Antivirals

Antiviral drugs are a class of medication used specifically for treating viral infections. Like antibiotics for bacteria, specific antivirals are used for specific viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development.

Antiviral drugs are one class of antimicrobials, a larger group which also includes antibiotic (also termed antibacterial), antifungal and ant parasitic drugs. They are relatively harmless to the host, and therefore can be used to treat infections. Antivirals also can be found in essential oils of some herbs, such as eucalyptus oil and its constituents.

Most of the antiviral drugs now available are designed to help deal with HIV, herpes viruses (best known for causing cold sores and genital herpes, and chicken pox), the hepatitis B and C viruses, which can cause liver cancer, and influenza A and B viruses.

Virus life cycle

Viruses consist of a genome and sometimes a few enzymes stored in a capsule made of protein (called a capsid), and sometimes covered with a lipid layer (sometimes called an 'envelope'). Viruses cannot reproduce on their own, and instead propagate by subjugating a host cell to produce copies of themselves, thus producing the next generation.

Researchers working on such "rational drug design" strategies for developing antivirals have tried to attack viruses at every stage of their life cycles; they all share a general pattern:

- Attachment to a host cell.
- Release of viral genes and possibly enzymes into the host cell.
- Replication of viral components using host-cell machinery.
- Assembly of viral components into complete viral particles.
- Release of viral particles to infect new host cells.

Anti-viral targeting

The general idea behind modern antiviral drug design is to identify viral proteins, or parts of proteins, that can be disabled. These "targets" should
generally be as unlike any proteins or parts of proteins in humans as possible, to reduce the likelihood of side effects.

**Approaches by life cycle stage:**

1. **Before cell entry**

   This stage of viral replication can be inhibited in two ways:
   
   - Using agents which simulate the virus-associated protein (VAP) and bind to the cellular receptors. This may include VAP anti-idiotypic antibodies, natural ligands of the receptor and anti-receptor antibodies.
   - Using agents which mimic the cellular receptor and bind to the VAP. This includes anti-VAP antibodies, receptor anti-idiotypic antibodies, extraneous receptor and synthetic receptor mimics.

2. **Entry inhibitor**

   A very early stage of viral infection is viral entry, when the virus attaches to and enters the host cell. A number of "entry-inhibiting" or "entry-blocking" drugs are being developed to fight human immunodeficiency virus (HIV).

3. **Uncoating inhibitor**

   Amantadine and rimantadine, have been introduced to combat influenza. These agents act on penetration/uncoating. Pleconaril works against rhinoviruses, which cause the common cold, by blocking a pocket on the surface of the virus that controls the uncoating process. This pocket is similar in most strains of rhinoviruses and enteroviruses, which can cause diarrhea, meningitis, conjunctivitis, and encephalitis.

4. **During viral synthesis**

   A second approach is to target the processes that synthesize virus components after a virus invades a cell.

   **a. Reverse transcription**

   One way of doing this is to develop nucleotide or nucleoside analogues that look like the building blocks of RNA or DNA, but deactivate the enzymes that synthesize the RNA or DNA once the analogue is incorporated.
The first successful antiviral, acyclovir, is a nucleoside analogue, and is effective against herpes virus infections. The first antiviral drug to be approved for treating HIV, zidovudine (AZT), is also a nucleoside analogue.

b. Integrase

Another target is integrase, which splices the synthesized DNA into the host cell genome.

c. Transcription

Once a virus genome becomes operational in a host cell, it then generates messenger RNA (mRNA) molecules that direct the synthesis of viral proteins.

Transcription /antisense

These are segments of DNA or RNA that are designed as complementary molecule to critical sections of viral genomes, and the binding of these antisense segments to these target sections blocks the operation of those genomes. A phosphorothioate antisense drug named fomivirsen has been introduced, used to treat opportunistic eye infections in AIDS patients caused by cytomegalovirus, and other antisense antivirals are in development.

Transcription /ribozymes

a set of drugs based on ribozymes, which are enzymes that will cut apart viral RNA or DNA at selected sites. In their natural course, ribozymes are used as part of the viral manufacturing sequence, but these synthetic ribozymes are designed to cut RNA and DNA at sites that will disable them.

d. Protease inhibitors

Some viruses include an enzyme known as a protease that cuts viral protein chains apart so they can be assembled into their final configuration. Protease inhibitors became available in the 1990s and have proven effective, though they can have unusual side effects, for example causing fat to build up in unusual places. Improved protease inhibitors are now in development. e.g. indinavir, ritonavir.
5. Assembly

Rifampicin acts at the assembly phase.

6. Release phase

The final stage in the life cycle of a virus is the release of completed viruses from the host cell, and this step has also been targeted by antiviral drug developers. Two drugs named zanamivir (Relenza) and oseltamivir (Tamiflu) that have been recently introduced to treat influenza prevent the release of viral particles by blocking a molecule named neuraminidase that is found on the surface of flu viruses, and also seems to be constant across a wide range of flu strains.

Immune system stimulation

A second category of tactics for fighting viruses involves encouraging the body's immune system to attack them, rather than attacking them directly. Some antivirals of this sort do not focus on a specific pathogen, instead stimulating the immune system to attack a range of pathogens.

One of the best-known of this class of drugs are interferons, members of the large cytokine family and that inhibit viral replication. They are produced very quickly (within hours) in response to viral infection which inhibit viral synthesis in infected cells. One form of human interferon named "interferon alpha" is well-established as part of the standard treatment for hepatitis B and C, and other interferons are also being investigated as treatments for various diseases. The different classes of IFN are produced by different cell types. IFN-α and IFN-β are synthesized by many cell types, but IFN-γ is produced mainly by lymphocytes, especially T cells and natural killer (NK) cells.

Vaccines

The purpose of viral vaccines is to use the immune response of the host to prevent viral disease. Several vaccines have proved to be remarkably effective at reducing the annual incidence of viral disease. Vaccination is the most cost effective method of prevention of serious viral infections.
<table>
<thead>
<tr>
<th>Virus</th>
<th>Drug of Choice</th>
<th>Alternate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza-A</td>
<td>Amantadine, Rimantadine</td>
<td>No alternative</td>
</tr>
<tr>
<td>Influenza A and B</td>
<td>Zanamivir, Oseltamivir</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex (keratitis)</td>
<td>Trifluridine (topical)</td>
<td>Idoxuridine (topical)</td>
</tr>
<tr>
<td>Herpes simplex (encephalitis)</td>
<td>Acyclovir</td>
<td>Foscarnet</td>
</tr>
<tr>
<td>CMV</td>
<td>Ganciclovir, Valganciclovir</td>
<td>Foscarnet</td>
</tr>
<tr>
<td>Herpes simplex (genital)</td>
<td>Acyclovir, Valacyclovir</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex (Acyclovir-resistant)</td>
<td>Foscarnet</td>
<td></td>
</tr>
<tr>
<td>Respiratory Syncytial Virus (RSV)</td>
<td>Ribavirin</td>
<td></td>
</tr>
<tr>
<td>Varicella-Zoster</td>
<td>Acyclovir, Valacyclovir</td>
<td>Foscarnet</td>
</tr>
<tr>
<td>Hepatitis-B (chronic)</td>
<td>IgG, Lamivudine, Interferon α</td>
<td>Entecavir/Adefovir</td>
</tr>
<tr>
<td>Hepatitis A,B and C. (HIV-coinfected)</td>
<td>INFα/PEG-INFα + ribavirin (ARV+Lamivudine/Adefovir)</td>
<td></td>
</tr>
</tbody>
</table>