VIROLOGY - CHAPTER NINE

ANTI-VIRAL CHEMOTHERAPY

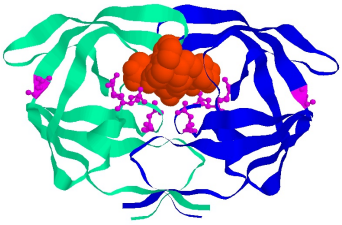
Dr Richard Hunt

TEACHING OBJECTIVES

To elucidate the drugs that are currently used as anti-viral agents and to determine why they are effective agents. The mode to action of these drugs will be discussed

SEE ALSO
Anti-HIV Chemotherapy chapter

Molecular Structure pop-up boxes show chemical and three-dimensional structures



Anti-bacterial drugs such as the penicillin antibiotics 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 replication enzymes. Even so, unfortunately, many anti-virals that are apparently effective *in vitro* are ineffective *in vivo*.

A successful anti-viral drug should:

(i) interfere with a virus-specific function (either because the function is unique to the virus or the similar host function is much less susceptible to the drug)
or
(ii) interfere with a cellular function so that the virus cannot replicate. To be specific, the anti-viral drug must only kill virus-infected cells. This could be done by restricting drug activation to virus-infected cells.

An ideal drug should be:

- Water-soluble
- Stable in the blood stream
- Easily taken up by cells

An ideal drug should NOT be:

- Toxic
- Carcinogenic
- Allergenic
- Mutagenic
- Teratogenic

Toxicity of an anti-viral drug may be acceptable if there is no alternative: such as, for example, in symptomatic rabies or hemorrhagic fever

Obviously, a good drug must show much more toxicity to the virus than the host cell. We measure selectivity by the therapeutic index of the drug

Therapeutic index (T.I.): Minimum dose that is toxic to cell
Minimum dose that is toxic to virus

Effective drugs have a T.I. of 100-1000 or better.

Just as with anti-bacterials, we must find a virus Achilles heel. This could be an enzyme that is unique to the virus so that the drug is not toxic to the host cell.

The following is a list of viruses that are known to code for their own enzymes. Among the *other* enzymes are: proteases, mRNA capping enzymes, neuraminidases, ribonucleases, kinases and uncoating enzymes.

Virus	RNA/DNA polymerase	Other
Picorna	+	+
Reo	+	+
Toga	+	+
Orthomyxo	+	+
Paramyxo	+	+
Rhabdo	+	+
Arena	+	?
Corona	+	+
Bunya	+	?
Parvo	-	+
Adeno	+	+
Herpes	+	+
Irido	+	+
Pox	+	+
Hepatitis B	+	+

The very first licensed anti-viral drug was idoxuridine (1963), a pyrimidine analog that inhibits viral DNA synthesis. It is still used topically for epithelial herpetic keratitis but has largely been replaced because other drugs are less toxic. It is toxic because it lacks specificity, i.e. the drug inhibits host DNA polymerization as well as that of the virus.

One of the better anti-viral drugs that we have dates from 1983: Acyclovir (acycloguanosine) which is a purine analog. It inhibits herpes DNA replication. It is also a nucleoside analog but, in contrast to idoxuridine, is highly specific and does not exhibit severe toxic side effects...for the reason for this, see below.

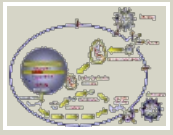

Cellular targets for drugs

Figure 1

POSSIBLE PHASES OF LIFE CYCLE ON WHICH ANTI-VIRAL ATTACK MIGHT BE LAUNCHED

The life cycle of a virus comprises several stages such as binding to the cell surface, replication, protein synthesis etc. and all of these stages may be the target of anti-viral drugs. Among the life cycle stages that have been targeted by potential therapeutic agents are:

- *Attachment of the virus to the cell surface, perhaps as a result of competition with a specific viral receptor.*
- *Uptake into intracellular vesicles (endosomes)*

WEB RESOURCES

Classes of anti-HIV drugs
NSAID

- *Uncoating of virus (loss of protein coat, fusion of lipid membrane with endosome/lysosome). Note: the endosome/lysosome compartment is acidic and inhibition of acidification of this compartment might be a good target.*
- *Integration of the viral DNA into chromosomal DNA of the host cell (where this occurs).*
- *Transcription of genome to new RNA or DNA (polymerases are the target).*
- *mRNA transcription*
- *mRNA processing (poly adenylation, methylation, capping, splicing)*
- *Translation to protein*
- *Post-translational modification of proteins (glycosylation, phosphorylation, fatty acylation, proteolysis). Some of these are essential for functional, infective viral progeny.*
- *Assembly of the components into the whole virus*

We shall look at each of these life-cycle stages (figure 1) in the following sections.

BINDING TO RECEPTOR OR UPTAKE INTO INTRACELLULAR VESICLES

There, were until recently, no good drugs that stop receptor binding by any virus (but see influenza sialidase inhibitor below). However, possibilities include the use a peptide that mimics the receptor such as soluble CD4 protein. This would bind HIV gp120 and stop it binding to the receptor on the cell surface. However, there is a stability problem. The soluble protein is rapidly broken down and cleared from the circulation, i.e. an efficacious concentration is not achieved for a useful period. Attempts have been made to stabilize proteins but little success has been achieved. There have been attempts to couple soluble CD4 to toxins to kill infected cells, again with little success. In some cases, soluble CD4 can make the virus more infectious in laboratory studies. It is not known why this happens but a possible explanation might be that binding to gp120 causes a conformational change in the latter giving it a higher affinity for the co-receptor that is important, along with CD4 antigen, in infection of a cell by HIV (see HIV, section 7). It is also possible that soluble CD4 bound to gp120 might promote fusion.

PRO 542 is a tetrameric form of soluble CD4 antigen genetically fused to an immunoglobulin for added stability. This CD4-immunoglobulin fusion protein comprises the D1 and D2 domains of human CD4 and the heavy and light chain constant regions of human IgG2. It has a high affinity for gp120.

For HIV to infect a cell, it must bind both to CD4 antigen and to a co-receptor, a chemokine receptor. The chemokine receptors bind chemokines and these can block binding to HIV gp120. Derivatives of one such chemokine (RANTES) have been used as agents to block virus binding. In addition to binding to the CCR5 chemokine receptor, these derivatives, like the natural chemokine, down-regulate the co-receptor by endocytosis, making it more difficult for the virus to bind. Chemokines such as RANTES are pro-inflammatory and chemotactic for leukocytes but these properties can be reduced by chemical modification at the N-terminus. Such chemokine derivatives are excellent antagonists of HIV binding and can protect monkeys that are exposed to HIV in the vagina. Anti-co-receptor monoclonal antibodies are also being developed to block virus binding. Another approach is to use peptides that are analogous to the transmembrane sequence of the co-receptor; these disrupt the interaction between the seven transmembrane alpha helices of the co-receptor protein.

AMD-3100
Chemical name: 1,4,8,11-Tetraazacyclotetradecane, 1,1'-(1,4-phenylenebis(methylene))bis-, octahydrochloride
In addition to peptide approaches to disrupt HIV-co-receptor interactions, some small molecule inhibitors have been developed. For example, AMD3100/JM-3100 appears to bind to the ligand binding site of the co-receptor known as CXCR4 (fusin) and blocks the interaction between CXCR4 and the V3 loop of gp120.

Maraviroc
Chemical name: 4,4-difluoro-N-{(1S)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide.
Maraviroc (brand-named Selzentry, or Celsentri outside the U.S.) was approved for use in HIV-infected patients in August 2007. It blocks the interaction between chemokine receptor CCR5 and HIV gp120. Because HIV can also use another co-receptor, CXCR4, an HIV tropism test is performed to determine if the drug will be effective. In a study comparing Maraviroc plus the conventional HAART triple combination of drugs with the standard of care HAART alone, use of HAART plus Maraviroc gave twice as many patients with HIV levels of fewer than 50 copies/ml compared to standard HAART.

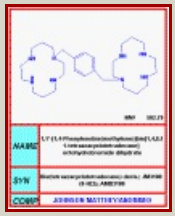


Figure 1a
AMD3100

FUSION OF VIRAL AND HOST CELL MEMBRANE

Agents that block fusion of HIV with the host cell by interacting with gp41

Enfuvirtide
Other names: DP-178, pentafuside, T-20, Fuzeon$^{\bar{U}}$.

Peptides derived from gp41 can inhibit infection, probably by blocking the interaction of gp41 with cell membrane proteins during fusion or by stopping the conformational change that results from the association of two gp41 molecules and which is necessary for fusion. Enfuvirtide (Fuzeon) is a 36 amino acid peptide that corresponds to residues 127-162 of gp41 and blocks this conformational change. In clinical trials, a nearly two log reduction in plasma viral levels was achieved. This drug was approved in 2003 but recent reports suggest low bioavailability and the emergence of resistant mutants.

There is a cavity on gp41 that could hold a small molecule inhibitor. Peptides containing D-amino acids that would fit this cavity have been identified and inhibit fusion.

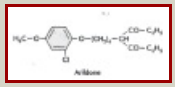
Others

RFI-641
Chemical Name: 4,4"-bis-{4,6-bis-[3-(bis-carbamoylmethyl-sulfamoyl)-phenylamino]-(1,3,5) triazin-2-ylamino}-biphenyl-2,2"-disulfonic acid
RFI-641 (biphenyl triazine) inhibits fusion of the membrane of respiratory syncytial virus (RSV) with the cell membrane. It seems to alter the conformation of the fusion (F) protein of the virus and is active *in vivo* in several animal models. It is active against RSV A and B strains. The drug is much better than ribovirin (the only routinely used drug in treating RSV infections) and seems to be RSV-specific. The drug has now been abandoned for routine use because of toxicity problems and delivery problems. It cannot be taken orally and so is delivered as an aerosol but elderly patients would likely find such a mode of delivery problematical. It may be of use in infants and derivatives may be less toxic.

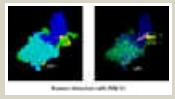
BMS-433771
Chemical Name: 2H-Imidazo(4,5-c)pyridin-2-one, 1-cyclopropyl-1,3-dihydro-3-((1-(3-hydroxypropyl)-1H-benzimidazol-2-yl)methyl)-
BMS-433771 is an RSV fusion inhibitor. It works by inhibition of viral F protein-induced membrane fusion and is active against both A and B groups of RSV. It is efficacious against RSV infection in two rodent models when dosed orally prior to infection and may be of clinical use.

More on RSV

UNCOATING


Arildone
Figure 2

Uncoating of the virus (i.e. the loss of the lipid envelope of membrane-containing viruses or the loss of nucleocapsid proteins in non-enveloped viruses) often occurs in low pH endosome or lysosomes, as the result of a pH-dependent fusogen. Note: Some viruses do not need an acidic environment for fusion and fuse with the plasma membrane; this is the case with herpes viruses and HIV and leads to the formation of syncytia.


Human rhinovirus with WIN V1 (arrows) buried in a pocket in the VP1 protein

Arildone and the WIN compounds
Chemical name: 4-(6-(2-Chloro-4-methoxy)phenoxy)hexyl-3,5-heptanedione
Arildone and the WIN compounds inhibit uncoating of picornaviruses, which do not have a lipid membrane. The drug inserts into a canyon in VPI protein of virus and blocks ion transport. For more information see chapter 10, part 3.


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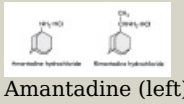
Figure 3

MOLECULAR

Pleconaril
Chemical name: 3-(3,5-Dimethyl-4-(3-(3-methyl-5-isoxazolyl)propoxy)phenyl)-5-(trifluoromethyl)-1,2,4-oxadiazole
Other names: Win 63843, Picovir
This acts like a WIN compound in that it fits into a hydrophobic pocket in the nucleocapsid and interrupts the replication of the virus by stopping the shedding of nucleocapsid proteins from the RNA. This orally taken compound is broadly active against a variety of entero- and rhinoviruses (picornaviruses) but the reduction in the duration of symptoms is small and only occurs in some populations. An intranasal formulation of pleconaril represents an optimized delivery approach, as compared to the earlier oral formulation.

STRUCTURE
Arildone
Pleconaril



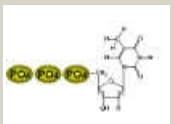
Amantadine (left)
Rimanadine (right)
Figure 4

WEB RESOURCES
Antiviral Drugs and the Flu
CDC

MOLECULAR STRUCTURE
Amantadine
Rimantadine

Acyclovir is phosphorylated first by a viral kinase to acycloGMP and then by cellular kinases to acycloGDP and acyclo GTP

Figure 5



Three phosphates are added to thymidine. The first is added by the viral enzyme and the remainder by cellular enzymes
Figure 6

Amantadine
Chemical name: tricyclo[3.3.1.1.^{3,7}]decane-1-amine hydrochloride
Other names: 1-adamantanamine, amantadine HCl, Symmetrel^{Ū}, Mantadix^{Ū}, Amantan^{Ū}

Rimantadine
Chemical name: alpha-methyltricyclo[3.3.1.1.^{3,7}]decane-1-methanamine hydrochloride
Other names: alpha-methyl-1-adamantanemethylamine HCl, Flumadine^{Ū}
These were originally thought to be lysosomotropic, that is they were thought to stop acidification of the endocytic vesicles and lysosomes. However, they are now known to act on a viral protein, the M2 ion channel, which is necessary for the acidification of the enveloped virus in the endosome, a process that must occur before uncoating of the virus. These drugs may also act on maturation of influenza HA glycoprotein so that progeny virions are poorly infective.

These drugs are good for oral prophylaxis against influenza A (but not influenza B). They are a good alternative to the vaccine in immunocompromised patients and the elderly. Other than this, they are not used much in western countries. Prophylactic rimantadine has been used a lot in countries of the former USSR. Both of these drugs are licensed for use in US. Interest in these drugs has rearisen because of the possibility of an avian flu pandemic since currently there is no vaccine for this type of influenza virus (H5N1) and it will take several months to develop a vaccine after the pandemic strain is identified.

In the 2005-2006 influenza season, 92% of H3N2 strains examined had a mutations that would confer resistance to these drugs as did 25% of the H1N1 strains tested. Similar problems were seen in 2006-2007 and so these drugs are not recommended until the per cent resistance in the major circulating types drops.

NUCLEIC ACID SYNTHESIS

The best anti-viral drugs that we have are of this type.

They are selective because:

- the virus may use its own enzyme to activate the drug
  and/or
- the viral polymerases may be much more sensitive to the drug than the corresponding host enzymes

Thymidine kinase substrates

The thymidine kinase (figure 6) of herpes simplex (and other) viruses allows the virus to grow in cells that do not have a high concentration of phosphorylated nucleic acid precursors. These are usually cells that are not replicating their genome (e.g. nerve cells). Resting cells do, however, have unphosphorylated nucleosides. By bringing in its own kinase, the virus can grow in non-dividing cells by phosphorylating the cells' nucleosides.

The name of the enzyme is a bit of a misnomer since it can work on other nucleosides than thymidine (thymidine happens to be the best substrate), i.e. the enzyme is non-specific as to substrate. This is in contrast to the host cell thymidine kinase which is very specific to thymidine since the cell has other enzymes to phosphorylate the other nucleosides. This lack of specificity of the viral enzyme allows it also to work on nucleoside-analog drugs and phosphorylate them. The host enzyme, because of its greater specificity, is much less good at this (and often does not phosphorylate the drug at all).

The fact that the viral enzyme is quite good at phosphorylating the drug has another advantage. We can administer the nucleoside-analog in a non-phosphorylated form. This is useful as it is difficult to get phosphorylated drug into the cell because plasma membranes are poorly permeable to phosphorylated compounds in the absence of a specific transport protein.

Thus the need for activation restricts use of drug to viruses with their own thymidine kinase or that cause cell to overproduce the endogenous enzyme (which may, if we are lucky, activate the drug to a lesser degree).

To recapitulate, the great use of these drugs results from the facts that:

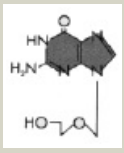
- they are only activated by the virus-infected cell
- the activated form of the drug is rendered even more specific as a result of the viral DNA polymerase being more sensitive to the drug than the host enzyme.

Most nucleic acid synthesis inhibiting drugs are nucleoside analogs with an altered sugar, base or both. Acyclovir (acycloguanosine) is the best example of such a drug and is used to treat herpes virus infections. It gets into the cell across the plasma membrane as the nucleoside form and is then specifically phosphorylated inside the cell by herpes virus thymidine kinase to an active form. It then blocks DNA synthesis by inhibiting polymerization; it is a chain terminator.

DNA Synthesis Inhibitors

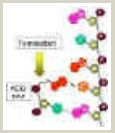
(1) Sugar modifications

Acyclovir/Acycloguanosine
Chemical name: 9-(2-hydroxyethoxymethyl)guanine, acycloguanosine (ACG)
Other names: Aciclovir (ACV), Zovirax™. (figure 7).
As noted above, this drug is very selective and one of our better anti-viral drugs. It is non-toxic to uninfected cells (except some renal dysfunction) because it is not activated by uninfected cells (because the drug is a poor substrate for the very specific cell thymidine kinase). Moreover, the DNA polymerase of herpes simplex virus is 10 times more sensitive than cellular DNA polymerase. This drug is a competitive inhibitor - it competes with dGTP - but it also acts in another way that is more important: When it gets incorporated into DNA, it acts as a chain terminator (figure 8). It is taken orally, topically or intra-venously.


Acyclovir
Figure 7

HSV-1, HSV-2 and VZV are susceptible to acyclovir.

Acyclovir is effective against herpes simplex keratitis, latent HSV, fever blisters (H. labialis), genital herpes. Acyclovir-resistant mutants are a problem after long term use and have been shown to result from changes in the thymidine kinase or polymerase gene.


Chain termination
Figure 8

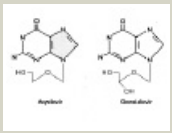
There is a prodrug form of acyclovir called Valaciclovir ((VACV), Zelitrex™, Valtrex™) which is an L- valine ester of the drug. This can be taken orally.

Penciclovir
Chemical Name: 9-(4-hydroxy-3-hydroxymethyl-but-1-yl)guanine
Other names: PCV, Denavir™, Vectavir™
Used against HSV-1 and -2 and VZV, Penciclovir is similar in action to acyclovir, that is it is a chain terminator. It can only be used as a topical cream because of insolubility.

MOLECULAR STRUCTURE
Acyclovir

Famciclovir
Chemical Name: diacetyl ester of 9-(4-hydroxy-3-hydroxymethyl-but-1-yl)-6-deoxyguanine
Other names: FCV, Famvir™.
This is a prodrug of Penciclovir and is converted to Penciclovir as a result of oxidation and the hydrolysis of the two ester groups. Because of the esterification, it is soluble in water and can be administered orally. It is also used for HSV-1 and -2 and VZV infections.

Ganciclovir
Chemical name: 9-(1,3-dihydroxy-2-propoxymethyl)guanine
Other names: DHPG, GCV, Cymevene™, Cytovene™ - figure 9
This drug is very similar to Acyclovir, it just has an extra -OH. It is also available as a prodrug called Valganciclovir which is an L-valine ester of Ganciclovir (Valcyte). Oral Valganciclovir will probably to replace intravenous Ganciclovir for therapy and prevention of cytomegalovirus (CMV) infections. Ganciclovir is active against CMV for which it is the drug of choice. Acyclovir has some activity against CMV in culture but has not found much use in therapy of these infections because of the superiority of Ganciclovir.


Acyclovir Gancyclovir
Figure 9

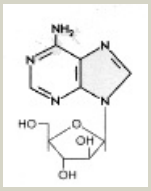
As with Acyclovir, Ganciclovir targets the viral DNA polymerase and acts as a chain terminator. In herpes virus-infected cells, it is phosphorylated first by the viral thymidine kinase and then by cell kinases to yield the triphospho form of the drug which is incorporated into and terminates the DNA chain. However, CMV does not encode a thymidine kinase. Instead, Ganciclovir is phosphorylated by a CMV-encoded protein kinase (UL97) which accounts for its specificity for infected cells. Selectivity is also achieved because the viral polymerase has 30 times greater affinity for Ganciclovir than the host enzyme.

MOLECULAR STRUCTURE
Ganciclovir

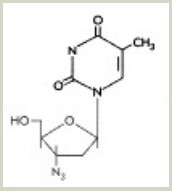
Normally, Ganciclovir is given intra-venously at a level of 10mg/kg per day or orally at 3000mg/day. It is often used for CMV retinitis in AIDS patients for whom there is an

intraocular (that is, intravitreal) implant known as Vitrasert. This contains 4.5 mg Ganciclovir for localized therapy.

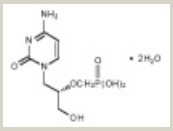
Adenosine arabinoside
Chemical name: 9-beta-D-Arabinofuranosyl-9H-purin-6-amine
Other names: Vidarabine, Ara-A - figure 10
Acyclovir and Ganciclovir are chain terminators because they do not have a complete sugar ring; the appropriate 3' -OH group needed to form a phosphodiester bond during DNA elongation is missing. Adenosine arabinoside has a complete sugar but it is arabinose rather than ribose. This drug has severe side effects and is only used in potentially lethal disease. In addition, it is easily deaminated in the bloodstream to a less effective form, ara-hypoxanthine


Ara-A
Figure 10

Zidovudine
Chemical name: 3′-azido-2′,3′-dideoxythymidine
Other names: Azidothymidine, AZT, RetrovirŪ - figure 11A
This drug is also a chain terminator. It is phosphorylated by a cell kinase and so it can be used against viruses without their own thymidine kinase (e.g. HIV). Reverse transcriptase (RNA-dependent DNA polymerase) is more sensitive to the drug than human DNA-dependent DNA polymerase accounting for the specificity but there are severe toxicity effects. It is used as an anti-HIV type 1 and type 2 drug (see HIV). Because of the use of RNA polymerase II in the synthesis of the viral genome of retroviruses and the consequent high rate of mutation of the virus, the selective pressure of the presence of the drug rapidly leads to the emergence of resistant viral mutants. All of these have mutations in reverse transcriptase. Because of the emergence of resistant mutants, AZT is administered in combination with other drugs.


AZT
Figure 11A

MOLECULAR STRUCTURE
AZT


Cidofovir
Figure 11B

Cidofovir
Chemical name: 1-[(*S*)-3-hydroxy-2-(phosphonomethoxy)propyl]cytosine dihydrate (HPMPC)
Other names: VistideŪ - figure 11B

Cidofovir is both a DNA chain terminator and DNA polymerase inhibitor. It is an acyclic nucleoside phosphonate (not a phosphate) in which the C-O-P bond in a nucleoside monophosphate has been replaced by a phosphonate (C-P) bond that provides an enzymatically stable derivative with a long half life.

The drug is administered in the phosphonomethoxy-nucleoside form and is phosphorylated twice intracellularly to the active diphosphate form using two cellular kinases (pyrimidine nucleoside monophosphate kinase and pyrimidine nucleoside diphosphate kinase. A viral kinase is not involved, in contrast to acyclovir which is administered as the nucleoside form and the first phosphate is added by viral thymidine kinase).

Cidofovir inhibits the DNA polymerases of a number of viruses at concentrations that are substantially lower than those needed to inhibit human DNA polymerases. It is active against herpes viruses with fewer side effects than Ganciclovir although it does show nephrocytotoxicity and a number of other side effects. It must be administered along with probenecid in order to block renal tubular secretion of the drug.

Cidofovir is particularly useful in the treatment of cytomegalovirus and is indicated for the treatment of CMV retinitis in patients with AIDS. It may be useful for treatment of acyclovir-resistant herpes infections. It is also active against pox viruses, including the *molluscum contagiosum virus,* BK virus, which is a polyoma virus, and adenoviruses. It is promising for the treatment of immunocompromised patients for gasteroenteritis caused by adenovirus, although no control studies have been carried out, and has been used as an adjunctive treatment in addition to HAART in the treatment of AIDS patients with progressive multifocal leukoencephalopathy (PML). The latter is caused by JC, another human polyoma virus.

Cidofovir was recently (March 2007) used (along with an experimental drug, ST-246) in treating a case of *eczema vaccinatum* in a two-year old boy. This is an unusual side effect of smallpox vaccination in which the live vaccinia virus in the vaccine can be passed to contacts of the vaccinee who are usually immunocompromised. It this case, because of the eczema, the virus was able to enter the patient's skin cells and replicate, initially causing a widespread rash and then blisters with a central dimple which is indicative of vaccinia infection. The rash encompassed 50% of the patient's keratinized skin. Although *eczema vaccinatum* can be fatal, the patient was discharged after 48 days in hospital.

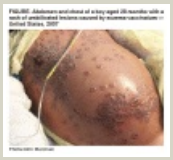
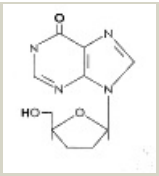


Figure 11C
Eczema vaccinatum in a 28 month old boy

WEB RESOURCES
Cidofovir
Medicinenet

CASE REPORT
Household Transmission of Vaccinia Virus from Contact with a Military Smallpox Vaccinee


DDI
Figure 12

MOLECULAR STRUCTURE
DDI

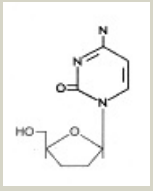
Other sugar modifications:

Dideoxyinosine
Chemical name: 2′,3′-dideoxyinosine
Other names: DDI, Didanosine, Videx® - figure 12
This is licensed for use against HIV in AZT-resistant patients and in combination drug treatments along with AZT.

Zalcitabine
Chemical name: 2′,3′-dideoxycytidine
Other names: Dideoxycytosine, DDC, Hivid®, - figure 13
DDC is also licensed for use with AZT in HIV patients. Again, as with AZT, there is pronounced toxicity because of lack of specificity to the viral polymerase and the rapid emergence of resistant HIV mutant strains.

Stavudine
Chemical name: 2′,3′-didehydro-2′,3′-dideoxythymidine
Other names: d4T, Zerit®.
This is also used in combination therapy, particularly in advanced HIV disease.

Lamivudine
Chemical name: (−)-β-$_{L}$-3′-thia-2′,3′-dideoxycytidine
Other names: 3TC, Epivir®, Zeffix®).
This is active against HIV types 1 and 2 and also against hepatitis B virus. In both cases it acts as a chain termination during reverse transcription. For HIV, 3TC can be administered with AZT in a combination drug (Combivir®) or with AZT and Abacavir (Trizivir®).


DDC
Figure 13

Abacavir
Chemical name: (1*S*,4*R*)-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol succinate
Other names: ABC, Ziagen®

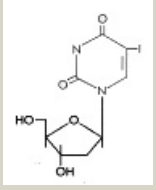
Emtricitabine
Chemical name: (−)-β-$_{L}$-3′-thia-2′,3′-dideoxy-5-fluorocytidine
Other names: (−)-FTC, Emtriva®.
This is another reverse transcriptase inhibitor that is active against HIV and hepatitis B virus.

Tenofovir disoproxil
Chemical name: Fumarate salt of bis(isopropoxycarbonyloxymethyl) ester of (*R*)-9-(2-phosphonylmethoxypropyl)adenine
Other names: bis(POC)PMPA, Viread®
Tenofovir is active against retroviral and hepatitis B reverse transcriptase and is a chain terminator. It is often used in combination with lamivudine and a non-nucleoside reverse transcriptase inhibitor, efavirrenz. It should not be used in combination with lamivudine and abacavir. In addition to being licensed for use in treating HIV infection, tenofovir is also approved for treating hepatitis B.

(2) Base modifications

These are pyrimidine analogs that are incorporated into DNA by the viral DNA polymerase. They form unstable base pairs and mis-translation results in mutant proteins. They are competitive inhibitors of the viral DNA polymerase after intracellular phosphorylation.

Bromovinyl deoxyuridine (Brivudin)
Chemical name: (*E*)-5-(2-bromovinyl)-2′-deoxyuridine, bromovinyldeoxyuridine
Other names: BVDU, Zostex®, Zonavir®, Zerpex®.
BVDU is used for treating HSV (type 1) and VZV. The drug is initially phosphoryalted by viral thymidine kinase, hence its specificity. It is used various HSV and VSV infections including HSV keratitis and genital herpes. It can be given orally or topically.


IDU
Figure 14

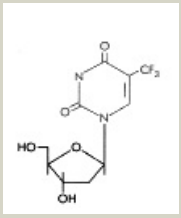
Iodo-deoxyuridine (Idoxuridine)
Chemical name: 5-iodo-2′-deoxyuridine
Other names: IDU, IUdR, Herpid®, Stoxil®, Idoxene®, Virudox® - figure 14
This is similar to BVDU and is now used mainly in eye drops or a topical cream for HSV

keratitis.

Trifluorothymidine (Trifluridine)
Chemical name: 5-trifluoromethyl-2′-deoxyuridine
Other names: TFT, Viroptic®. - figure 15
This is similar in its mode of action to BVDU and IDU. It also is activated by viral thymidine kinase. TFT is used as a topical cream or in eye drops for HSV keratitis.

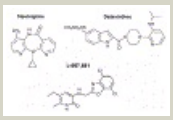
(3) Non-nucleoside inhibitors of reverse transcriptase

(See figure 16)


Trifluorothymidine
Figure 15

Because of the problems with AZT and the other nucleoside analogs in the treatment of HIV, interest has grown in another approach to inhibiting the same enzyme, reverse transcriptase. Alternative drugs might be useful in combination therapy since there is a limit to the number of mutations that reverse transcriptase can bear without losing function. Clearly, mutations resistant to a non-nucleoside non-competitive inhibitor of reverse transcriptase would be at a different site in the enzyme from the mutation that makes the enzyme resistant to a competitive nucleoside analog.

Non-nucleoside inhibitors are the most potent and selective reverse transcriptase inhibitors that we have, working at nanomolar concentrations. They have minimal toxicity in tests with cultured cells (anti-viral activity at 10,000 to 100,000-fold lower concentration than cytotoxic concentration) and have been shown to work synergistically with nucleoside analogs such as AZT. Moreover, they work against nucleoside-analog resistant HIV. Thus, these drugs have high therapeutic index and also show good bioavailablity so that anti-viral concentrations are readily achievable. They are non-competitive reverse transcriptase inhibitors that target an allosteric pocket on the reverse transcriptase molecule.


Non-competitive reverse transcriptase inhibitors
Figure 16

Not surprisingly, since these drugs target reverse transcriptase, resistant mutants rapidly emerge, even after only a few passages in cultured cells. In patients, resistant mutants also arise rapidly. They are therefore of little use in monotherapy; however, although resistant virus strains are cross resistant to other non-nucleoside reverse transcriptase inhibitors, they are not to nucleoside analog inhibitors. There is also some evidence that these drugs may be able to overcome resistance at the high concentrations that seem to be achievable.

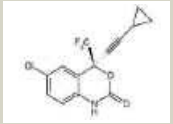
There is now a collection of such agents that are chemically distinct:

Nevirapine
Chemical name: 11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2′,3′-f][1,4]diazepin-6-one
Other names: NVP or BIRG-587, Viramune®
In monotherapy, this drug causes an initial fall in the number of HIV virions but resistance sets in and virus titers rise again to a high level. This drug has been approved for therapy in AIDS patients.

MOLECULAR STRUCTURE
Nevirapine
Efavirenz

Delavirdine
Chemical name: 1-(5-methanesulfonamido-1H-indol-2-yl-carbonyl)-4-[3-(1-methylethyl-amino)pyridinyl)piperazine monomethane sulfonate
Other name: Rescriptor®.
This is a bis (heteroaryl) piperazine compound. Considerable increases are observed in $CD4^+$ cells in combination therapy using this drug with AZT and 3TC. There have been promising results in patients with very low $CD4^+$ cells that have prior treatment with AZT. In combination with AZT and 3TC, DLV may delay emergence of resistance to AZT. The drug is absorbed rapidly. DLV is used in combination with a nucleoside analog such as AZT and the protease inhibitors discussed below.

Efavirenz
Chemical name: (−)6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2*H*-3,1-benzoxazin-2-one
Other names: Sustiva®, Stocrin®. Formerly known as DMP-266 - figure 17
Efavirenz used in combination with other drugs, can suppress viral load at least as well as the protease inhibitor Indinavir in the equivalent combination with nucleoside reverse transcriptase inhibitors. In a comparison of viral load reduction with Efavirenz plus AZT plus 3TC, vs. a standard-of-care control group treated with Indinavir plus AZT plus 3TC, the Efavirenz combination suppressed viral load to below 400 copies in a significantly higher proportion of the volunteers than the control arm, at all time points between week 2 and week 24.


Efavirenz (Sustiva)
Figure 17

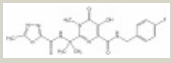
Guidelines for HAART treatment of treatment-naive patients

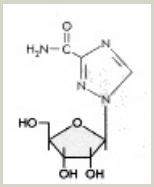

Foscarnet
Figure 18

MOLECULAR STRUCTURE
Foscarnet

4) Other non-nucleoside polymerase inhibitors

Foscarnet
Chemical name: trisodium phosphonoformate
Other names: Foscarnet sodium, Foscavir$^{\bar{U}}$, PFA, phosphono formic acid - figure 18
This is a competitive inhibitor of DNA polymerase - it binds to pyrophosphate site. Viral DNA polymerase is inhibited at 10-100x lower concentration than cell DNA polymerases giving *some* selectivity. It is used intravenously for CMV retinitis is AIDS patients and in other immunocompromised patients. It is useful when the infecting virus has gained resistance to other drugs such as Acyclovir.


Isentress (Raltegravir)
Figure 19a


Ribavirin
Figure 19b

DNA INTEGRATION

Retroviruses copy their RNA genome into DNA using reverse transcriptase. The DNA may remain as a circular provirus or may be integrated into the cellular DNA. The latter is necessary for transcription to genomic and messenger RNA . Thus, integration is required for viral replication. Integration of viral DNA is effected by the integrase enzyme which is encoded in the pol gene. The necessity of integration for replication means that the integrase would be a selective drug target. Recently, a specific integrase inhibitor has been approved.

Raltegravir
Chemical name: is N-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt.

Other names: Isentress$^{\bar{U}}$, MK-0518 - figure 19a
Isentress can be used as part of a HAART regimen when the patient is resistant to other drugs such as protease inhibitors. It was comparable to Sustiva (standard of care) in HAART over a period of 24 weeks. More than 80 percent of those who took the drug showed a drop in the blood level of virus to barely detectable levels It is not approved for HIV-infected children.

RNA SYNTHESIS INHIBITORS

Ribavirin
Chemical name: 1-β-$_D$-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide
Other names: Virazole$^{\bar{U}}$, Virazid$^{\bar{U}}$, Viramid$^{\bar{U}}$ - figure 19b
This drug is not a pyrimidine or a purine. It inhibits influenza RNA polymerase non-competitively *in vitro* but poorly *in vivo*. It may act as a guanosine analog and inhibit 5' cap formation on mRNA. The cap normally contains methyl guanosine. However, ribavirin is known to inhibit the production of infectious polio virus and this virus does not have a methyl guanosine cap; so there must be alternative mechanisms for ribavirin action. It is likely that this drug introduces multiple mutations into viral RNA rendering it incapable of a new round of cell infection

Ribavirin and mutation frequency

MOLECULAR STRUCTURE
Ribavirin

An aerosol form is used against RSV (respiratory syncytial virus) and the drug is used intra-venously against Lassa fever. N.B. Ribavirin can antagonize the effect of AZT as was found in some initial combination therapy trials against HIV**.**

Neplanocin A
Chemical name: 4-Cyclopentene-1,2-diol, 3-(6-amino-9H-purin-9-yl)-5-(hydroxymethyl)-, (1S,2R,3R)-
Other names: dihydropropyl adenine, Vidarabine
This drug, a potent inhibitor of S-adenosylhomocysteine hydrolase, may also inhibit capping of mRNA. S-adenosylhomocysteine hydrolase inhibitors have been shown to exert anti-viral activity against pox-, paramyxo-, rhabdo-, filo-, bunya-, arena-, and reoviruses. They also

interfere with the replication of HIV by inhibition of the Tat transactivation process.

Sofosbuvir
This drug (Gilead Sciences) inhibits hepatitis C virus's RNA polymerase enzyme. It is a chain-terminating nucleotide analog which is incorporated into newly synthesized viral RNA. Its effectiveness varies according to which genotype of hepatitis C, infects the patient. About a quarter of patients in the United States are infected with hepatitis C genotypes 2 and 3. These patients are treated with sofosbuvir in combination with ribavirin but without interferon. Since interferon has to be injected, this will be the first completely oral treatment for hepatitis C.

More than 70% of patients infected with hepatitis C in the United States are infected with genotype 1. They require interferon plus ribavirin together with sofosbuvir over a period of 12 weeks. In a clinical trial, about 90 percent of previously untreated patients taking sofosbuvir in combination with interferon and ribavirin showed no detectable virus in the blood at the end of treatment.

RNA CLEAVAGE ENZYMES

Ribozymes are RNA molecules that have catalytic properties among which are the specific cleavage of nucleic acids. Heptazyme is a ribozyme that cleaves hepatitis C RNA at highly conserved regions (thereby reducing the possibility of the development of resistance). It recognizes and cuts all known types of the hepatitis C virus, thereby stopping viral replication. Heptazyme has not been successful in clinical trials.

Catalytic RNAs - Ribozymes

PROTEIN SYNTHESIS INHIBITORS

Little progress has been made in the development of drugs that inhibit viral protein synthesis since viruses use host cell translation mechanisms. However, one drug in this class is available.

Fomivirsen
Chemical name: Anti-sense oligonucleotide
Other names: ISIS 2922, Vitravene$^{\tilde{U}}$.
Fomivirsin is an anti-sense oligonucleotide made of 21 nucleosides that are phosphorothioate stabilized. It can be administered as an intra-ocular injection for CMV retinitis. It specifically hybridizes to the mRNA for CMV immediate early 2 protein, blocking its translation.

PROTEIN PROCESSING INHIBITORS

Protease inhibitors


The process of retrovirus protease activity in which the protease starts as part of the POL polyprotein and then cleaves the polyprotein
Figure 20

Many viruses must cleave the proteins that they make. In the case of surface glycoproteins, this is usually carried out by a host protease in the secretory pathway (e.g. in Golgi body). In the case of internal proteins, such as the polymerase or the group-specific antigens (GAGs) of retroviruses and some other viruses, there is a viral protease that is encoded in the POL gene (figure 20).

Active site-directed inhibitors of the HIV aspartyl protease have been developed as this enzyme is not similar to known host proteolytic enzymes and therefore the inhibitors should show specificity to viral proteins. The action of the HIV protease is crucial to viral infectivity. Now we have the promise of a drug regimen that can suppress indefinitely the progress of disease.(see also anti-HIV drugs)

WEB RESOURCES
MECHANISM

The anti-HIV protease inhibitors are all substrate analogs (figure 22). When used individually they can drive down viral load to between one 30th and one 100th of initial value but sub-optimal doses of these inhibitors, when used alone, can result in loss of suppression after several months and an accumulation of multiple mutations in the protease gene giving a high level of drug resistance. However, it should be noted that patients with sustained suppression do not develop the resistant mutations. This seems to

Clickable mechanism of aspartyl protease mechanism. From Edward K. O'Neil and Charles M. Grisham at the University of Virginia in Charlottesville, Virginia

be because replication must be maintained for the development of such mutations under the selective pressure of the drug.

Saquinavir (SQ)
Chemical name: cis-N-tert-butyl-decahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[*N*-2-quinolylcarbonyl-$_L$-asparaginyl]-amino]butyl]-(4aS–8aS)-isoquinoline-3(*S*)-carboxamide methane sulfonate
Other names: Invirase^{Ū} (hard gel capsules), Fortovase^{Ū} soft gelatin capsules. (Hoffman-La Roche, figure 21).

This is a hydroxyethylamine transition-state analog of the cleavage site on a protein recognized by the HIV protease. It is the least bio-available of the present protease inhibitors and is the least effective. Nevertheless, SQ + AZT + ddC reduced viremia with a rise in T4 cells in individuals with a T4 cell count of 50 - 300/mm^3.

Ritonavir
Chemical name: [5S-(5R,8R,10R,11R)]-10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid 5-thiazolylmethyl ester
Other names: Norvir^{Ū} (Abbot Labs).

This drug reduces AIDS-defining events and death by 58% compared to placebo. It causes nausea in 25% of patients. It is used as part of a triple drug highly active anti-retroviral therapy (HAART).

Indinavir
Chemical name: [(1*S*,2*R*,5(*S*)-2,3,5-trideoxy-*N*-(2,3-dihydro-2-hydroxy-1*H*-inden-1-yl)-5-[2-[[(1,1-dimethylethyl)amino]carbonyl]-4-pyridinylmethyl)-1-piperazinyl]-2-(phenylmethyl-□-erythro)pentonamide
Other names: Crixivan^{Ū}. (Merke).

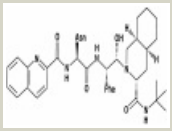

Saquinavir

Figure 21

Indinavir plus two anti-RT drugs (HAART) reduces HIV to such an extent that PCR cannot detect the virus in 85% of patients

Amprenavir
Chemical name: 3*S*)-tetrahydro-3-furyl-*N*-[(*S*,2*R*)-3-(4-amino-*N*-isobutylbenzene-sulfonamido)-1-benzyl-2-hydroxypropyl]carbamate
Other names: , Agenerase^{Ū}, Prozei^{Ū} (Glaxo)

This is another protease inhibitor used in combination HAART therapy


Structure of RSV protease bound to a peptide analog of the HIV cleavage site Requires a Chime plug-in. Get Chime here - Click on thumbnail to open file

Figure 22A

Nelfinavir
Chemical name: [3*S*-(3*R*,4a*R*,8a*R*,2′*S*)]-2-[2′-hydroxy-3′-phenylthiomethyl-4′-aza-5′-oxo-5′-[2′-methyl-3′-hydroxyphenyl)-pentyl]-3-(*N*-(*tert*-butyl)-carboxamide)-decahydro isoquinoline methane sulfonate
Other names: Viracept^{Ū}.

Lopinavir
Chemical name: N-(4(*S*)-(2-(2,6-dimethylphenoxy)-acetylamino)-3(*S*)-hydroxy-5-phenyl-1(*S*)-benzylpentyl)-3-methyl-2(*S*)-(2-oxo(1,3-diazaperhydroinyl)butanamine
Other names: ABT-378/r, Kaletra^{Ū}.

Lopinavir is administered combined with Ritonavir, another protease inhibitor at a 4/1 ratio. Again, it is used as part of HAART.

Atazanavir
Chemical name: 1-[4-(pyridin-2-yl)phenyl]-5(*S*)-2,5-bis-{[*N*-(methoxycarbonyl)-□-*tert*-leucinyl]amino}-4(*S*)-hydroxy-6-phenyl-2-azahexane
Other names: CGP 73547, BMS-232632, Reyataz^{Ū}. (Bristol-Myers Squibb)

Bevirimat
Chemical name: 3-O-(3′,3′-dimethylsuccinyl) betulinic acid
Other names: PA-457 (Panacos Pharmaceuticals)
The protease inhibitors described above are general inhibitors of the HIV aspartyl protease. Bevirimat is more specific but is also involved in the maturation of the virus.

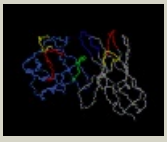
The assembly of the HIV virus budded from the cell into an infectious virion depends upon Pr55Gag, a precursor of the Gag proteins. Pr55Gag is assembled into the virus particle which buds from the cell and at the same time a maturation process occurs in which the

viral protease cleaves P55Gag to generate several smaller proteins including the immature capsid protein, the matrix protein, the nucleocapsid protein and p6. The immature capsid protein (p25) is cleaved to form mature capsid protein (p24). This maturation process results from a structural rearrangement in which the electron-dense conical core of the mature virion is formed. Bevirimat inhibits the cleavage that occurs in the maturation of p25 to p24. Specifically, the cleavage of the p25 to p24 is disrupted, resulting in the formation of defective, noninfectious virus particles.

MOLECULAR STRUCTURE
Indinavir

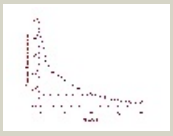
Highly active anti-retroviral therapies (HAART)

Combination therapies (triple drug cocktail, HAART) are very effective and can reduce viral load in the patient below detectable levels implying that HIV replication has ceased. One such HAART cocktail consists of zidovudine (AZT) , lamivudine (3TC), both nucleoside analog reverse transcriptase inhibitors, and Indinavir, a protease inhibitor. Viral RNA levels before treatment, which may be as high as 11 million copies per ml, are reduced to undetectable levels in few weeks by this drug combination (we can measure as low as 20 copies /ml) (figure 23). The evidence suggests that there is NO replicating virus in these patients and this is sustained for several years. When treatment is stopped, however, the virus comes back because of latent virus in memory T cells and possibly other cells.


HIV-1 Protease Complexed With A Macrocyclic Peptidomimetic Inhibitor
Requires a Chime plug-in. Get Chime here - Click on thumbnail to open file
Figure 22B

Another triple drug combination consists of two nucleoside analog reverse transcriptase inhibitors (tenofovir, (R)-9-(2-Phosphonylmethoxypropyl)adenine) and emtricitabine (2',3'-Dideoxy-5-fluoro-3'-thiacytidine) plus the non-nucleoside inhibitors of reverse transcriptase, efavirenz (Sustiva).

The trouble with all of these complicated drug regimens is compliance. The components of HAART must be taken at different times, sometimes in the middle of the night as well as during the day sand must be taken with different foods. For example, failure to take saquinavir within 2 hours of high fat meal leads to no absorption of drug. On the other hand, Indinavir must be ingested with minimal food intake.


Level of HIV RNA in serum as measured by PCR after treatment with HAART
Figure 23

In patients that fail to take the three drugs for a week, there is a marked rise in viral load. Non-compliance with protease inhibitor therapy is of serious concern as the new virus that emerges is resistant to the inhibitor being taken and also resistant to other protease inhibitors. This is a major problem since the new resistant mutants may be transmitted to others. Thus if a patient is known to be likely to be non-compliant he/she should probably not be offered the drugs since resistance can emerge so quickly and can be spread to contacts. The HAART is very expensive, for example the combination of zidovudine/lamivudine/protease inhibitor costs $12,000 per year.

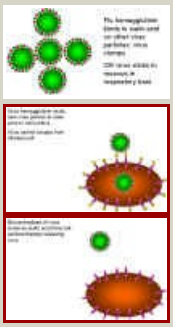
A single pill with three drugs

Can we cure an HIV infection with drug therapy?

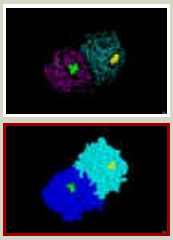
Some years ago this possibility would have been scoffed at. The drugs available then reduced viral load only to small extent and a double drug combination was thought to be acting well if it led to a rise in CD4 cells of 50/cu mm and the viral load was down 1.5 logs. Now these are considered to be very small changes. If, as seems likely, the triple drug therapy when taken correctly stops all HIV replication in the patient, we might be able to eliminate the virus as cells that harbor it in the latent form are turned over. There is evidence, however, that this may be difficult because latent reservoirs of HIV undoubtedly exist. When a CD4 cell leaves the thymus it may meet an antigen, activate and subsequently die but a small subset of these cells become memory T cells and revert to a resting state. They may stay in the body for many years and if they are HIV-infected they will harbor the provirus. These cells therefore form a reservoir for HIV in the patient. The infection rate of this subset of cells does not appear to be great, less than 1 in 10,000 harbor latent viral DNA. This means that only some 10,000,000 of the 1000 trillion lymphocytes in the body are latently infected. But these may persist of decades and they will be untouched by the triple therapy combination. In individuals that have been treated with the combination therapy for more than 3 years, the rate of latently infected cells remains the same (1 in 10,000). Interestingly, the archival virus had the same resistance patterns as those that infected the patient. This means that in more than 3 years there were probably no new rounds of HIV replication. However, the bad news is that this reservoir of cells may last decades.


This diagram derived from X-ray crystallography shows the dimeric HIV aspartyl protease (ribbons). Aspartate residues are shown as ball and sticks. Note that four aspartates are clustered at the active site of the enzyme. A protease inhibitor is shown fitting into the active site
Figure 24

Hepatitis C protease inhibitor



The requirement for neuraminidase in the life cycle of influenza virus
Figure 24



Influenza virus neuraminidase complexed with Relenza. Left: The enzyme is shown as strands. Relenza is space-filled. The single N-acetyl glucosamine residue on each chain of the dimer is shown as ball and stick. Right: The enzyme is space-filled showing the inhibitor at the active site in a cleft in the surface of the molecule.
Figure 25

WEB RESOURCES
Neuraminidase Inhibitors for Treatment of Influenza A and B Infections

MOLECULAR STRUCTURE
Castanospermine

Zanamivir Relenza
Oseltamivir

PROTEIN MODIFICATION INHIBITORS

- **Glycosylation**
  2-deoxyglucose and D-glucosamine interfere with glycosylation *in vitro* but, not surprisingly, have little effect *in vivo*. Castanospermine (a natural product derived from a species of Australian chestnut) interferes with glycosylation of HIV and other retroviruses. It leads to a dramatic decrease in syncytia. Interest in this drug as an anti-HIV agent has waned.

- **Phosphorylation**
  No good drugs that target viruses by altering the phosphorylation of their proteins have been found

- **Sialidation**
  Two glycoproteins are found on the surface of influenza viruses; the hemagglutinin and the neuraminidase (sialidase). The latter has several functions. It allows the virus to move through mucous secretions in the respiratory tract so that it may infect new cells. Since sialic acid is the influenza receptor, it is necessary to remove sialic acid from the surface of the infected cell and of the virus so that viral particles may escape (figure 24). The neuraminidase is therefore very important for the spread of the virus from cell to cell.

Zanamivir
Chemical name: 4-guanidino-2,4-dideoxy-2,3-didehydro-*N*-acetylneuraminic acid, 5-acetylamino-4-[(aminoiminomethyl)amino]-2,6-anhydro-3,4,5-trideoxy-$_D$-glycero-$_D$-galacto-non-2-enonic acid
Other names: CG 167, Relenza™
Zanamivir is an anti-viral agent for influenza announced in the fall of 1997. It is a potent inhibitor of the viral neuraminidase of types A and B influenza viruses (figure 25). This is important as the previously available drugs such as rimantadine are ineffective against influenza type B. The design of Zanamivir is based on the three-dimensional structure of the neuraminidase. Treatment of community-acquired type A and B influenza with Zanamivir shortens the duration of major symptoms by about one day in the study group as a whole and about three days in sicker patients if the drug is started early. Since no antiviral drug has been approved for the treatment or prevention of influenza B, Zanamivir could fill a niche in the control of influenza, but type B causes only about 35 percent of cases. Moreover, it has the disadvantage of requiring aerosol delivery to the respiratory tract, an approach that could prove difficult for many.

Oseltamivir
Chemical name: ethyl ester of (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(1-ethylpropoxy)-1-cyclohexane-1-carboxylic acid
Other names: GS 4104, Ro 64-0796, Tamiflu™
Another neuraminidase inhibitor, Oseltamivir is a carbocyclic sialic acid analogue that can be given orally.

OTHER TARGETS

In the retrovirus life cycle, the targeting of the specific protease that is necessary for the formation of an infectious virus particle has been particularly successful. Earlier, reverse transcriptase inhibitors had also been successful but the nucleoside analogs cause severe side effects because they also inhibit the host's DNA polymerase. In contrast, the non-nucleoside inhibitors of reverse transcriptase show excellent therapeutic indices. In each case, however, monotherapy leads to the rapid emergence of resistant mutants. Many other possible targets for intervention in the life cycles of viruses are under investigation and, of course, the goal is specificity. In the case of the retroviruses, in addition to those drugs described above, inhibitors of the integrase are being extensively studied but none has yet made it to the clinic as routine treatment.

Other interesting approaches can be found at the pages below

Tarvacin Hepatitis C and HIV

 Return to the Virology section of Microbiology and Immunology On-line

This page last changed on Wednesday, November 06, 2013
Page maintained by Richard Hunt

<<Previous Next>>