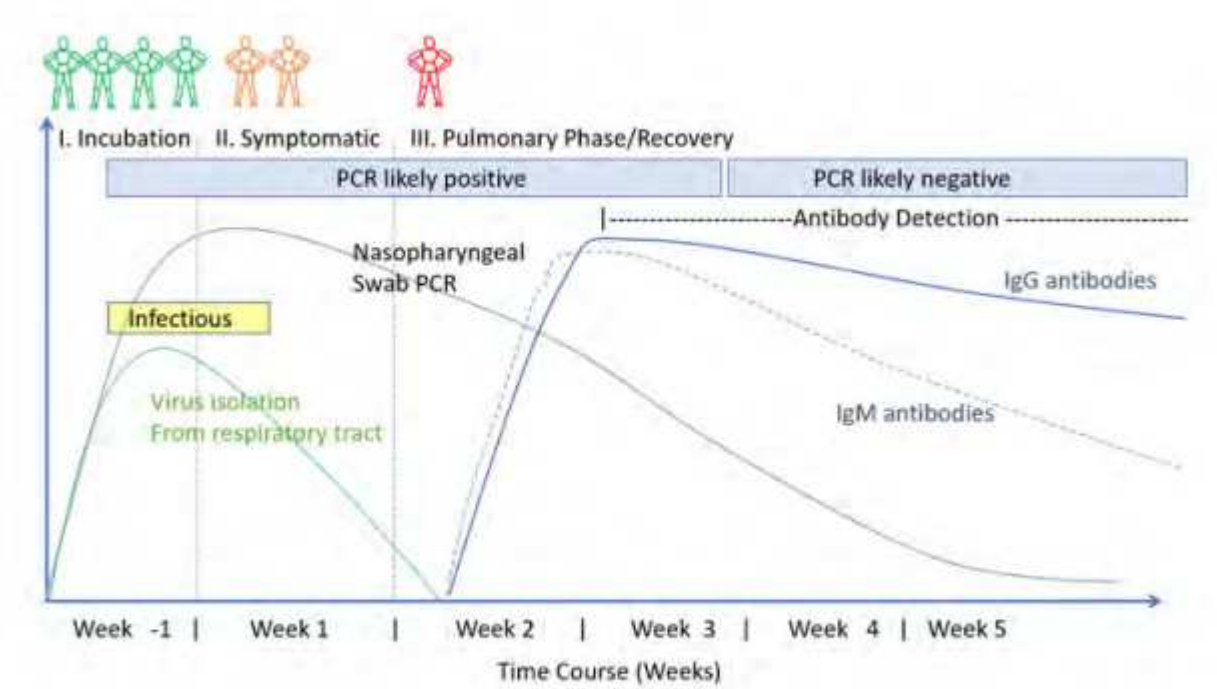
Figure 2. The Course of COVID-19 and General Approach to Treatment



Note. This time course was developed for the ancestral strain (Wuhan) as well as the Alpha, Gamma, and Delta strains. With the Omicron and newer strains, the time course has been compressed. Source: FLCCC

Accessed 01/18/2024

Figure 3. Time Course of Laboratory Tests for COVID-19



Note. This time course was developed for the ancestral strain (Wuhan) as well as the Alpha, Gamma, and Delta strains. With the Omicron and newer strains, the time course has been compressed. Source: FLCCC

Accessed 01/18/2024

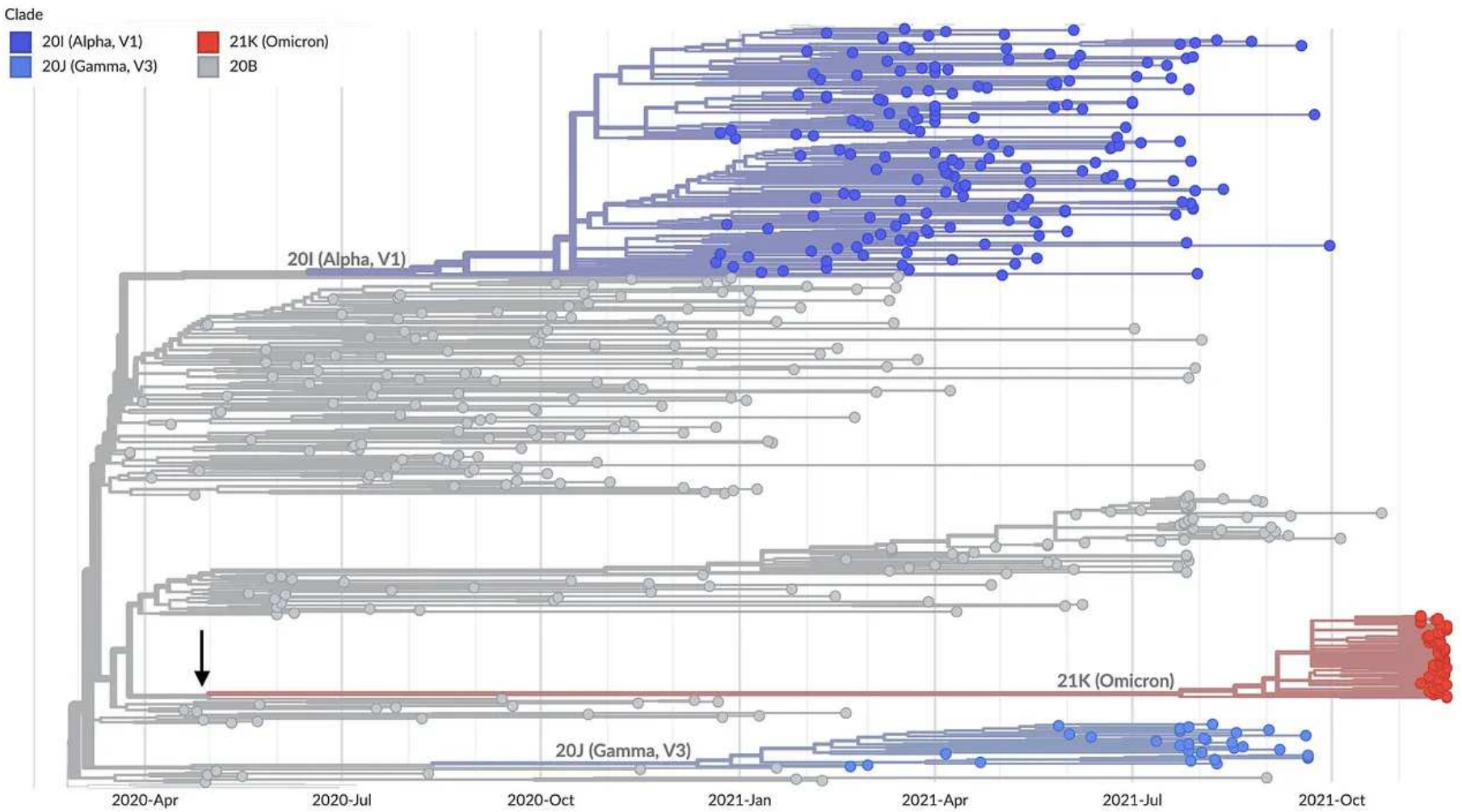

Clade
20I (Alpha, V1)
20J (Gamma, V3)
21K (Omicron)
20B
20I (Alpha, V1)
21K (Omicron)
20J (Gamma, V3)
2020-Apr
2020-Jul
2020-Oct
2021-Jan
2021-Apr
2021-Jul
2021-Oct

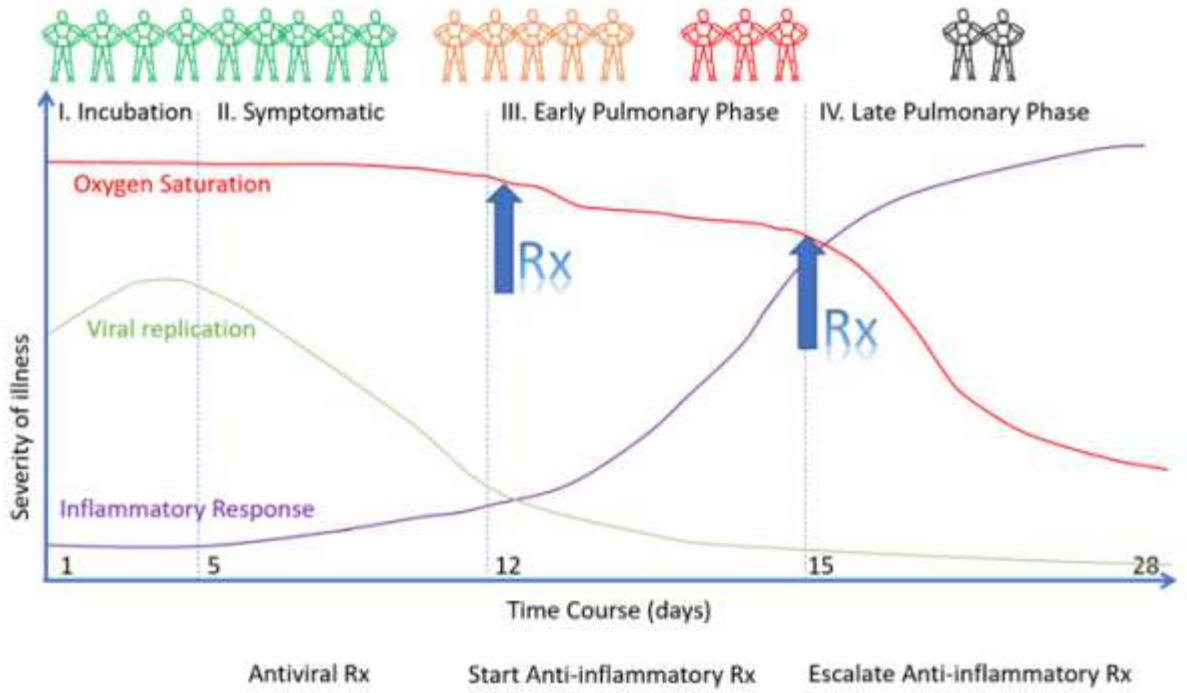
Table 1. Pharmacological Therapy for COVID-19 by Stage of Illness: What has worked and what has failed

	Pre-exposure/ Post-Exposure/Incubation	Symptomatic Phase	Pulmonary/ inflammatory phase
Ivermectin	BENEFIT	BENEFIT	BENEFIT
Hydroxychloroquine	Benefit**	Benefit**	?Trend to harm
Corticosteroids	n/a	Trend to harm	BENEFIT
Anti-androgen Rx	? Benefit	Benefit	BENEFIT
LMWH	n/a	n/a	BENEFIT
Paxlovid/Molnupiravir	n/a	No Benefit	n/a
Monoclonal Abs	No Benefit	No benefit	HARM
Lopivinar-Ritonavir	n/a	No benefit	No benefit
Tocilizumab	n/a	n/a	Unclear Benefit
Convalescent Serum	n/a	No benefit	Trend to harm
Colchicine	n/a	Unclear benefit	No Benefit

Source: FLCCC

Accessed 01/18/2024

Figure 3. Timing of the Initiation of Anti-Inflammatory Therapy



Source: FLCCC

Ivermectin, low molecular weight heparin (LMWH) and corticosteroids form the foundation of care for the hospitalized patient.

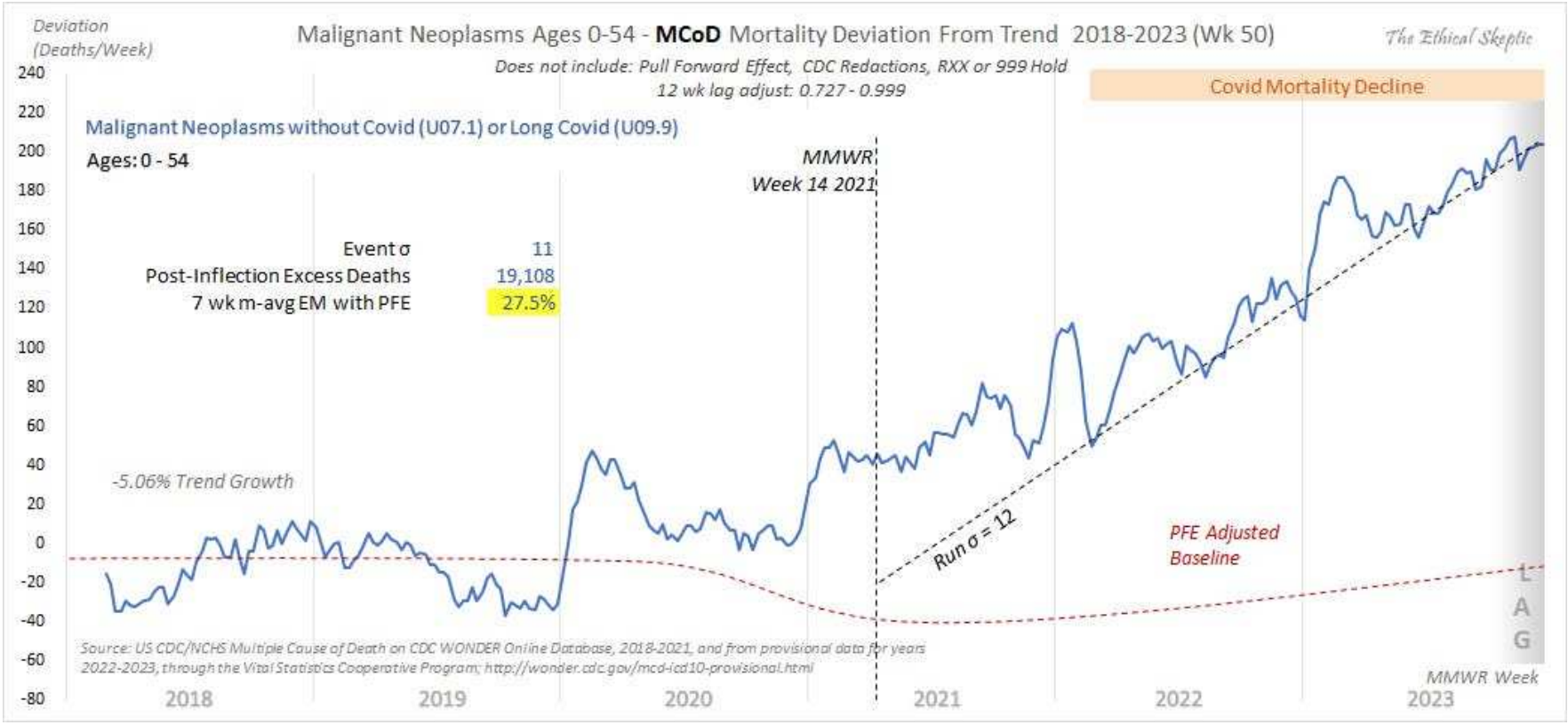
Accessed 01/18/2024

Severe Covid Pulmonary Disease

- I. Methylprednisolone 250 mg daily for at least 3 days, then titrate guided by clinical status and CRP
- II. Ivermectin 1 mg/kg for 5 days
- III. Melatonin 10 mg by mouth at night
- IV. Enoxaparin 60 mg daily; critically ill patients usually have some degree of renal impairment and will require a renally adjusted lower dose. Patients with very high D- dimer and or thrombotic complications may require full anticoagulant doses of Lovenox. It may be prudent to monitor Xa levels aiming for 0.4-0.8 IU/ml (a somewhat lower anti-Xa).
- V. Vitamin C 3 g every 6 hours to 25 g every 12 hours

Severe Covid Pulmonary Disease

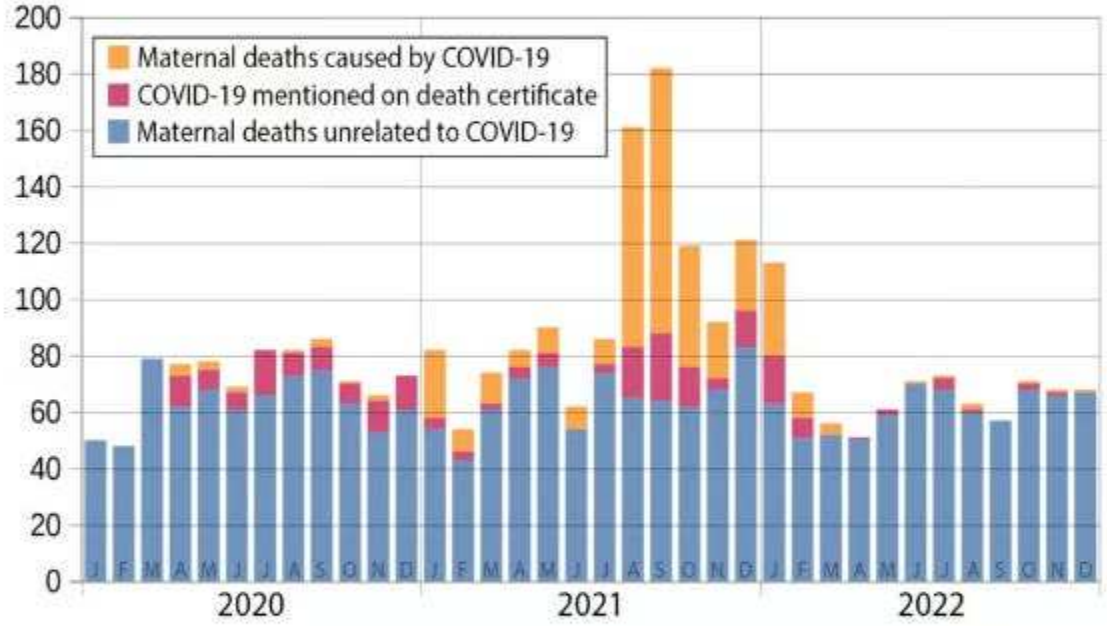
- Consider:
- VI. Cyproheptadine 4–8 mg by mouth every 6 hours
- VII. Fluvoxamine 50-100 mg twice daily
- VIII. Spironolactone 100 mg twice daily
- IX. Thiamine 200 mg every 12 hours
- X. NAC 1200 mg by mouth twice daily [154]
- XI. Finasteride 10 mg daily or dutasteride 2 mg day 1 then 1 mg daily or bicalutamide 150 mg daily
- XII. Omega-3 fatty acids 4 g/day
- XIII. Famotidine 40 mg twice daily
- XIV. Calcifediol (0.014 mg/kg) use as a single dose



Post roll-out of mRNA vaccine for Covid 19

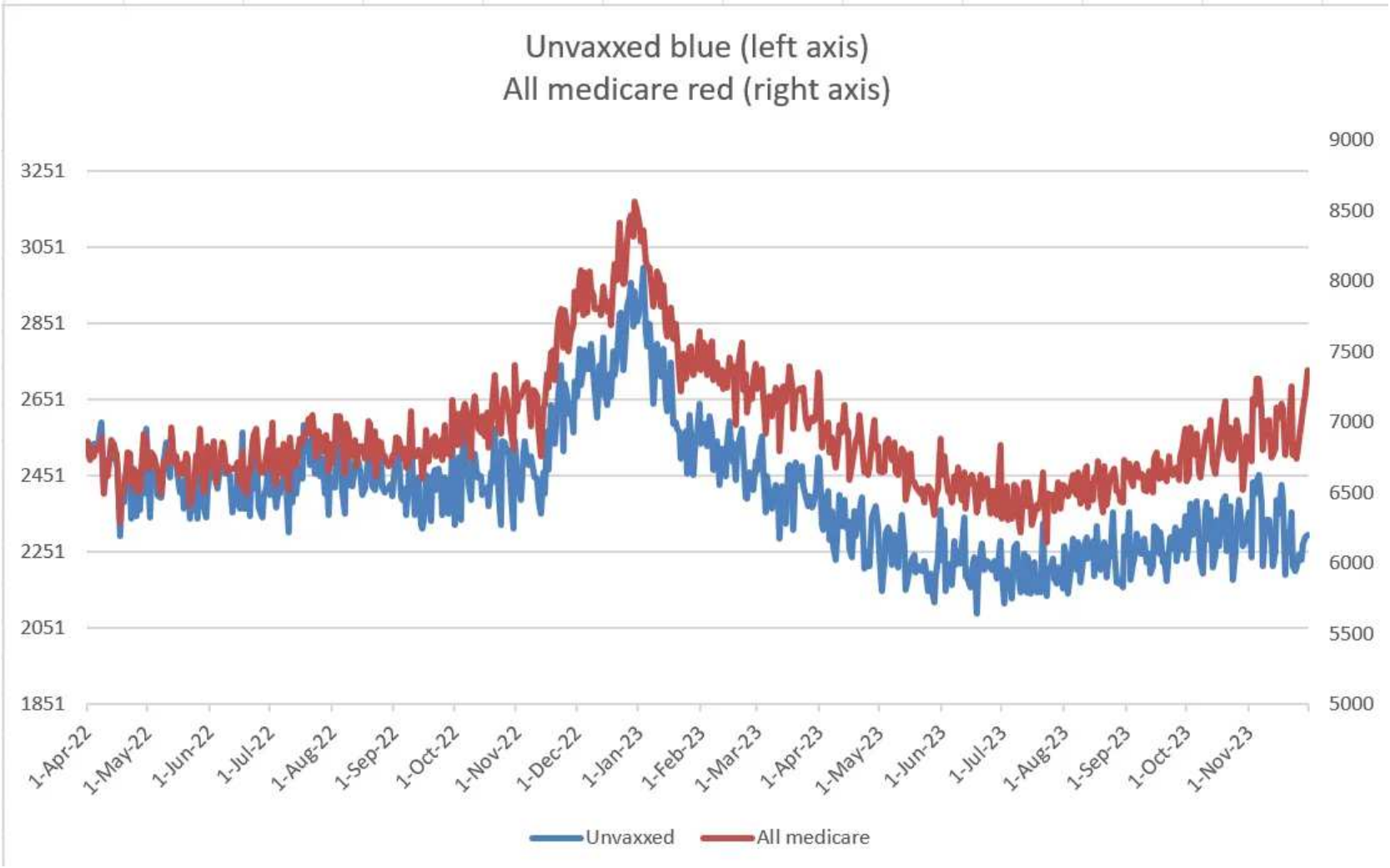
Covid Deaths in Pregnancy Rose 300 Percent During Delta. Blame The Toxic Combination of Covid Plus Vaccines.

PIERRE KORY, MD, MPA AND MARY BETH PFEIFFER



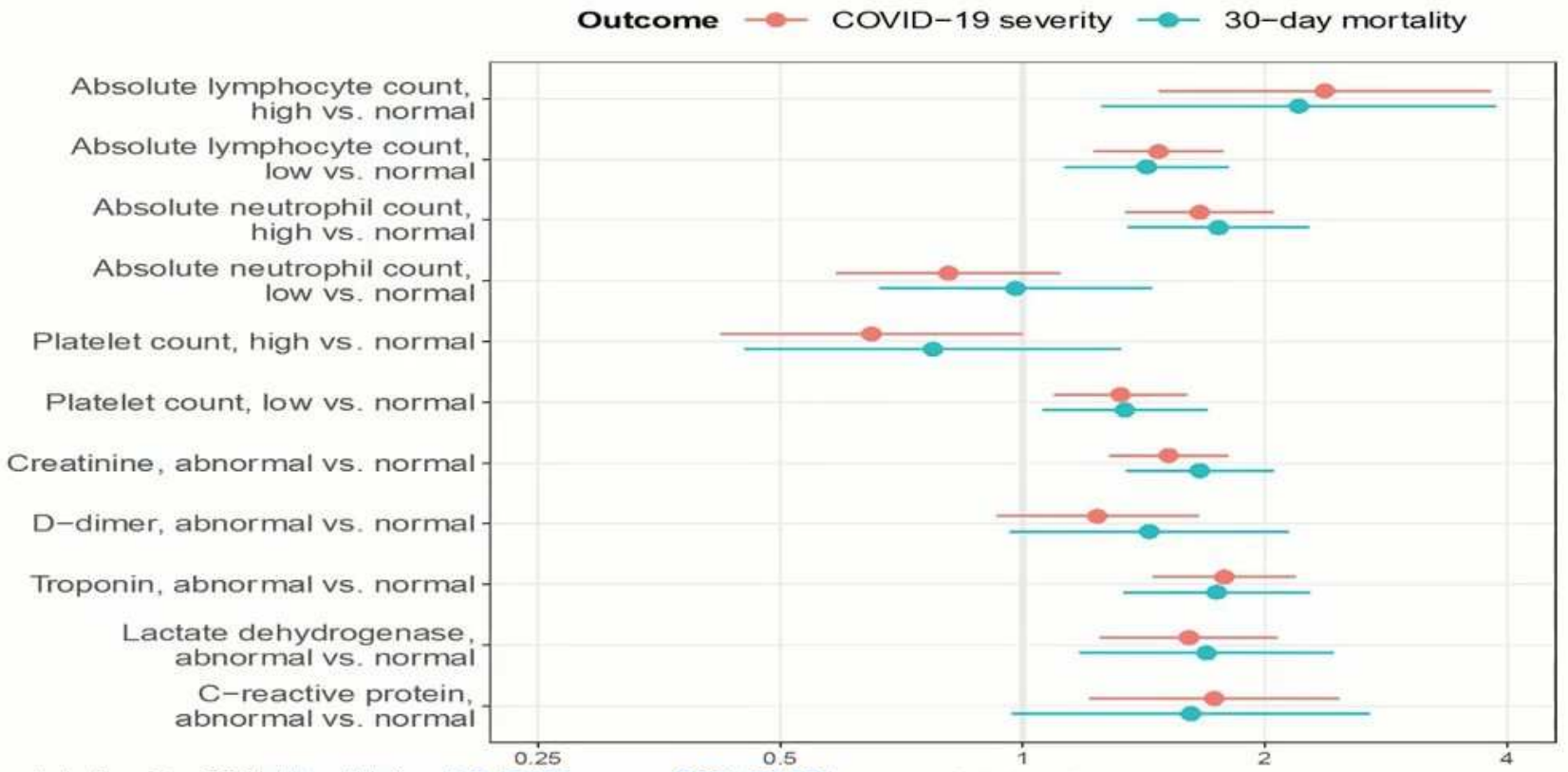
Source: CDC WONDER (data as of January 4, 2024) - Chart and research by Fabian Spieker

Maternal Deaths Across the USA: Pregnancy-related deaths rose sharply in 2021, driven by Covid-19 as the underlying cause (orange) and as a contributing factor (red). Half of the Covid deaths occurred in August and September, coinciding with the Delta wave and advisories for pregnant women to get vaccinated. Maternal Covid Deaths rose 321 percent from 2020 to 2021 while all Covid deaths rose 20 percent.



All cause death rates

Association of laboratory parameters with outcome in n=2872 **hospitalized patients**



Grivas et al. *Ann Onc* 2021 https://doi.org/10.1016/j.annonc.2021.02.024

Covid

- No benefit from vaccination against influenza or Covid (hospitalization or death) demonstrated in review of 9 million VA patient encounter records 2022-2023.
- Xie, Choi, Al-Aly, JAMA (2023) 329:1697-1699
- Vaccination deaths increased following introduction of vaccination; higher risk in those receiving multiple boosters.
- Alessandria, M, Malatesta, GM, Berrino, F, Donzelli, A, Microorganisms (2024) 12:1343

SARS-CoV-2 Spike protein

- Spike protein activation of the TLR4 signaling response and upregulation of miR-146a (proinflammatory) in neurons.
- The spike trimer directly binds to the TLR4 receptor with an affinity comparable to the binding strength of many virus-receptor interactions.
- The spike protein robustly induces the inflammatory agent Il-1β.

SARS-CoV-2 Spike protein

- TLR4 expression is high in the substantia nigra in association with PD, along with upregulation of the inflammatory cytokine IL-1β.
- Parkinson's patients also have enhanced expression of TLR4 in circulating monocytes and B cells.
- CD14+, CD16+ cells represented an extremely high percentage (37% on average) of the monocytes in their blood, compared with only 6.5% in HIV-negative controls
- SARS-CoV-2 spike protein has a sequence just above the furin cleavage site closely resembling Staphylococcal enteroxin B

SARS-CoV-2 Spike protein

- Human cells expressing the retrotransposon long interspersed nuclear element-1 (LINE-1) are able to reverse-transcribe the spike protein mRNA into DNA within six hours of exposure through transfection
- Nucleic acid binding Antimicrobial protein triggers reverse transcription by LINE-1 binding.
- PrP_{sc}'s cytotoxicity is dependent upon its ability to facilitate LINE-1 retrotransposition activity
- This leads to DNA double-strand breaks and cellular damage

SARS-CoV-2 Spike protein

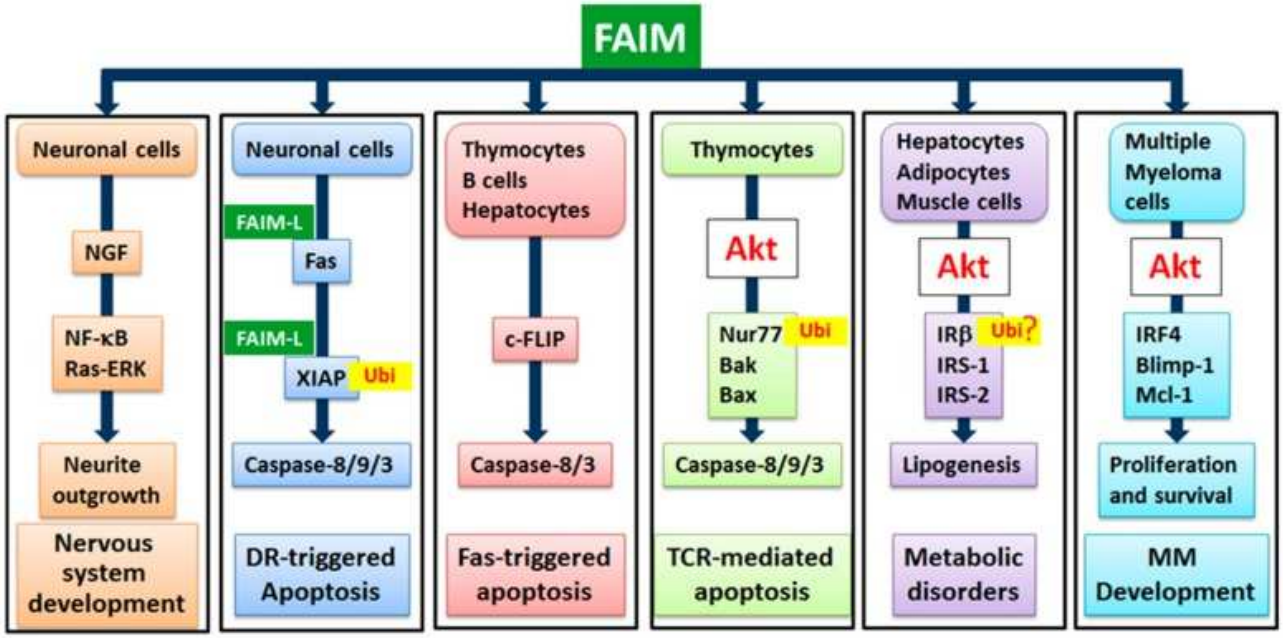
- By analogy, the spike protein itself, which is also an RNA-binding protein, may facilitate the retrotranscription of spike protein mRNA into DNA, mediated by LINE-1.
- While LINE-1 is inactive in most cells, neurons, like cancer cells and immune cells, actively express LINE-1, especially in association with neurodegenerative diseases.
- Promotes senescence in macrophages
- The presence of G4 forming motifs may be the link in the initial conversion of PrP^{C} to PrP^{SC}. Large numbers of G4 complexes in vaccines as compared to virus

SARS-CoV-2 Spike protein

- Platelets are the largest reservoir of prion protein in the blood.
- Platelet activation has been shown to induce platelets to release the prion protein and display it on the surface of exosomes
- May present as amyloid clots

SARS-CoV-2 Spike protein

- Fas Apoptosis Inibitory Molecule (FAIM) upregulated in activated B-cells blocks apoptosis
- If blocked, as with spike protein, mediation of AKT uncontrolled



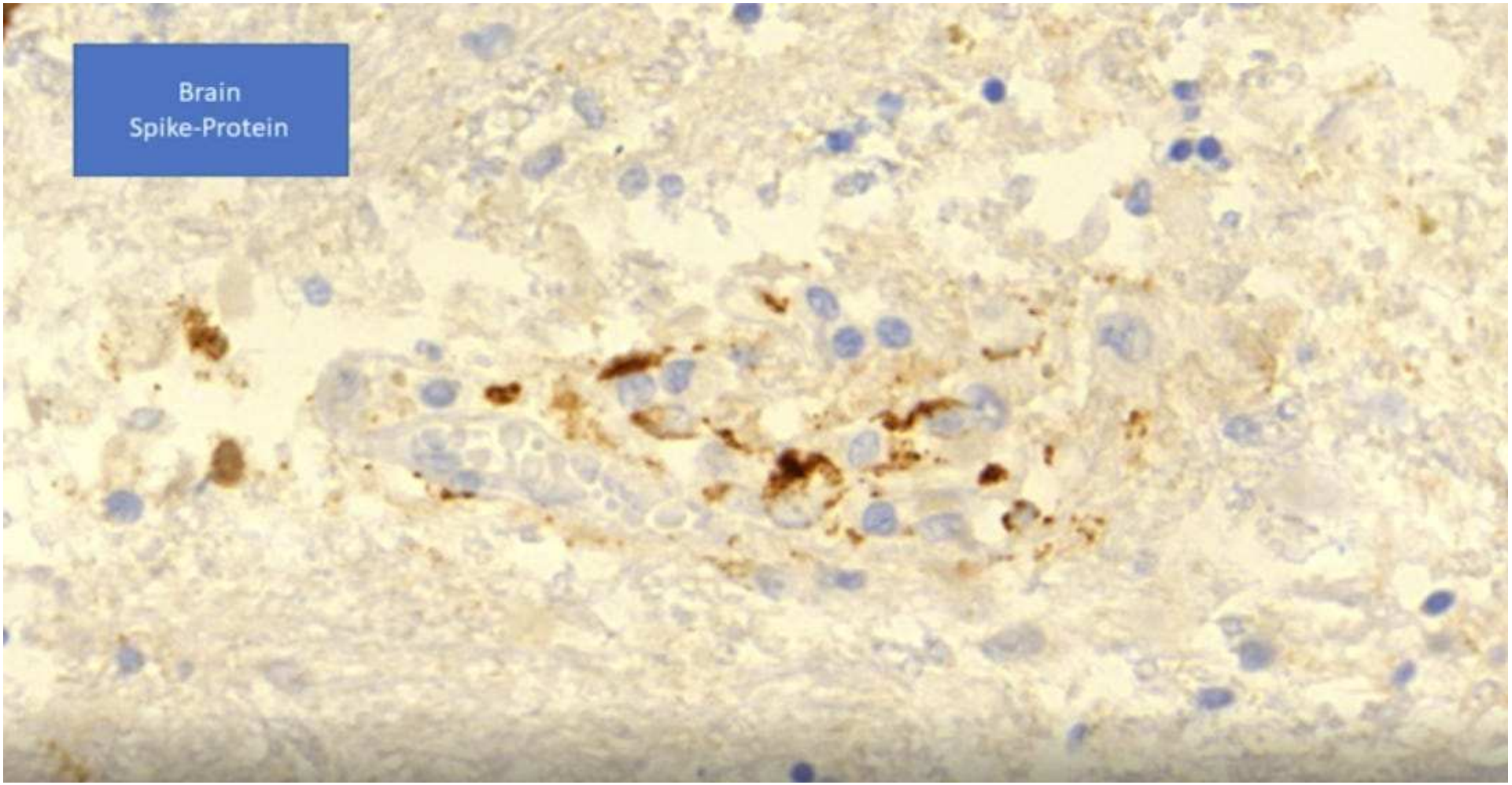
doi:10.3390/cells8060541

SARS-CoV-2 Spike protein

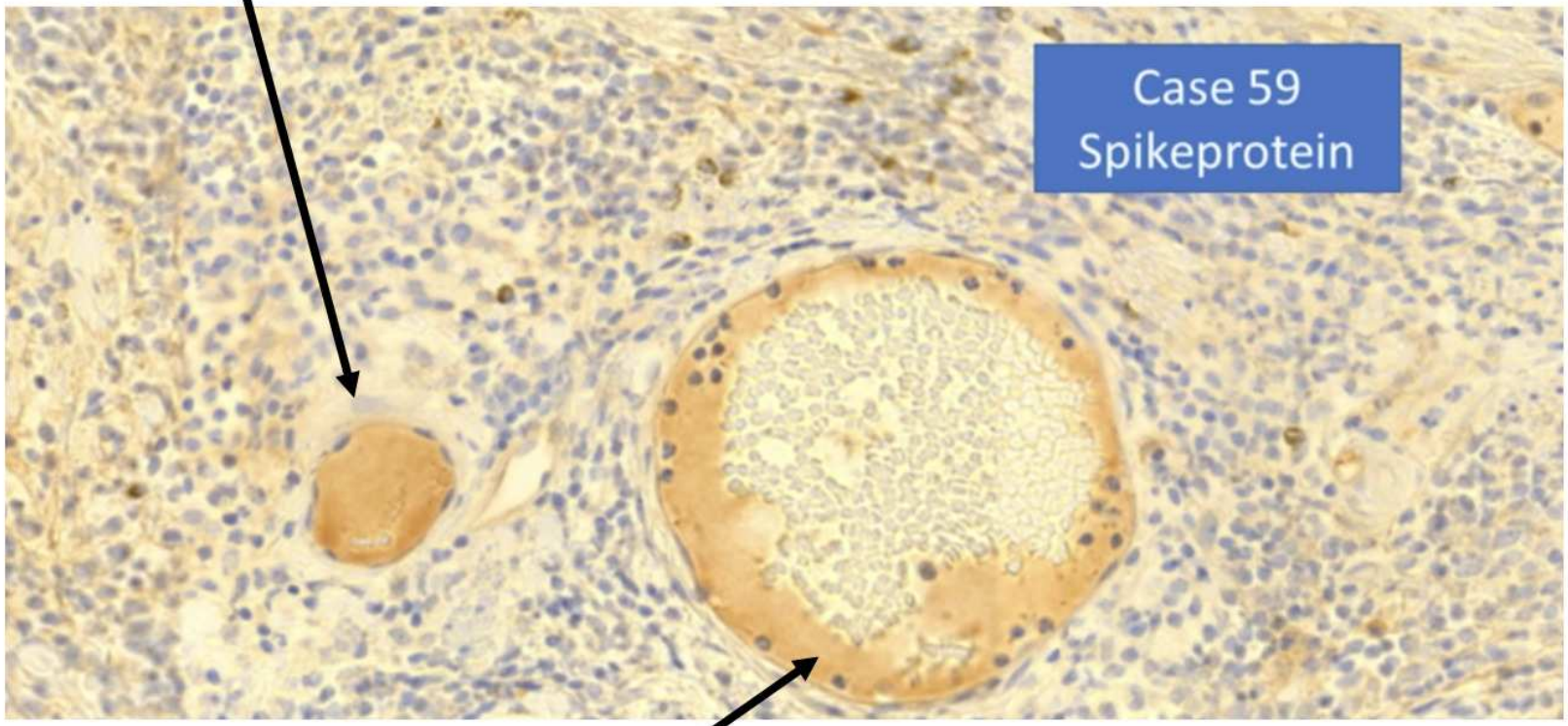
- Extracellular Hsp70/72 can bind antigens, and the complex is then recognized by antigen-presenting cells (APCs) via scavenger receptors.
- The APC takes up the complex, and bound Hsp70/72 sequesters the antigen until it reaches the proteosome.
- After processing, the antigen is transported to MHC class I molecules, triggering the activation of cytotoxic CD8+ T cells.

SARS-CoV-2 Spike protein

- The Hsp70/72-antigen complex can also be processed in the lysosome, leading to the presentation of antigen-derived peptides on MHC class II molecules, thus activating CD4+ T cells
- Febrile seizures, autoimmune disorders, myocarditis, fertility disorders, mental impairment among the many side effects described with spike protein
- Impaired insulin signaling leads to a deficient ability to induce HSR and the subsequent resolution of inflammation.

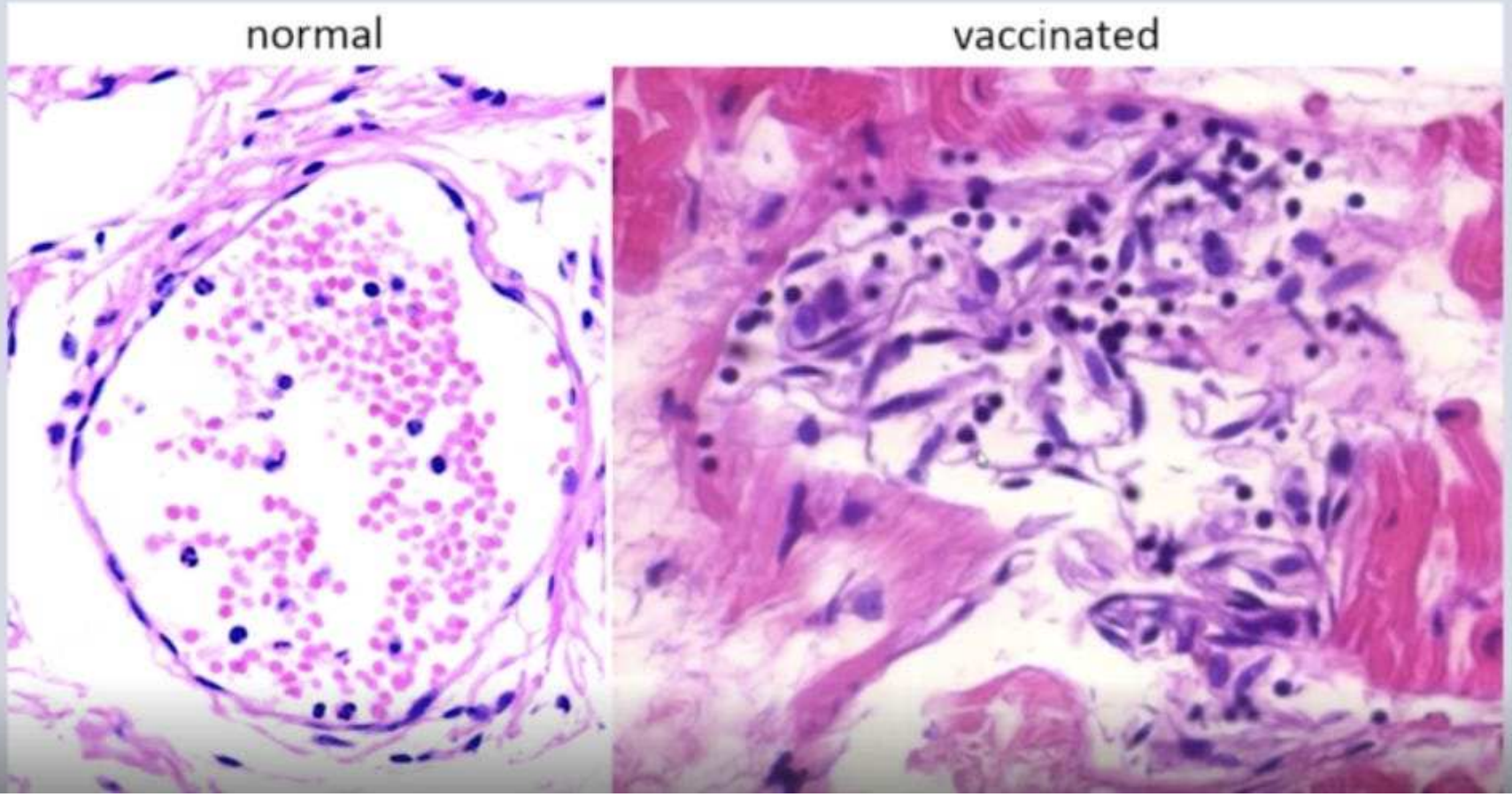

Brain
Spike-Protein

Spike-protein occluded capillary in the heart

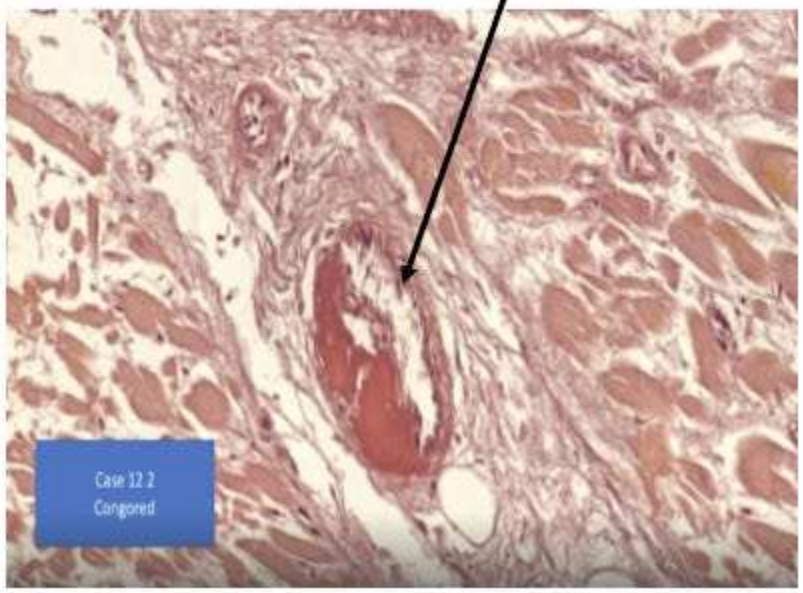


Spike protein filling and thickening a vessel wall

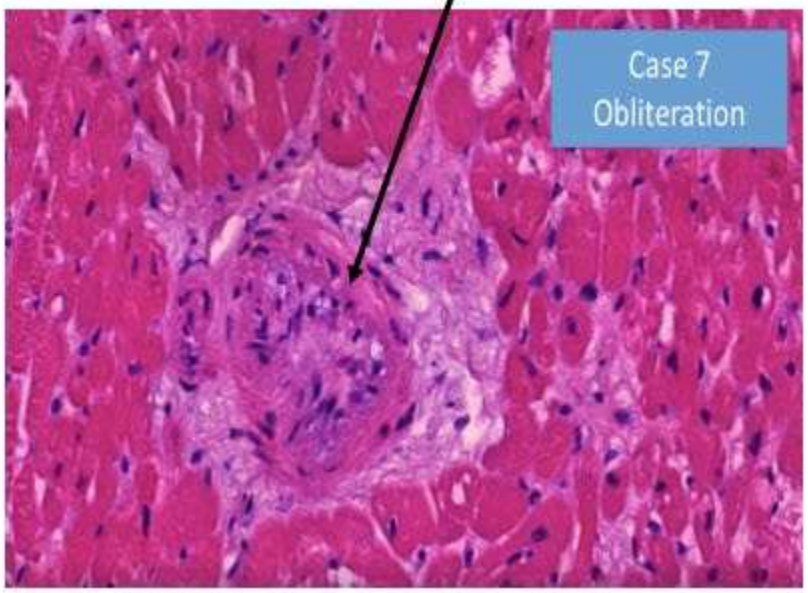
Endothelial stripping and destruction in a venule after vaccination (case 1)

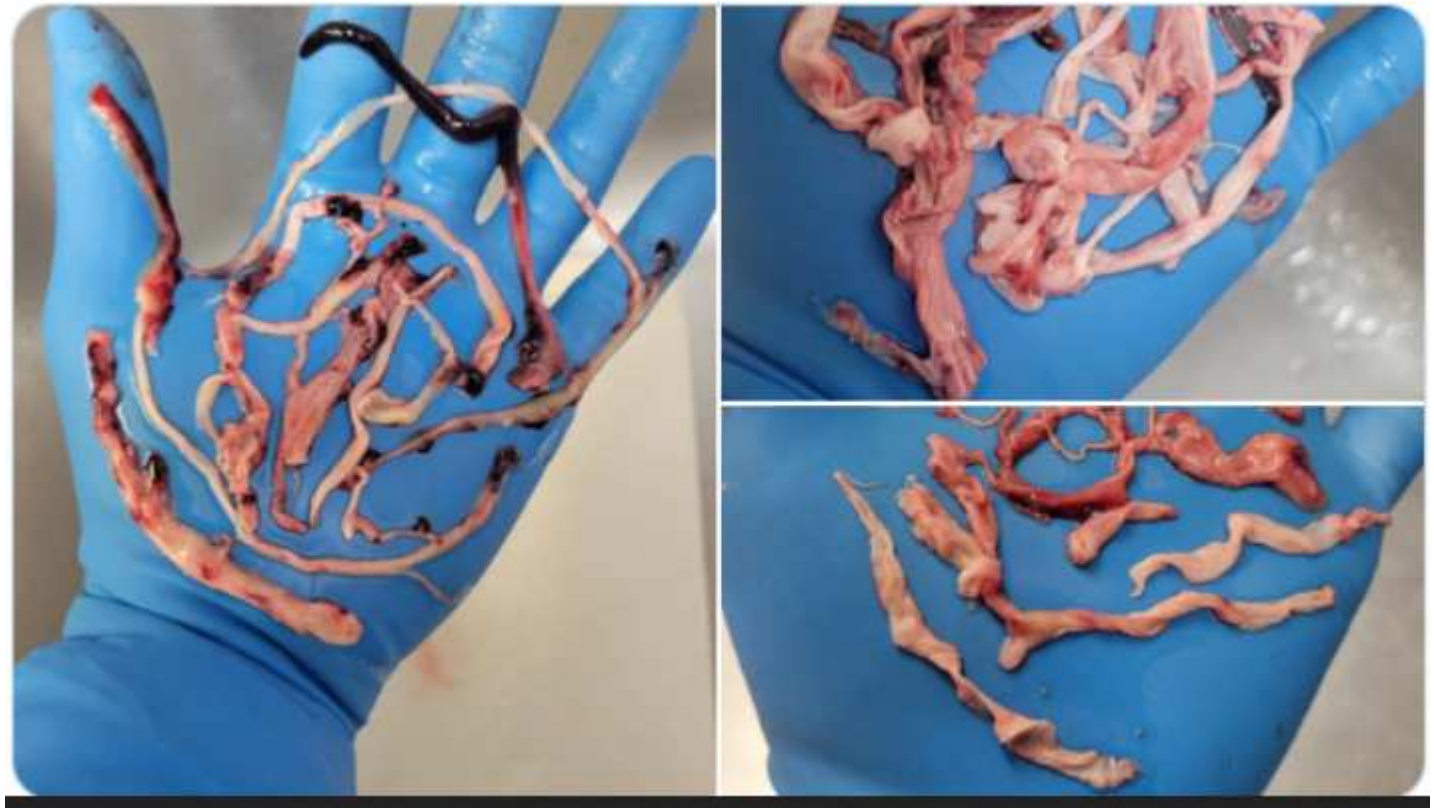


Amyloid Within a Vessel

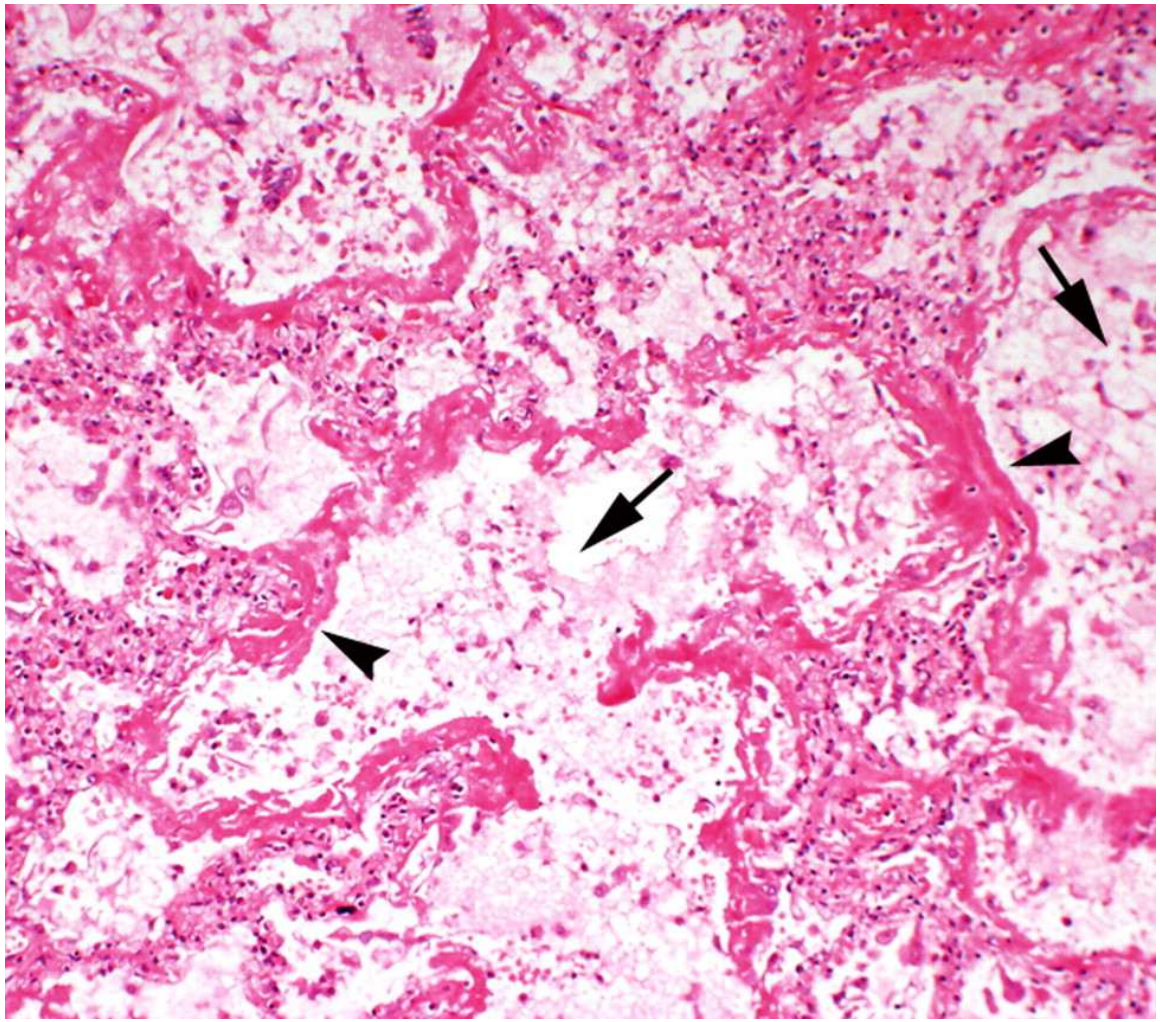


Amyloid Occluding a Vessel





SARS, MERS, Severe Covid 19



Diffuse alveolar damage with hyaline membrane formation (arrowhead).

Intra-alveolar edematous period is present (arrows).

https://pubs.rsna.org/doi/full/10.1148/radiol.11092149
Accessed 12/10/2019

Rabies

- Early specific neurologic symptoms include:
- Paresthesia, pain, or pruritus near the site of the exposure
- 20%, ascending paralysis
- 80%, atypical encephalitis
- Episodes of hyperexcitability are typically followed by periods of complete lucidity that become shorter as the disease progresses.

Rabies

- Brainstem involvement (nucleus ambiguus)
- Hydrophobia and aerophobia
- Hypersalivation
- 20%, acute flaccid paralysis
- Sphincter involvement

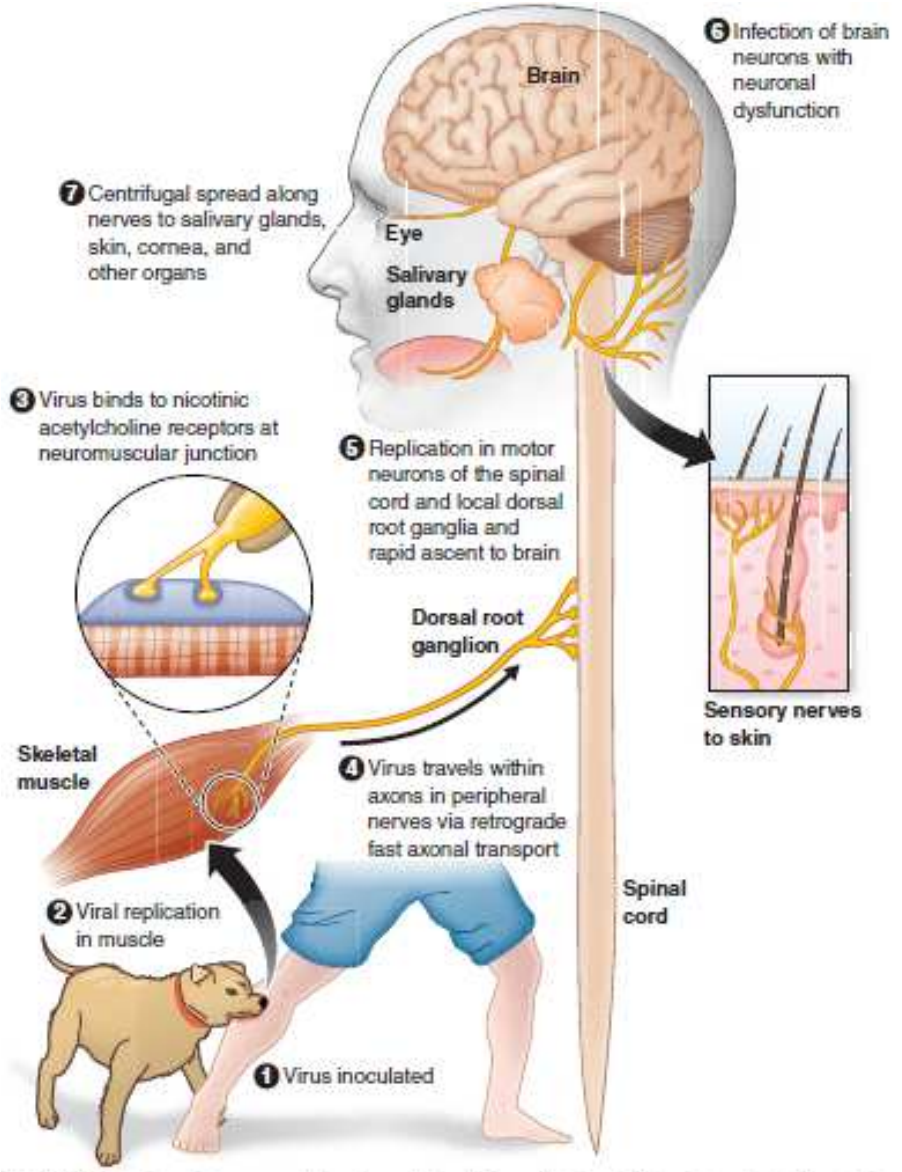


FIGURE 203-3 Schematic representation of events in rabies pathogenesis following peripheral inoculation of rabies virus by an animal bite. *(Adapted from AC Jackson: Human disease, in Rabies: Scientific basis of the disease and its management, 3rd ed. AC Jackson [ed], Oxford, UK, Elsevier Academic Press, 2013, pp 269–298; adapted with permission.)*

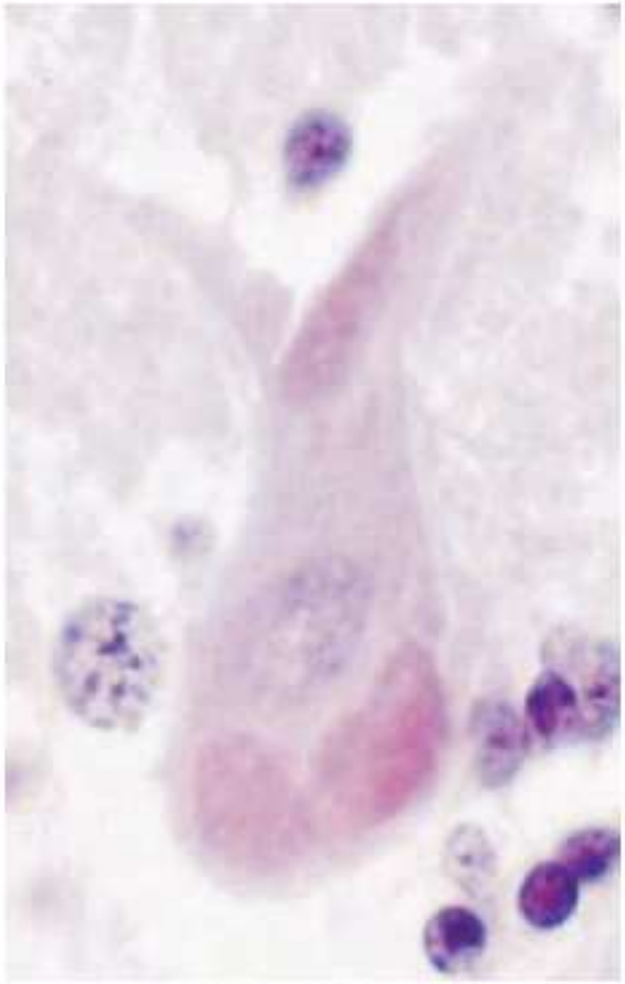


FIGURE 203-4 Three large Negri bodies in the cytoplasm of a cerebellar Purkinje cell from an 8-year-old boy who died of rabies after being bitten by a rabid dog in Mexico. *(From AC Jackson, E Lopez-Corella: N Engl J Med 335:568, 1996. © Massachusetts Medical Society.)*

HTLV 1

- Glut-1 transporter is viral receptor.
- Most effective transmission is cell to cell contact.
- Infects dendritic cells via neurophilin-1.
- Tax protein transcription leads to IL2, IL2R, IL15 production (and lymphocyte proliferation).
- Apoptosis is blocked (BCL-X).
- DNA polymerase and cell cycle controller p18 are repressed.
- There is also direct binding to TGF-β and cell cycle controller MOD-1.
- p53 is also affected.

HTLV 1

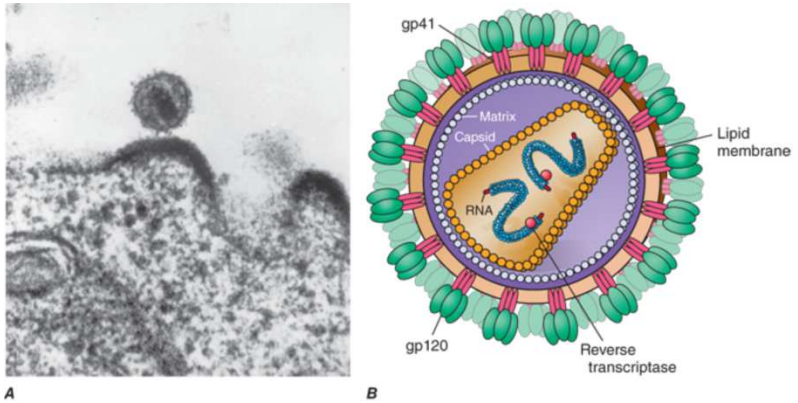
- Body fluid transmission leads to T cell leukemia/lymphoma.
- Blood transfusion transmission leads to myelopathy (paraparesis)

HIV

- HIV-1 common type associated with AIDS in the US, Europe, Central Africa
- HIV-2 common type associated with AIDS in West Africa and Asia
- Capsid is icosahedral.
- Retrovirus genomic RNA contains gag, pol, env genes.

- Gag and pol gene products cleaved by protease to yield mature proteins.
- The viral core contains the capsid proteins, two copies of single stranded genomic RNA, and, as well, protease, reverse transcriptase, and integrase.

HIV morphology



Accessed 02/03/2016

A. Electron micrograph of HIV. Figure illustrates a typical virion following budding from the surface of a CD4+ T lymphocyte, together with two additional incomplete virions in the process of budding from the cell membrane. B. Structure of HIV-1, including the gp120 envelope, gp41 transmembrane components of the envelope, genomic RNA, enzyme reverse transcriptase, p18(17) inner membrane (matrix), and p24 core protein (capsid). (Copyright by George V. Kelvin.) (Adapted from RC Gallo: Sci Am 256:46, 1987.) C. Scanning electron micrograph of HIV-1 virions infecting a human CD4+ T lymphocyte. The original photograph was imaged at 8000× magnification.
(Courtesy of Elizabeth R. Fischer, Rocky Mountain Laboratories, National Institute of Allergy and Infectious Diseases; with permission.)

HIV

- p24 is the capsid protein, and binds cyclophilin A.
- p7 is the nucleocapsid protein that binds RNA.
- p6 interacts with vpr, participates in terminal steps of virion budding.
- p17 is a matrix protein that surrounds the viral core and underlies the viral envelope and stabilizes it
- Helps target Gag proteins to lipid rafts, promoting virus assembly at cell surface.
- 50 copies of reverse transcriptase
- Reverse transcriptase is error prone
- Associated with high HIV mutation rate

HIV

- Gp 160 is the envelope protein that is cleaved in the endoplasmic reticulum.
- It yields, gp120, the surface protein that binds to CD4 on the host cell and then to one of the two chemokine receptors (CCR5 or CXCR4)
- It yields gp41, the transmembrane protein that permits fusion
- Gene specific to HIV include nef, rev, tat, vpr, vpu, and vif.
- The nef gene produces negative factor that downregulates MHC I expression on infected T_H cells, enhancing virion infectivity.

HIV

- The rev gene promotes nuclear export of incompletely spliced RNA into cytoplasm.
- The tat gene upregulates Pol-II mediated elongation of integrated viral DNA.
- The long terminal repeat is required for initiation of transcription.
- It contains control regions that bind transcription factors (e.g., NF-κB) as well as the RNA trans-acting response element (TAR) that binds tat.

HIV

- The presence of NF-κB binding sites in the genome promotes proviral transcription in the face of any environmental antigen exposure that activates T cells and macrophages.
- The rev gene promotes nuclear export of incompletely spliced RNA into cytoplasm.
- The tat gene upregulates Pol-II mediated elongation of integrated viral DNA.
- The long terminal repeat is required for initiation of transcription.

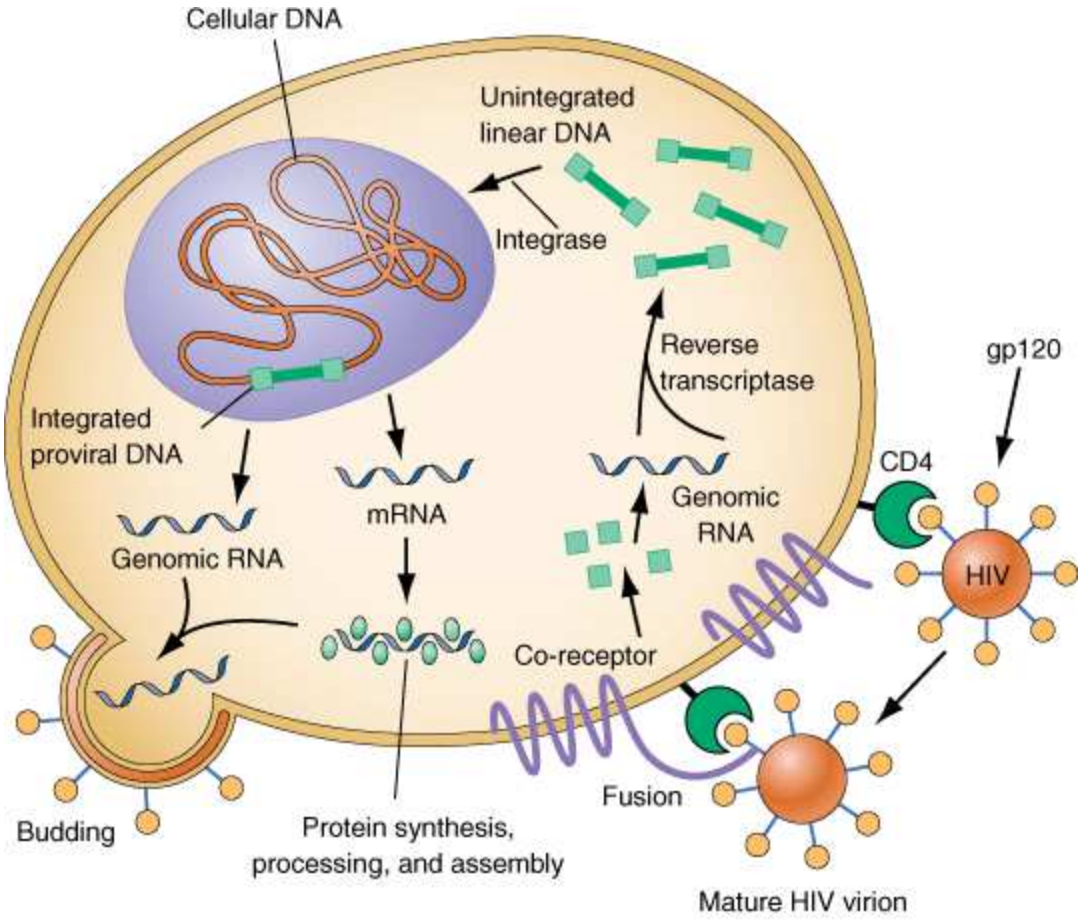
HIV

- It contains control regions that bind transcription factors (e.g., NF-κB) as well as the RNA trans-acting response element (TAR) that binds tat.
- The presence of NF-κB binding sites in the genome promotes proviral transcription in the face of any environmental antigen exposure that activates T cells and macrophages.

HIV

- The vpr gene increases viral replication as well as facilitates infection of mucosal dendritic cells (macrophages). Interacts with p6.
- The vpu gene promotes CD4 degradation and increases virion release.
- The vif gene produces an infectivity factor that overcomes the inhibitory effect of host factor (APOBEC3G) in unactivated T cells by binding to this cytidine deaminase and promoting its degradation by protease.

HIV replication cycle



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

(Adapted from Fauci AS: Host factors and the pathogenesis of HIV-induced disease. Nature 384:529, 1996

Fig. 182-3 Accessed 07/01/2010

HIV replication cycle

- gp120 binding to CD4 occurs first. Requires binding to other chemokine receptors to enter cell (CCR5, CXCR4)
- Conformational change leads to exposure of chemokine binding site and chemokine binding.
- Conformational change in gp41 exposes fusion peptide in hydrophobic region at gp41 tip. Fusion peptide penetrates cell membrane
- Fusion of HIV membrane with host cell membrane leads to entry of viral genome into cytoplasm
- Dendritic cells bind HIV with ganglioside Selgic-1 and present virus to T cell in that fashion.

HIV replication cycle

- Reverse transcriptase mediated synthesis of double stranded complementary (proviral) DNA.
- Remains in linear form in quiescent cell.
- In dividing cells, the cDNA circularizes, enters the nucleus, and integration of provirus into host cell genome occurs.
- HIV RNA transcripts leave nucleus for cytoplasm where virion assembled.
- Membrane budding and release of mature virion follows.

HIV tropism

- M-tropic R5 virus
- 90% of acutely infected individuals
- Attracted to CCR5 co-receptors; macrophages allow entry (early in infection).
- T-tropic X4 virus
- Attracted to CXCR4 co-receptors
- T-cells allow entry (late in infection)
- Infects even thymus T-cell precursors.
- Correlates to a more rapid progression to AIDS.
- Form syncytia in cell culture.

HIV tropism

- HIV persistence noted more frequently in those populations without HLA DRB1*1302 (Gambia).
- HIV progression associated with HLA B35, HLA A1, HLA B8, HLA DR3 antigens (and absence of HLA B27) not reproduced consistently.

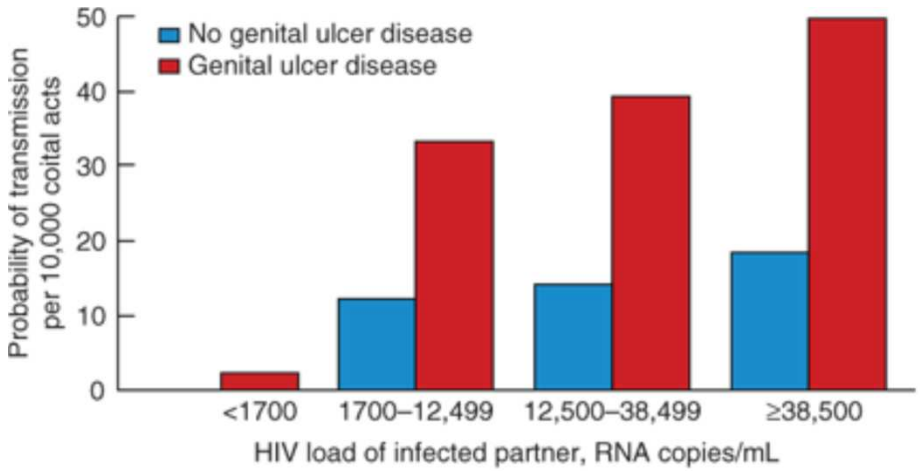
HIV

- Very rapid decrease in GALT CD4 lymphocytes.
- Slow progressive decrease in circulating CD4 lymphocytes (chronic activation of uninfected cells leads to apoptosis)
- Diminished antigen induced T-cell proliferation as well as a decrease in T_{H1} response (as opposed to T_{H2}) noted.
- Memory cell subset of T_H cells lost early in disease.

HIV

- 70% of patients experience a “mononucleosis syndrome” of fever, rash, sore throat, lymphadenopathy, and a flu-like syndrome with athralgia, headache, and diarrhea.
- EBV VCA and CMV antibody negative as clues.
- Virus present in semen, blood, body fluids.
- Markedly lower concentrations of virus present in cervical secretions
- Perhaps viral transmission occurs from female-to-male if other STD present.

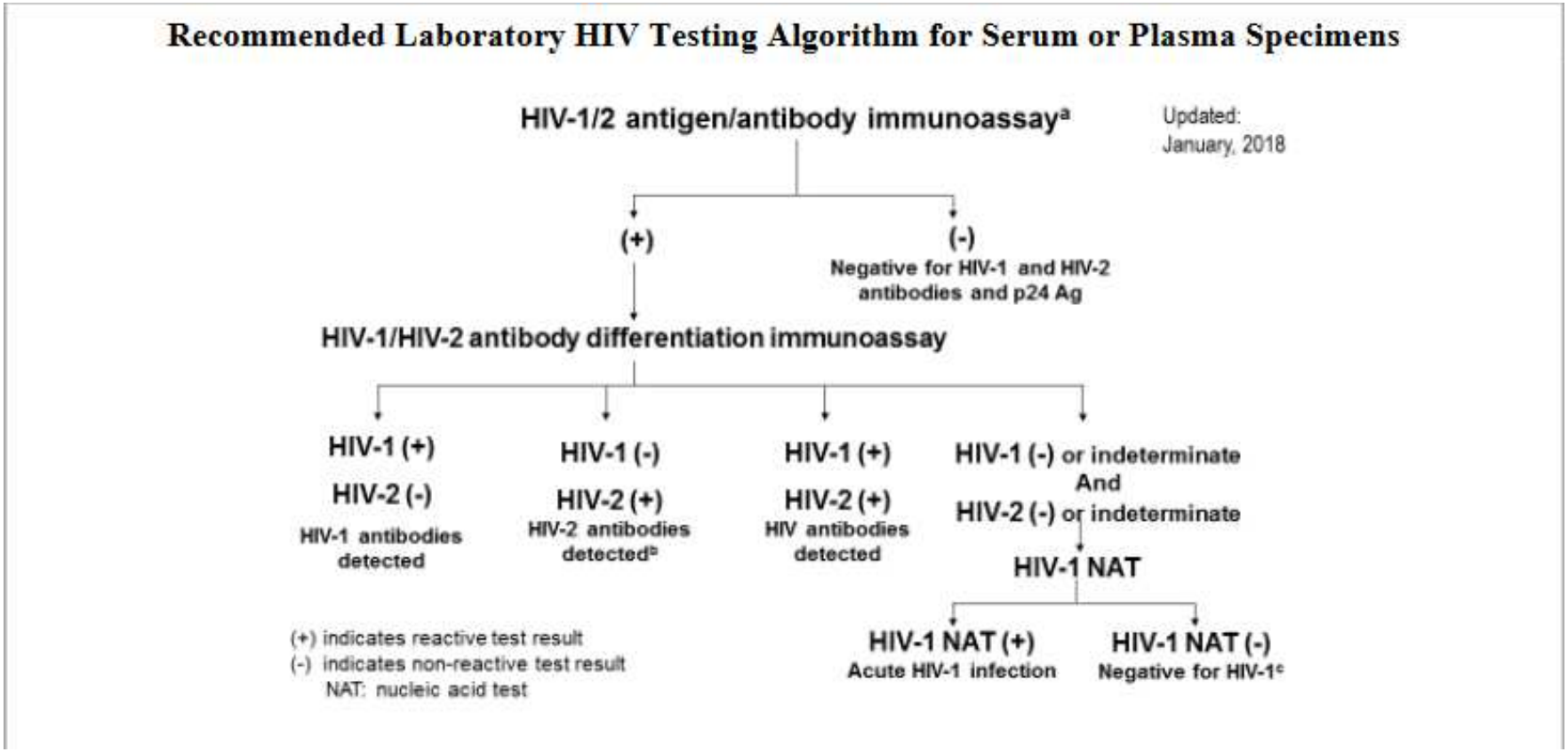
Probability of HIV transmission



Probability of HIV transmission per coital act among monogamous, heterosexual, HIV-serodiscordant couples in Uganda. (From RH Gray et al: Lancet 357:1149, 2001.)

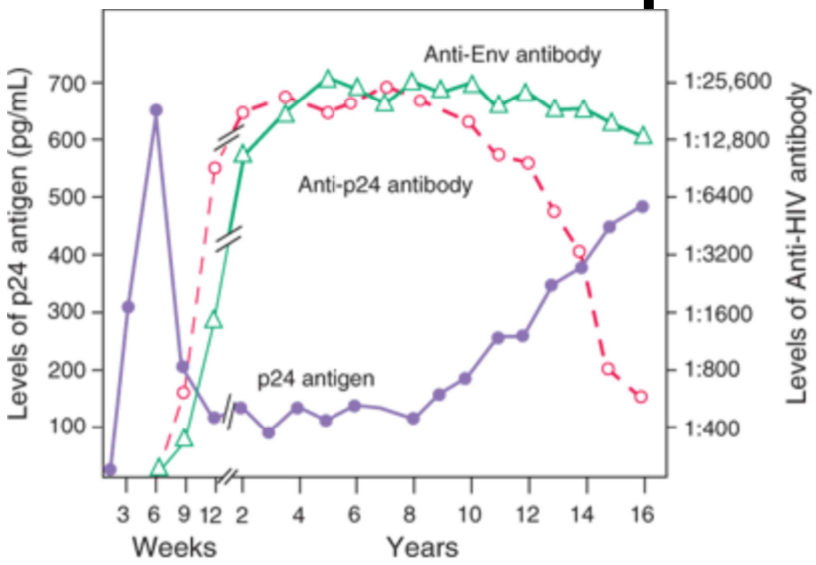
Accessed 02/03/2016

Antibodies to gp41 and p24 antigens are the first detectable serologic markers following HIV infection



https://stacks.cdc.gov/view/cdc/50872

Development of antibody response



Relationship between antigenemia and the development of antibodies to HIV. Levels of plasma HIV parallel those of p24 antigen. Antibodies to HIV proteins are generally seen 6–12 weeks following infection and 3–6 weeks after the development of plasma viremia. Late in the course of illness, antibody levels to p24 decline, generally in association with a rising titer of p24 antigen.

Accessed 02/03/2016

Percentage of patients progressing to AIDS within 3 years

	HIV RNA <500 copies/ml	HIV RNA >3000-10,000 copies/ml	HIV RNA >10,000-30,000 copies/ml	HIV RNA >30,000 copies/ml
CD4 >750 cells/uL	0	3.2	9.5	32.6
CD4 <750 cells/uL	3.7	8.2	40.1	47.9

When to initiate ART

- The optimal time to initiate antiretroviral therapy in adult patients with CD4 count >350 cells/μl is not well defined.
- For HIV-infected patients older than 50 years of age, antiretroviral therapy (ART) is recommended for all, regardless of CD4 cell count.
- Older patients frequently have a blunted immune response
- Older patients have high virologic response rates.
- Older patients have relatively poor CD4 cell increases in response to antiretroviral therapy as measured by an increase of CD4 count by 100 cells/fl

When to initiate ART

- Older HIV-infected patients have a greater risk of developing serious non-AIDS complications.
- Patients >55 years old may be at higher clinical risk even after starting therapy
- The administration of ART during pregnancy or intrapartum significantly reduces the risk of mother-to-child transmission
- A 96% reduction in transmission between sero-discordant heterosexual couples when the positive partner was receiving ART

Necessary testing

- 20-25% drug naïve patients possess resistant strains.
- Reverse transcriptase and protease genotypic resistance testing should be used to guide selection of a regimen
- If transmitted integrase strand transfer inhibitor resistance is a concern, testing should also include the integrase gene
- HLA-B*5701 testing should be performed before initiation of abacavir (ABC).
- Patients should be screened for hepatitis B and hepatitis C virus infection before initiating ART

Necessary testing

- A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered
- Co-receptor tropism testing is recommended for patients who exhibit virologic failure on a CCR5 antagonist
- A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage
- A genotypic tropism as an alternative
- A proviral DNA tropism assay can be utilized for patients with undetectable HIV-1 RNA when a CCR5 antagonist is considered for use

Monitor therapy

- HIV screening is recommended to begin at age 13
- Two surrogate markers are used to monitor people with HIV:
- Plasma HIV RNA (viral load) to assess level of HIV viremia
- CD4 T lymphocyte cell count to assess immune function.

Outcomes

- With maximally suppressed viral loads (200 copies/fl), life expectancy approaches that of non-HIV infected population
- Therapy that achieves a plasma viral load of < 50 copies/mL has been shown to provide a durable response to the therapy employed.

Outcomes

- Those with less cumulative time with detectable plasma viremia are less likely to suffer certain complications:
- Cardiovascular disease
- Neurocognitive dysfunction
- Decreased risk of severe bacterial infections
- Malignancies

ART complications

- ART initiation is associated with a risk of immune reconstitution inflammatory syndrome (IRIS).
- IRIS is a clinical syndrome characterized by new or worsening infectious and non-infectious complications observed after the initiation of ART
- The risk of IRIS increases when ART is begun:
- At low CD4 cell counts (<100 cells/fl)
- With the presence of cryptococcal or TB meningitis
- With cutaneous Kaposi's sarcoma

Monitor therapy

- HIV screening is recommended to begin at age 13
- Two surrogate markers are used to monitor people with HIV:
- Plasma HIV RNA (viral load) to assess level of HIV viremia
- CD4 T lymphocyte cell count to assess immune function.

Initial treatment regimen

- An antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active drug from one of three drug classes:
- An integrase strand transfer inhibitor (INSTI)
- A non-nucleoside reverse transcriptase inhibitor (NNRTI)
- A protease inhibitor (PI) with a pharmacokinetic (PK) enhancer (also known as a booster)

Pharmacologic therapy

- Six distinct classes of drugs:
- Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI, NtRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors (PI)
- Fusion inhibitors (Fis)
- CCR5 co-receptor antagonists
- Integrase strand transfer inhibitors (INSTI)

Drug names

- Nucleoside reverse transcriptase inhibitors (NRTI)
- ABC abacavir
- 3TC lamivudine
- FTC emtricitabine
- TAF tenofovir alafenamide
- TDF tenovir disoproxil fumarate
- Entry Inhibitors (EI)
- IBA ibalizumab
- MVC maraviroc

Drug names

- Protease Inhibitors (PI)
- DRV/c darunavir with cobicistat
- DRV/r darunavir with ritonavir
- Integrase strand inhibitors (INSTI)
- BIC bictegravir
- DTG dolutegravir
- RAL raltegravir
- EVG/c elvitegravir with cobicistat
- Non-nucleoside reverse transcriptase inhitibots (NNRTI)
- NVP nevarapine

Table 6a. Recommended Antiretroviral Regimens for Initial Therapy

Recommended Initial Regimens for Most People with HIV
Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.
INSTI plus 2 NRTIs: **Note**: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens. • BIC/TAF/FTC **(AI)** • DTG/ABC/3TC **(AI)—if HLA-B*5701 negative** • DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)** • RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC) **INSTI plus 1 NRTI**: • DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- EVG/c/(TAF or TDF)[a]/FTC **(BI)**

Boosted PI plus 2 NRTIs:

- In general, boosted DRV is preferred over boosted ATV
- (DRV/c or DRV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- (ATV/c or ATV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(BI)**
- (DRV/c or DRV/r) plus ABC/3TC—**if HLA-B*5701 negative (BII)**

NNRTI plus 2 NRTIs:

- DOR/TDF[a]/3TC **(BI)** or DOR plus TAF[a]/FTC **(BIII)**
- EFV plus (TAF or TDF)[a] plus (FTC or 3TC)
  - EFV 600 mg plus TDF plus (FTC or 3TC) **(BI)**
  - EFV 400 mg/TDF/3TC **(BI)**
  - EFV 600 mg plus TAF/FTC **(BII)**
- RPV/(TAF or TDF)/FTC **(BI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
- DRV/r plus RAL twice a day **(CI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**
- DRV/r once daily plus 3TC[a] **(CI)**

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children

Preferred Regimens			
Age	**Regimens**		**FDC Available** (see Appendix A, Table 1)
Infants, Birth to Age <14 Days[a,b]	Two NRTIs **plus** NVP		No
	Weight ≥2 kg	Two NRTIs **plus** RAL[c]	No
Children Aged ≥14 Days to <3 Years	Two NRTIs **plus** LPV/r[b]		No
	Weight ≥2 kg	Two NRTIs **plus** RAL[c]	No
Children Aged ≥3 Years	Weight <25 kg	Two NRTIs **plus** ATV/r	No
		Two NRTIs **plus** twice-daily DRV/r[d]	No
		Two NRTIs **plus** RAL[c]	No
	Weight ≥25 kg	Two NRTIs **plus** DTG[e]	Yes
		Two NRTIs **plus** EVG/c[f]	Yes
Adolescents Aged ≥12 Years with SMRs of 1–3	Weight ≥25 kg	Two NRTIs **plus** BIC[g]	Yes

Once daily dosing

Available as a Multi-Tablet Regimen with Once-Daily Dosing		
Tenofovir alafenamide/ emtricitabine *and* dolutegravir* (TAF 25 mg/FTC *and* DTG; Descovy *and* Tivicay)	• Initiate ***only*** in patients with CrCl ≥30 mL/min. • Documented DTG resistance after initiation in treatment-naive patients is rare. • Contains 25 mg of TAF, unboosted. • Magnesium- or aluminum-containing antacids may be taken 2 hours before or 6 hours after DTG; calcium-containing antacids or iron supplements may be taken simultaneously if taken with food.	A1
Tenofovir alafenamide/ emtricitabine *and* raltegravir (TAF 25 mg/FTC *and* RAL HD; Descovy *and* Isentress HD)	• Initiate ***only*** in patients with CrCl ≥30 mL/min. • To date, no clinical trials have been conducted with TAF and RAL; data are based on bioequivalence pharmacokinetic studies. • Contains 25 mg of TAF, unboosted. • Administer as TAF/FTC once daily and RAL HD 1200 mg once daily, dosed as two 600 mg HD tablets. • Magnesium- or aluminum-containing antacids are contraindicated; co-administration of calcium-containing antacids is not recommended with RAL HD.	

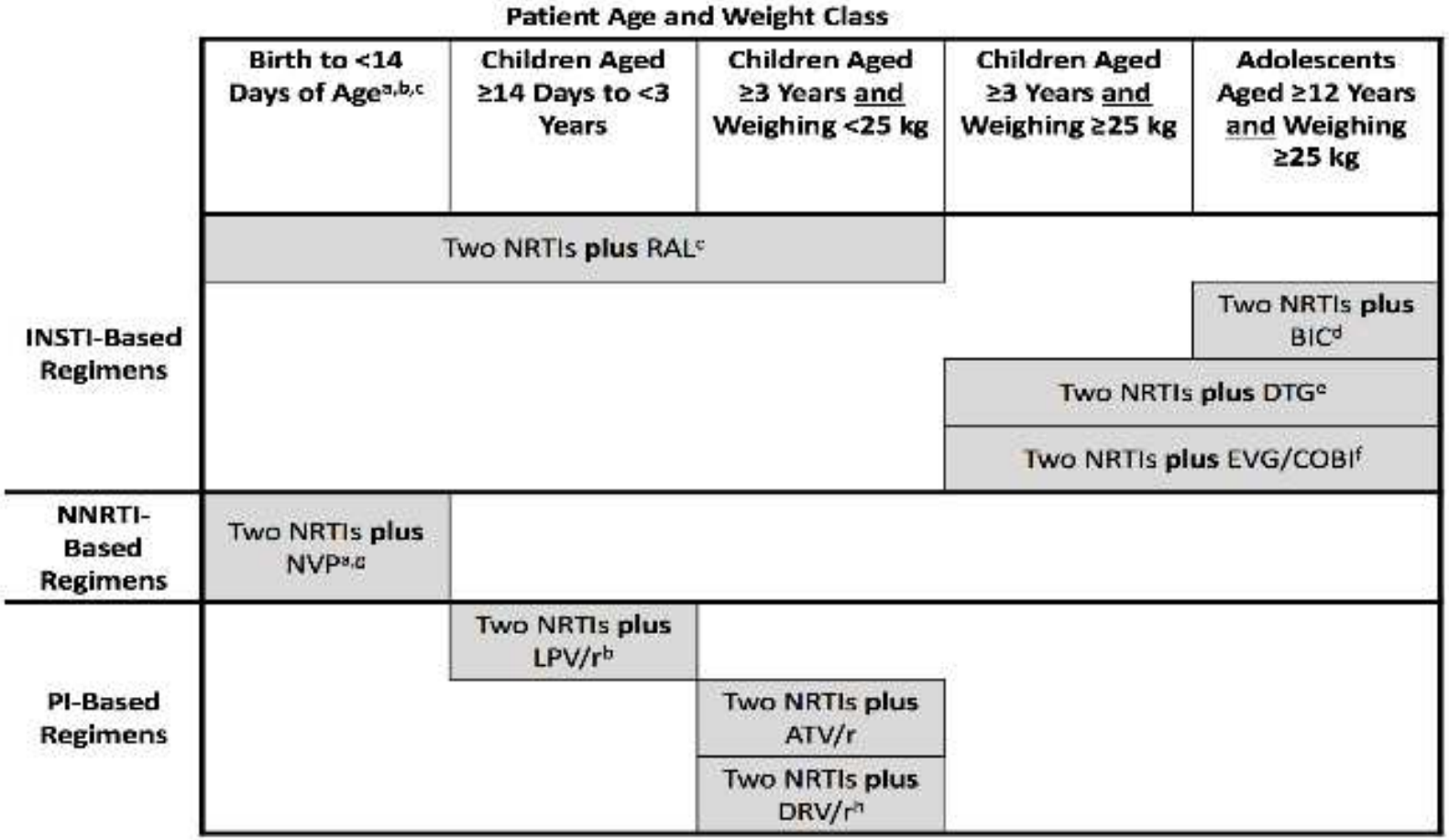
Nucleoside reverse transcriptase inhibitors

- Abacavir has the potential for serious hypersensitivity reactions (HSRs).
- Clinically suspected HSRs have been observed in 5%–8% of patients who start this drug.
- Risk highly associated with the presence of the HLA-B*5701 allele.

When to initiate ART therapy in children

- Antiretroviral therapy is initiated in infants <12 months of age regardless of clinical status, CD4 count, or viral load.
- The 1-year risk of AIDS or death is substantially higher in younger than older children at any given level of CD4 count, particularly for infants age <12 months.
- Always test for drug resistance.

Figure 1. Preferred Regimen by Age, Weight, and Drug Class



Nucleoside reverse transcription inhibitor

- Nucleoside reverse transcriptase inhibitors are not metabolized by the CYP450 mitochondrial system.
- Emtricitabine and lamivudine have few adverse effects, select for the M184V resistance mutation which confers high-level resistance, and improves susceptibility to tenofovir (also effective against Hepatitis B).
- These combinations are the backbone of therapy.
- Abacavir does not require adjustment for renal function.

Nucleoside reverse transcription inhibitor

- Triple NRTI regimens are biologically inferior.
- Dolutegravir is approved for use in children 12 years or older
- Zidovudine/lamivudine remains as the preferred option in pregnant women.
- This dual-nucleoside reverse transcriptase inhibitor regimen has the most safety and efficacy data for both mother and newborn.

Non-nucleoside reverse transcription based therapy

- Non-nucleoside reverse transcription inhibitors are metabolized by the CYP450 mitochondrial system.
- Non-nucleoside reverse transcription inhibitor based therapy is preferred in those in whom adherence to the other regimens is unlikely.
- Must use before drug resistance develops. HIV-2 infection is resistant to this therapy.
- Efavirenz/tenofovir/emtricitabine is the preferred initial choice.
- It is a fixed dose combination taken once daily.
- Neurotoxicity is a problem with efavirenz.

Non-nucleoside reverse transcription inhibitor

- Efavirenz is the non-nucleoside reverse transcriptase inhibitor employed except during first trimester of pregnancy or in women who are trying to conceive or who are sexually active with men and not using effective and consistent contraception.
- Its use is associated with a significant risk of neural tube defects in the fetus.
- Oral contraceptive use may interfere with antiretroviral drug functioning.
- IV zidovidine is administered to the mother at labor if RNA copies >400/ml.

Protease inhibitor based therapy

- Protease inhibitors are potent inhibitors of viral replication.
- Resistance slow to develop.
- Metabolized by CYP3A4 mitochrondrial system.
- Darunavir/ritonavir plus tenofovir /emtricitabine is the preferred regimen.
- Atazanovir may be substituted for darunavir in those patients with an allergy to sulfa drugs.
- Ritonavir has weak anti-HIV activity but is used to boost pharmacokinetic profile of protease inhibitor.
- Lipodystrophy associated with protease inhibitor use

Integrase strand transfer inhibitor based therapy

- Integrase inhibitor increases circulating 2-LTR circles of viral DNA even in those patients where virus is otherwise undetected.
- UGT1A1 metabolism generally.
- Elvitegravir metabolized by CYP3A4 mitochondrial system.
- Demonstrate the absence of HLA B*5701 if dolutegravir with abacavir/lamivudine is to be employed
- Abacavir use associated with hypersensitivity reaction.

Integrase strand transfer inhibitor based therapy

- Demonstrate the presence of normal renal function if elvitegravir/cobicistat/tenofovir/emtricitabine (fixed dose combination) is to be employed;
- Demonstrate the presence of a creatinine clearance >30ml/min
- If combination elvitegravir/cobicistat/tenofovir /emtricitabine

CCR5 antagonist

- Maraviroc selectively binds to human CCR5 receptor on the cell membrane, thus blocking the interaction of the HIV gp120 and the CCR5 receptor for CCR5-tropic HIV.
- However, it does not block viral entry of CXCR4 tropic HIV or HIV that uses both CCR5 and CXCR4 for cell entry.
- Viral tropism testing must be performed to confirm that the patient's virus only uses the CCR5 co-receptor.
- Co-receptor usage may change over time of HIV infection and must be monitored.
- CYP3A4 metabolism.

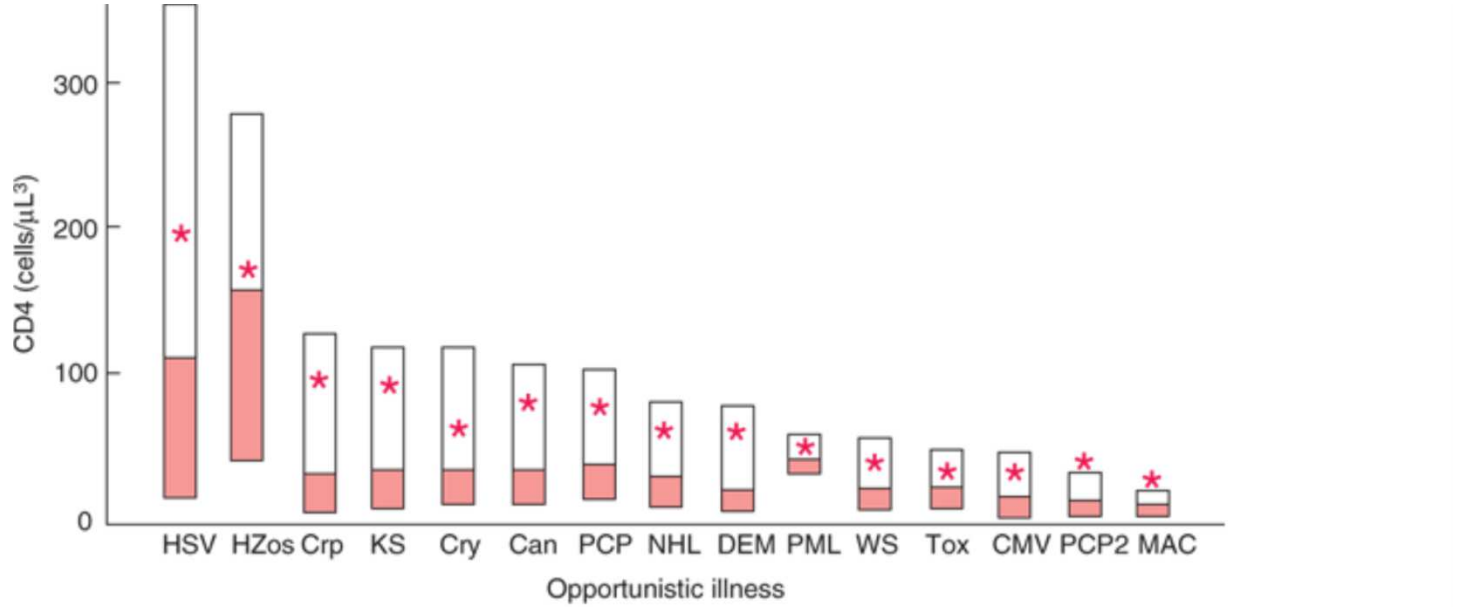
Fusion inhibitor

- The fusion inhibitor enfuvirtide interferes with this fusion process by binding to the first heptad-repeat (HR1) in the viral envelope glycoprotein gp41, thus preventing conformational changes necessary for the fusion of the viral and cellular membrane.
- Because of its unique mechanism of action, there is no cross resistance with other antiretroviral drugs.
- CYP3A4 metabolism.
- Injectable only.
- Used in cases of multiple drug resistance where oral administration of drugs is not possible.

Exposure prophylaxis

- Pre-exposure prophylaxis with tenofovir and emtricitabine.
- Post-exposure prophylaxis with a 28 day course of ART therapy.
- This is not 100% effective in blocking HIV infection.

CD4 counts and development of opportunistic infections



Boxplot of the median (line inside the box), first quartile (bottom of the box), third quartile (top of the box), and mean (asterisk) CD4+ lymphocyte count at the time of the development of opportunistic disease.

Can, candidal esophagitis; CMV, cytomegalovirus infection; Crp, cryptosporidiosis; Cry, cryptococcal meningitis; DEM, AIDS dementia complex; HSV, herpes simplex virus infection; HZos, herpes zoster; KS, Kaposi's sarcoma; MAC, Mycobacterium avium complex bacteremia; NHL, non-Hodgkin's lymphoma; PCP, primary Pneumocystis jiroveci pneumonia; PCP2, secondary P. jiroveci pneumonia; PML, progressive multifocal leukoencephalopathy; Tox, Toxoplasma gondii encephalitis; WS, wasting syndrome. (From RD Moore, RE Chaisson: Ann Intern Med 124:633, 1996.)

Opportunistic infections

- Isoniazid and vitamin B6 for 12 months if PPD>5mm.
- Treatment of drug-susceptible tuberculosis should include a standard regimen that consists of isoniazid AND rifabutin AND pyrazinamide AND ethambutol given for 2 months, followed by isoniazid AND rifabutin for 4 to 7 months
- Trimethoprim-sulfisoxazole or dapsone (PCP prophylaxis) if CD4<200 or thrush is present. Add pyrimethamine and folic acid if the CD4<100 and Toxoplasma serologic tests are positive.
- Clarithromycin or azithromycin if CD4<75 (Mycobacterium Avium Complex prophylaxis).

Prophylaxis of opportunistic infections

- Patients with CD4 counts below 200 cells/μL, a CD4 lymphocyte percentage below 14%, or weight loss or oral candidiasis should be offered primary prophylaxis for Pneumocystis pneumonia.
- Patients with a history of Pneumocystis pneumonia should receive secondary prophylaxis until they have had a durable virologic response to HAART for at least 3–6 months and maintain a CD4 count of > 250 cells/μL.

Prophylaxis of opportunistic infections

- Patients whose CD4 counts fall to below 75–100 cells/μL should be given prophylaxis against M avium complex infection.
- Prophylaxis against M avium complex infection may be discontinued in patients whose CD4 counts rise above 100 cells/μL in response to HAART and whose plasma viral load has been optimally suppressed to < 50–75 copies/mL.

Prophylaxis of opportunistic infections

- Isoniazid, 300 mg daily, plus pyridoxine, 50 mg orally daily, for 9-12 months should be given to all HIV-infected patients with positive PPD reactions (defined as > 5 mm of induration for HIV-infected patients).
- Toxoplasmosis prophylaxis is desirable in patients with a positive IgG toxoplasma serology and CD4 counts below 100 cells/μL.

Prophylaxis of opportunistic infections

- Oral ganciclovir (1000 mg orally three times daily with food) is approved for CMV prophylaxis among HIV-infected persons with advanced disease (eg, CD4 counts below 50 cells/μL).
- Causes neutropenia.
- Decreased incidence of cryptococcal disease with prophylaxis using fluconazole, 200 mg orally daily

Pediatric HIV therapy

- Transplacental spread, infection in the birth canal, infection through breast milk most common causes of transmission to child.
- Chorioamnionitis increases risk of transmission.
- Antiretroviral therapy is initiated in infants <12 months of age regardless of clinical status, CD4 count, or viral load.
- The 1-year risk of AIDS or death is substantially higher in younger than older children at any given level of CD4 count, particularly for infants age <12 months.
- Always test first for drug resistance.

HIV treatment results

- HAART treatment of HIV infection is very expensive. When does one initiate treatment?
- Early treatment of HIV infection with HAART is associated with increased life expectancy regardless of viral load if the patient is <30 years old and CD4 count is >200 cells/mm^3.
- Life expectancy ranges from 14.5 years if viral load >300,000 copies/ml
- (and rises) to 18.2 years if viral load <10,000 copies/ml and CD4 >500 cells/mm^3.

HIV treatment results

- Early treatment of HIV infection with HAART in patients OVER 40 YEARS OF AGE is associated with a life expectancy of 11.4 years if CD4 counts are >200cells/mm³ AND viral loads are >300,000 copies/ml, rising to 12.9 years if CD4 counts are >500cells/mm³ AND viral loads are <10,000 copies/ml.
- Little improvement in the life expectancy of 9.2 years of those patients OLDER THAN 50 YEARS is seen with early treatment with HAART.
- 70% of infants <12 months of age progress.

PRIMARY PROPHYLAXIS AGAINST OI'S IN HIV INFECTED PATIENTS

I. Strongly recommended as **Standard of Care**:

Pneumocystis jiroveci (carinii)	$CD_4 < 200$ **or oral pharyngeal candidiasis**	TMP-SMZ	1 DS po q.d or 1 DS po t.i.w
		Allergy to above	Dapsone 50 mg po QD
Mycobacterium tuberculosis	Reaction > 5mm	Isoniazid	300 mg po + pyridoxine 50 mg q.d X **9 mo**
Toxoplasma gondii	$CD_4 < 100$ **& IgG +**	TMP-SMZ	1 DS po q.d
		Allergy to above	Pyrimethamine 50 mg po Q Week Leucovorin 25 mg po Q Week
Mycobacterium avium complex	$CD_4 < 50$	Biaxin Zithromax	500 mg po b.i.d. 1200 mg po q.w.
Varicella zoster	Sig. Exposure	Vericella zoster immune globulin	

II. Generally recommended:

Streptococcus pneumoniae	**$CD_4 \geq 200$**	Pneumococcal Vaccine	
Hepatitis B	All Susceptible	Hepatitis B Vaccine; 3 doses	
Influenza	All	Inactivated vaccine / Oseltamivir,Rimantadine,amantadine	
Hepatitis A	**All Susceptible with Chronic Hep C**	**Hep A Vaccine**	**2 doses**

III. Not routinely indicated

Bacteria	Neutropenia	Granulocyte-colony-stimulating-factor
Cryptococcus neoformans	$CD_4 < 50$	Fluconazole
Histoplasma capsulatum	$CD_4 < 100$	Itraconazole
Cytomegalovirus	$CD_4 < 50$ CMV Ab +	Oral gancyclovir

Guidelines fot Preventing Opportunistic Infections Among HIV-Infected Persons --- 2002
Recommendations of the US Public Health Service and the Infectious Disease Society of America
MMWR, June 14, 2002

Related neoplasias

- Kaposi's sarcoma (with HHV 8).
- Infects endothelial cells and B-cell.
- Proliferation of small vascular channels that may arise from primitive mesenchyme.
- Factor VIII can be demonstrated in endothelial cells.
- Incidence diminished with HAART therapy.

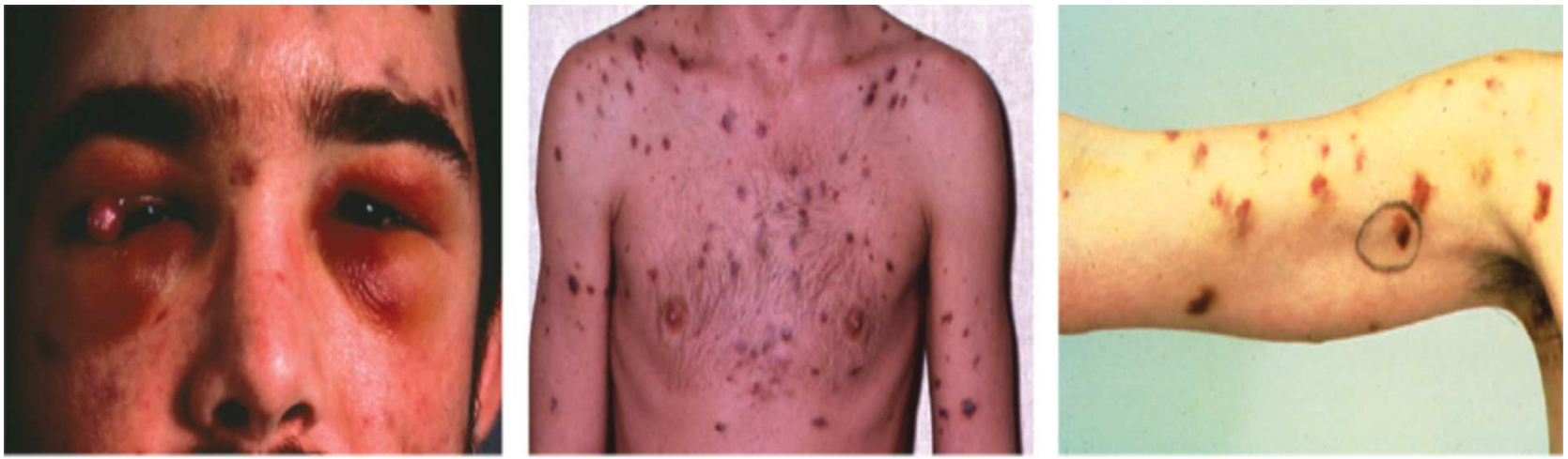
Related neoplasias

- B-cell lymphoma (with Epstein-Barr virus).
- Primary CNS lymphoma, lymphomas at extranodal sites.
- EBV LMP-1 behaves as constitutively activated CD40 receptor
- EBNA-2 behaves as constitutively activated Notch receptor
- Viral IL-10 blocks T-cell activation.

Related neoplasias

- Cervical and anal cancer (HPV 16 and 18).
- E6 protein degrades p53 and stimulates expression of telomerase.
- E7 protein binds to RB protein, promoting progression through the cell cycle.

Kaposi's sarcoma



Kaposi's sarcoma in three patients with AIDS demonstrating (A) periorbital edema and bruising; (B) classic truncal distribution of lesions; and (C) upper extremity lesions.

Accessed 02/03/2016

Slow virus infections

- Progressive multifocal leukoencephalopathy
- JC virus, a papoavirus distinct from human papilloma virus, infects and kills oligodendroglia and causes syncytia in astrocytes.
- Virus persists in kidney and is excreted in urine.
- Subacute sclerosing panencephalitis

  Incompletely replicating measles virus variant that persists in previously measles infected children.
- Rubella
- Human immunodeficiency virus

Prions

- Infectious particles comprised totally of protein.
- They are encoded by a cellular gene.
- If the protein produced is a β-pleated sheet rather than in an α-helix configuration, they aggregate into filaments that disrupt neuronal function and lead to neuronal death.
- Resistant to heat, ultraviolet light.
- Do not elicit inflammatory or antibody response as are normal human proteins.

Prions

- Progressive vacuolation in neurons and astrocytes.
- Spongiform appearance as neuronal loss in gray matter.
- Concomitant with appearance of many vacuoles.
- Deposition of amyloid plaques (distinct from those in Alzheimer's).
- Onset over age 50 years.
- Decades long incubation for CJD and kuru; once symptoms evident, death is rapid.

PrP^{C}

- Normal protein found on neuron surface.
- PrP^{Sc} neuronal protein differs at two codons.
- Has a different tertiary structure
- Aggregates
- Abnormally resistant to degradation.
- Conversion of normal protein occurs with introduction of PrP^{Sc}
- May contribute to vacuolar change

Crutzfeldt-Jakob disease

- 10% of CJD cases are familial.
- Aspartic acid to arginine at codon 178; valine at codon 129 in PRNP gene.
- Rare plaque formation.
- Dementia, hallucinations, myoclonus, cerebellar ataxia, muscle weakness, hyper-reflexia, blindness.
- New variant CJD has extensive plaque formation with high concentrations of PrP^{Sc} .
- Onset 19-24 years
- Death in months.

Crutzfeldt-Jakob disease

- In Creutzfeldt-Jakob disease, spongiform change is found in the cerebral cortex, caudate, putamen, thalamus, and molecular layer of the cerebellum.
- Astrocytic gliosis is present throughout the brain.
- In kuru, as well as variant Creutzfeldt-Jakob disease, florid plaques are found in the brain.
- These are vacuoles in a petal fashion about an PrP^{Sc} amyloid core.

Other human prion diseases

- Gerstmann-Straussler-Scheinker syndrome (GSS).
- Rare subset of inherited form of CJD.
- Earlier onset (35-55), slower progression (3-5 years).
- Fatal familial insomnia (FFI)
- Aspartic acid to arginine at codon 178; methionine at codon 129 of PRNP gene.
- Wide age range of onset (20-70 yrs old).
- Symptoms for 6-30 months.
- Distinct from CJD, there is an inability to sleep.
- Myoclonus, ataxia, dementia are seen.
- Spongiform degeneration may not always occur.

SPONGIFORM ENCEPHALOPATHIES

Disease	Pathogenesis	Important Features
Kuru	Infectious protein	Neural tissue (sheep, human)
Variant Cruetzfeld-Jakob disease	Infectious protein	Neural tissue (cow, human)
Cruetzfeld-Jakob disease	Sporadic	Most common form though germ cell mutation has also been found
Gerstmann-Sträussler- Scheinker syndrome	Hereditary	Germ cell mutation
Fatal familial insomnia	Hereditary	Germ cell mutation