Antiviral Therapy

Introduction:

- Viruses are among the smallest micro-organisms varying in size from 0.02-0.04μm and can be seen and identified by electron microscopes.
- They are simply nucleic acid (either DNA or RNA), which constitutes the genetic material; surrounded by a protein shell (the whole structure is called the nucleocapsid). The protein coat, the capsid, exists to facilitate insertion of the nucleic acid into host cells, where it then directs production of more viruses. Eventually the new viruses will lyse the host cell, killing it, and spread onto new cells.
- Life threatening viral diseases have been well controlled by vaccines and other immunological methods during the last half of the 20th century.
- The clinical outcome of a viral infection depends on which host cells the virus has an affinity for.
- Most of the new antivirals available are a result of efforts to fight the HIV virus, and other viral infections that AIDS patients are susceptible to.

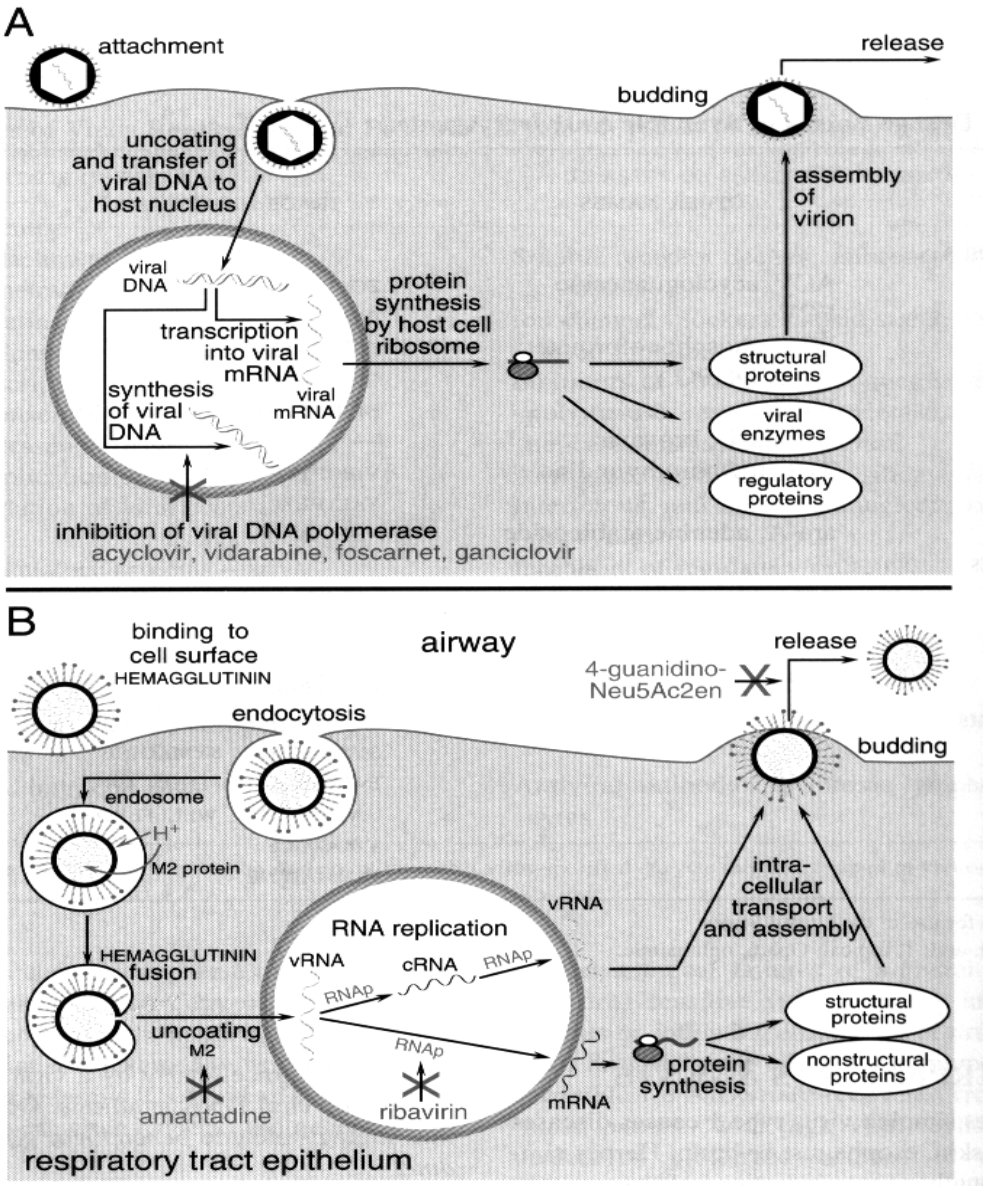
Common Viral Pathogens
(for which we have antiviral drugs)

1. Herpesviridae - Double Stranded DNA viruses

2. Respiratory Syncytial Virus
   RSV - Causes lung infection in infants. A double-stranded RNA virus.

3. Influenza Virus
   Types A & B - Single-stranded RNA viruses that cause the flu.
4. Hepatitis B
   Double stranded DNA virus that causes hepatitis. Picked up from blood. Very hardy virus that will survive drying. Chronic infection is common and can lead to hepatocellular carcinoma.
5. Hepatitis C
   Single stranded RNA virus that causes hepatitis. Initial infection is often asymptomatic. Many (~50%) go on to chronic hepatitis with a risk of developing cirrhosis.
6. Human Immunodeficiency Virus
   HIV -A single-stranded RNA retrovirus.

Possible Methods of Antiviral Attack



A. Replicative cycles of herpes simplex virus, an example of a DNA virus, and the probable sites of action of antiviral agents.

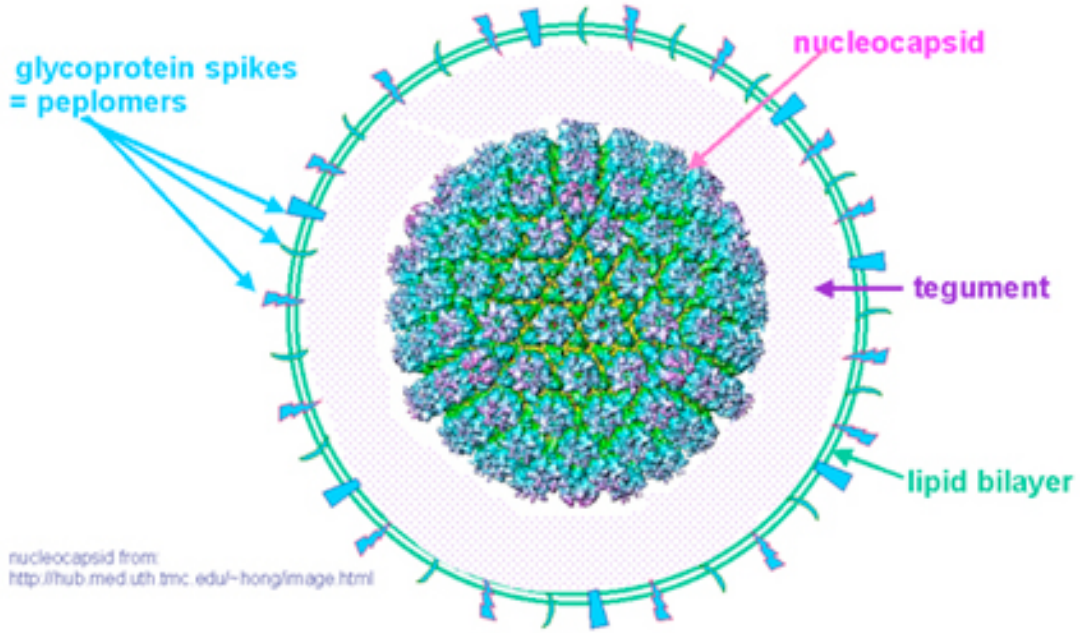
B. Replicative cycles of influenza, an example of an RNA virus, and the loci for effects of antiviral agents.

Herpesviridae

Large, DNA-containing enveloped viruses. Members of the herpesvirus family have been identified in more than 80 different animal species. Eight have been identified as human pathogens

Herpes viruses are a leading cause of human viral disease, second only to influenza and cold viruses

Herpes viruses infect most of the human population and persons living past middle age usually have antibodies to many of the human herpesviruses.



Herpesviridae

After the primary infection, herpesviruses establish latency in the infected host. Once a patient has become infected by herpes virus, the infection remains for life. Intermittently, the latent genome can become activated, in response to various stimulus, to produce infectious virions.

Herpesviridae –

- Herpes simplex 1 (HSV-1 - cold sores)
- Herpes simplex 2 (HSV-2 - genital)
- Varicella-zoster (VZV - Chicken-pox, shingles)
- Epstein Barr (EBV - mono)
- Cytomegalovirus (CMV)– mostly subclinical infection but in immunosuppressed, can be severe. HIV patients get retinitis while organ transplants get pneumonia.

Herpesviridae- Infection and Disease

Designation	Common Name	Subfamily	Associated Diseases
HHV-1	HSV-1	Alpha	Oral Herpes (cold sore), Genital Herpes
HHV-2	HSV-2	Alpha	Genital Herpes
HHV-3	VZV	Alpha	Chicken Pox, Shingles
HHV-4	EBV	Gamma	Mononucleosis, Lymphoma, Carcinoma
HHV-5	CMV	Beta	Mononucleosis, Retinitis, Transplant Rejection
HHV-6	HHV-6	Beta	Roseola infantum, Mononucleosis syndrome, Chronic fatigue syndrome, Multiple Sclerosis?
HHV-7	HHV-7	Beta	Roseola infantum , Mononucleosis syndrome?
HHV-8	KSHV	Gamma	Kaposi's Sarcoma

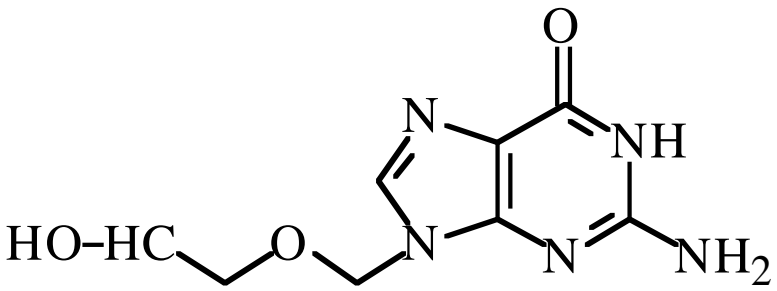
Human Simplex Virus (HSV)- Treatment

Nucleoside Analogs

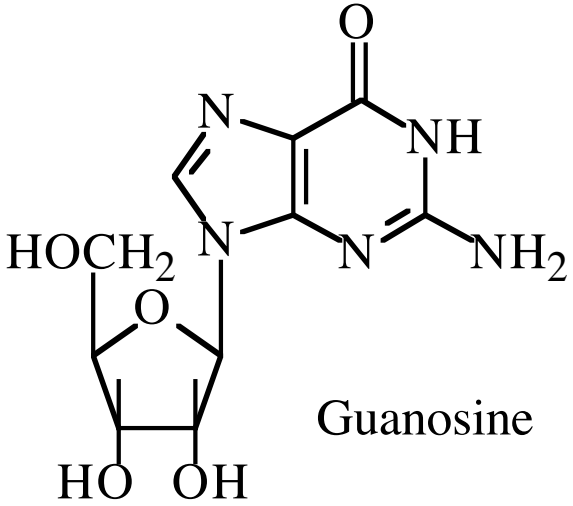
Acyclovir (Zovirax® and generics on UW formulary)
Valacyclovir (Valtrex®; L-valyl ester of acyclovir)
Famciclovir (Famvir®; diacetyl ester of 6-deoxy penciclovir)

All suffer from the appearance of resistant HSV mutants. Fortunately, the mutant strains are less virulent

The drugs are ineffective against latent virus

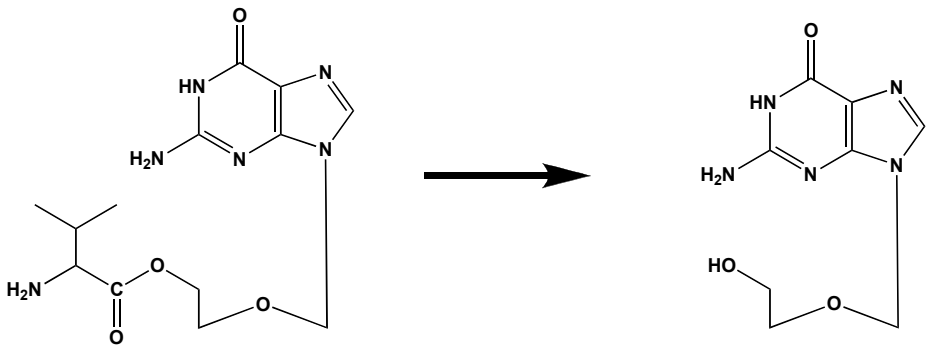


Acyclovir



Guanosine

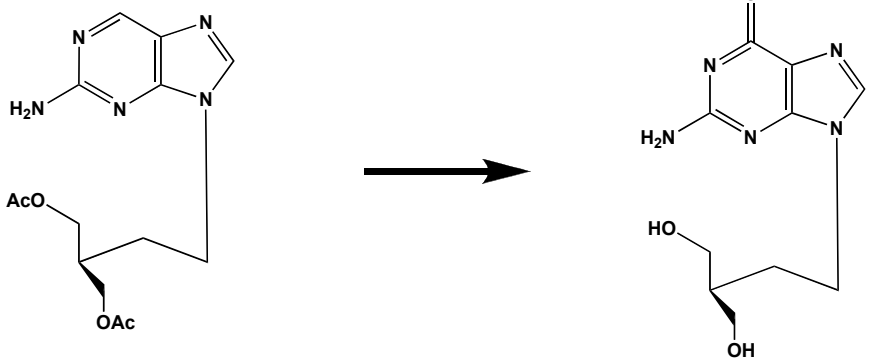
Examples of Prodrugs of Neocloside analogs



Valacyclovir **Acyclovir**

Valacyclovir, valine ester prodrug of acyclovir.

Has a more prolonged "release" of acyclovir and can give fewer doses per day

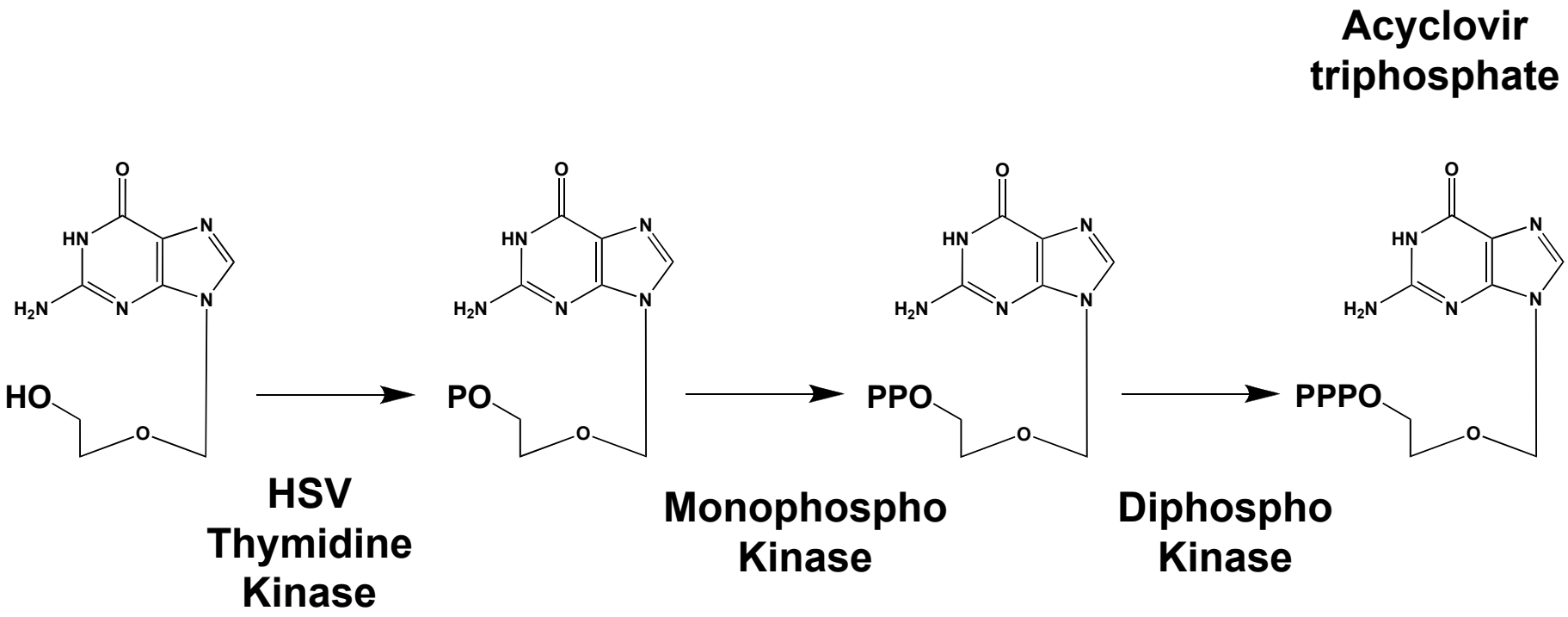


Famciclovir **Penciclovir**

Famciclovir, the diacetate ester prodrug of penciclovir

penciclovir is not absorbed orally but when given IV has similar activity to acyclovir; penciclovir is not commercially available for IV use
not chain terminating but has high intracellular concentrations.

Nucleoside Analogs- MOA



Acyclovir is phosphorylated (viral thymidine kinase) to acyclovir monophosphate then with cell kinases to ACV-triphosphate. Acyclovir triphosphate then blocks uptake of guanosine into the growing DNA chain by competing for binding sites at the viral DNA-polymerase, thus terminating DNA chain proliferation. Resistance may occur by production of low levels of thymidine kinase during prolonged therapy in immunocompromised patients.

Cytomegalovirus (CMV)

The virus is spread via most secretions, particularly saliva, urine, vaginal secretions and semen

CMV may also be spread by blood transfusion and organ transplant

CMV causes no symptoms in children and mild disease in adults

The virus elicits both humoral and cell-mediated immunity but the infection is not cleared

The virus may reactivate, particularly in cases of

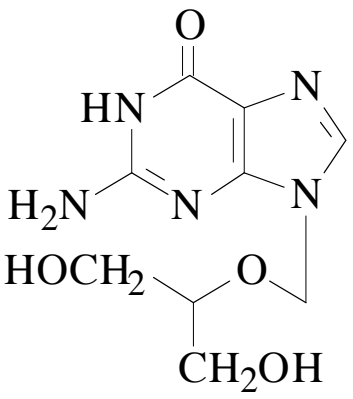
- Organ transplant patients
- Immunosuppressive disease

(**CMV-retinitis** occurs in up to 15% of all AIDS patients; also pneumonia, colitis, esophagitis and encephalitis)

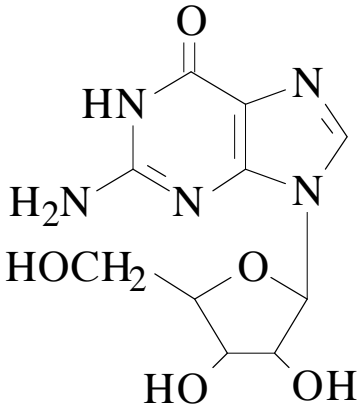
Drugs Against CMV

Ganciclovir (Cytovene® Roche) (UW Formulary)

active against herpes viruses but especially cytomegalovirus (CMV) infections, which typically cause retinitis, and may cause pneumonia, colitis, esophagitis, and hepatitis in immunocompromised patients



Ganciclovir



Guanosine

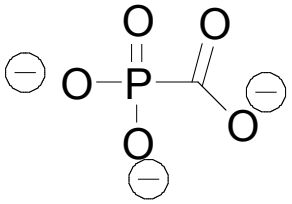
Guanine analog structurally very similar to acyclovir. Ganciclovir is phosphorylated to ganciclovir-triphosphate which blocks the uptake of guanosine into the growing viral DNA by competing for binding sites. It is not a chain terminator like acyclovir.

Ganciclovir is teratogenic and carcinogenic in animals. Should be given by slow IV infusion to avoid reaching toxic blood levels of this drug, and the dose needs to be adjusted in renal failure.

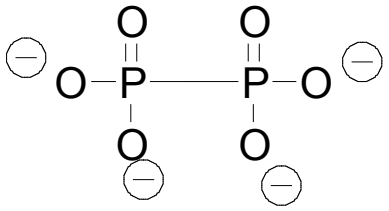
Foscarnet

Foscarnet (Foscavir ® Astra) (UW formulary)

Foscarnet sodium is a trisodium phosphate that inhibits DNA polymerase of herpes viruses including CMV although gancilcovir is usually tried first. It is FDA approved for treatment of CMV retinitis in AIDS patients. In combination with ganciclovir, the results have been promising even in progressive disease with gancivlovir-resistant strains Foscarnet is an organic analog of inorganic pyrophosphate, which is necessary for phosphorylation of nucleotides in DNA/RNA chain proliferation. Foscarnet works by inhibiting the binding of pyrophosphate at viral-specific DNA polymerases. At the concentrations given foscarnet does not bind to eukaryotic DNA polymerases.



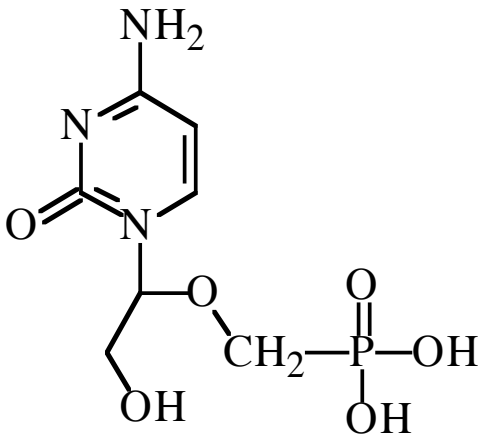
Foscarnet



Pyrophosphate

Cidofovir

Cidofovir (Vistide ® Gilead) (UW formulary)
synthetic acyclic purine nucleotide analog of cystosine nucleoside when phosphorylated to the diphosphate, inhibits CMV DNA polymerase and blocking viral replication. Diphosphate has 2-3d T 1/2. Indicated for treatment of CMV retinitis.



Cidofovir

Boxed warning on renal toxicity. Avoid use with other nephrotoxic drugs. Hydrate the patient well. Give with probenecid to decrease nephrotoxicity.

Also active against HSV, VZV and HPV.

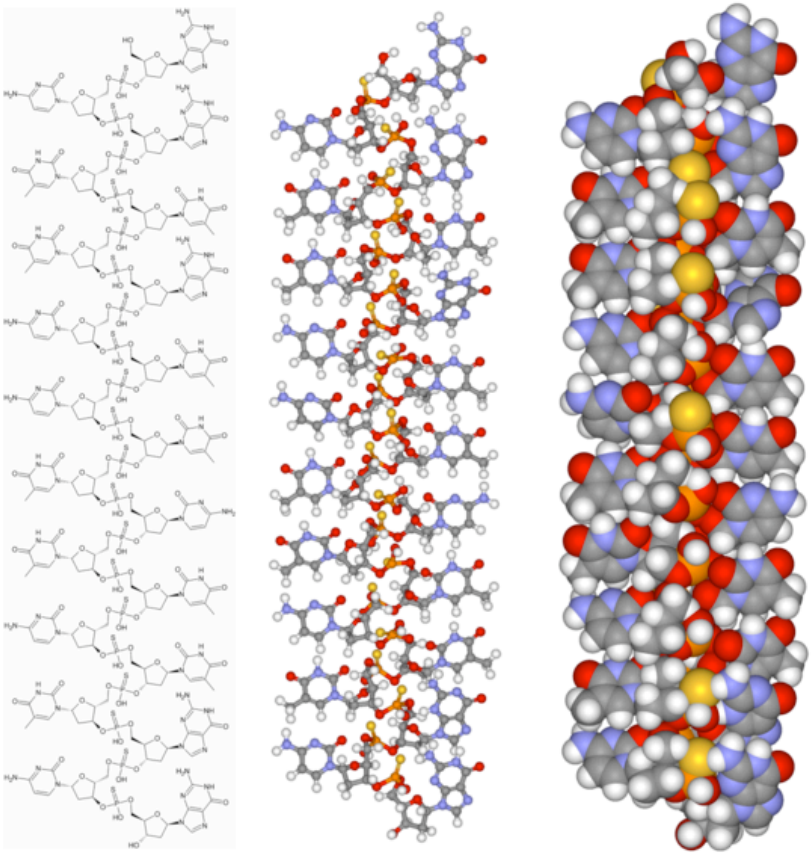
Bioterrorism – a hexadecycloxypropyl derivative is absorbed orally and is active against pox viruses. It is active in cowpox infected mice. May be helpful for use with smallpox exposure.

Fomivirsen

Fomivirsen (Vitravene®, Novartis)

for intravitreal injection (intraocular injection) to treat CMV retinitis

First “antisense” oligonucleotide agent approved as an alternateive medicine for patients with CMV. It binds to target viral on RNA. It works by inhibiting the synthesis of proteins responsible for the regulation of viral gene expression that is involved in infection of CMV retinitis. Has several side effects including: eye inflammation, abnormal vision, cataract, eye pain, as well as stomach pain, fever, headache, vomiting and liver dysfunction.

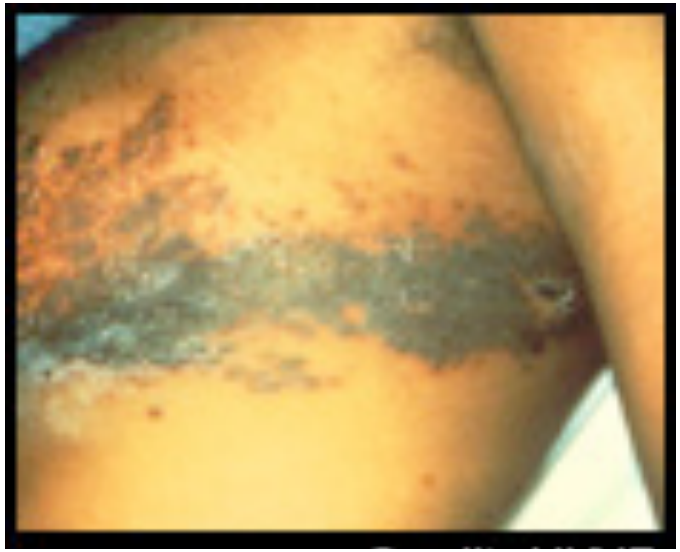


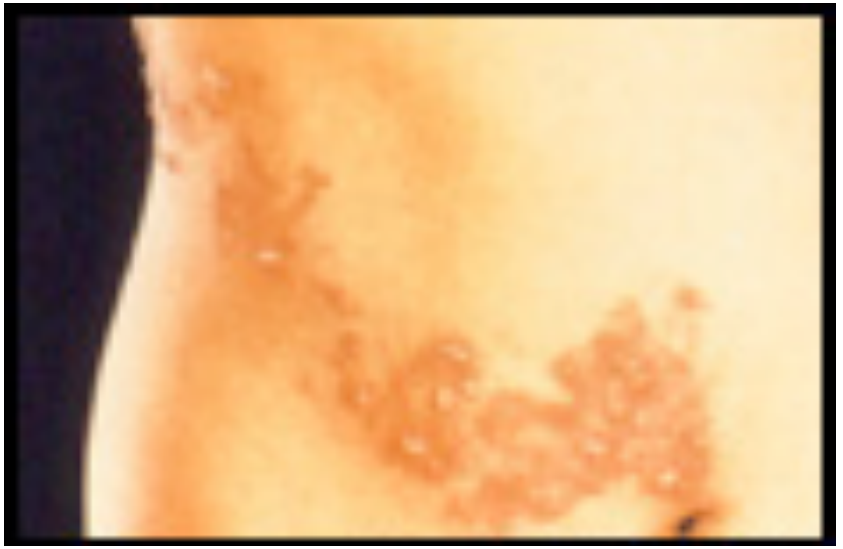
Varicella-Zoster Virus (VZV)

Initial infection usually in childhood with Varicella virus (HHV-3)
-> ***Chicken Pox***

It is spread by respiratory aerosols or direct contact with lesions. The virus establishes latency within the dorsal root ganglia

Years or decades later, the virus (Herpes zoster) may reactivate -> ***Shingles***





Zoster means girdle, from the characteristic rash that forms a belt around the thorax

Pathology and Treatment

Trigeminal nerve reactivation

- uveitis, keratitis, conjunctivitis

Cranial nerve reactivation

- **Bells palsy:** a condition that causes the facial muscles to weaken or become paralyzed. It's caused by trauma to the 7th cranial nerve and is not permanent.

- **Ramsay-Hunt syndrome:** virus spread to facial nerves. Characterized by intense ear pain, a rash around the ear, mouth, face, neck, and scalp, and paralysis of facial nerves. Symptoms may include hearing loss, vertigo, and tinnitus.

Post-herpetic neuralgia: chronic burning or itching pain; hyperesthesia (increased sensitivity to touch)

Treatment:
Acyclovir, valacyclovir, and famciclovir are approved for the treatment of VZV

Epstein Barr Virus (EBV)

EBV (HHV-4) is responsible for **infectious mononucleosis**

The primary infection is often asymptomatic, but the patient may shed infectious virus for many years

Some patients develop symptoms after 1-2 months

- malaise
- lymphadenopathy
- tonsillitis
- enlarged spleen and liver
- fever
- occasional rash

The severity of disease often depends on age, but usually resolves in 1 to 4 weeks

EBV may be transmitted by blood transfusion

Influenza

Influenza is an infectious disease commonly called "the flu”. It is an infection of the respiratory tract caused by the influenza virus.

Symptoms of Influenza

- •fever (typically 100ºF to 103ºF in adults)
- •cough, sore throat, runny/stuffy nose
- •muscle aches, extreme fatigue

Symptoms usually resolve over 1-2 weeks.

(Note: ”Stomach flu" is sometimes used to describe GI illnesses resulting from infection by other organisms)

Pneumonia is a serious and potentially life-threatening complications (young, old, immunocompromised)

Influenza virus

Influenza viruses belong to the orthomyxovirus family

These are enveloped, segmented, negative-strand RNA viruses

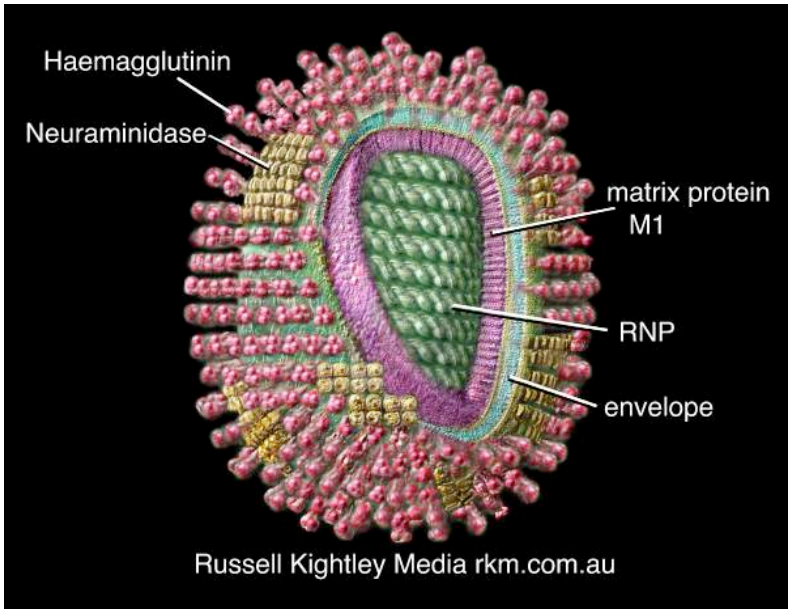
Neuraminidase (NA) is an envelope glycoprotein that may help the virus penetrate mucus to reach epithelial cells.

NA is also critical to virus escape from the infected cell.

There are nine major antigenic NA types.

The virus adsorbs to receptors on the cell surface, mediated by a second envelope glycoprotein, hemagglutinin (HA).

There are 13 major antigenic HA types.



Influenza Virus- Classification

There are three types of influenza viruses: A, B, and C.

Influenza Type A

Influenza type A viruses can infect people, birds, pigs, horses, seals, whales, and other animals, but wild birds are the natural hosts for these viruses.

Influenza type A viruses are divided into subtypes based on HA and NA subtypes

Only some influenza A subtypes (i.e., H1N1, H1N2, and H3N2) are currently in general circulation among people

Other subtypes are found most commonly in other animal species. (i.e., H5N1 causes severe illness in birds)

Influenza Virus- Classification Cont.

Influenza Type B

Influenza B viruses are normally found only in humans

Although influenza type B viruses can cause human epidemics, they have not caused pandemics

Influenza Type C

Influenza type C viruses cause mild, often asymptomatic illness in humans; they do not cause epidemics or pandemics.

Influenza types A and B are responsible for annual epidemics of respiratory illness, and substantial morbidity and mortality

Influenza Virus- Mechanisms of Resistence

Antigenic Drift

•mutations occur over time that cause a gradual change in the virus (HA/NA) (every 2-3 years)

•"old" antibodies no longer recognizes the "new" virus, and provide only partial protection

•constant change enables the virus to evade the immune system, and people remain susceptible throughout life

Antigenic Shift

•an abrupt change in the HA and/or NA proteins, resulting in the sudden emergence of a new subtype

•the population is “naïve” and epidemics/pandemics occur (every 10-15 years)

Influenza A viruses undergo both kinds of changes, while influenza type B viruses change only by antigenic drift

Drugs Against Influenza

Drugs to treat and prevent influenza. For treatment, best given shortly after onset of symptoms (24-48h).
For prevention, must take every day.

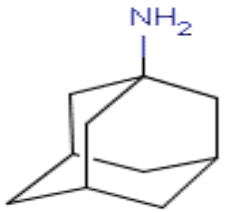
Vaccine vs. drug? Vaccine is best of course because it is better to prevent than to treat. Role is when one fails to vaccinate or have vaccine failure (e.g. when new "shift" virus comes).

Drugs may be lifesavers in the face of an Influenza pandemic. Vaccine failures increase with increasing age.

Flu can be very serious in the elderly and infants, therefore these drugs have some applications in high risk and elderly patients.

Anti-Influenza Drugs

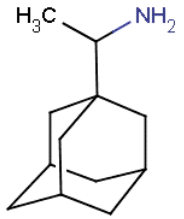
Amantadine (Symmetrel ®)
As an antiviral: Prevention/Treatment of Influenza A virus (not B). Prevention has efficacy of ~70%. CNS effects limit wide use.



Amantadine

Mechanism of Action: It appears to be virustatic by preventing uncoating of virus particle, leading to no viral replication and no infection (ideally). It affects maturation of influenza HA glycoprotein in trans-Golgi network.

Side effects: Dopaminergic effects may cause insomnia, dizziness, nervousness, nausea and vomiting. Decrease dose in renal failure.

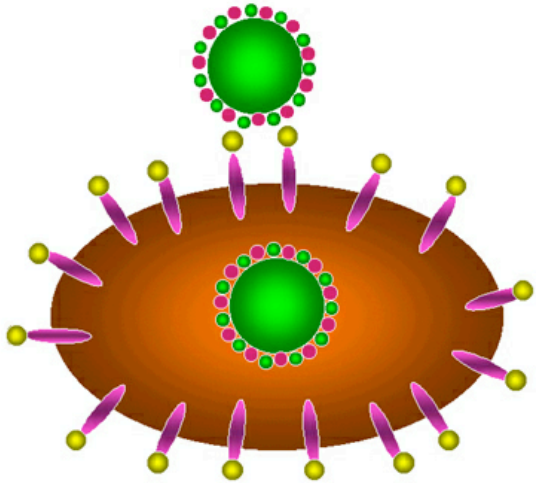


Rimantadine

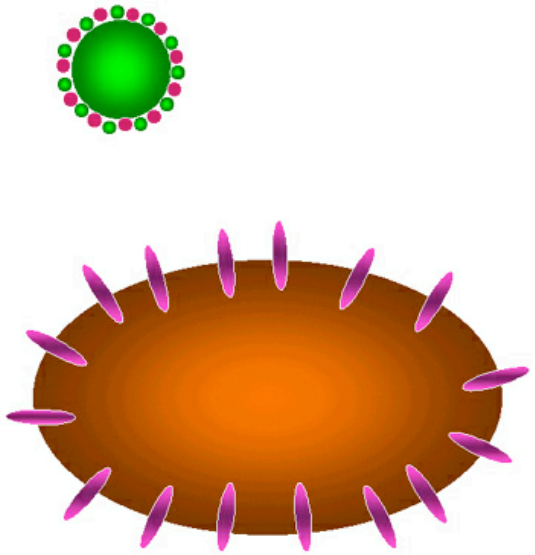
Rimantadine (Flumadine ® Forest)
Same as Amanadine but with fewer side effects

Neuraminidase inhibitors

Neuraminidase breaks the bonds that hold new virus particles to the outside of an infected cell by cleaving sialic acid from the cell surface. This releases new viruses that can infect other cells and spread infection. Neuraminidase inhibitors prevent viral cleavage of sialic acid thereby preventing new virus particles from being released, thereby limiting the spread of infection.



Hemagglutinin sticks to cellular sialic acid



Neuraminidase degrades cellular sialic acid

Neuraminidase inhibitors cont.

Shorten flu duration 1-2 days if started within 48 h of onset.

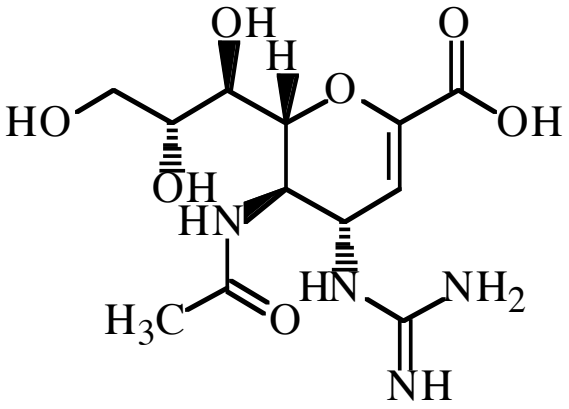
Zanamivir (Relenza ® Glaxo Wellcome)
Inhibit influenza A and B viruses.

Given as 10 mg micronized powder by inhalation “Diskhaler”, BID for 5 days

5 mg/inhalation thus dose is 2 inhalation BID x 5d. Start within 48 h of onset, not absorbed orally

Well tolerated unless have underlying airway disease

propylaxis – 67% decrease in incidence in a 4 week study
treatment – 84% decrease in fever and symptoms with treatment.



Zanamivir

Neuraminidase inhibitors cont.

Oseltamivir (Tamiflu ® Roche) (UW Formulary)

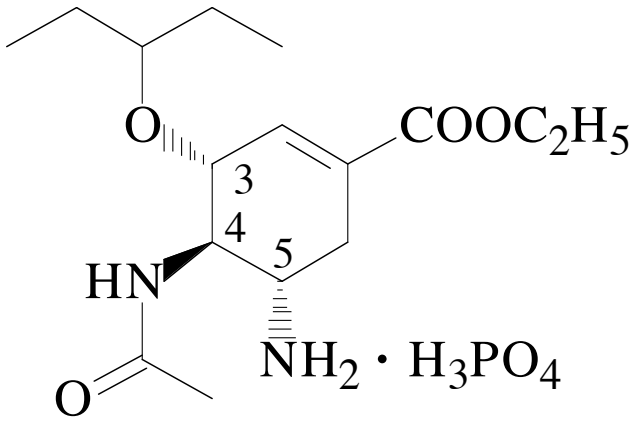
Given as 75 mg capsules or suspension BID for 5 days; start within first 2 days of symptoms

It is an ethyl ester prodrug that is hydrolyzed in vivo

For prophylaxis if exposed, 75mg/d for ≥ 7d and oral suspension 12mg/ml

Pregnancy category C and not for < 1 year of age (safety not established)

Well tolerated; some GI upset



Oseltamivir

Drugs Against Respiratory Syncytial Virus (RSV) and Hepatitis

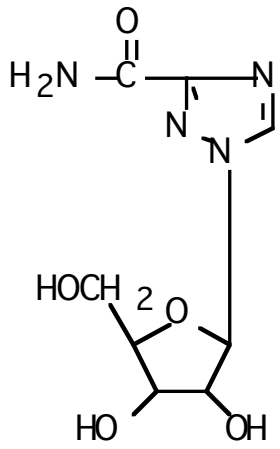
RSV: Two subtypes, A and B, have been identified. Subtype B are characterized as the asymptomatic strains of the virus that the majority of the population experiences. The more severe clinical illnesses involve subtype A strains, which tend to predominate in most outbreaks. RSV affects the upper and lower respiratory tracts, but is most prevalent in lower respiratory illnesses such as pneumonia and bronchiolitis.

Most adults have antibodies against RSV so no apparent infection is common. In the very young and in premature infants the infection can be serious.

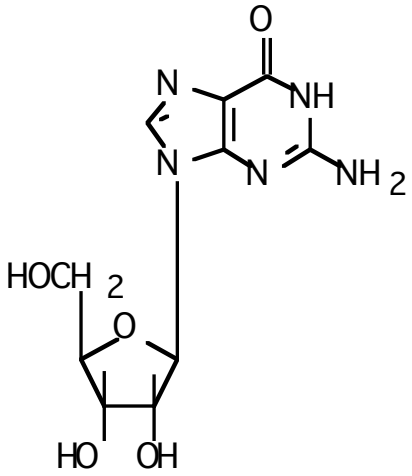
We will cover Hepatitis in detail when we cover vaccines

Ribavirin

Ribavirin:
Active against many DNA/RNA viruses and highly active against influenza A and B, but is only approved for treating RSV in infants and young children by aerosol and hepatitis C together with interferon. Clinically Ribavirin was shown to delay the onset of full-blown AIDS in patients with early symptoms of HIV infection



Ribavirin



Guanosine

Ribavirin mechanism of action

Mechanism of action:

Ribavirin is a guanine analog that is phosphorylated by adenosine kinase to its most active form, ribavirin-triphosphate. This compound inhibits viral RNA-polymerase preferentially at therapeutic doses by competing with adenosine-triphosphate and guanine-triphosphate for binding sites at the polymerase, as well as inhibiting transferases necessary for the addition of guanine.

Toxicity:

Ribavirin is quite teratogenic in animals - do not give to a patient who is pregnant (must test and patient must use 2 methods of birth control). May cause headaches/dizziness - advise health care workers to wear mask when administering this drug by aerosol. May worsen COPD-like symptoms in some patients.

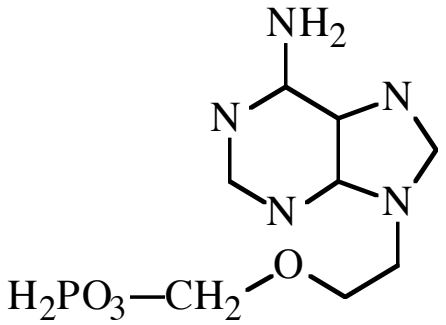
Ribavirin and other products

Virazole® Schering - lyophilized ribavirin powder for aerosolization by small particle aerosol generator (SPAG-2). Used by inhalation in infants and small children with significant RSV infection

Ribavirin oral capsules 200mg Rebetrol® (Schering)
-for use in patients with chronic hepatitis C

Peginterferon alpha 2a (Pegasys® Roche) Once weekly dose of Peg interferon 2α to treat adults with chronic hepatitis C

Adefovir (Hepsera® Gilead) (UW Formulary)
for chronic hepatitis B with evidence of active viral replication 10 mg/day.



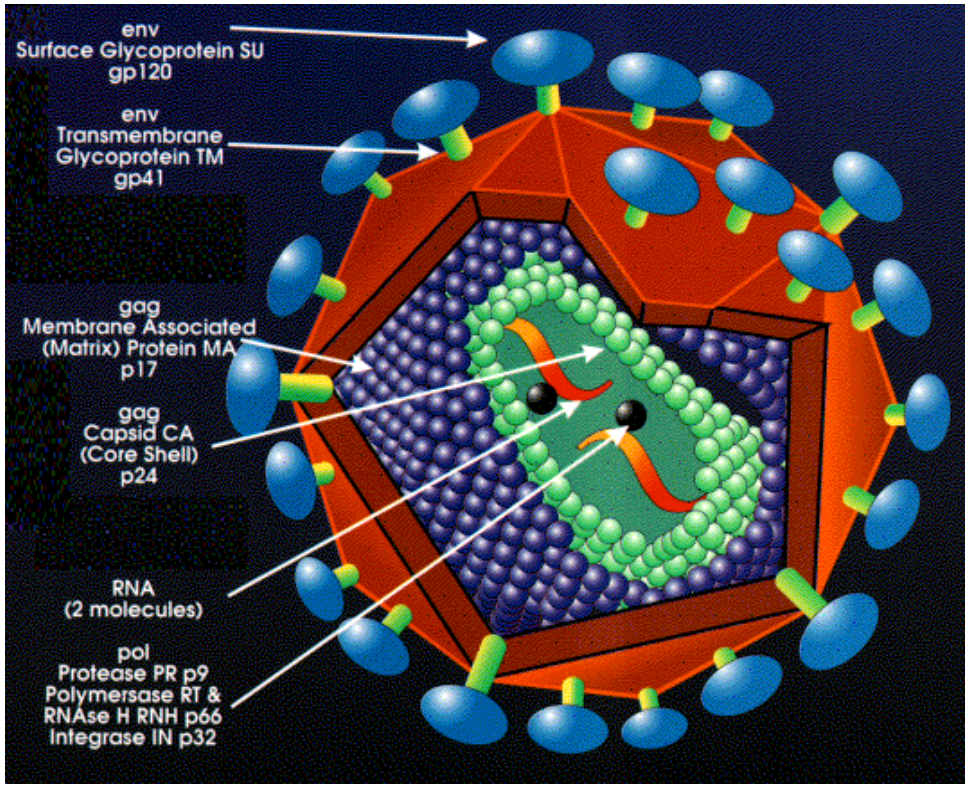
Adefovir

Human Immunodeficiency Virus (HIV)

Infection with HIV is associated with a disease known as ***Acquired Immuno Deficiency Syndrome*** (***AIDS***)

HIV is a typical retrovirus

The nucleocapsid contains two copies of the RNA genome (capped and polyadenlyated)



Anti-HIV Drug Therapy

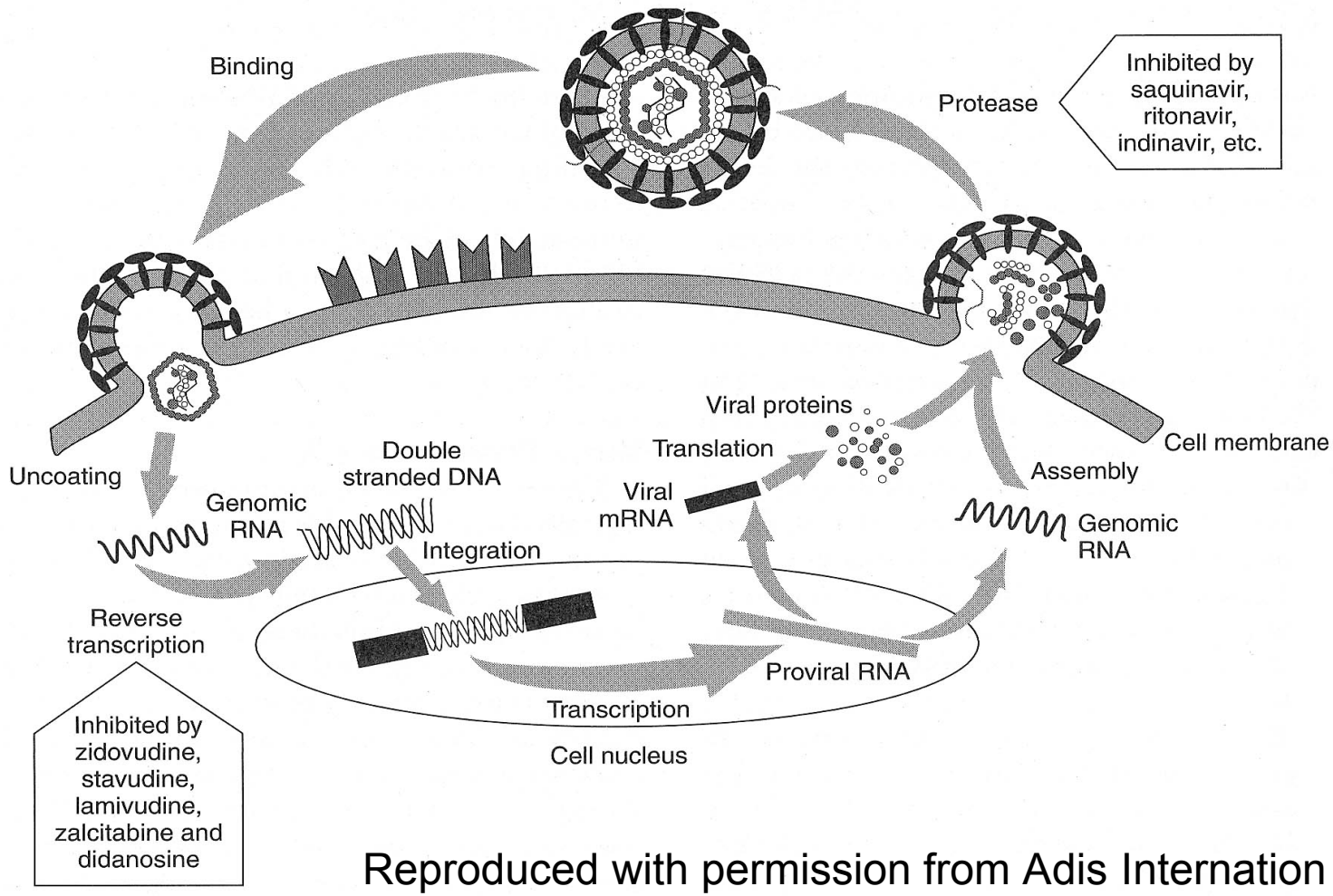
Although a variety of drugs have been developed for treating AIDS patients none have proven successful in curing the disease. Difficulties experienced with this viral infection are due to the ability of the virus to mutate leading to rapid drug resistance. Anti-HIV drugs are classified according to the mode of action:

Drugs inhibiting Reverse Transcriptase (RT) interfere with replication of HIV and stop synthesis of infective viral particles. They are classified in nucleoside and non-nucleoside RT inhibitors.

Drugs inhibiting Proteases block release of viral particles from the infected cells.

Drugs that inhibit gp41 Membrane Fusion.

The life cycle of HIV and the site of action of Anti HIV agents



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Reverse Transcriptase Inhibitors (RTI)

All are 2,3 dideoxynucleosides. All competitively inhibit DNA dependent RNA polymerase (reverse transcriptase). All block early events in virus replication. All are chain terminators (like Acylcovir). Once viral DNA is integrated into host cell genome, they don't work.

Resistance develops due to changes in enzyme. High virus load results in mutants that are resistant. Cross resistance is not complete so can switch from one inhibitor to another or use in combination to decrease resistance. BUT don't use two drugs together with same adverse effect.

The high rate of RT mutation and resistance to the nucleoside inhibitors led to the development of non-nucleoside inhibitors

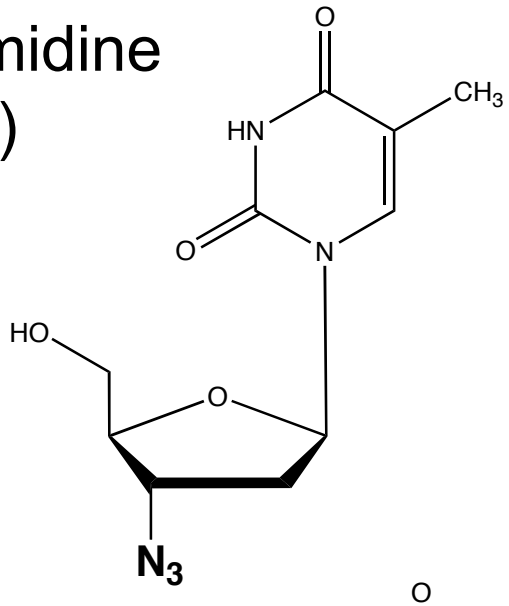
These drugs are ***non-competitive inhibitors*** of reverse transcriptase

The idea is that mutations in RT leading to resistance to nucleoside inhibitors would be different than those leading to resistance of the non-nucleoside inhibitors

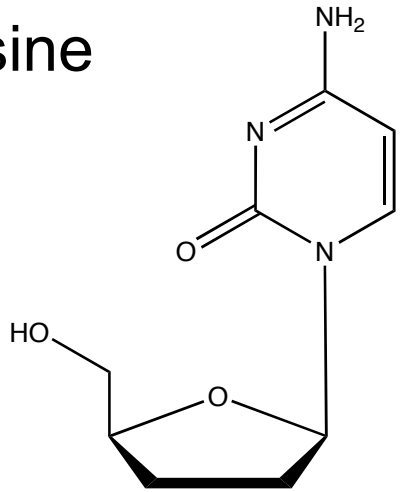
Thus, the nucleoside and non-nucleoside RT inhibitors could be used in combination therapy.

Examples of Nucleoside RT Inhibitors

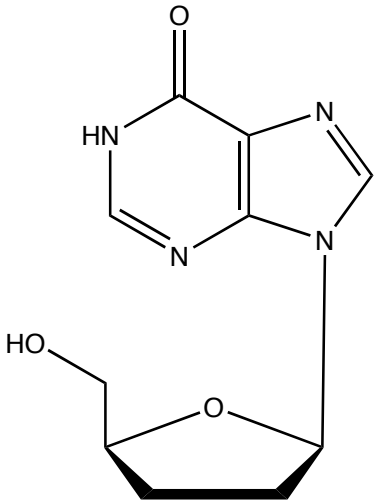
Azidothymidine (AZT)



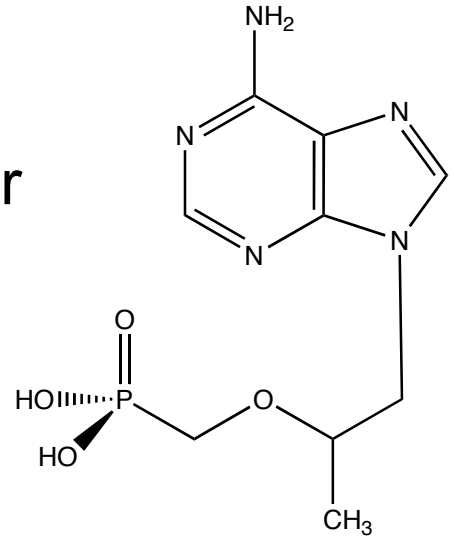
Dideoxycytosine (DDC)



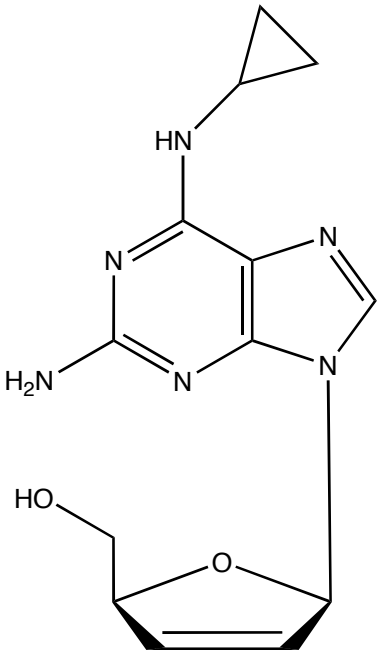
Dideoxyinosine (DDI)



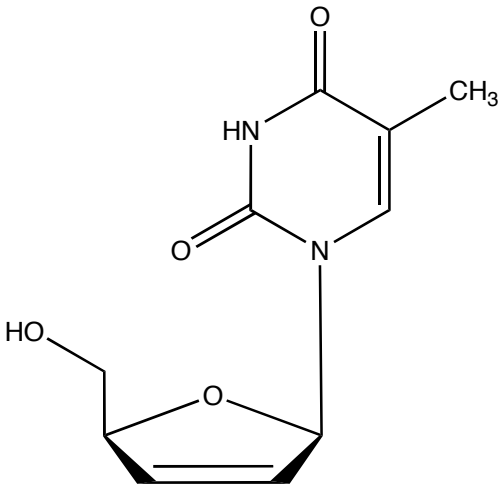
Tenofovir



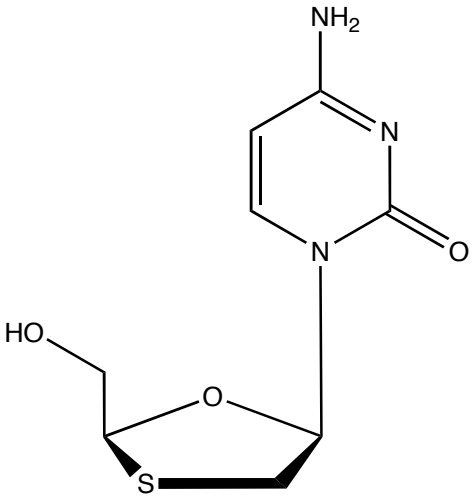
Examples of Nucleoside RT Inhibitors



Abacavir



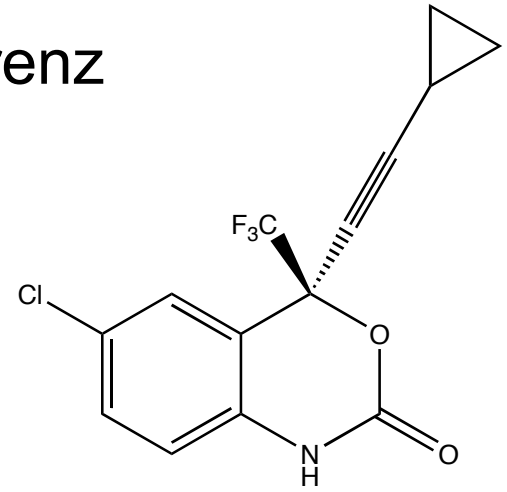
Didehydrothymidine
(d4T)

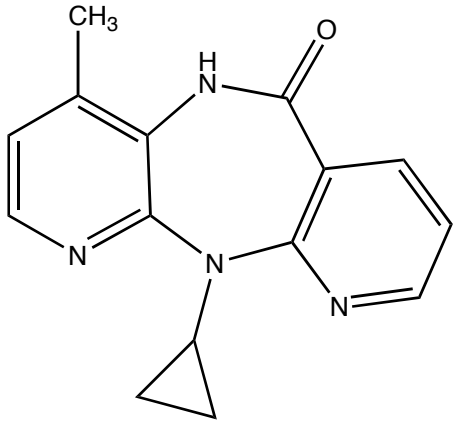


2'-deoxy-3'-thiacytidine
(3TC)

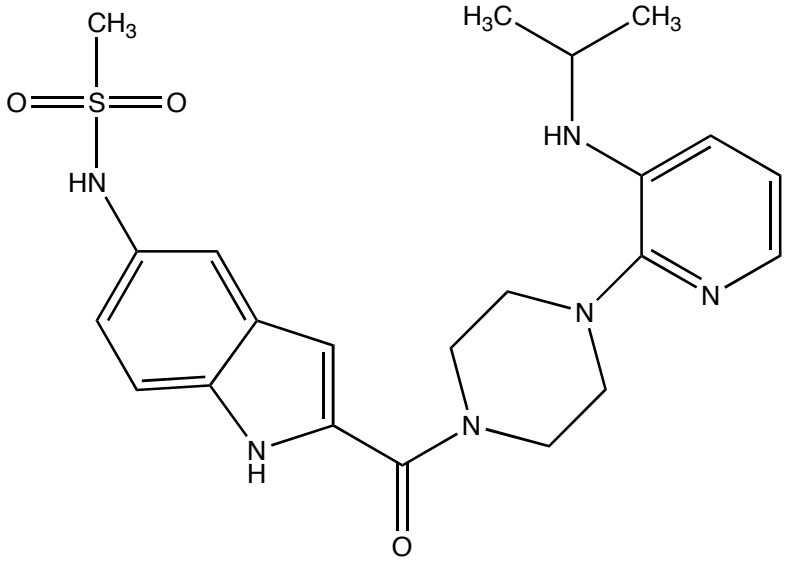
Examples of Non-Nucleoside RT Inhibitors

Efavirenz





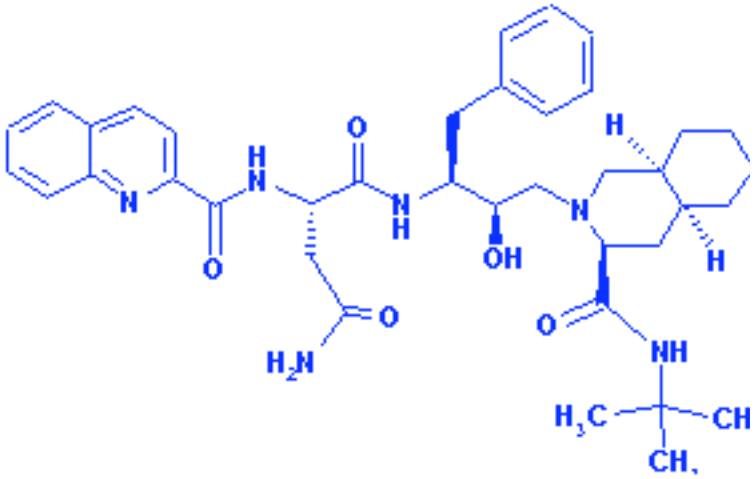
Nevirapine
(NVP)



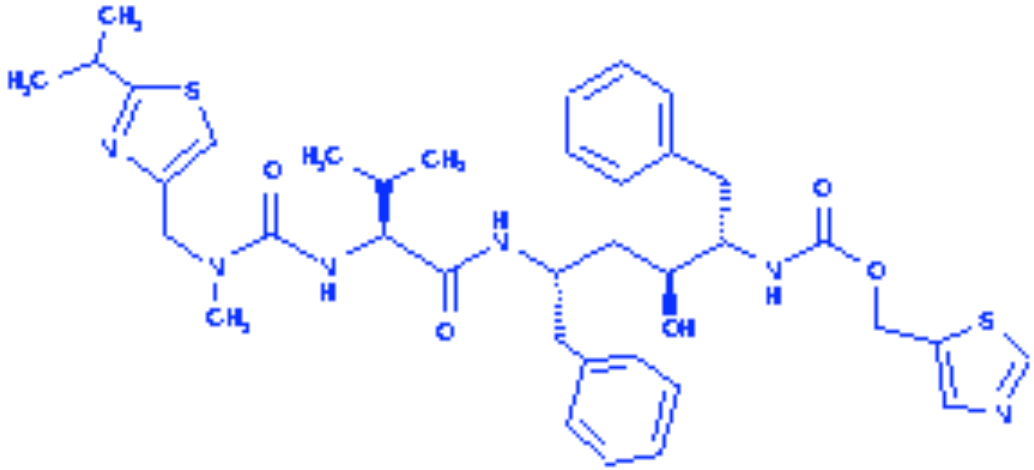
Delavirdine
(DLV)

Viral Protease Inhibitors

This approach has resulted in useful HIV treatment. The protease cleaves a huge protein called "gag-pol" (based on the gene segment coding for it) into capsid, reverse transcriptase, integrase. Molecular modeling of the enzyme's active site has lead to several inhibitors. All of these drugs mimic the peptide substrates for the enzyme. Several are approved now (approved via a fast track process). Resistance is a problem when agents are used alone. When combined with a RTI, have two different mechanisms of activity and decreased resistance and enhanced antiviral effect. They block cell to cell spread of HIV.

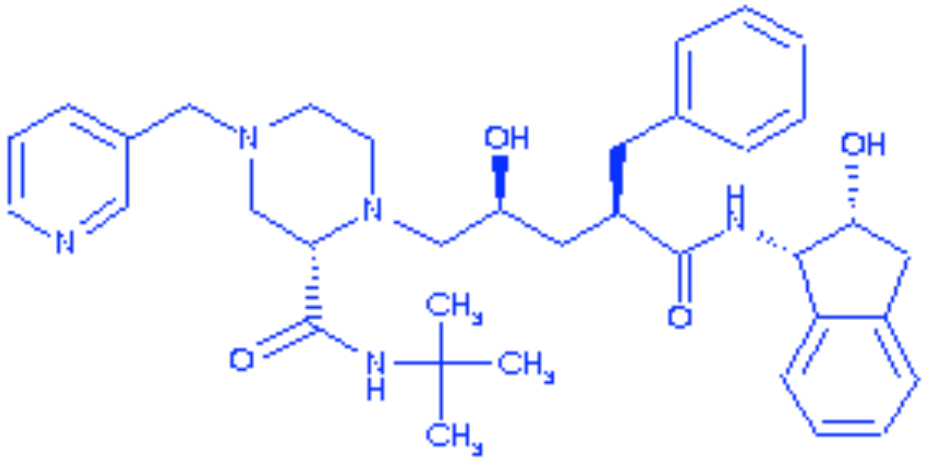


Saquinavir
(SQ)



Ritonavir

Other Protease Inhibitors



Indinavir

Other agents:

Nelfinavir

Amprenavir

Lopinavir

NEW Viral Fusion Inhibitors

Enfuvintide Fuzeon ® Approved Mar 03. It blocks fusion of HIV-1 with CD-4 cells, i.e. blocks viral entry: binds to gp41 viral envelope glycoprotein and interferes with its ability to approximate the two membranes. It is also referred to as a "fusion inhibitor

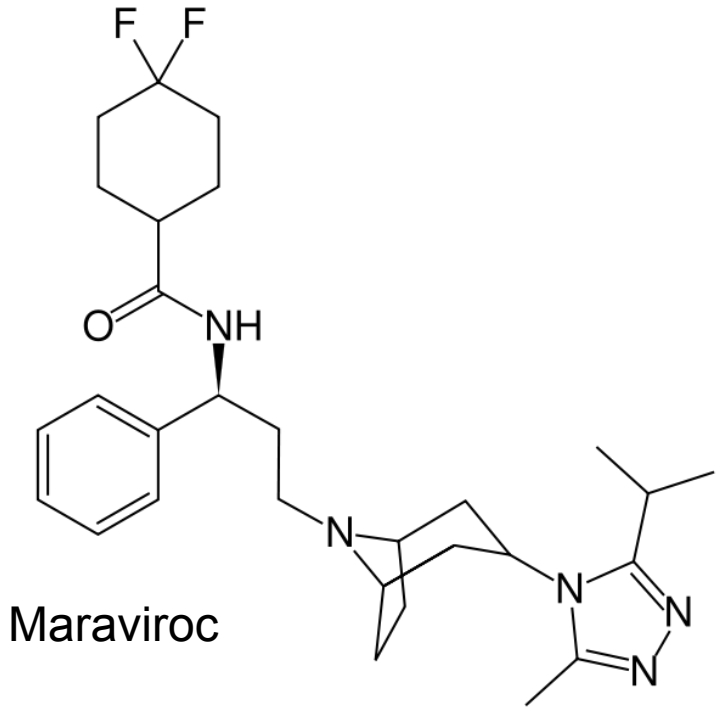
It is the first drug in a new class. It stops HIV from "fusing" with a cell it has attached to. This prevents HIV from infecting the cell. Enfuvirtide helps control HIV, even when it is resistant to other medications.

Enfuvirtide has to be injected under the skin twice daily. Almost everyone who uses it gets skin reactions where it is injected. Most of these are not serious.

Ac-YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF

New Entry Inhibitor

Maraviroc (Selzentry), binds to CCR5, preventing an interaction with gp120. It is a "chemokine receptor antagonist." New agent approved in 2007. Indicated for treatment-experienced adult patients infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents. Given orally



Maraviroc