Antiviral drugs

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Last update: 13.04.2011

Viruses

- Viruses are the smallest infective agents, consisting essentially of nucleic acid (either RNA or DNA) enclosed in a protein coat or capsid.

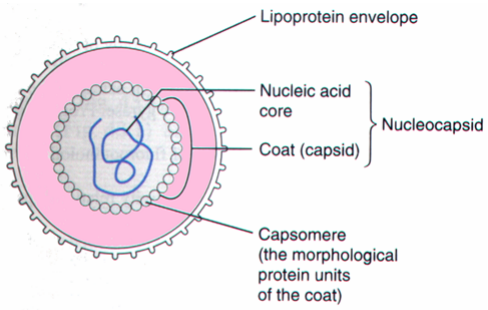

Fig. 44.1 Schematic diagram of the components of a virus particle or virion.

- Some important examples of viruses and the diseases they cause are as follows:

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DNA viruses

- Pox viruses (smallpox)
- Herpes viruses (chickenpox, herpes etc.)
- Adenoviruses (sore throat, conjunctivitis)
- Hepadnaviruses (serum hepatitis)
- Papillomaviruses (warts)

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RNA viruses

- Orthomyxoviruses (influenza)
- Paramyxoviruses (measles, mumps)
- Rubella virus (German measles)
- Rhabdoviruses (rabies)
- Picornaviruses (colds, meningitis, poliomyelitis)
- Retroviruses (AIDS, T-cell leukemia)
- Arenaviruses (meningitis, Lassa fever)
- Arboviruses (arthropod-borne encephalitis, yellow fever)

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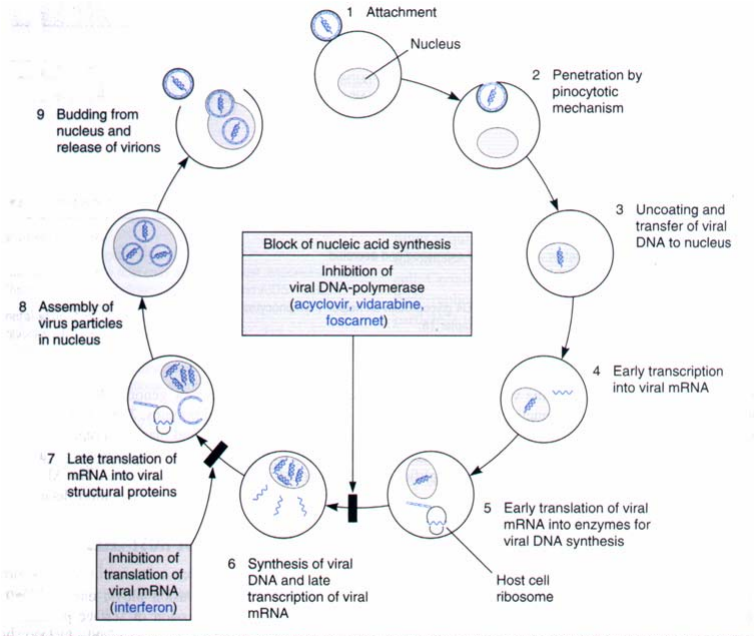

Fig. 44.2 Schematic diagram of replication of a DNA virus (e.g. herpes simplex) in a host cell with the probable sites of action of antiviral agents. Viral components are shown in blue. In some viruses, assembly (stage 8) takes place in the host cell cytoplasm.

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Mechanism of action of antiviral drugs

Inhibition of penetration of host cell

- **Amantadin** and also ***rimantadin*** inhibit uncoating and are effective against influenza A virus.
- **Gammaglobulins** ″neutralize″ viruses.

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Antiviral mechanism of action: Inhibition of nucleic acid synthesis I

Acyclovir a guanosine derivative selectively inhibits viral DNA polymerase; effective against herpes viruses; minimal unwanted effects.

- **Gancyclovir**, also a guanosine derivative is phosphorylated and then incorporated into viral DNA, supressing its replication; used in cytomegalovirus infections; especially CMV retinitis in AIDS patients.

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Antiviral mechanism of action: Inhibition of nucleic acid synthesis II

- ***Vidarabine***, an adenosine derivative, is a relatively selective inhibitor of viral DNA polymerase; effective against *Herpes simplex* and *Varicella zoster*; can have serious unwanted effects.
- **Ribavirin** is similar to guanosine and is thought to interfere with synthesis of viral DNA; can inhibit many DNA and RNA viruses.

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Antiviral mechanism of action: Inhibition of nucleic acid synthesis III

- ***Foscarnet*** inhibits viral DNA polymerase by attaching to the pyrophosphate binding site; approved for CMV infections.
- **Zidovudine**, an analogue of thymidine, inhibits reverse transcriptase and is relatively effective in HIV infection.
- **Zalcitabine** and **didanosine** are reverse transcriptase inhibitors used in HIV infection.

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Neuramidase inhibitors

- **Zanamivir** and **oseltamivir** inhibits neuramidase which is essential for virus replication.
- They are used against influenza A and B.
- They are for avian and swin influenza (H5N1 and H1N1 respectively) which are influenza A subtypes.
- Zanamivir is used by inhalation; oseltamivir orally.

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Immunomodulators

- Interferons induce, in the host cells' ribosomes, enzymes which inhibit viral mRNA; they are used in hepatitis B infections and may be useful in AIDS.
- Pavilizumab is a monoclonal antibody against fusion proteins of respiratory syncytial virus.
- Imiquimod is a immune response modulator used topically against genital and perianal warts.

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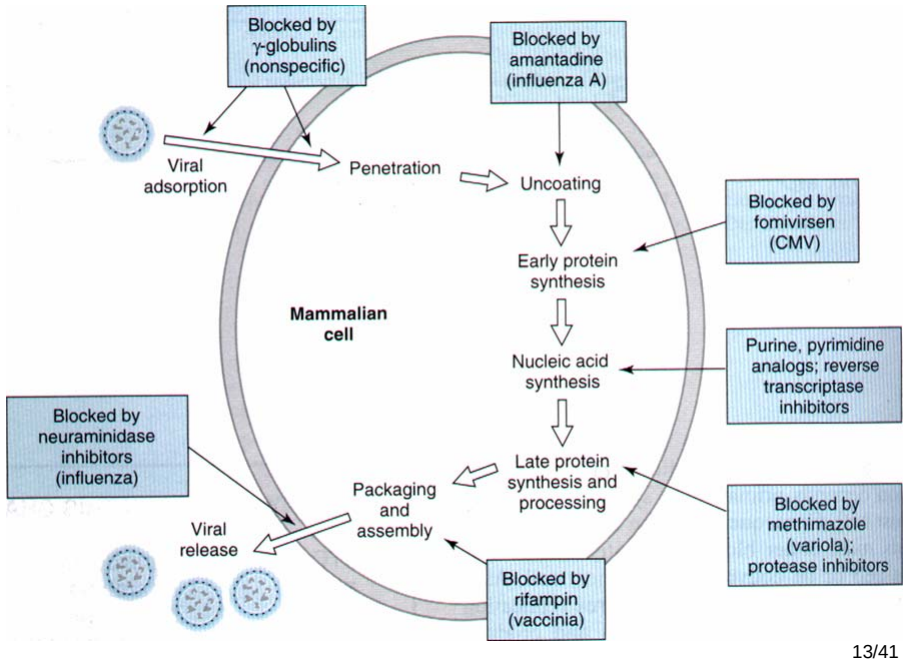

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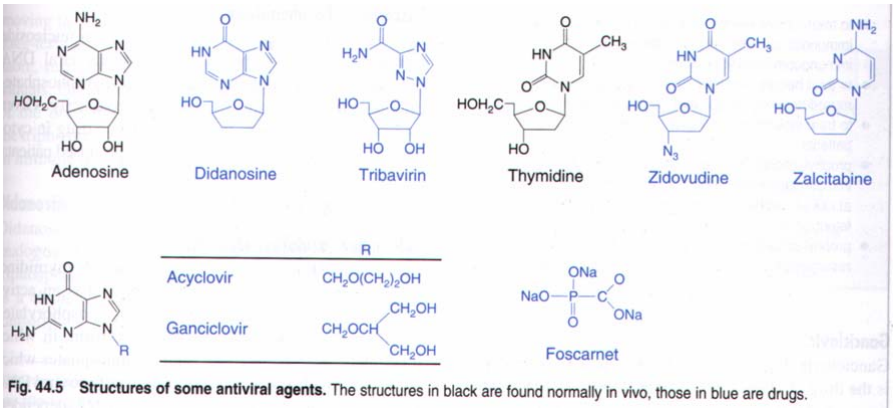

Fig. 44.5 Structures of some antiviral agents. The structures in black are found normally in vivo, those in blue are drugs.

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The human immunodeficiency virus (HIV) and AIDS

- Infection with HIV results in the acquired immune deficiency syndrome (AIDS).
- In 1997 it was estimated that nearly 30 million adults world-wide were infected with HIV, with the number of HIV infections increasing by five every minute.
- The epidemic is overwhelmingly centered on sub-Saharan Africa, where about 7% of the population is infected.

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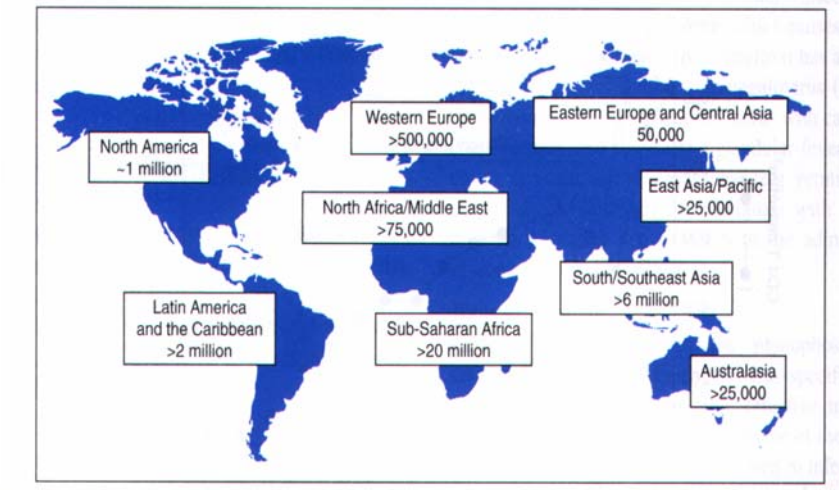

Fig. 44.3 Figures from the United Nations AIDS programme for the number of individuals with HIV infection in 1997. (McIlwain 1997 Nature 390: 326)

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The interaction of HIV with the host's immune system

- The interaction of HIV with the host's immune system is complex.
- Cells of the immune system have the equivalent of “name badges” that identify them.
- The surface glycoprotein CD4 is the name badge of a particular group of helper T lymphocytes; it also occurs on macrophages and dendritic cells.

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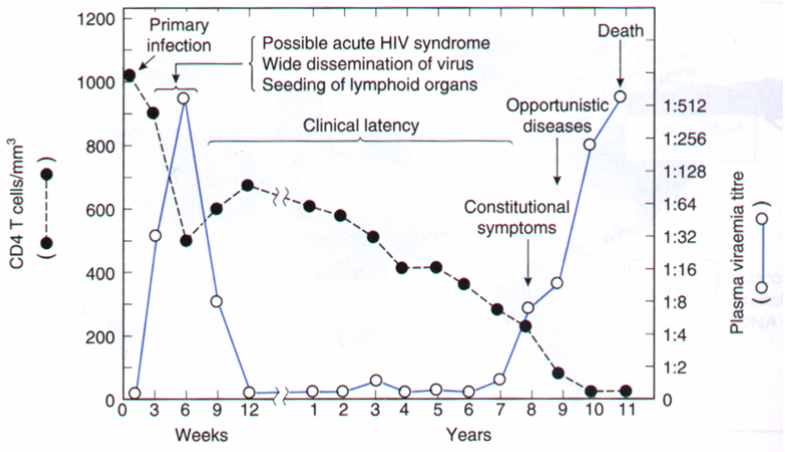

Fig. 44.4 Schematic outline of the course of HIV infection. (Adapted from Pantaleo et al. 1993)

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Highly active antiretroviral therapy I

- The advent of highly active antiretroviral therapy (HAART) has changed the prognosis, in countries that can afford it.
- HAART is a combination of three antiviral drugs including at least one protease inhibitor.
- There are 20 anti-HIV drugs available; six nucleoside reverse transcriptase inhibitors, four non-nucleoside reverse transcriptase inhibitors, one nucleotide reverse transcriptase inhibitor, eight protease inhibitors, and one fusion inhibitor. Most are discussed below.

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Highly active antiretroviral therapy II

- With a HAART regime, HIV replication is inhibited -its presence in the plasma being reduced to undetectable levels- and patient survival is prolonged; but the regime is complex, difficult to adhere to and may well have to be lifelong.
- It is also extremely expensive-which effectively prevents its use in developing countries.
- In any case, with the high mutation rate of the virus, resistance is an important problem. HIV has certainly not yet been outsmarted.

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Anti-AIDS Drugs
Reverse Transcriptase Inhibitors

- Nucleoside:
  Abacavir
  Didanosine
  Lamivudine
  Stavudine
  Zalcitabine
  Zidovudine
- Non-nucleoside
  Neviparine
  Delavirdine
  Efavirenz
  Loviride
- Nucleotide
  Tenefovir

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Zidovudine (azidothymidine, AZT)

- Zidovudine is an analogue of thymidine. In retroviruses -such as the HIV virus- it is an active inhibitor of reverse transcriptase.
- It is phosphorylated by cellular enzymes to the triphosphate form, in which it competes with equivalent cellular triphosphates which are essential substrates for the formation of proviral DNA by viral reverse transcriptase (viral RNA-dependent DNA polymerase); its incorporation into the growing viral DNA strand results in chain termination.

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Zidovudine (continued)

- Mammalian alpha DNA polymerase is relatively resistant to the effect.
- However, gamma DNA polymerase in the host cell mitochondria is fairly sensitive to the compound and this may be the basis of unwanted effects.

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Pharmacokinetic aspects of zidovudine I

- Given orally, the bioavailability of zidovudine is 60-80% and the peak plasma concentration occurs at 30 minutes.
- It can also be given intravenously.
- Its half-life is 1 hour, and the intracellular half-life of the active triphosphate is 3 hours.

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Pharmacokinetic aspects of zidovudine II

- Zidovudine enters mammalian cells by passive diffusion and in this is unlike most other nucleosides which require active uptake.
- The drug passes into the CSF and brain.
- Most of the drug is metabolized to inactive glucuronide in the liver, only 20% of the active form being excreted in the urine.

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Unwanted effects of zidovudine I

- Anaemia and neutropenia are common, particularly with long-term administration.
- Administration of erythropoietin and GM-CSF may alleviate these problems.

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Unwanted effects of zidovudine II

- Other unwanted effects include gastrointestinal disturbances, paraesthesia, skin rash, insomnia, fever, headaches, abnormalities of liver function and, more particularly, myopathy.
- Confusion, anxiety, depression and a flu-like syndrome are also reported.
- The prophylactic use of the drug, short-term, in fit individuals, after specific exposure to the virus, is associated with only minor, reversible unwanted effects.

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Resistance to the antiviral action of zidovudine

- Because of rapid mutation the virus is a constantly moving target, thus the therapeutic response wanes with long-term use, particularly in late-stage disease.
- Furthermore, resistant strains can be transferred between individuals.
- Other factors which underlie the loss of efficacy of the drug are decreased activation of zidovudine to the triphosphate and increased virus load due to reduction in immune mechanisms.

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Didanosine (dideoxyinosine, ddI)

- Didanosine is a synthetic purine dideoxynucleoside analogue. It is phosphorylated in the host cell to the triphosphate, dideoxyadenosine, in which form it acts as a chain terminator and inhibitor of the viral reverse transcriptase.
- It is used to treat AIDS.

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Pharmacokinetic aspects of didanosine

- Didanosine is given orally, rapidly absorbed and is actively secreted by the kidney tubules.
- The plasma half-life is 30 minutes but the intracellular half-life is more than 12 hours.
- The cerebrospinal fluid/plasma ratio is 0.2.

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Unwanted effects of didanosine

- The main unwanted effect -occurring in >30% of patients-is dose-related pain and sensory loss in the feet.
- Dose-related pancreatitis occurs in 5-10% of patients and has been fatal in a few cases.
- Headache and gastrointestinal disturbance are also common and insomnia, skin rashes, bone marrow depression (less marked than with AZT) and alterations of liver function have been reported.

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Zalcitabine (dideoxycytidine, ddC)

- Zalcitabine, a synthetic nucleoside analogue, is used in combination with zidovudine for the therapy of AIDS.
- It is a reverse transcriptase inhibitor and it is activated in the T cell by a different phosphorylation pathway from zidovudine.
- It is given orally, its plasma half-life is 20 minutes, its intracellular half-life is nearly 3 hours and its cerebrospinal fluid/plasma ratio is ~0.2.

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Unwanted effects of zalcitabine

- The most important unwanted effect is a dose-related neuropathy (which can increase for several weeks after the drug has been stopped).
- Other unwanted effects include gastrointestinal disturbances, headache, mouth ulcers, nail changes, edema of the lower limbs and general malaise.
- Skin rashes occur but may resolve spontaneously.
- Pancreatitis has been reported.

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Other reverse transcriptase inhibitors

- New nucleoside reverse transcriptase inhibitors now in use include **lamuvidine,** and **stavudine**.
- Non-nucleoside reverse transcriptase inhibitors now in use include **nevirapine,** and **delavirdine**.
- All are given orally.

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Protease inhibitors

- Host mRNAs code directly for functional proteins, but in HIV, the RNA is translated into biochemically inert polyproteins.
- A virus-specific protease then converts the polyprotein into various structural and functional proteins by cleavage at the appropriate positions.
- Since this protease does not occur in the host, it is a good target for chemotherapeutic intervention.

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Protease inhibitors (continued)

- Several protease inhibitors have now been developed, and their use, in combination with reverse transcriptase inhibitors, has transformed the therapy of AIDS.
- Examples of current protease inhibitors are: **amprenavir, *atazanavir,* indinavir, *fosemprenavir, nelfinavir,* ritonavir,** and ***saquinavir.***

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Protease inhibitors (continued)

- They are all given orally and all can cause gastrointestinal disorders: nausea, vomiting and diarrhea.
- Raised concentrations of liver enzymes in the blood are reported with ritonavir and indinavir.
- Ritonavir can cause paraesthesias around the mouth, and in the hands and feet, and patients on indinavir may develop kidney stones.

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Protease inhibitors (continued)

- All inhibit the cytochrome P450 enzymes (indinavir and saquinavir to a lesser extent than ritonavir) and can interact with other drugs handled by this system, and all can increase the plasma concentration of benzodiazepines.
- Preliminary evidence suggests that long-term use may lead to an unusual redistribution of cutaneous fat.

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Fusion inhibitors

- **Enfuvirtide** inhibits the entrance of HIV virus into host cells.
- It is applied subcutaneusly in combination with other anti-AIDS drugs.

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Principles of HIV/AIDS therapy

1. Monitor plasma viral load and CD4 count.
2. Start treatment before immunodeficiency becomes evident.
3. Aim to reduce plasma viral concentration as much as possible for as long as possible.
4. Use combinations of at least three drugs, e.g. two reverse transcriptase inhibitors and one protease inhibitor.
5. Change to a new regime if plasma viral concentration increases.

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Thank you…

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