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| **Antiviral drugs**  |

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| **OVERVIEW**  |

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| **This chapter deals with drugs used to treat infections caused by viruses. We give first some necessary information about viruses: a simple outline of virus structure, a list of the main pathogenic viruses and a brief summary of the life history of an infectious virus. We then continue with a consideration of the host-virus interaction: the defences deployed by the human host against viruses and the strategies employed by viruses to evade these measures. We then describe the various types of antiviral drugs and their mechanisms of action, with particular reference to the treatment of AIDS, an infection caused by the human immunodeficiency virus (HIV).**  |
| **BACKGROUND INFORMATION ABOUT VIRUSES**  |

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| AN OUTLINE OF VIRUS STRUCTURE  |

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| Viruses are small (usually in the range 20-30 nm) infective agents that are incapable of reproduction outside their host cells. The free-living (e.g. outside its host) virus particle is termed a *virion*, and consists of segments of nucleic acid (either RNA or DNA) enclosed in a protein coat comprised of symmetrical repeating structural units and called a *capsid* ([Fig. 47.1](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047002)). The viral coat, together with the nucleic acid core, is termed the *nucleocapsid*. Some viruses have, in addition, a further external lipoprotein envelope, which may be decorated with antigenic viral glycoproteins or phospholipids acquired from its host when the nucleocapsid buds through the membranes of the infected cell. Certain viruses also contain enzymes that initiate their replication in the host cell.  |

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| Viruses are generally characterised either as *DNA* or *RNA viruses* depending on the nature of their nucleic acid content. These two broad categories are conventionally subdivided into some six subclasses, which classify viruses according to whether they contain single- or double-stranded nucleic acids and how this functions during replication.  |

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| EXAMPLES OF PATHOGENIC VIRUSES  |

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| Viruses can infect virtually all living organisms. Humans are no exception, and such infections are common.  |

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| * Some important examples of the diseases they cause are as follow.
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| * *DNA viruses*: poxviruses (smallpox), herpesviruses (chickenpox, shingles, cold sores, glandular fever), adenoviruses (sore throat, conjunctivitis) and papillomaviruses (warts).
* *RNA viruses*: orthomyxoviruses (influenza), paramyxoviruses (measles, mumps, respiratory tract infections), rubella virus (German measles), rhabdoviruses (rabies), picornaviruses (colds, meningitis, poliomyelitis), retroviruses (acquired immunodeficiency syndrome [AIDS], T-cell leukaemia), arenaviruses (meningitis, Lassa fever), hepadnaviruses (serum hepatitis) and arboviruses (arthropod-borne encephalitis and various febrile illnesses, e.g. yellow fever).
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| Figure 47-1 **Schematic diagram of the components of a virus particle or virion.** |

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| VIRUS FUNCTION AND LIFE HISTORY  |

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| As viruses have no metabolic machinery of their own, they have to attach to and penetrate a living host cell-animal, plant or bacterial-and use the victim's own metabolic processes to replicate. The first step in this process is facilitated by polypeptide binding sites on the envelope or capsid, interacting with receptors on the host cell. These 'receptors' are normal membrane constituents-receptors for cytokines, neurotransmitters or hormones, ion channels, integral membrane glycoproteins, etc. Some examples of host cell receptors utilised by particular viruses are listed in [Table 47.1](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=T047001#T047001).  |

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| Following attachment, the receptor-virus complex enters the cell (often by receptor-mediated endocytosis), during which time the virus coat may be removed by host cell enzymes (often lysosomal in nature). Some bypass this route. Once in the host cell, the nucleic acid of the virus then uses the host cell's machinery for synthesising nucleic acids and proteins that are assembled into new virus particles. The actual way in which this occurs varies between DNA and RNA viruses.  |

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| **Table 47-1. Some host cell structures that can function as receptors for viruses** |

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| **Host cell structure**a | **Virus(es)** |
| Body\_ID: **T047001.50** |  |
| Helper T-lymphocytes CD4 glycoprotein | HIV (causing AIDS) |
| Body\_ID: **T047001.100** |  |
| CCR5 receptor for chemokines MCP-1 and RANTES | HIV (causing AIDS) |
| Body\_ID: **T047001.150** |  |
| CXCR4 chemokine receptor for cytokine SDF-1 | HIV (causing AIDS) |
| Body\_ID: **T047001.200** |  |
| Acetylcholine receptor on skeletal muscle | Rabies virus |
| Body\_ID: **T047001.250** |  |
| B-lymphocyte complement C3d receptor | Glandular fever virus |
| Body\_ID: **T047001.300** |  |
| T-lymphocyte interleukin-2 receptor | T-cell leukaemia viruses |
| Body\_ID: **T047001.350** |  |
| β-Adrenoceptors | Infantile diarrhoea virus |
| Body\_ID: **T047001.400** |  |
| MHC molecules | Adenovirus (causing sore throat and conjunctivitis)T-cell leukaemia viruses |
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| aFor more detail on complement, interleukin-2, the CD4 glycoprotein on helper T lymphocytes, MHC molecules, etc., see Chapter 13. For SDF-1, see [Chapter 22](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=C02269116#C02269116).MCP-1, monocyte chemoattractant protein-1; MHC, major histocompatibility complex; RANTES, regulated on activation, normal T-cell-expressed and secreted; SDF-1, stromal cell-derived factor-1.  |

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| ***Replication in DNA viruses***  |

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| Viral DNA enters the host cell nucleus, where transcription into mRNA occurs catalysed by the host cell RNA polymerase. Translation of the mRNA into virus-specific proteins then takes place. Some of these proteins are enzymes that then synthesise more viral DNA, as well as proteins comprising the viral coat and envelope. After assembly of coat proteins around the viral DNA, complete virions are released by budding or after host cell lysis.  |

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| ***Replication in RNA viruses***  |

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| Enzymes within the virion synthesise its mRNA from the viral RNA template, or sometimes the viral RNA serves as its own mRNA. This is translated by the host cell into various enzymes, including RNA polymerase (which directs the synthesis of more viral RNA), and also into structural proteins of the virion. Assembly and release of virions occurs as explained above. With these viruses, the host cell nucleus is usually not involved in viral replication, although some RNA viruses (e.g. orthomyxoviruses) replicate exclusively within the host nuclear compartment.  |

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| ***Replication in retroviruses***  |

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| The virion in retroviruses1 contains a *reverse transcriptase* enzyme (virus RNA-dependent DNA polymerase), which makes a DNA copy of the viral RNA. This DNA copy is integrated into the genome of the host cell, and it is then termed a *provirus*. The provirus DNA is transcribed into both new viral genome RNA as well as mRNA for translation in the host into viral proteins, and the completed viruses are released by budding. Many retroviruses can replicate without killing the host cell.  |

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| The ability of several viruses to remain dormant within, and be replicated together with, the host genome is responsible for the periodic nature of some viral diseases, such as those caused by *herpes labialis* (cold sores) or the *varicella zoster* (chickenpox and shingles) virus, which recur when viral replication is reactivated by some factor (or when the immune system is compromised in some way). Some RNA retroviruses can transform normal cells into malignant cells.  |
| **THE HOST-VIRUS INTERACTION**  |

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| HOST DEFENCES AGAINST VIRUSES  |

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| Figure 47-2 **The mechanisms whereby a CD8+ T cell kills a virus-infected host cell.** The virus-infected host cell expresses a complex of virus peptides plus major histocompatibility complex class I product (MC H-I) on its surface. This is recognised by the CD8+ T cell, which then releases lytic enzymes into the virus-infected cell and also expresses a Fas ligand. This trigers apoptosis in the infected cell by stimulating its Fas 'death receptor'. |

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| The first defence is the simple barrier function of intact skin, which most viruses are unable to penetrate. However, broken skin (e.g. at sites of wounds or insect bites) and mucous membranes are more vulnerable to viral attack. Should the virus gain entry to the body, then the host can deploy both the innate and subsequently the adaptive immune response ([Ch. 13](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=C01369116#C01369116)). The infected cell presents, on its surface, viral peptides complexed with major histocompatibility complex (MHC) class I molecules. This complex is recognised by T lymphocytes, which then kill the infected cell ([Fig. 47.2](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047010)). This may be accomplished by the release of lytic proteins (such as *perforins*, *granzymes*) or by triggering the apoptotic pathway in the infected cell by activation of its Fas receptor ('death receptor' see p. 79). The latter may also be triggered indirectly through the release of a cytokine such as tumour necrosis factor (TNF)-α. If the virus escapes immune detection by cytotoxic lymphocytes by modifying the expression of the peptide-MHC complex (see below), it may still fall victim to natural killer (NK) cells. This reaction to the absence of normal MHC molecules might be called the 'mother turkey' strategy (kill everything that does not sound exactly like a baby turkey; see footnote on [p. 206](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=P0206#P0206)). But some viruses also have a device for evading NK cells as well (see below).  |

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| Within the cell itself, a sophisticated mechanism known as *gene silencing* may also provide a further level of protection (see Schutze, [2004](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047018#r047018)). Short double-stranded fragments of RNA, such as those that could arise as a result of the virus's attempts to recruit the host's transcription/translational machinery, actually cause the gene coding for the RNA to be 'silenced'-to be switched off, probably by DNA phosphorylation. This means that the gene is no longer able to direct further viral protein synthesis, thus interrupting the replication cycle. This mechanism can be exploited for experimental purposes in many areas of biology, and tailored siRNA (small-or short-interfering RNA) is a cheap and useful technique to suppress temporarily expression of a particular gene under investigation. Attempts to harness the technique for viricidal purposes have met with some success (see Barik, [2004](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047029#r047029)).  |

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| VIRAL PLOYS TO CIRCUMVENT HOST DEFENCES  |

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| Viruses have evolved a variety of strategies to ensure successful infection, some entailing redirection of the host's response for the advantage of the virus (discussed by Tortorella et al., [2000](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047015#r047015)).  |

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| ***Subversion of the immune response***  |

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| Viruses can inhibit the action of the cytokines, such as interleukin-1, TNF-α and the antiviral interferons (IFNs; see p. 223), that normally coordinate the innate and adaptive immune responses. Following infection, for example, some poxviruses express proteins that mimic the extracellular ligand-binding domains of cytokine receptors. These *pseudoreceptors* bind cytokines, preventing them from reaching their natural receptors on cells of the immune system and thus moderating the normal immune response to virus-infected cells. Other viruses that can interfere with cytokine signalling include human cytomegalovirus, Epstein-Barr virus, herpesvirus and adenovirus.  |

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| ***Evasion of immune detection and attack by killer cells***  |

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| Once within host cells, viruses may also escape immune detection and evade lethal attack by cytotoxic lymphocytes and NK cells in various ways, such as the following.  |

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| * *Interference with the surface protein markers on the infected cells essential for killer cell attack.* Some viruses inhibit generation of the antigenic peptide and/or the presentation of MHC-peptide molecules. This turns off the signal that the cells are infected, enabling the viruses to remain undetected. Examples of viruses that can do this are adenovirus, herpes simplex virus, human cytomegalovirus, Epstein-Barr virus and influenza virus.
* *Interference with the apoptotic pathway.* Some viruses (e.g. adenovirus, human cytomegalovirus, Epstein-Barr virus) can subvert this pathway for their own purposes.
* *Adopting the 'baby turkey' ploy.* Some viruses (e.g. cytomegalovirus) get round the mother turkey approach of NK cells by expressing a homologue of MHC class I (the equivalent of a turkey chick's chirping) that is close enough to the real thing to hoodwink NK cells.
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| It is evident that evolution has equipped pathogenic viruses with many efficacious tactics for circumventing host defences, and understanding these in more detail is likely to suggest new types of antiviral therapy. Fortunately, the biological arms race is not one-sided, and evolution has also equipped the host with sophisticated counter-measures. In most cases these prevail, with viral infections eventually generally resolving spontaneously, except in an immunocompromised host. The situation does not always end happily though; some viral infections, such as Lassa fever and Ebola virus infection, have a high mortality, and we now discuss a further, grave example of this group: the HIV virus. This is appropriate because HIV exhibits many of the features common to other viral infections, and the sheer scale of the global AIDS problem has pushed HIV to the top of the list of antiviral targets.  |
| **HIV AND AIDS**  |

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| **Viruses** |

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| * Viruses are small infective agents consisting of nucleic acid (RNA or DNA) enclosed in a protein coat.
* They are not cells and, having no metabolic machinery of their own, are obligate intracellular parasites, utilising the metabolic processes of the host cell they infect to replicate.
* *DNA viru*s*es* usually enter the host cell nucleus and direct the generation of new viruses.
* *RNA viruses* direct the generation of new viruses, usually without involving the host cell nucleus (the influenza virus is an exception in that it does involve the host cell nucleus).
* *RNA retroviruses* (e.g. HIV, T-cell leukaemia virus) contain an enzyme, reverse transcriptase, which makes a DNA copy of the viral RNA. This DNA copy is integrated into the host cell genome and directs the generation of new virus particles.
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| HIV is an RNA retrovirus. Two forms are known. *HIV-1* is the organism responsible for human AIDS. The *HIV-2* organism is similar to the HIV-1 virus in that it also causes immune suppression, but it is less virulent. HIV-1 is distributed around the world, whereas the HIV-2 virus is confined to parts of Africa. We will consider them together in this section.  |

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| * In 2004, the World Health Organization estimated that almost 40 million people were living with AIDS, and that women and children constituted approximately half that total number. During the same year, some 3 million people died of the disease (including 0.64 million children under 15 years), and there were a further 5 million new cases of AIDS infection reported. The epidemic is overwhelmingly centred on sub-Saharan Africa, which accounts for two-thirds of the total global number of infected persons, and where the adult prevalence is 7.4% (compared with 0.3% in Europe). For a review of the pathogenesis of AIDS, see Mindel & Tenant-Flowers ([2001](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047011#r047011)).
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| The interaction of HIV with the host's immune system is complex, and although it involves mainly cytotoxic T lymphocytes (CTLs, CD8+ T cells) and CD4+ helper T lymphocytes (CD4 cells), other immune cells, such as macrophages, dendritic cells and NK cells, also play a part. Antibodies are produced by the host to various HIV components, but it is the action of the CTLs and CD4 cells that initially prevents the spread of HIV.  |

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| **Cytotoxic T lymphocytes** directly kill virally infected cells and produce and release antiviral cytokines ([Fig. 47.2](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047016)). The lethal event is lysis of the target cell, but induction of apoptosis by interaction of Fas ligand ('death ligand' see [Fig. 5.5](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047016)) on the CTL with Fas receptors on the virally infected cell can also play a part. **CD4**+ **cells** have an important role as helper cells, and it is the progressive loss of these cells that is the defining characteristic of HIV infection ([Fig. 47.4](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047016)). Recent work suggests that CD4 cells may themselves have a direct role (e.g. lysis of target cells) in the control of HIV replication (Norris et al., [2004](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047012#r047012)).  |

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| Once within the cell, HIV is integrated with the host DNA (the provirus form), undergoing transcription and generating new virions when the cell is activated ([Fig. 47.3](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047016)). In an untreated subject, a staggering 1010 new virus particles may be produced each day. Intracellular HIV can remain silent (latent) for a long time.  |

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| * The priming of naive T cells to become CTLs during the induction phase involves interaction of the T-cell receptor complex with antigenic HIV peptide in association with MHC class I molecules on the surface of antigen-presenting cells (APCs; see [Figs 13.3](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047016) and [13.4](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047016)). Priming also requires the presence and participation of CD4+ cells. It is thought that both types of cell need to recognise antigen on the surface of the same APC ([Fig. 13.3](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047016)).
* The CTLs thus generated are effective during the initial stages of the infection but are not able to stop the progression of the disease. It is believed that this is because the CTLs have become 'exhausted' and dysfunctional. Two different mechanisms may be involved, and these are summarised in simple terms below.

One possible mechanism has been suggested on the basis of recent research into a different viral infection. The study shows that the assistance of CD4+ cells *during the initial priming process* may be essential for the secondary expansion of CTLs on autonomous restimulation. The evidence is that, during priming, CD4+ cells help determine the development of the relevant CTL memory and the ability of CTLs to mount a secondary response. Without this, most CTL cells may, on interacting with antigen again, themselves become exhausted and enter apoptosis (Jansen et al., [2004](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047010#r047010)). This throws new light on the role of CD4+ cells in the immune response to HIV.* + Another possible explanation for CD8+ T-cell exhaustion, also based on recent work with another viral infection, is that these cells overexpress an apoptotic gene. Administration of an antibody that blocked the interaction between this factor and its receptor restored the ability of T cells to proliferate and kill infected cells, thus reducing the viral load. This notion also suggests a novel and potentially effective immunological strategy for treatment of chronic viral infections such as that caused by the HIV viruses (Barber et al., [2006](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047007#r047007)).

 The HIV virion cannily attaches to proteins on the host cell surface to gain entry to the cells. The main targets are CD4 (a glycoprotein marker of a particular group of helper T lymphocytes) and CCR5 (a coreceptor for certain chemokines, including monocyte chemoattractant protein-1 and RANTES [regulated on activation normal T-cell expressed and secreted]). CD4+ cells normally orchestrate the immune response to viruses, but by entering these cells and using them as virion factories, HIV virtually cripples this aspect of the immune response. + T cell. Infected activated CD4 T cells in lymphoid tissue form the major source of HIV production in HIV-infected individuals; infected macrophages are another source.* As for CCR5, evidence from exposed individuals who somehow evade infection indicates that this surface protein has a central role in HIV pathogenesis. Compounds that inhibit the entry of HIV into cells by blocking CCR5 are in phase III clinical trials and may soon be available commercially (Charo et al., [2006](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047009#r047009)).
* When immune surveillance breaks down, other strains of HIV arise that recognise other host cell surface molecules such as CD4 and CXCR4. A surface glycoprotein, gp120, on the HIV envelope binds to CD4 and also to the T-cell chemokine coreceptor CXCR4. Another viral glycoprotein, gp41, then causes fusion of the viral envelope with the plasma membrane of the cell ([Fig. 47.3](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047016)).
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| Figure 47-3 **Schematic diagram of infection of a CD4+ T cell by an HIV virion, with the sites of action of the two main classes of anti-HIV drugs.** The 10 steps of HIV infection, from attachment to the cell to release of new virions, are shown. The virus uses the CD4 coreceptor and the chemokine (Ck) receptor CXCR4 as binding sites to facilitate entry into the cell, where it becomes incorporated into host DNA (steps 1-5). When transcription occurs (step 6), the T cell itself is activated and the transcription factor nuclear factor κB initiates transcription of both host cell and provirus DNA. A viral protease cleaves the nascent viral polypeptides (steps 7 and 8) into structural proteins and enzymes (integrase, reverse transcriptase, protease) for the new virion. The new virions are assembled and released from the cells, initiating a fresh round of infection (steps 9 and 10). The sites of action of the currently used anti-HIV drugs are shown. |

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| Viral replication is error-prone, and there are a large number of mutations daily at each site in the HIV genome, so HIV soon escapes recognition by the original cytotoxic lymphocytes. Although other cytotoxic lymphocytes arise that recognise the altered virus protein(s), further mutations, in turn, allow escape from surveillance by these cells too. It is suggested that wave after wave of cytotoxic lymphocytes act against new mutants as they arise, gradually depleting a T-cell repertoire already seriously compromised by the loss of CD4+ helper T cells, until eventually the immune response fails.  |

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| There is considerable variability in the progress of the disease, but the usual clinical course of an untreated HIV infection is shown in [Figure 47.4](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047016). An initial acute influenza-like illness is associated with an increase in the number of virus particles in the blood, their widespread dissemination through the tissues, and the seeding of lymphoid tissue with the virion particles. Within a few weeks, the *viraemia* is reduced by the action of cytotoxic lymphocytes as specified above.  |

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| The acute initial illness is followed by a symptom-free period during which there is reduction in the viraemia accompanied by silent virus replication in the lymph nodes, associated with damage to lymph node architecture and the loss of CD4+ lymphocytes and dendritic cells. Clinical latency (median, 10 years) comes to an end when the immune response finally fails and the signs and symptoms of AIDS appear-opportunistic infections (e.g. with *Pneumocystis carinii* or the tubercle bacillus), neurological disease (e.g. confusion, paralysis, dementia), bone marrow depression and cancers. Chronic gastrointestinal infections contribute to the severe weight loss. Cardiovascular damage and kidney damage can also occur. In an untreated patient, death usually follows within 2 years. The advent of complex combination drug regimens has changed the prognosis-at least in countries that are able to deploy them.  |

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| There is evidence that genetic factors play an important role in determining the susceptibility-or resistance-to HIV (see Flores-Villanueva et al., [2003](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047030#r047030)).  |

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| **ANTIVIRAL DRUGS**  |

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| Because viruses hijack many of the metabolic processes of the host cell itself, it is difficult to find drugs that are selective for the pathogen. However, there are some enzymes that are virus-specific, and these have proved to be useful drug targets. Most currently available antiviral agents are effective only while the virus is replicating. Because the initial phases of viral infection are often asymptomatic, treatment is often delayed until the infection is well established, and one therefore begins therapy at a tactical disadvantage. As is often the case with infectious diseases, an ounce of prevention is worth a pound of cure.  |

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| Many antiviral drugs are available, and we cannot discuss all these in detail for space reasons. However, most fall into only a few groups with similar mechanisms of action and often similar side effects too. [Table 47.2](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=T047002#T047002) shows the commonest antiviral drugs, their mechanisms of action and some of the diseases they are used to treat. Some common side effects are shown in [Table 47.3](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=T047003#T047003). We will discuss each group briefly.  |

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| **NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS**  |

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| This currently comprises a large group of nucleoside analogues all of which are phosphorylated by host cell enzymes to give the 5'-trisphosphate derivative. This moiety competes with the equivalent host cellular trisphosphate substrates for proviral DNA synthesis by viral reverse transcriptase (viral RNA-dependent DNA polymerase). Eventually, the incorporation of the 5'-trisphosphate moiety into the growing viral DNA chain results in chain termination. Mammalian α-DNA polymerase is relatively resistant to the effect. However, γ-DNA polymerase in the host cell mitochondria is fairly sensitive to the compound, and this may be the basis of some unwanted effects. The main utility of these drugs is the treatment of HIV, but a number of them have useful activity against other viruses also. Some examples of nucleoside reverse transcriptase inhibitors are given below.  |

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| ***Zidovudine***  |

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| Figure 47-4 **Schematic outline of the course of HIV infection.** The CD4+ T-cell titre is often expressed as cells/mm3. (Adapted from Pantaleo et al. 1993 N Engl J Med 328: 327-335.) |

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| **Table 47-2. Principal classes of antiviral drugs and some common therapeutic uses** |

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| Body\_ID: None |
| **Type** | **Common therapeutic indication(s)** |
| Body\_ID: **T047002.50** |  |
| Nucleoside reverse transcriptase inhibitors: *abacavir, adefovir* *dipivoxil, didanosine, emtricitabine, lamivudine, stavudine,* *tenofovir, zalcitabine, zidovudine* | Mainly HIV, generally in combination with other retroviralsLamivudine and adefovir are also used in the treatment of hepatitis B |
| Body\_ID: **T047002.100** |  |
| Non-nucleoside reverse transcriptase inhibitors: *efavirenz, nevirapine* | HIV, generally in combination with other retrovirals |
| Body\_ID: **T047002.150** |  |
| Protease inhibitors: *amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir* | HIV, generally in combination with other retrovirals |
| Body\_ID: **T047002.200** |  |
| Viral DNA polymerase inhibitors: *aciclovir*† ,*cidofovir\*,famciclovir*† ,*foscarnet*† ,*ganciclovir\*, idoxuridine*† ,*penciclovir*†*,* | Treatment of herpes†, cytomegalovirus\*, or hepatitis C and respiratory syncitial virus infections‡ *ribvarin*‡ ,*valaciclovir\**† ,*valganciclovir\** |
| Body\_ID: **T047002.250** |  |
| Inhibitors of HIV fusion with host cells: *enfurvitide* | HIV, generally in combination with other retrovirals |
| Body\_ID: **T047002.300** |  |
| Inhibitors of viral coat disassembly and neuraminidase inhibitors: *amantadine\*, oseltamivir, zanamivir* | Influenza A\* or A and B |
| Body\_ID: **T047002.350** |  |
| Biologics and immunomodulators: *interferon-*α ,*pegylated* *interferon-*α ,*inosine pranobex\*, palivizumab*† | Treatment of hepatitis B and C, herpes\* and respiratory syncitial virus† |
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| **Table 47-3. Principal common unwanted effects of some antiviral drugs** |

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| Body\_ID: None |
| **Drug type** | **Principal common unwanted effects** | **Comments** |
| Body\_ID: **T047003.50** |  |  |
| Nucleoside reverse transcriptase inhibitors: *zidovudine, abacavir,* *didanosine, emtricitabine, lamivudine,* *stavudine, tenofovir, zalcatabine* | Gastrointestinal disturbances including nausea, vomiting, abdominal pain and diarrhoea Central nervous system and related effects including headache, insomnia and dizziness, and neuropathyMusculoskeletal and dermatological effects including fatigue, myalgia, arthralgia, rash, urticaria and feverBlood disorders including anaemia, neutropenia and thrombocytopeniaMetabolic effects including pancreatitis, liver damage and lipodystrophy | - |
| Body\_ID: **T047003.100** |  |  |
| Non-nucleoside reverse transcriptase inhibitors: *efavirenz, nevirapine* | Dermatological effects including rash and urticaria Central nervous system and related effects including fatigue, headache, sleep disturbances, depression and dizzinessGastrointestinal disturbances including nausea, vomiting, abdominalpain and diarrhoeaBlood disorders including anaemia, neutropenia and thrombocytopeniaaMetabolic effects including pancreatitis, raised cholesterol, liver dysfunction and lipodystrophy | High (15-25%) incidence of rash |
| Body\_ID: **T047003.150** |  |  |
| Protease inhibitors: *amprenavir,* *atazanavir, indinavir, lopinavir*,*nelfinavir, ritonovir, saquinavir* | Gastrointestinal disturbances including nausea, vomiting, abdominal pain and diarrhoea Central nervous system and related effects including fatigue, headache, sleep disturbances and dizziness, taste disturbances and paraesthesiaMusculoskeletal and dermatological effects including myalgia, arthralgia, rhabdomyolysis, rash, urticaria and fever Blood disorders including anaemia, neutropenia and thrombocytopeniaMetabolic effects including pancreatitis, liver dysfunction and lipodystrophy | - |
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| aAdministration of epoietin (erythropoietin) and molgramostim (recombinant human granulocyte macrophage colony-stimulating factor; see [Ch. 22](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=C02269116#C02269116), p. 354) may alleviate these problems.  |

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| **Zidovudine** is an analogue of thymidine. It can prolong life in HIV-infected individuals and diminish HIV-associated dementia. Given to the parturient mother and then to the newborn infant, it can reduce mother-to-baby transmission by more than 20%. It is generally administered orally twice daily but can also be given by intravenous infusion. The bioavailability is 60-80%, and the peak plasma concentration occurs at 30 minutes. Its half-life is 1 hour, and the intracellular half-life of the active trisphosphate is 3 hours. The concentration in cerebrospinal fluid (CSF) is 65% of the plasma level. Most of the drug is metabolised to the inactive glucuronide in the liver, only 20% of the active form being excreted in the urine.  |

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| *Resistance to the antiviral action of zidovudine*  |

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| 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 that underlie the loss of efficacy of the drug are decreased activation of zidovudine to the trisphosphate and increased virus load owing to reduction in the host immune response.  |

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| ***Didanosine***  |

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| **Didanosine** is an analogue of deoxyadenosine. It is given orally, is rapidly absorbed and is actively secreted by the kidney tubules. The level in the CSF reaches ∼20% of the plasma concentration. The plasma half-life is 30 minutes, but the intracellular half-life is more than 12 hours.  |

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| ***Zalcitabine***  |

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| **Zalcitabine** is a homologue of cytosine. 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, and its intracellular half-life is nearly 3 hours; the CSF level is 20% of that in the plasma.  |

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| ***Lamivudine***  |

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| **Lamivudine** is an analogue of cytosine. It is given orally, is well absorbed and most is excreted unchanged in the urine. The CSF level is 20% of the plasma concentration. Used alone, it could select for HIV mutants that are resistant to both the drug itself as well as other reverse transcriptase inhibitors. Lamivudine is also used in the therapy of hepatitis B infection.  |

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| ***Stavudine***  |

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| **Stavudine** is a thymidine analogue. It is given orally, has a plasma half-life of 1 hour, and most is eliminated via the kidney by active tubular secretion. The CSF level is 55% of that in the plasma.  |

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| ***Abacavir***  |

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| **Abacavir** is a guanosine analogue and has so far proved to be more effective than most other nucleoside reverse transcriptase inhibitors. It is well absorbed after oral administration and is metabolised in the liver to inactive compounds. The CSF level is 33% of that in the plasma.  |

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| **NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS**  |

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| Non-nucleoside reverse transcriptase inhibitors are chemically diverse compounds that bind to the reverse transcriptase enzyme near the catalytic site and denature it. Most non-nucleoside reverse transcriptase inhibitors are inducers, substrates or inhibitors, to varying degrees, of the liver cytochrome P450 enzymes. Currently available drugs **nevirapine** are and **efavirenz**.  |

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| ***Nevirapine***  |

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| Nevirapine is given orally, its bioavailability is >90%, and its CSF level is 45% of that in the plasma. It is metabolised in the liver, and the metabolite is excreted in the urine. Nevirapine can prevent mother-to-baby transmission of HIV if given to the parturient mother and the neonate.  |

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| ***Efavirenz***  |

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| Efavirenz is given orally, once daily because of its plasma half-life (∼50 hours). It is 99% bound to plasma albumin, and its CSF concentration is ∼1% of that in the plasma. It is inactivated in the liver.  |

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| **PROTEASE INHIBITORS**  |

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| In HIV and many other viral infections, the mRNA transcribed from the provirus is translated into two biochemically inert *polyproteins*. A virus-specific protease then converts the polyproteins into various structural and functional proteins by cleavage at the appropriate positions (see [Fig. 47.3](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047017)). Because this protease does not occur in the host, it is a useful target for chemotherapeutic intervention. HIV-specific protease inhibitors bind to the site where cleavage occurs, and their use, in combination with reverse transcriptase inhibitors, has transformed the therapy of AIDS. Examples of current protease inhibitors are shown in [Table 47.2](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=T047002#T047002) and are exemplified by drugs such as **saquinavir**, **nelfinavir**, **indinavir**, **ritonavir** and **amprenavir**.  |

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| ***Pharmacokinetic aspects***  |

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| The drugs are generally given orally, saquinavir being subject to extensive first-pass metabolism. CSF levels are negligible with saquinavir and highest with indinavir (76% of the plasma concentration). Nelfinavir and ritonavir are best taken with food, and saquinavir within 2 hours of a meal.  |

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| *Unwanted effects* are also similar (see [Table 47.3](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=T047003#T047003)).  |

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| **DNA POLYMERASE INHIBITORS**  |

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| ***Aciclovir***  |

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| The era of effective selective antiviral therapy began with **aciclovir**. This agent is a guanosine derivative with a high specificity for herpes simplex and varicella zoster viruses. Herpes simplex can cause cold sores, conjunctivitis, mouth ulcers, genital infections2 and, rarely but very seriously, encephalitis; in immunocompromised patients, it is much more aggressive. Varicella zoster viruses cause shingles and chickenpox. Herpes simplex is more susceptible to aciclovir than varicella zoster. Epstein-Barr virus (a herpesvirus that causes glandular fever) is also slightly sensitive. Aciclovir has a small but reproducible effect against cytomegalovirus-a herpesvirus that can affect the fetus with catastrophic consequences, can cause a glandular fever-like syndrome in adults and severe disease (e.g. retinitis, which can result in blindness) in immunocompromised individuals.  |

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| *Mechanism of action*  |

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| Aciclovir is converted to the monophosphate by thymidine kinase, and happily the virus-specific form of this enzyme is very much more effective in carrying out the phosphorylation than the enzyme of the host cell; it is therefore only activated adequately in infected cells. The host cell kinases then convert the monophosphate to the trisphosphate. It is the aciclovir trisphosphate that inhibits viral DNA polymerase, terminating the nucleotide chain. It is 30 times more potent against the herpesvirus enzyme than the host enzyme. Aciclovir trisphosphate is fairly rapidly broken down within the host cells, presumably by cellular phosphatases. Resistance caused by changes in the viral genes coding for thymidine kinase or DNA polymerase has been reported, and aciclovir-resistant herpes simplex virus has been the cause of pneumonia, encephalitis and mucocutaneous infections in immunocompromised patients.  |

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| *Pharmacokinetic aspects*  |

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| Aciclovir can be given orally, intravenously or topically. When it is given orally, only 20% of the dose is absorbed and peak plasma concentrations are reached in 1-2 hours. The drug is widely distributed, reaching concentrations in the CSF that are 50% of those in the plasma. It is excreted by the kidneys, partly by glomerular filtration and partly by tubular secretion.  |

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| *Unwanted effects*  |

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| These are minimal. Local inflammation can occur during intravenous injection if there is extravasation of the solution. Renal dysfunction has been reported when aciclovir is given intravenously; slow infusion reduces the risk. Nausea and headache can occur and, rarely, encephalopathy.  |

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| There are now many other drugs with a similar action to aciclovir (see [Table 47.2](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=T047002#T047002)). This group includes **valaciclovir**, a prodrug of aciclovir, and **famciclovir**, which is metabolised to the active compound **penciclovir** in vivo. Other viral DNA polymerase inhibitors include the following.  |

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| ***Ganciclovir***  |

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| This acyclic analogue of guanosine is the drug of choice for *cytomegalovirus* infection. This is a frequent opportunistic infection in immunocompromised or AIDS patients and has been a formidable obstacle to successful transplantation of organs and bone marrow (which necessitates immunosuppressive therapy). Like aciclovir, **ganciclovir** has to be activated to the trisphosphate, and in this form it competes with guanosine trisphosphate for incorporation into viral DNA. It suppresses viral DNA replication, but unlike aciclovir it does not act as a chain terminator and has a longer duration of action, persisting in infected cells for 18-20 hours.  |

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| **Clinical uses of drugs for herpes viruses (e.g. aciclovir, famciclovir, valaciclovir)** |

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| * *Varicella zoster* infections (chickenpox, shingles):
	+ orally in immunocompetent patients
	+ intravenously in immunocompromised patients.
* *Herpes simplex* infections (*genital* herpes, *mucocutaneous* herpes and herpes *encephalitis*).
* Prophylactically:
	+ patients who are to be treated with immunosuppressant drugs or radiotherapy and who are at risk of herpesvirus infection owing to reactivation of a latent virus
	+ in individuals who suffer from frequent recurrences of genital infection with herpes simplex virus.
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| *Pharmacokinetic aspects*  |

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| Ganciclovir is given intravenously. It is excreted in the urine and has a half-life of 4 hours.  |

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| *Unwanted effects*  |

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| Ganciclovir has serious unwanted actions, including bone marrow depression and potential carcinogenicity, and is consequently used only for life- or sight-threatening cytomegalovirus infections in patients who are immunocompromised. Oral administration can be used for maintenance therapy in AIDS patients.  |

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| ***Tribavirin (ribavirin)***  |

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| **Tribavirin** is a synthetic nucleoside, similar in structure to guanosine. It is thought to act either by altering virus nucleotide pools or by interfering with the synthesis of viral mRNA. It inhibits a wide range of DNA and RNA viruses, including many that affect the lower airways. In aerosol form, it has been used to treat influenza and infections with *respiratory syncytial virus* (an RNA paramyxovirus). It has also been shown to be effective in hepatitis C as well as Lassa fever, an extremely serious *arenavirus* infection. When given promptly to victims of the latter disease, it has been shown to reduce to 9%, a case fatality rate previously 76%.  |

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| ***Foscarnet (phosphonoformate)***  |

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| **Foscarnet** is a synthetic non-nucleoside analogue of pyrophosphate that inhibits viral DNA polymerase by binding directly to the pyrophosphate-binding site. It can cause serious nephrotoxicity. Given by intravenous infusion, it is a second-line drug in cytomegalovirus eye infection in immunocompromised patients.  |

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| **INHIBITORS OF HIV FUSION WITH HOST CELLS**  |

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| There is only one drug in this group: **enfurvirtide**. The drug is generally given by subcutaneous injection in combination with others to treat HIV when resistance becomes a problem or when the patient is intolerant of other antiretrovirals.  |

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| *Unwanted effects*  |

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| These include flu-like symptoms, central effects such as headache, dizziness, alterations in mood, gastrointestinal effects and sometimes hypersensitivity reactions.  |

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| **NEURAMINIDASE INHIBITORS AND INHIBITORS OF VIRAL COAT DISASSEMBLY**  |

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| Body\_ID: **HC047045** |

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| Viral neuraminidase is one of three transmembrane proteins coded by the influenza genome. Infection with these RNA viruses begins with the attachment of the viral haemaglutinin to neuraminic (sialic) acid residues on host cells. The viral particle then enters the cell by an endocytic process. The endosome is acidified following influx of H+ through another viral protein, the *M2 ion channel*. This facilitates the disassembly of the viral structure, allowing the RNA to enter the host nucleus, thus initiating a round of viral replication. Newly replicated virions escape from the host cell by budding from the cell membrane. Viral neuraminidase promotes this by severing the bonds linking the particle coat and host sialic acid.  |

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| The neuraminidase inhibitors **zanamivir** and **oseltamivir** are active against both influenza A and B viruses, and are licensed for use at early stages in the infection or when use of the vaccine is impossible. Zanamivir is available as a powder for inhalation, and oseltamivir as an oral preparation. At the time of writing, governments around the world are stockpiling this latter drug in the expectation that it may offer some defence against 'bird flu', should this mutate into an organism capable of infecting humans.  |

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| *Unwanted effects* of both include gastrointestinal symptoms (nausea, vomiting, dyspepsia and diarrhoea), but these are less frequent and severe in the inhaled preparation.  |

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| **Amantadine**,3 quite an old drug (1966) and seldom recommended today, effectively blocks the M2 ion channels, thus inhibiting viral disassembly. It is active against influenza A virus (an RNA virus) but has no action against influenza B virus. The closely related **rimantadine** is similar in its effects.  |

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| *Pharmacokinetic aspects.* Given orally, amantadine is well absorbed, reaches high levels in secretions (e.g. saliva) and most is excreted unchanged via the kidney. Aerosol administration is feasible.  |

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| *Unwanted effects* are relatively infrequent, occurring in 5-10% of patients, and are not serious. Dizziness, insomnia and slurred speech are the most common adverse effects.  |

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| **BIOLOGICS AND IMMUNOMODULATORS**  |

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| A number of other agents have been recruited in the fight against virus infections, including immunoglobulin preparations, IFNs, immunomodulators and monoclonal antibodies.  |

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| ***Immunoglobulin***  |

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| Pooled immunoglobulin contains antibodies against various viruses present in the population. The antibodies are directed against the virus envelope and can 'neutralise' some viruses and prevent their attachment to host cells. If used before the onset of signs and symptoms, it may attenuate or prevent measles, infectious hepatitis, German measles, rabies or poliomyelitis. *Hyperimmune* globulin, specific against particular viruses, is used against hepatitis B, varicella zoster and rabies.  |

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| ***Palivisumab***  |

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| Related in terms of its mechanism of action to immunoglobulins is **palivisumab**, a monoclonal antibody (see [Chs 13](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=C01369116#C01369116) and [55](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=C05569116#C05569116)) directed against a glycoprotein on the surface of respiratory syncytial virus. It is used (as an intramuscular injection) in infants to prevent infection by this organism.  |

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| ***Interferon***  |

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| **Interferons** are a family of inducible proteins synthesised by mammalian cells and now generally produced commercially using recombinant DNA technology. There are at least three types, α, β, and γ, constituting a family of hormones involved in cell growth and regulation and the modulation of immune reactions. IFN-γ, termed *immune interferon* (see [p. 223](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=P0223#P0223)), is produced mainly by T lymphocytes as part of an immunological response to both viral and non-viral antigens, the latter including bacteria and their products, rickettsiae, protozoa, fungal polysaccharides and a range of polymeric chemicals and other cytokines. IFN-α and IFN-β are produced by B and T lymphocytes, macrophages and fibroblasts in response to the presence of viruses and cytokines. The general actions of the IFNs are described briefly in [Chapter 13](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=C01369116#C01369116).  |

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| *Mechanism of antiviral action*  |

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| The IFNs bind to specific ganglioside receptors on host cell membranes. They induce, in host cell ribosomes, the production of enzymes that inhibit the translation of viral mRNA into viral proteins, thus halting viral replication. They have a broad spectrum of action and inhibit the replication of most viruses in vitro.  |

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| *Pharmacokinetic aspects*  |

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| Given intravenously, IFNs have a half-life of 2-4 hours. With intramuscular injections, peak blood concentrations are reached in 5-8 hours. They do not cross the blood-brain barrier.  |

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| *Clinical use*  |

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| Interferon-α-2a is used for treatment of hepatitis B infections and AIDS-related Kaposi sarcomas; IFN-α-2b is used for hepatitis C. There are reports that IFNs can prevent reactivation of herpes simplex after trigeminal root section and can prevent spread of herpes zoster in cancer patients. Preparations of IFNs conjugated with polyethylene glycol (pegylated IFNs) have a longer lifetime in the circulation.  |

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| *Unwanted effects*  |

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| Unwanted effects are common and include fever, lassitude, headache and myalgia. Repeated injections cause chronic malaise. Bone marrow depression, rashes, alopecia and disturbances in cardiovascular, thyroid and hepatic function can also occur.  |

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| ***Inosine pranobex***  |

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| Immunomodulators are drugs that act by moderating the immune response to viruses or use an immune mechanism to target a virus or other organism. **Inosine pranobex** may interfere with viral nucleic acid synthesis but also has immunopotentiating actions on the host. It is sometimes used to treat herpes infections in mucosal tissues or on the skin.  |

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| COMBINATION THERAPY FOR HIV  |

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| Two main classes of antivirals are used to treat HIV: reverse transcriptase inhibitors and protease inhibitors. As they have different mechanisms of action ([Fig. 47.3](http://www.studentconsult.com/content/bookcontent.cfm?ID=HC047017)), they can usefully be used in combinations and this technique has dramatically improved the prognosis of the disease. The combination treatment is known as highly active antiretroviral therapy (HAART). A typical HAART combination would involve two nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or one or two protease inhibitors.  |

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| Using a HAART protocol, HIV replication is inhibited, the presence in the plasma of HIV RNA is reduced to undetectable levels, and patient survival is greatly prolonged. But the regimen is complex and has many unwanted effects. Compliance is difficult and treatment is lifelong. The virus is not eradicated but lies latent in the host genome of memory T cells, ready to reactivate if therapy is stopped.  |

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| Unwelcome interactions can occur between the three component drugs of HAART combinations, and there may be interindividual variations in absorption. Some drugs penetrate poorly into the brain, and this could lead to local proliferation of the virus. At present, there is no cross-resistance between the three groups of drugs, but it needs to be borne in mind that the virus has a high mutation rate-so resistance could be a problem in the future. The HIV virus has certainly not yet been outsmarted.  |

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| **Antiviral drugs** |

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| * Most antiviral drugs generally fall into the following groups:
	+ nucleoside analogues that inhibit the viral reverse transcriptase enzyme, preventing replication (e.g. lamivudine, zidovudine)
	+ non-nucleoside analogues that have the same effect (e.g. efavirenz)
	+ inhibitors of proteases that prevent viral protein processing (e.g. saquinavir, indinavir)
	+ inhibitors of viral DNA polymerase that prevent replication (e.g. aciclovir, famciclovir)
	+ inhibitors of viral capsule disassembly (e.g. amantidine)
	+ inhibitors of neuraminidase that prevent viral escape from infected cells (e.g. oseltamivir)
	+ immunomodulators that enhance host defences (e.g. interferons and inosine pranobex)
	+ immunoglobulin and related preparations that contain neutralising antibodies to various viruses.
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| **Drugs for HIV infections** |

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| * Reverse transcriptase inhibitors (RTIs):
	+ *nucleoside RTIs* are phosphorylated by host cell enzymes to give the 5´-trisphosphate, which competes with the equivalent host cellular trisphosphates that are essential substrates for the formation of proviral DNA by viral reverse transcriptase (examples are zidovudine and abacavir); they are used in combination with protease inhibitors.
	+ *non-nucleoside RTIs* are chemically diverse compounds that bind to the reverse transcriptase near the catalytic site and denature it; an example is nevirapine.
* Protease inhibitors inhibit cleavage of the nascent viral protein into functional and structural proteins. They are often used in combination with reverse transcriptase inhibitors. An example is saquinavir.
* Combination therapy is essential in treating HIV; this characteristically comprises two nucleoside RTIs with either a non-nucleoside RTI or one or two protease inhibitors.
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| **Treatment of HIV/AIDS** |

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| * A consensus on the use of retroviral therapy in AIDS has emerged based on the following principles:
	+ monitor plasma viral load and CD4+ cell count
	+ start treatment before immunodeficiency becomes evident
	+ aim to reduce plasma viral concentration as much as possible for as long as possible
	+ use combinations of at least three drugs (e.g. two reverse transcriptase inhibitors and one protease inhibitor)
	+ change to a new regimen if plasma viral concentration increases.
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| The choice of drugs to treat pregnant or breast-feeding women is difficult. The main aims are to avoid damage to the fetus and to prevent transmission of the disease to the neonate. Therapy with zidovudine alone is often used in these cases. Another area that requires special consideration is prophylaxis for individuals who may have been exposed to the virus accidentally. Specific guidelines have been developed for such cases, but they are beyond the scope of this chapter.  |

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| PROSPECTS FOR NEW ANTIVIRAL DRUGS  |

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| At the beginning of the 1990s, there were only five drugs available to treat viral infections; 15 years later, this number has increased some sevenfold. New strategies-based on the growing understanding of the biology of pathogenic viruses and their action on and in host cells-could well, if vigorously implemented, have the potential to target the viruses causing most viral diseases (see de Clercq, [2002](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047020#r047020)). However, the ultimate weapon in the fight against the virus is vaccination. This has proved to be stunningly effective in the past against diseases such as polio and smallpox, and more recently against influenza (both types) and hepatitis B. However, while there have been many clinical trials, the prospect of a vaccine against HIV (or indeed many other viruses) still seems rather remote. Part of the problem is *antigenic drift*, a process whereby the virus mutates, thus presenting different antigenic structures and minimising the chance of an effective and long-lasting immune response or the production of a vaccine. The whole problem is the subject of numerous reviews (see Stratov et al., [2004](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047035#r047035); Tonini et al., [2005](http://www.studentconsult.com/content/bookcontent.cfm?xrefID=r047036#r047036)).  |