

VII. ANTIVIRALS

A. Introduction

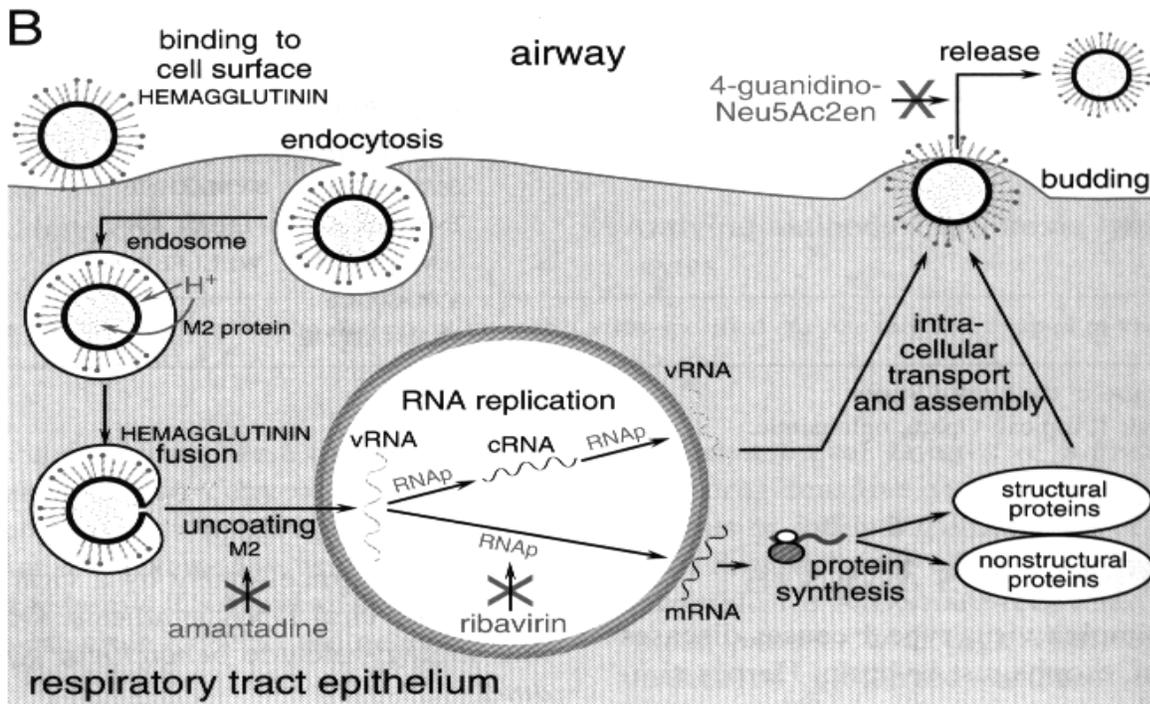
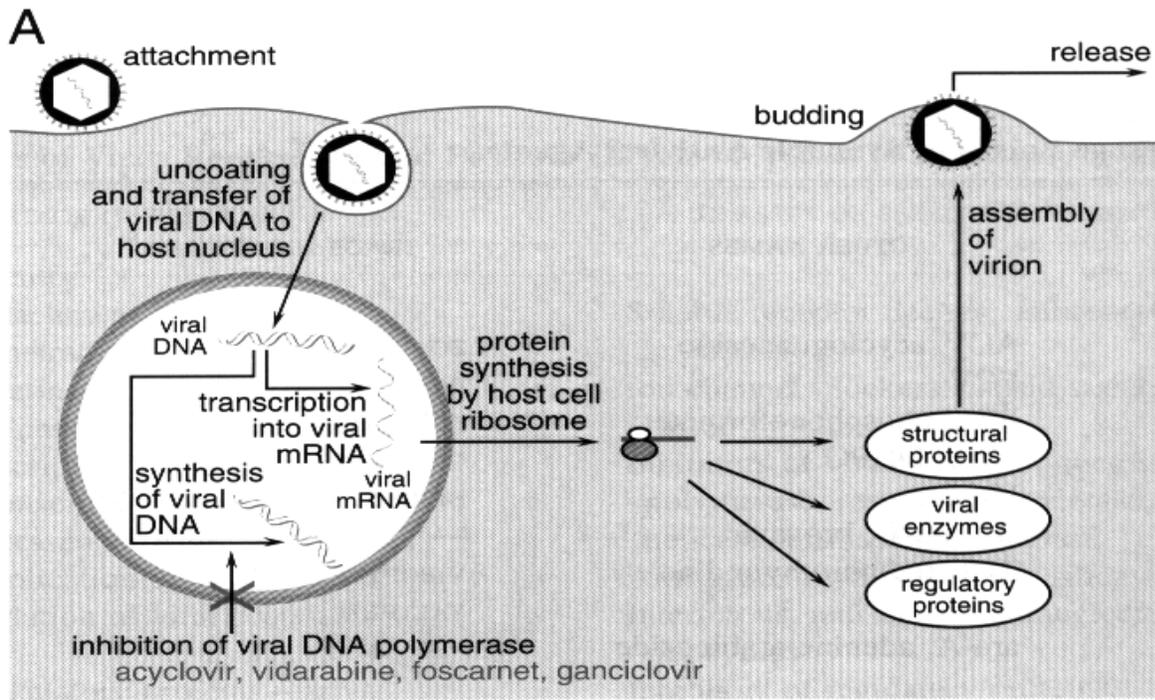
Viruses are among the smallest micro-organisms varying in size from 0.02-0.04 μm and can be seen and identified by electron microscopes. They are simply nucleic acid (either DNA or RNA), which constitutes the genetic material; surrounded by a protein shell (the whole structure is called the nucleocapsid). 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. The clinical outcome of a viral infection depends on which host cells the virus has an affinity for.

Life threatening viral diseases have been well controlled by vaccines and other immunological methods during the last half of the 20th century. However, with the onset of the HIV virus, and organ transplant related immunosuppression, patients have been increasingly threatened by opportunistic viral diseases for which we have no effective vaccination. These days, most of the new antivirals available are a result of our effort to fight the HIV virus, and other viral infections that AIDS patients are susceptible to.

Anti-bacterial drugs have proved very successful since they act against a bacterial structure, the cell wall, that is not present in eukaryotic cells. In contrast, most anti-viral agents have proved of little use therapeutically since the virus uses host-cell metabolic reactions and thus, for the most part, anti-viral agents will also be anti-cell agents. Thus, the alternative approach of stimulating the host's immune responses using vaccines has been most often pursued. Nevertheless, there are activities (i.e. enzymes) that are virus-encoded and therefore offer potential *virus-specific* targets. This is particularly the case with the viruses that have large genomes and code for their own replicative enzymes. Even so, unfortunately, many apparent anti-virals that are effective *in vitro* are ineffective *in vivo*.

It is beyond the scope of this course to cover anti HIV therapy in detail. This will be covered in the therapeutics course. Instead the emphasis will be on an overview of antiviral therapy with *some* detail given on agents used to treat Herpes virus infections and influenza.

B. Possible Methods of Antiviral Attack (see diagram)



The replicative cycles of herpesvirus (A) and influenza (B) are given as examples of DNA-encoded and RNA-encoded viruses, respectively. Sites of action of antiviral agents also are shown. Key: mRNA, messenger RNA; cDNA, complementary DNA; vRNA, viral RNA; DNAp, DNA polymerase; RNAp, RNA polymerase; cRNA, complementary RNA. An X on top of an arrow indicates a block to virus growth.

A. Replicative cycles of herpes simplex virus, an example of a DNA virus, and the probable sites of action of antiviral agents. Herpesvirus replication is a regulated, multistep process. After infection, a small number of so-called immediate-early genes are transcribed; these genes encode proteins that regulate their own synthesis and are responsible for synthesis of so-called early genes that are involved in genome replication, such as thymidine kinases, DNA polymerases, etc. After DNA replication, the bulk of the herpesvirus genes (called "late" genes) are expressed and encode proteins that either are incorporated into or aid in the assembly of progeny virions.

B. Replicative cycles of influenza, an example of an RNA virus, and the loci for effects of antiviral agents. The M2 protein of influenza virus allows an influx of hydrogen ions into the virion interior, which in turn promotes dissociation of the RNP segments and release into the cytoplasm (uncoating). Influenza virus mRNA synthesis requires a primer cleared from cellular mRNA and used by the viral RNAP complex. The neuraminidase inhibitor, 4-guanidino-Neu5Ac2en, specifically inhibits release of progeny virus. Small capitals indicate virus proteins.

C. Common Viral Pathogens (for which we have antiviral drugs)

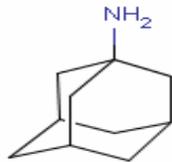
1. Herpesviridae - Double Stranded DNA viruses (once infected, virus stays for life)
 - Herpes simplex 1 (HSV-1 - cold sores)
 - Herpes simplex 2 (HSV-2 - genital)
 - Varicella-zoster (VZV - Chicken-pox, shingles)
 - Epstein Barr (EBV - mono)
 - Cytomegalovirus – mostly subclinical infection but in immunosuppressed, can be severe. HIV patients get retinitis while organ transplants get pneumonia.
2. Respiratory Syncytial Virus
 - RSV - Causes lung infection in infants. A double-stranded RNA virus.
3. Human Immunodeficiency Virus
 - HIV -A single-stranded RNA retrovirus.
4. Influenza Virus
 - Types A & B - Single-stranded RNA viruses that cause the flu.
5. 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.
6. 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.

D. Drugs Against Influenza

1. Introduction:

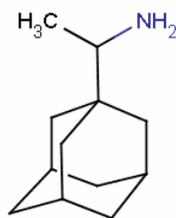
Drugs to treat and prevent influenza. For treatment, best given shortly after onset of symptoms (24-48h). For prevention, must take every day. Vaccine vs. drug? Vaccine is best of course because it is better to prevent than to treat. Role is when one fails to vaccinate or have vaccine failure (e.g. when 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.

2. Amantadine (Symmetrel[®])



- a) Place in Therapy: As an antiviral: Prevention/Treatment of Influenza A virus (not B). Prevention has efficacy of ~70%. CNS effects limit wide use.
- b) Mechanism of Action: Mostly unknown. It appears to be virustatic by preventing uncoating of virus particle, leading to no viral replication and no infection (ideally).
- c) Dose/Route: 100 mg PO - may be given at same time as the flu vaccine. Treat for at least 10 days and up to 90 days.
- d) Toxicity: Dopaminergic effects may cause insomnia, dizziness, nervousness, nausea and vomiting. Decrease dose in renal failure.
- e) Other: Sometimes used in mild Parkinson's disease.

3. **Rimantadine** (Flumadine[®] Forest)



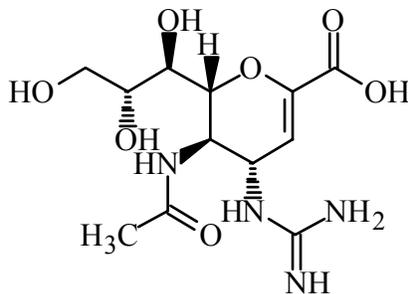
Approved in USA in 1993.

Same as amantadine but with fewer adverse effects.

4. **Neuraminidase inhibitors** – shorten flu duration 1-2 days if started within 48 h of onset.

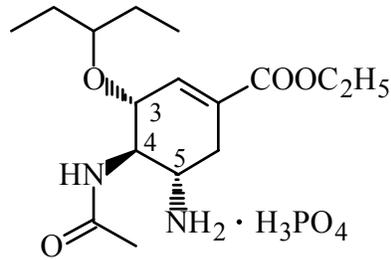
Neuraminidase breaks the bonds that hold new virus particles to the outside of an infected cell by cleaving sialic acid from the cell surface. This releases new viruses that can infect other cells and spread infection. Neuraminidase inhibitors prevent viral cleavage of sialic acid thereby preventing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

a) **Zanamivir** (Relenza[®] Glaxo Wellcome) Inhibit influenza A and B viruses.



1. given as 10 mg micronized powder by inhalation “Diskhaler”, BID for 5 days
2. 5 mg/inhalation thus dose is 2 inhalation BID x 5d
3. start within 48 h of onset
4. not absorbed orally
5. well tolerated unless have underlying airway disease
6. prophylaxis – 67% decrease in incidence in a 4 week study
7. treatment – 84% decrease in fever and symptoms with treatment

b) **Oseltamivir** (Tamiflu[®] Roche) (UW Formulary)

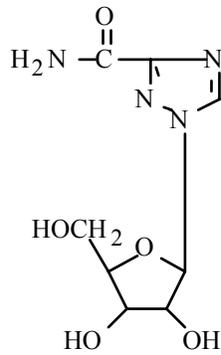


1. Given as 75 mg capsules or suspension BID for 5 days; start within first 2 days of symptoms
2. is an ethyl ester prodrug that is hydrolyzed in vivo
3. for prophylaxis if exposed, 75mg/d for $\geq 7d$ and oral suspension 12mg/ml
4. pregnancy category C and not for < 1 year of age (safety not established)
5. well tolerated; some GI upset

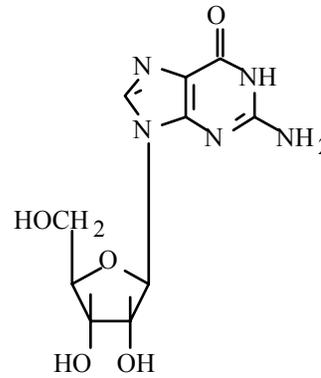
E. Drugs Against Respiratory Syncytial Virus (RSV) and Hepatitis (* indicates UW formulary drug)

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.

1. Ribavirin



Ribavirin



Guanosine

- a) Place in Therapy: Activity 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.
- b) 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.
- c) 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.
- d) *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

- most adults have antibodies against RSV so inapparent infection is common. In the very young and in premature infants the infection can be serious.

- 20mg/ml via aerosol for 12-18h/d for 3-7d using SPAG-2 aerosol generator

e) *Ribavirin oral capsules 200mg Rebetrol® (Schering)

- for use in patients with chronic hepatitis C

- usually used in combination with interferon 2α and this is taken for ~48 weeks (SQ 3x/week x 48 weeks)

- PEG - interferon 2β Peg-Intron (Schering) is on the UW formulary - there are many adverse effects including neuropsychiatric changes

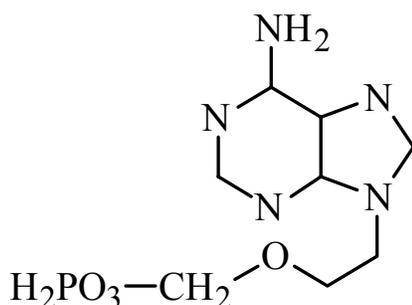
f) A monoclonal antibody (Palivizumab, Synagis®) is approved for RSV. A polyclonal antibody (RSV immune globulin, RespiGam®) is also available.

2. **Peginterferon** alpha 2a (Pegasys® Roche)

Once weekly dose of Peg interferon 2α to treat adults with chronic hepatitis C

3. ***Adefovir** (Hepsera® Gilead) (UW Formulary)

for chronic hepatitis B with evidence of active viral replication 10 mg/day



a) acyclic nucleotide of adenosine.

- b) phosphorylated to inhibit Hep B DNA polymerases.
- c) is a chain terminator.
- d) is only a weak inhibitor of human DNA polymerase.
- e) renal toxicity may be a problem, requires monitoring.

F. Drugs Against Herpes Viruses

Double Stranded DNA viruses (once infected, virus stays for life)

Herpes simplex 1 (HSV-1 - cold sores)

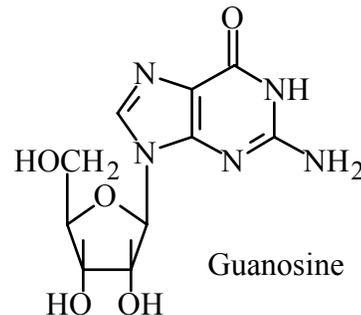
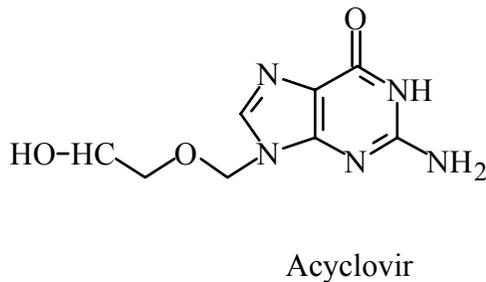
Herpes simplex 2 (HSV-2 - genital)

Varicella-zoster (VZV - Chicken-pox, shingles)

Epstein Barr (EBV - mono)

Cytomegalovirus – mostly subclinical but in immunosuppressed, can be severe.

1. Acyclovir (Zovirax ® and generic) (UW Formulary)



a) Place in Therapy:

Parenteral

- Initial and recurrent mucosal and cutaneous HSV-1 & 2 and varicella zoster infections in immunocompromised adults and children.
- Severe genital herpes infections (HSV-2) in adults (usually first episode).
- Herpes simplex encephalitis in patients older than 6 months of age.

Oral

- Management of genital herpes and herpes zoster.
- Acyclovir cream used for recurrent cold sores (HSV-1).

- b) Mechanism of Action: Acyclovir is a guanine analog which is phosphorylated (viral thymidine kinase) to acyclovir monophosphate then cell kinase 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.

c) Dose/Route:

Parenteral

- Herpes simplex: 12 years and older - 5 mg/kg Q8H for 7 days.

Under 12 years -

250 mg/m² Q8H for 7 days

- Herpes simplex encephalitis & Herpes zoster: Double the above dose

Oral

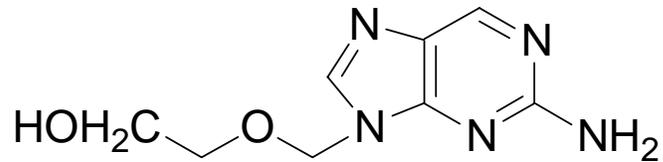
- Herpes simplex: 200 mg 5 times a day for 7-10 days or until resolution. For chronic suppressive therapy for recurrent HSV, the dose is 400 mg BID for 12 months

- Herpes zoster: 800 mg 5 times a day for 7-10 days starting within 48 hours of rash.

d) Activity against HSV1 > HSV2 > varicella > CMV. The need to give 5 x/d is a problem; 400mg TID is a more reasonable dose commonly prescribed.

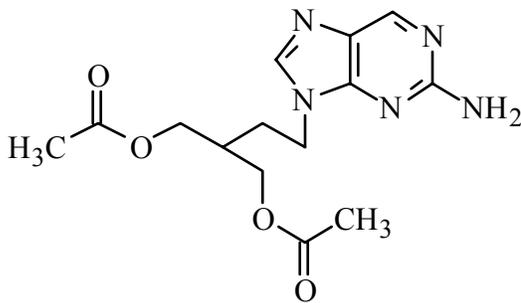
e) Toxicity: Decrease dosage in renal failure. Keep patient hydrated and administer IV slowly to decrease renal toxicity. Give IV slowly (1-2 hrs) - phlebitis may occur if given too fast. Headache is common (about 10%); nausea/vomiting occurs in about 5% of patients. Given with zidovudine may cause severe lethargy and drowsiness.

6-Deoxyacyclovir a pro-drug of Acyclovir. It is rapidly metabolized to Acyclovir by xanthine oxidase. Drug has the advantage of improved solubility and is used in the treatment of varivella-zoster infection.



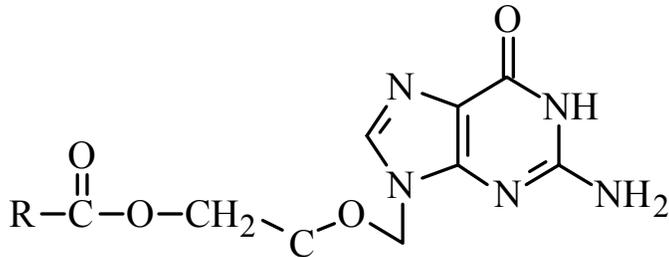
6-Deoxyacyclovir

2. **Famciclovir** (Famvir® Novartis) (UW Formulary)



- diacetate ester of penciclovir
- is a 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
- **uses:**
 - herpes zoster – 500mg TID x7d; reduces pain and time to healing and “post herpetic neuralgia”; start as soon as possible
 - recurrent genital herpes – reduces viral shedding and time to heal, 125mg BIDx5d
 - suppressive therapy – 250 BID for 1 year

3. **Valacyclovir** (Valtrex® Glaxo Smith Kline) (UW Formulary)



- valene ester of acyclovir

- prodrug of acyclovir

- has a more prolonged “release” of acyclovir and can give fewer doses per day

- indications for:

herpes zoster – 1g TID, start within 72h of symptom onset x7d

genital herpes

primary – 1g BID X 10d

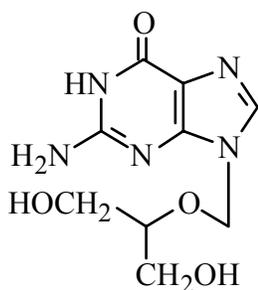
recurrent – 500mg BID X 3d

suppressive therapy – 500mg-1g daily for 1 year (HIV patients 500mg BID x 6 mos)

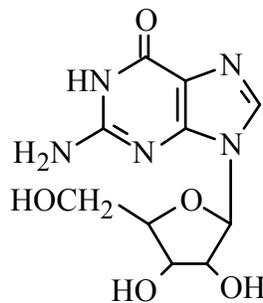
cold sores – 2g BID x1d

G. Drugs Against CMV

1. **Ganciclovir** (Cytovene® Roche) (UW Formulary)



Ganciclovir



Guanosine

- a) Place in Therapy: active against herpes viruses but especially cytomegalovirus (CMV) infections, which typically cause retinitis, and may cause pneumonia, colitis, esophagitis, and hepatitis in immunocompromised patients.
- b) Mechanism of Action: Ganciclovir is a guanine analog structurally very similar to acyclovir, differing only by the addition of a hydroxymethyl group on the purine side chain. Ganciclovir is phosphorylated to ganciclovir-triphosphate which blocks the uptake of guanosine into the growing viral DNA by competing for binding sites. Ganciclovir is active against all herpes viruses, but is especially useful for cytomegalovirus (CMV). It is not a chain terminator like acyclovir.

c) Dose/Route:

Induction: 5 mg/kg Q12H slow IV infusion.

Maintenance: 5 mg /kg ZD or 6 mg/kg 6 days/week slow IV infusion

Ganciclovir tablets

Used for maintenance – 1g TID or 500mg 6X/d with food

Poor bioavailability - ~6%

Intraocular implant is now available

- d) Toxicity: The most common dose-limiting reaction myelosuppression (granulocytopenia, thrombocytopenia, anemia). Usually interruption of therapy will result in a rebound of the blood count in 3-7 days. Other adverse effects are confusion, headache, nausea/vomiting, and retinal detachment (rare). Ganciclovir is teratogenic and carcinogenic in animals. Ganciclovir 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. Avoid use with other drugs adversely affecting the bone marrow (e.g. zidovudine).

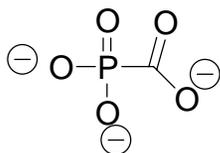
2. **Valganciclovir** (Valcyte ® Roche) (UW formulary)

- a) 450mg tablets now available
- b) valine ester of ganciclovir (prodrug) similar to Valacyclovir.

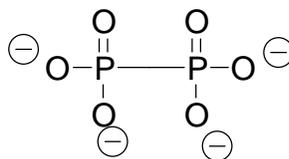
- c) ~60% bioavailable
- d) used for CMV retinitis treatment, 900mg BID x 21d with food
- e) used for maintenance to avoid recurrences, 900mg qd with food
- f) same limitations and concerns as ganciclovir

4. **Foscarnet** (Foscavir ® Astra) (UW formulary)

Foscarnet sodium is a trisodium phosphate that inhibits DNA polymerase of herpes viruses including CMV and retroviral RT.



Foscarnet



Pyrophosphate

- a) **Place in Therapy:** Used for treatment of all CMV infections; however, ganciclovir is usually tried first. FDA approved for treatment of CMV retinitis in AIDS patients. In combination with ganciclovir, the results have been promising even in progressive disease with ganciclovir-resistant strains. Foscarnet does not require phosphorylation to become active, and therefore it is thought that this drug may be effective for CMV infections that are resistant to ganciclovir
- b) **Mechanism of Action:** 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 inhibits replication of all herpes virus DNA *in vitro*.
- c) **Dose/Route:** IV only

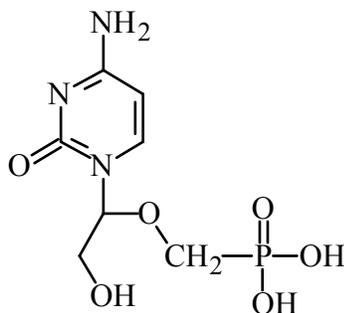
Induction: 60 mg/kg Q8H IV (over 1 hour) for 2-3 weeks.

Maintenance: 90-120 mg/kg/day IV (over 2 hours)

- d) **Toxicity**: The major dose-limiting toxicity of foscarnet is renal impairment. 33% of patients with AIDS in clinical trials developed significant renal impairment when given this drug. The induction dose must be adjusted if the patient has renal impairment. Renal function must be monitored during therapy and adjusted based on the patient's renal response.

Foscarnet has been associated with electrolyte imbalances, such as hypocalcemia, hypomagnesemia, hypokalemia, hypophosphatemia and hyperphosphatemia. These problems may be alleviated by giving a hydration drip with therapy.

5. **Cidofovir** (Vistide ® Gilead) (UW formulary)



- a) A synthetic acyclic purine nucleotide analog of cytosine 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.
- b) Given IV for treatment. 1g week x 2 weeks then 1g on alternate weeks. Given with probenecid to decrease renal tubular secretion.
- c) Can be used every 2 weeks for maintenance therapy; has long T 1/2.

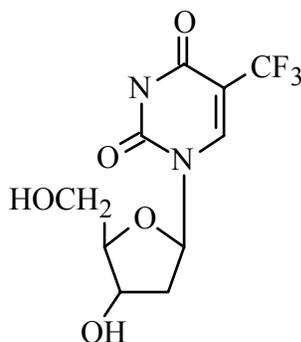
- d) Boxed warning on renal toxicity. Avoid use with other nephrotoxic drugs. Hydrate the patient well. Give with probenecid to decrease nephrotoxicity.
- e) Also active against HSV, VZV and HPV.
- f) Bioterrorism – a hexadecyloxypropyl derivative is absorbed orally and is active against pox viruses. It is active in cowpox infected mice. May be helpful for use with smallpox exposure.

5. **Fomivirsen** (Vitravene®, Novartis)

- a) for intravitreal injection to treat CMV retinitis
- b) First “antisense” oligonucleotide agent approved as an alternative 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.

6. **Trifluorothymidine** (UW formulary)

Flourinated pyridine nucleoside. Potent specific inhibitor of replicaion of HSV 1. Like other antiherpes drugs, it is first phosphorylated by thymidine kinase to the triphosphate which is then incorporated into viral DNA in place of thymidine to stop formation of late virus mRNA and subsequent synthesis of virion proteins.



Trifluorothymidine

- a) Greater water solubility makes it active against HSV-1 and HSV-2. Useful for treatment of CMV and VZV infections.
- b) topical use to treat primary keratoconjunctivitis and recurrent epithelial keratitis. Useful for some cases of herpetic iritis and established stromal keratitis. Plasma half-life 18 minutes and is mostly excreted in urine unchanged.
- c) Side effects include temporary burning, localized edema and bone marrow toxicity.

H. Drugs Against HIV (All are on UW formulary)

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 Protease inactivate RT activity and block release of viral particles from the infected cells.

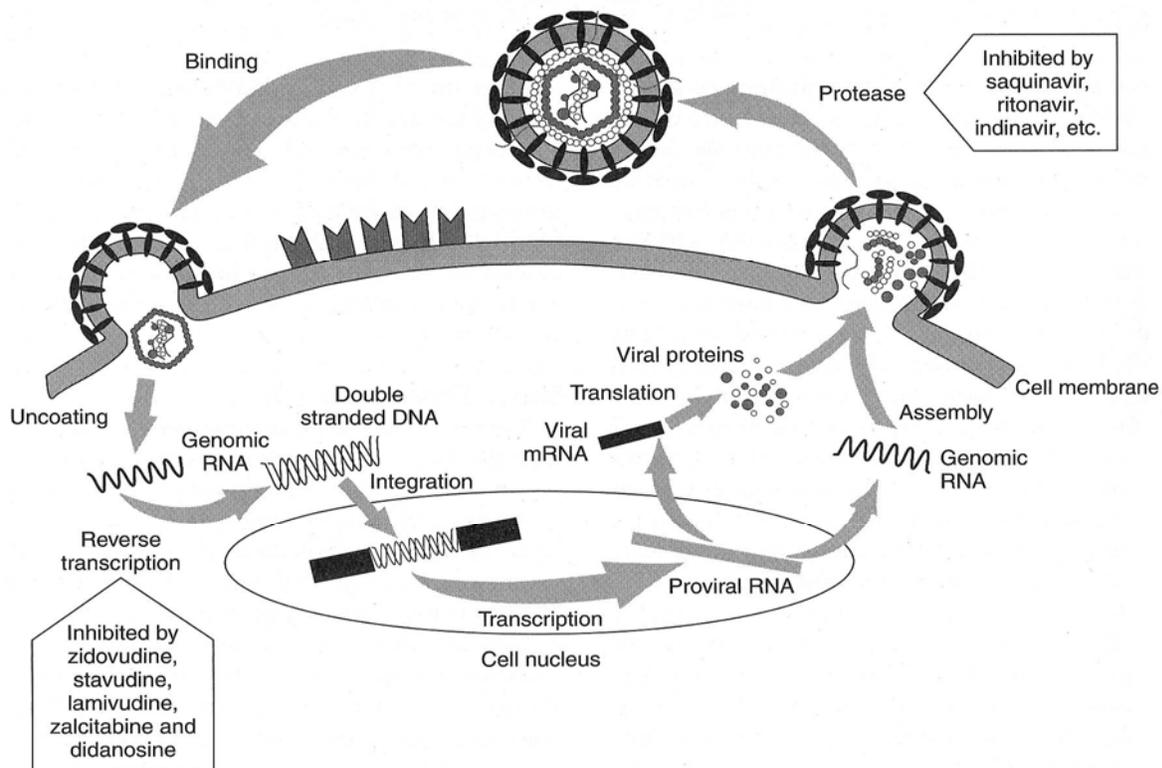
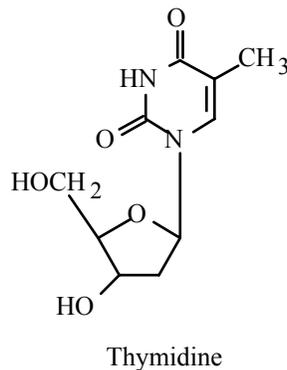
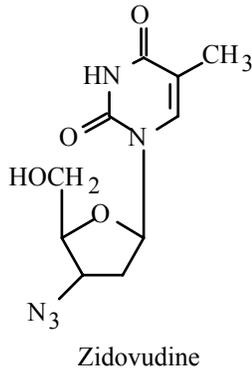


Fig. 39.2: The life cycle of HIV and the site of action of nevirapin and other antiretroviral agents. PI= protease inhibitors (e.g. nelfinavir, indinavir, ritonavir, saquinavir) RTI = Reverse transcriptase inhibitors (e.g., didanosine, lamivudine, stavudine, zalcitabine, zidovudine, efavirenze, dleviradine, veriapine). Reproduced with permission from Adis Internation Ltd., New Zealand from original article by M. Barry in *Clinical Pharmacokinetics* 1997, 32(3):194-209.

- Reverse Transcriptase Inhibitors (RTI)** - All are 2,3 dideoxynucleosides. All inhibit DNA dependent RNA polymerase (reverse transcriptase). All block early events in virus replication. All are chain terminators (like ACV). Once viral DNA is integrated into host cell genome, they don't work. The non-nucleoside inhibitors bind to sites separate from the substrate binding site.

(See diagram for sites where HIV can be hit in theory.) 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.

For example:



Here are the agents available now.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Abacavir

Ziagen ®

Didanosine

Videx ®

Lamivudine*

Epivir ®

Stavudine

Zerit ®

Zalcitabine

Hivid ®

Zidovudine (AZT)

Retrovir ®

Limiting adverse effects

fatigue, headache, myopathy, skin

pancreatitis, peripheral neuropathy

abdominal pain, malaise

peripheral neuropathy

peripheral neuropathy

anemia, bone marrow, myopathy

Emtricitabine	Emtriva ®	lactic acidosis, hepatomegaly
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*approved also as agent to treat chronic hepatitis B

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Limiting adverse effects

Delavirdine	Rescriptor ®	rash, fever, kidney, P450 3A4 inducer
Efavirenz	Sustiva ®	rash, CNS, P450 3A4 inducer
Nevirapine	Viramune ®	rash, fatigue, P450 3A4 inducer

2. Drugs Against HIV - HIV Protease Inhibitors

This approach has resulted in useful HIV treatment. See figure to see that the protease is involved in **maturation** of the virus after it exits the cell. These drugs hit virus outside the cell. The protease cleaves a huge protein called "gag-pol" (based on the gene segment coding for it) into capsid, reverse transcriptase, integrase (see handout). Molecular modeling of the enzyme's active site has led to several inhibitors. Six 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.

Agent	Trade name	Limiting Adverse Effects
Saquinavir	Fortovase ®	nausea, diarrhea, CYP 3A4 inhibitor
Indinavir	Crixivan ®	nausea, diarrhea, CYP 3A4 inhibitor
Ritonavir	Novir ®	numbness, nausea, diarrhea, strong CYP 3A4 inhibitor
Nelfinavir	Viracept ®	diarrhea, CYP 3A4 inhibitor
Amprenavir	Agenerase ®	rash, numbness, CYP 3A4 inhibitor
Atazanavir	Reyataz ®	diabetes, PR interval prolonged

3. Fusion inhibitors - NEW

Enfuvirtide	Fuzeon ®	Approved Mar 03; blocks fusion of HIV-1 with CD-4 cells, i.e. blocks viral entry; binds to gp41 subunit of viral envelope glycoprotein. Local pain at injection site, and reports of increased pneumonia are reported problems.
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Enfuvirtide 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.