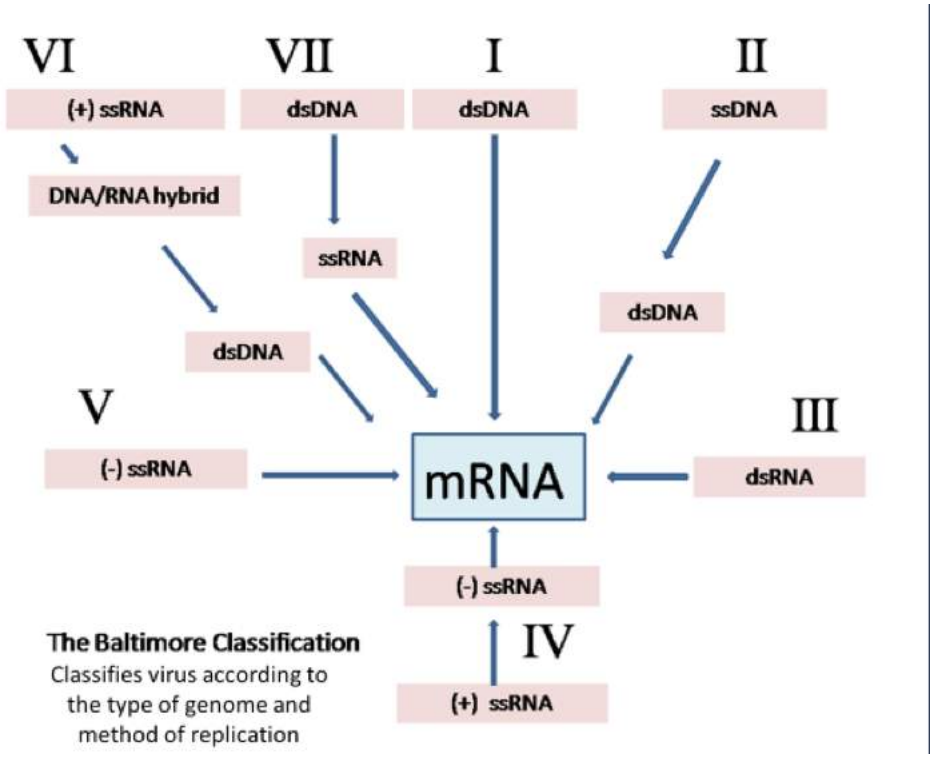
Overview

ML Medicine Learning



Viral Map

This organization is offered to link viruses to both their genomic categorization as well as the most closely associated clinical diseases.
Viruses with oncogenic potential are noted with °

RNA Viruses				
ssRNA				dsRNA
Respiratory	**GI-Liver**	**Systemic**	**CNS**	*Rotavirus*
Influenza A/B	*Poliovirus*	*Rubeola (Measles)*	*Rabies*	
Parainfluenza	*Norovirus*	*Rubella*	*Enteroviruses*	**Retrovirus**
RSV	*Yellow Fever*	*Mumps*	*CNS Arbo viruses: Zika, West Nile, St. Louis E, Japanese E, EEE, WEE, California*	*HIV*
Rhinovirus	*Hepatitis A, C, D, & E*	*Coxsackie*		*HTLV-1°*
Coronavirus (MERS, SARS)		*Dengue*		
Metapneumovirus		*Ebola*		
		Marburg		

DNA Viruses	
ssDNA	**dsDNA**
Parvovirus	*Herpes simplex 1-2*
	Herpes zoster
	HHV 6-8°
	EBV°
	CMV
	Adenovirus
	Hepatitis B°
	HPV°
	Molluscum
	JC virus
	BK virus
	Smallpox

DNA Viruses

ML Medicine Learning

dsDNA

Herpesviridae

dsDNA viruses that all cause persistent infections, mostly in a latent form. Their tissue tropism predicts clinical manifestations and latent forms.

Herpes Simplex 1 & 2

Cause cutaneous vesicular eruptions and are transmitted through contact with oral or genital secretions or direct contact with actively infected vesicle

HSV 1 is most often associated with oral-labial lesions and HSV 2 is associated with genital herpes.
After exposure, the virus replicates in epithelial cells then travels retrograde up axons where it becomes latent in the sensory ganglia (trigeminal or sacral). Reactivation can be stimulated by stress, trauma, fever, and sunlight. Viruses reactivate in the sensory ganglia and travel anterograde down the sensory nerve where cutaneous eruptions arise in the skin, characterized by non-scarring vesicles. Frequent and recurrent reactivations are commonplace. Asymptomatic viral shedding also occurs and is an important part of human-to-human transmission.

Ocular disease can occur during reactivation in the trigeminal ganglia, leading to keratitis with potential for corneal scarring and vision loss.

Exposure to genital secretions during birth can lead to HSV-2 transmission to the neonate leading to local ocular or cutaneous disease, CNS infection, and/or disseminated disease with multiorgan failure.
CNS disease can occur in primary or reactivation. HSV-1 causes encephalitis with temporal lobe involvement and high morbidity/mortality. HSV-2 causes a mild aseptic meningitis that can recur with recurrent outbreaks; severe disease is uncommon.

Diagnosis is often made presumptively based on appearance of typical lesions. Otherwise, identification of organism is usually accomplished by PCR of involved fluid. Tzank smears of the cells from the base of the vesicle is non-specific and not frequently used (but you may still see it in textbooks).
Treatment is acyclovir, valacyclovir. Neither have any effect on latent virus.

Varicella Zoster Virus (VZV)

Transmitted via respiratory droplets

Primary infection leads viremia and dissemination and manifests as a diffuse vesicular rash known as chicken pox. The virus then establishes latency in sensory ganglia (dorsal nerve roots, trigeminal ganglia, other cranial nerve roots). Reactivation occurs with advancing age and/or immunosuppression and causes a local vesicular eruption that occurs within the dermatome of involved ganglia, this is called shingles. Reactivation in cranial nerve ganglia can lead to other abnormalities including hearing deficits (Ramsay-hunt), facial nerve paralysis (Bell's palsy), and ocular involvement with V1 reactivation.

Reactivation of zoster is infrequent, in fact, having more than one episode of shingles is very uncommon.

Persons with advanced immunosuppression (e.g. stem cell transplant, AIDS) can develop disseminated disease with organ dysfunction during reactivation.
Treatment is with acyclovir or valacyclovir. Higher doses are required compared to HSV.

Vaccination against chickenpox is routine for children. Shingles vaccine is recommended for persons >50years, regardless of varicella vaccination.

Human Herpesviruses 6 &7

Transmitted via oral secretions and is acquired in the first 5 years of life for most humans

Latency is within lymphoid tissue and CD4 lymphocytes. HHV-6 is well documented cause of exanthem subitum. HHV-7 may cause asymptomatic or mild disease during infection.

Initial infection causes exanthem subitum (roseola) with 3-days of high fevers, followed by diffuse maculopapular rash that develops at the abrupt resolution of fevers. The high fever makes this a common cause of febrile seizures and is one of the six classic childhood exanthems.

Reactivation is of concern in patients with advanced immunosuppression where it has been associated with graft-vs-host disease and bone marrow suppression.

No treatment is currently available.

Humans Herpesvirus 8

Least prevalent herpes virus in the US but prevalence varies geographically. It is endemic in Central African and Mediterranean areas. It is transmitted via saliva but requires prolonged contact and is linked with intimate contact (such as kissing between sexual partners). HHV-8 latency is primarily within B-cells though a latent and lytic process occurs in other cells.

Primary infection is asymptomatic, but HHV-8 causes Kaposi sarcoma, a spindle cell tumor of endothelial origins. In the US, this is primarily seen in patients with advanced AIDS; the course is aggressive and life-threatening without immune restoration. Prior to AIDS epidemic, KS cases were predominantly seen in males of Mediterranean or central African origins. Other associated clinical diseases related to HHV-8 are primary effusion lymphoma and multicentric castleman's disease.

Treatment options are limited and immune restoration is key. Foscarnet and ganciclovir have anti-viral activity.

Cytomegalovirus

Named for the typical cytopathic effect produced in cell cultures, described as "owl's eyes"

Up to 70% of adults in the US are infected with CMV which usually occurs in the first 5 years of life. CMV can be found in many bodily fluids including saliva and genital secretions. Latent infection occurs in leukocytes and immature leukocytes.

Clinical findings of acute CMV infection can range from minimally symptomatic to mononucleosis-syndrome. Reactivation is subclinical in the immunocompetent. More severe disease is found in immunosuppressed conditions, such as pneumonia and hepatitis. In persons with AIDS, CMV reactivation in the eye causes a severe, rapidly progressive retinitis.

CMV can also be spread transplacentally from mother to fetus and is the most common cause of congenital abnormalities in the US. Disease in the fetus is worse if primary infection occurs during pregnancy (as opposed to asymptomatic reactivation) and infections early in pregnancy carry higher risk of abnormalities. A variety of congenital defects include hepatosplenomegaly, jaundice, cytopenias, low birth weight, microcephaly, and chorioretinitis, hearing loss may be a late manifestation.

Since asymptomatic lytic phase is common, identification of the organism by PCR in the serum is not always diagnostic and evidence of CMV-related cytopathic changes or PCR of affected tissue are needed.

Ganciclovir is used to treat serious CMV infections.

Epstein-Barr Virus

Transmitted via oral secretions and establishes latency in B-lymphocytes

Primary infection, “Infectious Mononucleosis” leads to a proliferation of non-specific B-cells and results in fever, pharyngitis, lymphadenopathy. Abundant atypical lymphocytes can be found in peripheral blood and a heterophile antibody (monospot test) is usually present – though both of these findings can be found in other conditions. EBV-specific antibodies develop in sequence after acute infection, the presence of Viral capsid antibodies is suggestive of acute infection.

In its latent form, EBV has oncogenic potential from somewhat unclear mechanisms, but may include immortalization of B-cell close. EBV is associated with African Burkitt’s lymphoma (due to c-myc translocation), Posttransplant lymphoproliferative disease, nasopharyngeal carcinoma, and primary CNS lymphoma in persons with AIDS. EBV also causes oral hairy leukoplakia (a benign condition) in persons with AIDS.

There is no specific antiviral therapy for EBV.

Poxviridae

Some of the largest viruses.

Molluscum contagiosum

Spread by direct contact with infected skin, and commonly seen in athletics, daycares, and sexual contact. Molluscum causes a benign cutaneous wart-like eruption with central umbilication. Disease does not disseminate, but persons with immune dysfunction are at risk of particularly severe and/or prolonged lesions.

Small pox

Also referred to as viariola, is transmitted by respiratory droplets or direct contact with active skin lesions
After inhalation, the virus disseminates to visceral organs and skin, and results in a robust immune response. The enormous inflammatory response is accountable for main characteristics of illness. Hallmark skin findings are vesiculo-pustular rash in which all lesions are in the same stage. Infections are associated with high mortality.
Vaccination (with Vaccinia, a related virus) has been very effective and smallpox is considered eradicated.

Polyomaviridae

JC Virus

Found worldwide and infection is commonplace. Primary infection is generally asymptomatic. JC Virus causes Progressive multifocal leukoencephalopathy (PML) immunosuppression, specifically AIDS and use of certain monoclonal antibody therapies (natalizumab most famously). PML is characterized by a progressive neurologic deterioration with dementia, hemiparesis, vision loss, and seizures. Death usually occurs within 3-6months of onset.

BK Virus

Closely related to JC virus and is also very common infection in humans with worldwide distribution. The virus is tropic to renal cells and is asymptomatic except in advanced immunosuppression where it can cause hemorrhagic cystitis, severe nephropathy, renal vasculopathy and is of particular concern among renal transplant where active viral replication can lead to graft loss. Cidofovir is a potential treatment for BK Virus.

Adenoviridae

Adenovirus

Naked capsid dsDNA virus that is frequently grouped in with respiratory viruses

There are over 68 different serotypes that infect humans and cause a variety of diseases beyond the respiratory tract. It can survive for prolonged periods on surfaces and can be spread among humans by respiratory droplets, fecal-oral, contract with fomites, and perinatally in the birth canal. In addition, asymptomatic and prolonged viral shedding make Adenovirus a very effective human pathogen and adenovirus outbreaks among young children and adults in close living quarters are well recognized.
Key clinical syndromes associated with adenovirus include: childhood febrile syndrome, pharyngitis often with conjunctivitis, pneumonia, keratoconjunctivitis, acute gastroenteritis, and hemorrhagic cystitis and interstitial nephritis (more commonly seen in immunosuppressed patients).
There is currently no antiviral therapy for adenovirus. Vaccine for serotypes 4 &7 are offered to military recruits to prevent respiratory infections.

Papillomaviridae

Human Papilloma Virus

Naked capsid dsDNA virus with at least 60 types that infect humans, most have tropism for epithelial cells where they cause papillomas (warty lesions)

Transmission is from direct skin contact, fomites, and/or genital secretions. Genes expressed early in viral replication E6 and E7 encode proteins that inhibit activity of tumor suppressive gene proteins, making HPV and oncovirus. Cancers caused by HPV include cervical cancer, anal cancer, vaginal cancer, and squamous cell cancer of oropharynx. There is significant genetic diversity with differing affinity for tumor suppressor gene products. Genotypes 16 and 18 are considered highest risk for the development of malignant transformation. While genotype 6 and 11 are the most common of 40 types of benign genital warts. Other genotypes are linked with warts on the hands, plantar warts, and flat warts.

Diagnosis of cervical HPV relies on appearance of cytopathic changes as detected on the Papanicolaou smear (pap smear). Viral antigen detection or PCR is also commonly used to detect the presence of high-risk HPV subtypes, even before onset of cervical epithelial changes.
There is no specific antiviral therapy for HPV. Treatment of lesions is either cytotoxic or surgical.

Hepadnaviridae

Hepatitis B Virus

An enveloped virus with incomplete circular dsDNA

It is transmitted through blood and bodily fluids (sexual contact, shared needles, blood derived products, and mother-to-child). It can cause chronic infection in the liver where the vast majority of disease is caused by immune response to the pathogen. There are three important antigens the surface antigen (which is used to measure chronic disease), the core antigen (which is not measurable in serum, but anti-core antibodies denote HBV exposure), and the e antigen (used diagnostically as a measure of infectivity).

Natural history of disease is dependent on the age of infection. Worldwide, infections occur most commonly in children <5years old; most are asymptomatic during acute infection and up to 90% will develop chronic infection. By contrast, in the US infection more often occurs in adults where acute infection can lead to hepatitis and jaundice, and chronicity occurs in <20%.
Chronic infection leads to cirrhosis and hepatocellular. The latter may be related to integration of HBV viral DNA into hepatocyte.

Antiviral therapy (nucleotide reverse transcriptase inhibitors) are used to treat chronic infection. Virologic suppression can be achieved but curative treatment is rare.
Immunization for HBV is highly effective. Hyperimmune serum globulins can be used as passive immunity for infants and others without immunity after exposure.

ssDNA

Parvovirus

Small naked ssDNA virus. It is transmitted by respiratory droplets and can be transmitted transplacentally. Virus preferentially infects erythroblasts. In immunocompetent, primary infection causes a self-limited viral syndrome (Fifth disease) that is described as causing 'slapped cheeks' and a fleeting reticular rash. In young adults, the infection can cause associated immune complex conditions with arthritis and rash. In persons with hemoglobinopathies or immunodeficiency, severe anemia, including aplastic anemia.

Congenital infection causes hydrops fetalis – severe anemia, heart failure, and edema.

RNA Viruses

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dsRNA

Rotavirus

Segmented dsRNA virus

The segmented RNS allows for genetic reassortment and is utilized in vaccine formation. It is transmitted by fecal-oral route where its double-layered capsid resists digestion by stomach acid. Primary site of infection is duodenum and proximal jejunum where villi are destroyed, leading to decreased absorptive surface.

It is one of the most important causes of diarrheal illness in children and can cause severe disease and death due to dehydration in infants. Interestingly, newborns (0-2months) are relatively resistant to disease caused by rotavirus infection. Diagnosis is made by viral PCR of the stool during acute infection.

Treatment is supportive. A live vaccine is given to infants with 85-98% efficacy in preventing disease.

Retroviruses

RNA viruses that use viral encoded reverse transcriptase, a polymerase that converts RNA to proviral DNA

Retroviruses also uniquely carry integrase enzymes that allow insertion of proviral DNA into the host cell genome. Host cell machinery is used for transcription and translation. While there are numerous orders and families of retroviruses that have co-evolved with living organisms for millions of years, the most important retrovirus in human disease is HIV infection and HTLV infection is also worth note. The steps in viral replication are important targets for treatment of HIV virus.

Human T-lymphocytic Virus

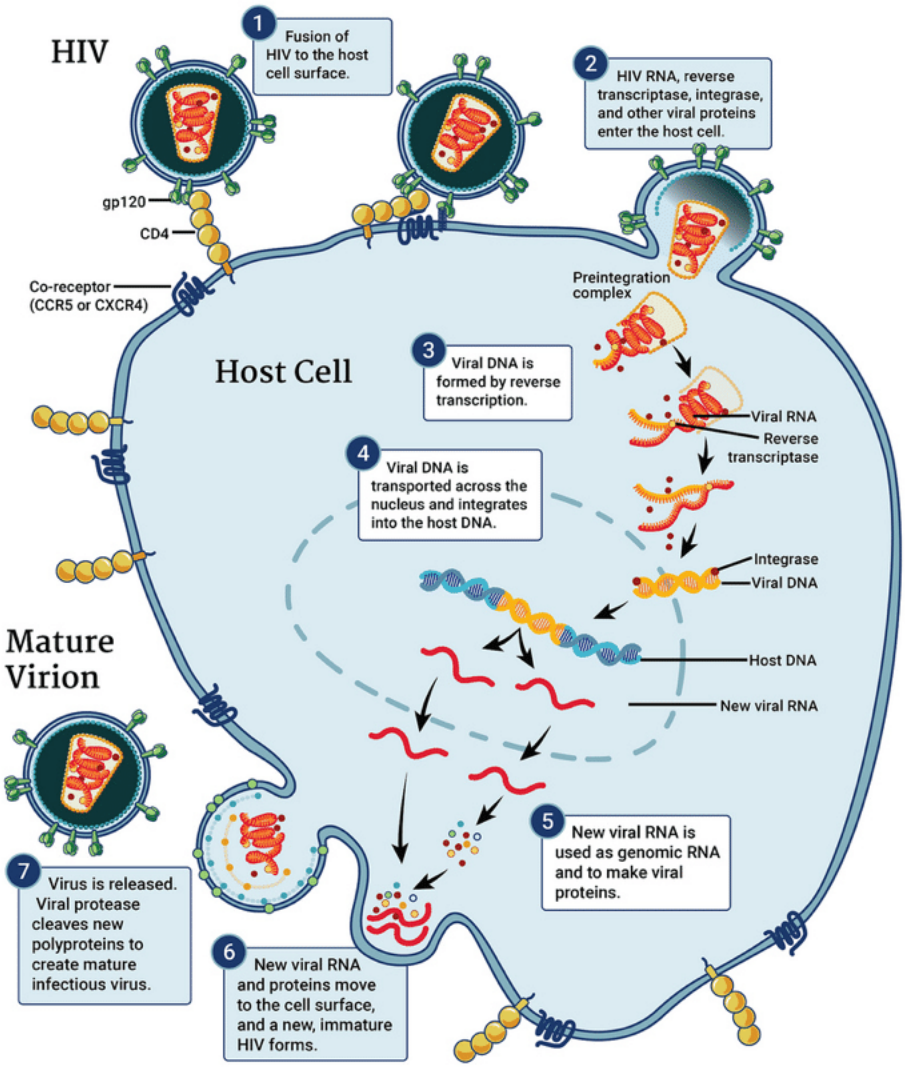
Oncoretrovirus

While it appears the virus has a worldwide distribution, clinical disease is rare and more commonly found in Japan, Africa, and Caribbean. HLTV-1 causes a rare adult T-cell leukemia and lymphoma which is associated with cutaneous disease (Sezary syndrome). Infection is also associated with neurologic disease known as Tropical spastic paresis.

Human Immunodeficiency Virus (HIV)

Enveloped virus with diploid ssRNA genome

The virus requires 2 receptors to enter a cell: the CD4 protein and a co-receptor (CCR5 or CXCR4 depending on the tropism of the virus). While CD4 lymphocytes are the most abundant viral target, and their depletion is the primary mode of disease, a plethora of other cells have available receptors, including astrocytes, macrophages, cells in the reproductive tract and colon. HIV is transmitted through blood and body fluids (sex, blood products, shared needles, transplacentally, peri-natal, breast milk).



This infographic illustrates the HIV replication cycle, which begins when HIV fuses with the surface of the host cell. A capsid containing the virus's genome and proteins then enters the cell. The shell of the capsid disintegrates and the HIV protein called reverse transcriptase transcribes the viral RNA into DNA. The viral DNA is transported across the nucleus, where the HIV protein integrase integrates the HIV DNA into the host's DNA. The host's normal transcription machinery transcribes HIV DNA into multiple copies of new HIV RNA. Some of this RNA becomes the genome of a new virus, while the cell uses other copies of the RNA to make new HIV proteins. The new viral RNA and HIV proteins move to the surface of the cell, where a new, immature HIV forms. Finally, the virus is released from the cell, and the HIV protein called protease cleaves newly synthesized polyproteins to create a mature infectious virus.
Credit NIAID

After initial infection, the virus establishes widespread infection throughout hematopoietic system. Acute retroviral infection may be asymptomatic, but may also cause symptoms of acute viral syndrome with fevers, pharyngitis, lymphadenopathy, and a rash. It then remains clinically quiescent for several years. If untreated, CD4 depletion occurs leading to defects in cell-mediated immunity as well as dysfunction of adaptive immunity. Opportunistic infections are myriad and are the primary cause of death.

Current diagnosis of HIV infection uses serologic testing for antibodies to HIV as well as the presence of p24 antigen. Confirmation is with PCR to detect viral RNA in the blood. In established infections, the viral load is used to monitor therapy. The goal of therapy is a sustained undetectable viral load.

Treatment of HIV infection requires multiple anti-retroviral (ARV) agents with different mechanisms of activity to avoid rapid adaptation of the virus through mutations. There are six main classes of ARVs: nucleot/side reverse transcriptase inhibitors (NRTIs), Non-nucleotide reverse transcriptase inhibitors (NNRTIs), Integrase strand transfer inhibitors (INSTIs), protease inhibitors (PIs), Co-receptor CCR5 inhibitor, and fusion inhibitors. Most common regimens involve a backbone of 2 NRTIs, plus one agent from INSTI, PI, or NNRTI. CCR5 inhibitors and fusion inhibitors are used as salvage therapy.

Antiretroviral agents by class		
NRTIs	**NNRTIs**	**Protease Inhibitors**
Tenofovir (TDF)	Efavirenz (EFV)	Atazanavir/Ritonavir (ATV/r)
Emtricitabine (FTC)	Nevirapine (NVP)	Darunavir/Ritonavir (DRV/r)
Lamivudine (3TC)	Delavirdine (DLV)	Lopinavir/Ritonavir (LPV/r)
Zidovudine (AZT)	Etravirine (ETR)	Fosamprenavir/Ritonavir (FPV/r)
Abacavir (ABC)	Rilpivirine (RPV)	Saquinavir/Ritonavir
Didanosine (ddI)	Doravirine (DOR)	Nelfinavir/Ritonavir (NFV/r)
Stavudine (d4T)		
Integrase Inhibitors	**Fusion Inhibitor**	**CCR5 Inhibitor**
Raltegravir (RAL)	Enfuvirtide (t-20)	Maraviroc (MVC)
Elvitegravir (EVT)	Ibalizumab (monoclonal Ab)	
Dolutegravir (DTG)		
Caboegravir (CAB)		Pharmacologic booster (non-antiretroviral)
Bicetegravir (BIC)		Cobicistat
Chart updated 11/2019		

Patients with HIV and AIDS can develop disease in nearly every organ system and the differential diagnosis for any chief complaint in persons with immunodeficiency is much more broad compared to those with intact immunity. In the case of HIV infection, in addition to common and unusual opportunistic infection, clinical disease can arise from direct effect of the virus itself and importantly, side effects and complications of disease treatment must also be considered. It is helpful to think about the types of infections and conditions that present primarily in certain systems.

Opportunistic Infections/HIV manifestations by System: Pulmonary

Opportunistic Infections
TB
Pneumocystis jirovecii
Recurrent bacterial pneumonias – typical and atypical
Non-TB mycobacterium (rapid growers)
Endemic Fungi
Cryptococcus
Nocardia
Aspergillus
CMV

HIV-Related Disorders
Pulmonary Hypertension
Lymphocytic Interstitial Pneumonia (peds)

Neoplasms
Kaposi Sarcoma (HHV8)
Primary effusion lymphoma (HHV8)
Lung Cancer

Medications

Opportunistic Infections/HIV-manifestations by System: Ophthalmic

Opportunistic Infections
CMV
Toxoplasmosis
VZV ophthalmicus and retinopathy
HSV keratitis and Acute outer retinal necrosis
Syphilis uveitis
TB uveitis
Candida endophthalmitis and keratitis
Cryptococcus chorioretinitis
Pneumocystis choroiditis (rare)

HIV-Related
HIV retinitis

Neoplasms
Kaposi Sarcoma (HHV8)*

Medications

Opportunistic Infections/HIV manifestations by System: Neurologic

Opportunistic Infections
TB - meningitis
Toxoplasmosis
Cryptococcus – meningitis (cryptococcoma, rare)
HSV/VZV
CMV
JC Virus - Progressive Multifocal Leukoencephalopathy
Bacterial Meningitis
Neurosyphilis
Nocardia
Coccidioidomycosis

HIV-Related Disorders
HIV-associated Neurocognitive Disorder (HAND) - Dementia
Polyneuropathy
Mononeuritis Multiplex
Aseptic Meningitis

Neoplasms
Primary CNS Lymphoma (EBV)

Medications
NRTIs -Peripheral neuropathies
EFV – psychiatric symptoms

Opportunistic Infections/Manifestations of HIV by System: Heme-Onc

Opportunistic Infections
Bone Marrow Infections
• ***Mycobacterium avium complex***
• Parvovirus B19
• ***Endemic Fungi (Histoplasmosis, Coccidioidomycosis, Blastomycosis)***
• Cryptococcus
• ***Tuberculosis***
Anemia of Chronic Disease (any systemic infection)

Medications
AZT - anemia

HIV-Related Disorders
Persistent Generalized Lymphadenopathy
Immune Thrombocytopenic Purpura (ITP)
Thrombotic Thrombocytopenic Purpura (TTP)

Neoplasms
Kaposi Sarcoma (HHV8)*
Non-Hodgkin Lymphoma (EBV)*
Invasive Cervical Cancer*
Hodgkin Lymphoma (11x increased risk)
Hepatocellular Carcinoma (HBV, HCV) (5x increased risk)
Anorectal Squamous Cell Ca (HPV 16, 18) (29x increased risk)

* AIDS-defining malignancy

Opportunistic Infections/HIV manifestations by System: GI

Opportunistic Infections
TB
Candida (thrush)
Oral hairy leukoplakia (EBV-related)
HSV stomatitis
CMV
Enteric bacterial infection: Shigella, Salmonella, Campylobacter
Mycobacterium avium complex
Histoplasmosis
Cryptosporidium, Cyclospora, Microsporidium
Anorectal wars

Medications
MOST OF THEM! Protease inhibitors most commonly implicated

Opportunistic Infections - hepatobiliary
Chronic hepatitis (HBV, HCV)
Infectious Cholangiopathy: MAC, Cryptosporidium

HIV-Related Disorders
Chronic Diarrhea/AIDS Enteropathy
HIV Cholangiopathy

Neoplasms
Kaposi Sarcoma (HHV8)
Non-Hodgkin Lymphoma (EBV)
Hepatocellular Carcinoma (HBV, HCV)
Anorectal Squamous Cell Ca (HPV 16, 18)

Opportunistic Infections/HIV-manifestations by System: Dermatologic

Opportunistic Infections
Bacillary angiomatosis (KS mimic) - Bartonella
Staph aureus SSTIs
HSV
VZV
Secondary Syphilis
Crusted scabies
Molluscum contagiosum
Warts
Adverse drug reactions

Medications
Drug Rash: NNRTIs, Darunavir (sulfa-moiety)

HIV-Related
Pruritic popular eruption (tropics)
Seborrheic dermatitis
Xerosis (dry skin)
Psoriasis
Eosinophilic folliculitis

Neoplasms
Kaposi Sarcoma (HHV8)
Basal cell carcinomas
Squamous cell carcinoma

Opportunistic Infections/HIV manifestations by System: Renal

Opportunistic Infections
Acute renal failure
• Systemic infections, Sepsis
• Medication to treat infections

HIV-Related Disorders
HIV-Associated Nephropathy (HIVAN)
• ***Collapsing focal segmental glomerular sclerosis***

Medications
Tenofovir – renal proximal tubular acidosis (Fanconi syndrome)
TMP-SMX – nephrotoxic in high doses

Opportunistic Infections/HIV manifestations by System: Cardiac

Opportunistic Infections
Pericarditis: TB, Viral, Bacterial, Primary Effusion Lymphoma (HHV8)
Endocarditis

HIV-Related Disorders
Dilated Cardiomyopathy
Early Coronary Artery Disease

Neoplasms
Kaposi Sarcoma (HHV8)

Medications
?Cardiovascular disease with NRTI exposure

Opportunistic Infections/HIV manifestations by System: Endocrine/Metabolic

Opportunistic Infections
Adrenal Failure
• TB (most common) • CMV, Cryptococcus

HIV-Related Disorders
Hypogonadism
• Low testosterone

Medications
Lactic acidosis - NRTIs
Dyslipidemia – Protease inhibitors

Opportunistic Infections/HIV manifestations by System: Rheumatologic & Musculoskeletal

Opportunistic Infections
Pyomyositis – *S. aureus*
TB – osteomyelitis, arthritis

HIV-Related
Sjogren's-like syndrome (Diffuse infiltrative lymphocytosis, DILS)
Polymyositis
Osteonecrosis/Avascular necrosis of hip

Medications
AZT - myopathy
Tenofovir (TDF) – decreased bone density

ssRNA

Respiratory

Influenza

Enveloped segmented ssRNA virus
There are three types, A, B, and C. Segmented genome allows for reassortment between viruses that infect different mammals this is called antigenic shift and accounts for major epidemics- Influenza A is the only type capable of this as others are restricted to humans only. Mutations in RNA segments leads to antigenic drift and accounts for the seasonal variations. Two important antigens are Hemagglutinin (HA) and Neuraminidase (NM) that facilitate viral attachment to respiratory epithelium and release of new particles respectively.

Transmission of influenza is by respiratory droplets. Clinical disease is characterized by abrupt onset of fevers, chills, myalgias and cough. Severe disease can in the very young, elderly, immunocompromised, co-morbid cardiac or pulmonary disease, and pregnant females. Severe disease includes viral pneumonia, respiratory distress, and multi-organ failure – most of which is mediated by a dysregulated immunopathologic response.

Diagnosis in symptomatic persons is PCR from nasopharyngeal swab.
Primary treatment is neuraminidase inhibitors, though their efficacy in treating severe disease is relatively limited.
Several vaccination options are available and are adjusted seasonally to reflect circulating strains while aiming to maintain immunogenicity.

Parainfluenza

Enveloped ssRNA virus in the same family as influenza. Unlike influenza, the antigenicity of hemagglutinin and neuraminidase is stable.

There are four sub-types. Transmission is via respiratory droplets and is a common infection in children.
Clinical infection causes fever and cough. In young children, parainfluenza is the most common cause of croup, which is characterized by a barking cough that is frequently worse at night. In infants, parainfluenza can cause bronchiolitis and respiratory distress similar to RSV. In adults, infection is generally limited to symptoms of the common cold.
Treatment is supportive.

Respiratory Syncytial Virus (RSV)

Enveloped ssRNA virus that is transmitted via respiratory droplets

Unlike other paramyxoviridae, RSV does not have hemagglutinin. Instead a fusion protein facilitates attachment and accounts for the cytopathologic features of fused cells that form multinucleated giant cells. There are two serotypes.
It is the most important cause of bronchiolitis and pneumonia in the first year of life. Sloughing of respiratory epithelial cells in the tiny airways of the infant lung leads to air-trapping, wheezing, and respiratory distress. In older children, RSV is a common cause of otitis media. Diagnosis is made by PCR of respiratory secretions. Therapy is mostly supportive, and aerosolized ribavirin is used for severely ill.

Rhinovirus

Naked ssRNA virus that is transmitted by aerosolized droplets and hand-to-nose contact
Infection is limited to the respiratory epithelium. And since virus replicates best at cooler temperatures, lower respiratory infections do not occur. There are over 100 serotypes.
Clinical disease is the common cold: rhinorrhea, congestion, pharyngitis.

Coronavirus

Enveloped ssRNA virus with 2 serotypes. Transmission is via respiratory droplets and immunity is not sustained, so reinfection can occur.

Most common clinical disease is simple common cold. Novel mutants have been associated with outbreaks and severe disease (e.g. SARS and MERS). These are frequently zoonotic in origin, viral mutation allows the 'jump' to humans and limited immunity facilitates outbreaks.

Human Metapneumovirus

Enveloped ssRNA virus that is transmitted via respiratory droplets
Similar to RSV, a fusion protein on the envelope facilitates attachment and creates fused multinucleated giant cells.

Most common clinical disease is the common cold. In infants, bronchiolitis similar to RSV is possible, and viral pneumonia in immunocompromised patients is a risk.

Diagnosis is by PCR of respiratory secretions. Treatment is supportive.

GI/Liver

Rotavirus

See dsRNA viruses above.

Norovirus

Nonenveloped ssRNA virus and part of calcivirus family
In contrast to the respiratory viruses of similar structure, norovirus is resistant to destruction by stomach acid. Transmission is fecal-oral route. There are many serotypes and immunity is brief.
Norovirus is the most common viral cause of acute diarrheal gastroenteritis. The virus is highly infectious and outbreaks are common, especially among families or closed settings (cruise ships, hospitals, schools, etc).
Treatment is supportive. There is no vaccine available.

Hepatitis A

Naked ssRNA virus with single serotype
Transmission is fecal-oral. The virus replicates in GI tract then spreads to liver during brief viremic phase. Replication within hepatocytes incites immune response which leads to fevers, immune mediated cellular injury, and jaundice. Infection is generally self-limited and viral clearance occurs with subsequent immunity (no chronicity). Diagnosis is made based on serology.
Treatment is supportive. Vaccination is recommended for those at risk. Hepatitis A immune globulin is available and may mitigate disease when given after exposure in a non-immune person.

Hepatitis C Virus (HCV)

Enveloped virus with single piece of ssRNA that is part of flavivirus family

There are multiple serotypes. It is transmitted primarily through blood; sexual and perinatal infection is also possible, though less common route. It is the most prevalent blood-borne pathogen in the US.

The natural history is dependent on age of infection and is the opposite of that seen for hepatitis B. Acute infection in children is more often symptomatic and progression to chronic infection is the exception. In contrast, adult infections (most common in US) are usually asymptomatic and progression to chronic infection occurs in 80-90%. Chronic hepatitis C leads to progressive hepatocellular injury and cirrhosis. The chronic inflammatory state in cirrhosis is linked to increased risks of hepatocellular carcinoma (in contrast to hepatitis B which is has direct oncogenic transformation potential).

Diagnosis begins with screening IgG antibody and confirmatory RNA PCR for those with positive results.

There is no vaccine for HCV. Treatment of hepatitis C has greatly simplified in the last 10 years. Interferon is rarely, if ever, used anymore, though may have a role for patients with confirmed acute HCV. Direct acting antivirals that inhibit viral enzymes, NS5A, NS5B (polymerase), and viral protease. Combination therapy is highly successful at achieving cure.

Hepatitis D Virus (HDV)

Defective virus with one piece of ssRNA
It is transmitted through blood and body fluids. HDV requires Hepatitis B protein coat. It can only replicated in cells that are infected with Hepatitis B and chronic carrier state can occur.
HDV is an important risk in persons with chronic HBV infection where it can cause flare or decompensation of liver disease during acute infection with HDV. There is no specific treatment for HDV, but immunization and prevention of HBV infection reduces HDV infection as well.

Hepatitis E Virus (HEV)

RNA virus that is similar to HAV in many ways: transmission is fecal-oral, and infection is limited/no chronic carrier state exists. HEV is more common in low-middle income countries where outbreaks can occur. Acute infection is usually mild and symptoms are due to immune response during viral clearance.

Yellow Fever

Also an arbovirus, is enveloped with ssRNA that is part of flavivirus family
It is geographically distributed in tropical areas through Caribbean, central America, and central zone of Africa. It is spread by Aedes aegypti mosquito and is a threat to SW US where that mosquito is endemic. Clinical infection is often asymptomatic but can cause abrupt onset fevers, chills, myalgias and hepatocellular injury leading to jaundice. Multiorgan failure and bleeding diasthesis can occur in severe disease and associated with up to 50% mortality. There is generally no long-term sequelae for those that recover. Treatment is supportive. A live virus vaccine is available and recommended for travelers to endemic areas.

Rashes/Systemic

Measles (Rubeola)

Enveloped ssRNA virus with single serotype
It is spread via respiratory droplets where it initially infects respiratory epithelium then spreads to local lymph nodes and then disseminates in the blood. Measles is one of the most contagious viruses among humans and was a common childhood infection prior to vaccination campaigns,

Initial symptoms of measles are cough, coryza, and conjunctivitis with fever. Koplik spots can be seen on buccal mucosa in first day or two of illness. As the fever resolved, a diffuse maculopapular rash erupts that spreads from head and neck downward. Severe complications can develop during initial infection and include pneumonia, encephalitis, meningitis, sinusitis, and bleeding disorders. Infants, immunosuppressed and malnourished persons are at greatest risk of severe infection. Infection with measles specifically downregulates IL-12 and cell-mediated immunity, and secondary opportunistic infections with bacteria, fungi, or mycobacteria contributes to the high morbidity/mortality of measles worldwide. Late immunologic sequelae such as blindness or subacute sclerosing panencephalitis are rare but untreatable, irreversible, and devastating.

Diagnosis of measles requires high index of suspicion, PCR of pharyngeal swab is preferred during acute symptoms. There is no specific treatment for measles. Vaccination with live attenuated vaccine is highly effective at preventing infection.

Rubella

Enveloped ssRNA virus with single serotype and member of the Togavirus family
It is transmitted via respiratory droplets and transplacentally from mother to fetus. Similar to measles, after respiratory transmission, the virus replicates in nasopharynx, spreads to local lymph nodes, then disseminates through bloodstream. Symptoms are generally mild with fever, rash, and arthralgia (over arthritis can be seen). Severe sequelae are uncommon. The serious risk with Rubella is congenital syndromes. When transmitted to a fetus early in pregnancy, it can cause severe malformations: cardiac, ocular defects, deafness, microcephaly, hepatosplenomegaly, and thrombocytopenia. There is no specific treatment. Live attenuated vaccine is highly effective.

Coxsackie

Member of the Enteroviruses and is naked ssRNA virus

There are multiple serotypes. It is transmitted via fecal-oral route where it replicates within GI tract, crossing into bloodstream where it disseminates. Acute febrile syndrome can occur. Coxsackie viruses can cause several different clinical syndromes and most closely associated with: Herpangina, Hand Foot and Mouth disease, myocarditis, pericarditis, and aseptic meningitis.

Treatment is supportive. There is no vaccine.

Dengue Virus

Flavivirus with 4 serotypes (DEN 1-4) with widespread geographic distribution in tropical climates across the world. It is transmitted through Aedes aegypti mosquito. Symptoms of Dengue fever are characterized by high fever, severe headache, retroorbital pain, myalgias, and bone pain. Progressive disease can occur leading to capillary leak syndrome and shock with bleeding diathesis, Dengue hemorrhagic fever. Children are at higher risk of severe disease. Immunity is life-long, but serotype specific. Subsequent infection with different serotype is risk for severe disease, due to antibody-dependent enhancement.

Treatment is supportive. Dengue vaccine is actively sought among researchers.

Ebola and Marburg Viruses

Enveloped ssRNA filamentous and pleomorphic filoviruses. Both cause highly fatal hemorrhagic fevers with rapid viral replication in vascular endothelial cells and profound suppression of normal immune responses. They are zoonotic with animal reservoir in mammals such as monkeys and bats. Geographically, they have been found mostly in the African continent.

Major outbreaks of Ebola have occurred in Africa with mortality rates of nearly 50%. Transmission mechanisms from animals are incompletely understood. Transmission between humans is through blood and bodily fluids.
Treatment is supportive. The 2015 outbreak in West Africa stimulated aggressive and fast-tracked research for Ebola vaccine and treatments.

CNS

Rabies Virus

Bullet-shaped enveloped ssRNA virus

Zoonotic transmission to humans occurs from the bite of an infected animal (urban cycle = unimmunized dogs/cats; sylvatic cycle = bats, skunks, raccoons). The viral receptor is Acetylcholine receptor. After transmission, the virus replicates locally in muscle tissue, then enters the peripheral nerves then transported retrograde up axon to the CNS where viral replication rapidly occurs in the grey-matter where it causes encephalitis. Anterograde transportation takes virus to salivary glands, adrenals, kidneys, and other organs.

Clinically, rabies has a prolonged incubation period (up to 90 days), followed by a prodromal stage with nonspecific flu-like symptoms. The acute neurologic stage presents with acute encephalitis, often with agitated state including hallucinations, hyperactivity, aggression, and hydrophobia that results from difficulty swallowing and diaphragmatic spasm after drinking water – leading to the classic description of "foaming at the mouth." Symptoms progress to coma and death in over 90%. There is no specific antiviral treatment. Rabies vaccination and immunoglobulin is given after a suspicious bite in effort to prevent viral infection of the CNS. There have been no deaths in the US when post-exposure prophylaxis was given promptly after exposure.

Enteroviruses

Picornaviruses, naked capsid with ssRNA
The group includes coxsackie viruses and polioviruses. Unlike rhinoviruses that are also picornaviruses, enteroviruses are resistant to the acidic pH of the stomach and transmission in humans is fecal-oral. Disease outbreaks are more common where hygiene may be sub-optimal or more frequent chances for exposure: among young children, daycares or long-term care facilities, crowded households, or other group-living. There is seasonal variation with dominant epidemic strains that come and go and are responsible for particular outbreaks. After replication in respiratory or GI mucosa, viruses are capable of widespread dissemination. Clinical disease depends on viral tropism, but may include disease in the CNS, heart, synovial tissues, skin, mucous membranes.

Enteroviruses are the most common cause of viral (aseptic) meningitis that tends to occur in summer or fall. Symptoms include abrupt onset of headache, fever, photophobia, and meningismus. Clinical disease is generally mild compared to other forms of meningitis, and longterm sequelae is very uncommon.

CNS Abroviruses

Transmitted to humans through arthropods and have tropism for the CNS and come from a variety of viral families. All CNS arboviruses maintain a sylvatic life cycle that includes non-human vertebrates which may serve as reservoirs or blind end hosts. Humans are incidental hosts. Notable CNS Arboviruses include: St. Louis encephalitis, Eastern and Western equine encephalitis, California encephalitis, Japanese encephalitis, and LaCrosse Virus. They are all spread via mosquitos (differing species) and geographically distributed according to their names. All cause a febrile syndrome with variable degrees of encephalitis.

- *West Nile Virus* is notable for broad distribution across the northern hemisphere. It is spread by mosquito virus with birds as the principle host. It can be transmitted by bodily fluids during viremic phase. There are three clinical outcomes of infection – asymptomatic, west nile fever (self-limited febrile illness), or neuroinvasive disease. Neuroinvasive disease can manifest as meningitis, encephalitis, or combination of both. Certain neurologic manifestations

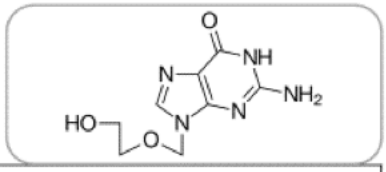
of interest are described: Asymmetric flaccid paralysis, Tremor, Myoclonus, and Parkinsonism symptoms distinguish neuroinvasive WNV from other CNS arboviruses.

Antiviral Agents

ML Medicine Learning

1

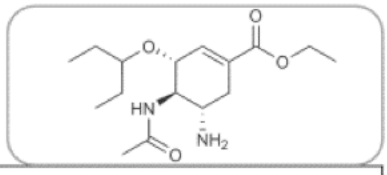
Acyclovir
(Zovirax)



Class(es)	Antiviral
Clinical Use(s)	FDA approved: Herpes zoster, herpes simplex virus (HSV), varicella, genital herpes, recurrent herpes simplex labialis Off-label / clinical use: chickenpox pneumonia, Bell's palsy, HSV (immunocompromised), eczema herpeticum
Mechanism(s) of Action	Stops replication of herpes viral DNA by competitive inhibition of viral DNA polymerase, incorporation into and termination of the growing viral DNA chain, and inactivation of the viral DNA polymerase
Key Adverse Effects	Malaise, renal failure, headache
Key Drug / Food Interactions	Nephrotoxic agents
Special Considerations	Renally adjusted: CrCl < 25 ml/min

2

Oseltamivir
(Tamiflu)

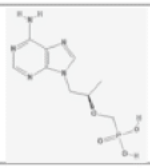


Class(es)	Antiviral
Clinical Use(s)	FDA approved: Influenza virus type A and B (treatment and prophylaxis) Off-label / clinical use: Avian influenza (treatment and prophylaxis)
Mechanism(s) of Action	Inhibits influenza virus neuraminidase which affects viral particle release
Key Adverse Effects	Headache, vomiting, nausea
Key Drug / Food Interactions	Warfarin
Special Considerations (e.g., genomic, pharmacokinetic or formulation issues, dose adjustment for disease state)	Renally adjusted: CrCl < 60 ml/min

Highly Active Antiretroviral Therapy (HAART)

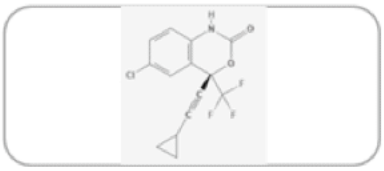
Class(es)	Antiretrovial
Clinical Use(s)	HIV/Aids treatment and pre-exposure prophylaxis
Mechanism(s) of Action	Decreases and controls viral load
Key Adverse Effects	Many common and severe.
Key Drug / Food Interactions	Tons! Check each drug for specific interactions.
Special Considerations (e.g., genomic, pharmacokinetic or formulation issues, dose adjustment for disease state)	**Drug classes used in treatment-naïve patients —** 4 classes typically used in initial regimens: ●Nucleoside reverse transcriptase inhibitors (NRTIs) ●Non-nucleoside reverse transcriptase inhibitors (NNRTIs) ●Protease inhibitors (PIs) ●Integrase strand transfer inhibitors (INSTIs)

Tenofovir Alfenamide, Tenofovir Disoproxil Fumarate (Vemlidy, Viread)



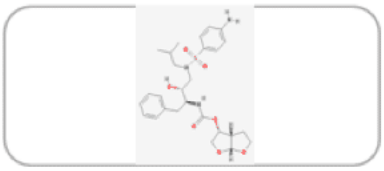
Class(es)	Nucleotide reverse transcriptase inhibitor
Clinical Use(s)	FDA approved: HIV, Hepatitis B Off-label / clinical use:
Mechanism(s) of Action	Tenofovir diphosphate competes with the natural substrate deoxyadenosine 5′-triphosphate for incorporation into the viral DNA strand. After incorporation into viral DNA, tenofovir diphosphate inhibits the activity of HIV-1 reverse transcriptase and HBV polymerase by terminating the DNA chain.
Key Adverse Effects	TDF: Rash, pruritus, nausea, asthenia, depression TAF: abdominal pain, backache, headache, fatigue Serious: lactic acidosis, hepatomegaly w/ steatosis
Key Drug / Food Interactions	NSAIDS
Special Considerations (e.g., genomic, pharmacokinetic or formulation issues, dose adjustment for disease state)	BBW: severe acute exacerbations of hepatitis B TDF: renal impairment adjust CrCl <50 ml/min TAF: renal impairment mild to severe – no adjustment, ESRD – use not recommended, hepatic impairment Child-Pugh A – no adjustment, Child-Pugh B or C use not recommended

Efavirenz
(Sustiva)



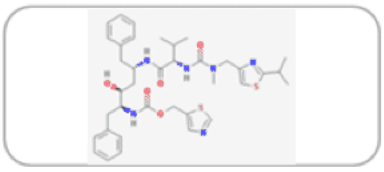
Class(es)	Non-nucleoside reverse transcriptase inhibitor
Clinical Use(s)	FDA approved: HIV Off-label / clinical use:
Mechanism(s) of Action	Through noncompetitive inhibition of HIV-1 reverse transcriptase.
Key Adverse Effects	Rash, ALT/AST elevation, cholesterol/triglyceride elevation, diarrhea, N/V
Key Drug / Food Interactions	St John's Wort, carbamazepine, voriconazole
Special Considerations (e.g., genomic, pharmacokinetic or formulation issues, dose adjustment for disease state)	Hepatic impairment moderate or severe: use not recommended

Darunavir
(Prezista)



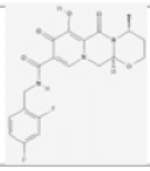
Class(es)	Protease inhibitor
Clinical Use(s)	FDA approved: HIV Off-label / clinical use:
Mechanism(s) of Action	Protease inhibitor that prevents the cleavage of Gag and Gag-Pol polyprotein yielding immature, noninfectious virus.
Key Adverse Effects	Rash, diarrhea, N/V, headache, SJS
Key Drug / Food Interactions	Phenobarbital, carbamazepine, colchicine + many more
Special Considerations (e.g., genomic, pharmacokinetic or formulation issues, dose adjustment for disease state)	Hepatic impairment severe – use not recommend

Ritonavir
(Norvir)



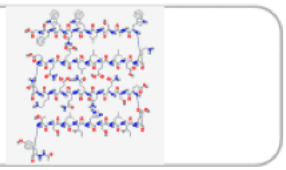
Class(es)	Protease inhibitor
Clinical Use(s)	FDA approved: HIV Off-label / clinical use:
Mechanism(s) of Action	Inhibits both human immunodeficiency virus proteases (HIV-1 and HIV-2), which leaves these enzymes incapable of processing the gag-pol polyprotein precursor. This leads to the production of noninfectious immature HIV particles.
Key Adverse Effects	Pruritus, rash, abdominal pain, N/V, altered sense of taste, arthralgia, asthenia, dizziness, paresthesia, cough
Key Drug / Food Interactions	Sildenafil, colchicine, carbamazepine, amiodarone + many more
Special Considerations (e.g., genomic, pharmacokinetic or formulation issues, dose adjustment for disease state)	BBW: Coadministration with several classes such as sedative hypnotics, antiarrhythmics, or ergot alkaloids may result in potentially life threatening events Hepatic impairment Child-Pugh C – use is not recommended

Dolutegravir
(Tivicay)



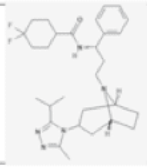
Class(es)	Integrase inhibitor
Clinical Use(s)	FDA approved: HIV Off-label / clinical use:
Mechanism(s) of Action	Integrase strand transfer inhibitor that blocks retroviral DNA integration in the HIV replication cycle.
Key Adverse Effects	Hyperglycemia, increased serum lipase, insomnia
Key Drug / Food Interactions	Dofetilide, carbamazepine, rifampin, metformin
Special Considerations (e.g., genomic, pharmacokinetic or formulation issues, dose adjustment for disease state)	Hepatic impairment Child-Pugh C – use not recommended

Enfuvirtide
(Fuzeon)



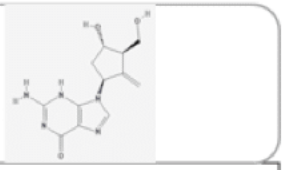
Class(es)	Fusion protein inhibitor
Clinical Use(s)	FDA approved: HIV Off-label / clinical use:
Mechanism(s) of Action	Interferes with the entry of HIV-1 into cells by inhibiting fusion of viral and cellular membranes. It prevents conformational changes required for fusion of viral and cellular membranes.
Key Adverse Effects	Injection site reaction, N/V, diarrhea, fatigue
Key Drug / Food Interactions	Tipranavir
Special Considerations (e.g., genomic, pharmacokinetic or formulation issues, dose adjustment for disease state)	Injectable only

Maraviroc
(Selzentry)



Class(es)	CCR5 antagonist
Clinical Use(s)	FDA approved: HIV (CCR5-tropic positive) Off-label / clinical use:
Mechanism(s) of Action	The antiviral mechanism of action of maraviroc is exclusively CCR5-mediated by preventing the interaction of HIV-1 glycoprotein (gp)120 and CCR5 necessary for CCR5-tropic HIV-1 to enter cells.
Key Adverse Effects	Rash, N/V, infectious disease, cough, URTI, fever
Key Drug / Food Interactions	Carbamazepine, fluconazole, 3A4 inducers/inhibitors
Special Considerations (e.g., genomic, pharmacokinetic or formulation issues, dose adjustment for disease state)	BBW: hepatotoxicity, severe rash, and systemic allergic reaction Renal impairment: CrCl <30 ml/min + 3A4 inhibitors or inducers - contraindicated

Entecavir
(Baraclude)



Class(es)	Nucleoside reverse transcriptase inhibitor
Clinical Use(s)	FDA approved: HIV Off-label / clinical use:
Mechanism(s) of Action	By inhibiting HBV polymerase and subsequently reverse transcriptase, entecavir inhibits HBV replication by 3 different mechanisms: base priming, reverse transcription of the negative strand from the pregenomic messenger RNA, and synthesis of the positive strand of the HBV DNA.
Key Adverse Effects	Nausea, dizziness, headache, fatigue Serious: lactic acidosis, hepatomegaly w/ steatosis
Key Drug / Food Interactions	Food may decrease exposure of entecavir
Special Considerations (e.g., genomic, pharmacokinetic or formulation issues, dose adjustment for disease state)	BBW: potential for hepatitis B reactivation and severe acute exacerbations in discontinuation of therapy Renal impairment: CrCl <50 ml/min – dose adjust