Our markedly improved understanding of factors involved in viral replication (attachment, fusion, uncoating, assembly) has lead to the selection of numerous targets for antiviral treatment. Within the past two decades, substantial advances in the development of compounds that specifically interfere with viral targets have resulted in the development of a vast armamentarium for use against viral infections. Unlike antibiotics, most antiviral drugs target a viral process that is only functional in one specific virus or a small group of viruses. We have therefore chosen to divide this chapter by viral pathogens and discuss the antiviral compounds under the group of viruses for which the drug has been used predominantly.

**DRUGS ACTIVE AGAINST CYTOMEGALOVIRUS**

### Cidofovir

Cidofovir (S-1-3-hydroxy-2-phosphonomethoxypropylcytosine), also known as HPMPC, is a nucleotide analog with potent activity against cytomegalovirus (CMV) in vitro and in vivo.

**Urinary system** The main adverse effect associated with intravenous administration of cidofovir is renal tubular damage. Proteinuria seems to be an early indicator of this adverse effect. Other laboratory abnormalities associated with nephrotoxicity are glycosuria, reduced serum phosphate, uric acid, and bicarbonate, and increased serum creatinine. Serious and potentially irreversible nephrotoxicity can generally be prevented by the concomitant administration of intravenous saline and oral probenecid, monitoring the blood and urine immediately before each infusion of cidofovir, and withdrawing the drug for low-threshold increases in either urinary protein or serum creatinine concentrations (15). Concomitant use of other nephrotoxic drugs should be avoided.

**Special senses** Two cases of iritis shortly after intravenous administration of cidofovir have been reported (28). Intravitreal administration of cidofovir delays the progression of CMV retinitis, but may be associated with reduced intraocular pressure or vitreitis (35).

### Foscarnet

A pyrophosphate analog, foscarnet (trisodium phosphonoformate hexahydrate, PFA) interacts with the enzymatic action of polymerases and inhibits the cleavage of pyrophosphate from the nucleoside triphosphate. Because of this mechanism, the antiviral activity of the drug is broad. Foscarnet is a non-competitive inhibitor of herpesvirus DNA polymerase, hepatitis B virus DNA polymerase, and reverse transcriptases (48). Intravenous foscarnet has been used for the treatment of mucocutaneous disease due to acyclovir-resistant *Herpes simplex* (55) and for the treatment of severe CMV infection (55, 75). Foscarnet has been shown to be as effective as ganciclovir in the treatment of gastrointestinal CMV and CMV retinitis in patients with AIDS (85). The two drugs differ, however, in their respective toxicity profile, and in a comparison in CMV retinitis, ganciclovir was better tolerated (95). Treatment-limiting adverse effects are renal toxicity, hypocalcemia, and mucosal ulceration.

**Urinary system** Alterations in creatinine clearance or acute renal insufficiency occur in 10—20% of patients with AIDS receiving intravenous foscarnet (105), due to acute tubular damage. Severe renal insufficiency can be prevented in most cases by careful hydration before and during therapy (118). To minimize the residual incidence of nephrotoxicity, the dose of foscarnet should be frequently recalculated, based on the estimated creatinine clearance.

**Mineral and fluid balance** The second most common adverse effect is symptomatic hypocalcemia, which may be responsible for the cardiac dysrhythmias and seizures that occur after acute overdose or excessively rapid infusion of foscarnet. Foscarnet stimulates the release of parathyroid hormone, which raised concerns about long-term administration (128). However, in a study of seven patients receiving a 14-day foscarnet induction regimen, there were no changes in calcium or phosphate metabolism (135).
Skin and appendages  Painful oral, penile, and vulvar ulceration can occur during foscarnet therapy (14), most probably due to local accumulation of the drug (SEDA-17, 338). Penile ulcers have been reported to be the reason for discontinuation of foscarnet therapy in up to 10% of patients (15).

Ganciclovir

Ganciclovir (dihydroxypropoxymethylguanine, DHPG) is a nucleoside analog with antiviral activity in vitro against herpesviruses. Intracellular phosphorylation of ganciclovir to its triphosphate derivative, which acts as a competitive inhibitor of deoxyguanosine triphosphate, leads to the inhibition of viral DNA synthesis. Because its toxicity profile is more favorable than those of foscarnet and cidofovir, it should be considered first-line treatment of life-threatening or sight-threatening cytomegalovirus (CMV) infections in immunocompromised patients. Ganciclovir is administered by infusion or by intravitreal injection (16). Oral ganciclovir as maintenance therapy for CMV retinitis in patients with AIDS has been reviewed (17). Oral ganciclovir has also been the subject of a pilot study in hepatitis B infection (18).

The proportion of patients in whom ganciclovir therapy is subsequently interrupted or withdrawn because of adverse effects is estimated at 32% (16). Neutropenia is the most frequent adverse effect and is dose-dependent, usually occurring before a total dose of 200 mg/kg has been given. Other hematological adverse effects include thrombocytopenia, anemia, and lymphopenia. Pure red cell aplasia has been reported in one bone-marrow transplant recipient (21) and hemolysis has been observed in two other patients (19). The adverse hematological effects of ganciclovir are generally rapidly reversible after withdrawal (16). Since ganciclovir maintenance treatment is often necessary, concomitant use of G-CSF is often required in patients with AIDS with ganciclovir-associated neutropenia (22).

Neurologic system  Adverse effects involving the central nervous system occur in about 5% of patients and include confusion, seizures, abnormal thinking, psychosis, hallucinations, nightmares, anxiety, tremor, dysesthesia, ataxia, coma, headache, and somnolence (16, 19, 20).

Hematological  Neutropenia is the most frequent adverse effect and is dose-dependent, usually occurring before a total dose of 200 mg/kg has been given. Other hematological adverse effects include thrombocytopenia, anemia, and lymphopenia. Pure red cell aplasia has been reported in one bone-marrow transplant recipient (21) and hemolysis has been observed in two other patients (19). The adverse hematological effects of ganciclovir are generally rapidly reversible after withdrawal (16). Since ganciclovir maintenance treatment is often necessary, concomitant use of G-CSF is often required in patients with AIDS with ganciclovir-associated neutropenia (22).

Special senses  Adverse effects reported in patients receiving intravitreal ganciclovir include foreign body sensation, conjunctival hemorrhage, mild conjunctival scarring, scleral induration, bacterial endophthalmitis, and retinal detachment (16).

Sexual function  Animal data suggest that ganciclovir may inhibit spermatogenesis and fertility (23), but one clinical study did not find significant changes in serum gonadotropin hormone concentrations in 32 men during ganciclovir therapy (24).

Miscellaneous  Fever, rash and abnormal liver function values are each reported to occur in about 2% of ganciclovir recipients (16). Other infrequently reported adverse effects, which may or may not be associated with ganciclovir, include chills, edema, malaise, vomiting, anorexia, diarrhea, dyspnea, reduced blood glucose, alopecia, impaired renal function, and inflammation, pain, or phlebitis at the infusion site (16). These effects may also be due to the underlying illness in such patients.

Interactions  Drugs that inhibit the replication of rapidly dividing cells should not be administered concomitantly with ganciclovir, unless the potential benefits outweigh the risks. Zidovudine and ganciclovir have overlapping toxicity profiles with respect to adverse hematological effects. Severe life-threatening hematological toxicity has been reported in 82% of patients treated with a combination of zidovudine and ganciclovir (25). The combination of ganciclovir with didanosine was much better tolerated (26).

DRUGS ACTIVE AGAINST HERPES SIMPLEX AND VARICELLA ZOSTER VIRUSES

Aciclovir

Aciclovir (9-[2-hydroxyethyl]guanine, acyclovir, ACV), is an acyclic purine nucleoside. Its antiviral activity depends upon intracellular phosphorylation to its triphosphate derivative. Because of its higher affinity for viral thymidine kinase, aciclovir is phosphorylated at a much higher rate by the viral enzyme. Thus, it is almost exclusively active in infected cells, fulfilling one of the selectivity principles of antiviral drugs. In addition, aciclovir triphosphate serves as a better substrate for viral than for host-cell DNA polymerase and thereby causes preferential termination of viral DNA synthesis (27).

Aciclovir is active against Herpes simplex virus type 1 (HSV-1), HSV-2, Varicella zoster virus (VZV), Herpesvirus simiae, and to a lesser degree Epstein-Barr virus (EBV). Resistant strains of HSV may arise owing to the emergence of thymidine kinase-deficient mutants. Other forms of resistance patterns are less common (28, 29).

Aciclovir is used topically or systemically, orally or intravenously. Its therapeutic potential is most im-
pressive in active parenchymal or systemic HSV infections. The latency stage of the viral infection is not affected. Since the blood–brain barrier is well penetrated, aciclovir is the treatment of choice for HSV encephalitis.

Very few adverse effects, generally of minor importance, have been reported (30R). In immunosuppressed patients abnormal liver function, encephalopathy and myelosuppression have been observed; however, it is unclear at present whether these adverse effects are related to the drug itself or to the underlying disorder (31C)–(33C).

Nervous system Neurotoxicity secondary to aciclovir is rare and is associated with high plasma concentrations (SEDA 18, 299). One report described reversible psychiatric adverse effects in three dialysis patients receiving intravenous aciclovir (8–10 mg/kg/day) (34C).

Urinary system Renal impairment has been associated with the use of intravenous aciclovir. Transient increases in serum creatinine and urea have been observed in 14% of patients treated with bolus injections (35C). These are related to crystal formation in the lower renal tubules when the solubility of aciclovir in urine is exceeded. Slow (1-hour) intravenous infusion and adequate hydration are therefore mandatory. Bolus doses are to be avoided. Dosage modifications for patients with renal insufficiency are based on creatinine clearance (30R). Renal toxicity has not been described in infants treated with intravenous aciclovir, 5–10 mg/kg every 8 hours for 5–10 days (36), in children receiving aciclovir 500 mg/m² intravenously (8C) or orally (30R).

Immunological and hypersensitivity reactions A case of possible acyclovir-induced Stevens–Johnson syndrome has been reported in an HIV-positive patient with mycobacterial disease (37C). However, Stevens–Johnson syndrome is associated with Herpes simplex infection and can be prevented by aciclovir (38C).

Special senses Local application of 3% ophthalmic ointment can cause mild transient stinging. Diffuse, superficial, punctate, non-progressive keratopathy can develop. This quickly resolves after withdrawal (39R, 40R).

Miscellaneous Local necrosis and inflammation can occur due to extravasation of the drug at the site of injection (41R).

Second-generation effects Animal data suggest that aciclovir is probably safe in pregnancy. There are no reports of teratogenicity in humans, and a report of 312 pregnant women exposed to aciclovir showed no increase in the number of birth defects compared with the numbers expected in the general population (42C). However, data from larger numbers of human pregnancies are not available to draw reliable conclusions about the safety of aciclovir in pregnancy.

Famciclovir

Famciclovir is an oral prodrug of penciclovir, a selective antiviral drug with activity against Varicella zoster virus, Herpes simplex virus types 1 and 2, and Epstein–Barr virus, as well as human hepatitis B virus. After oral administration, famciclovir is well absorbed (systemic availability 77%), with little intersubject variability, and is rapidly converted to penciclovir. This compares favorably with aciclovir, the absorption of which is slow and incomplete, with a highly variable systemic availability of only 10–20%.

An integrated safety analysis of 1607 patients who had taken famciclovir for the treatment of Herpes zoster or genital herpes has shown that famciclovir is extremely well tolerated, with an adverse effect profile similar to placebo (43R). Headache, nausea, and diarrhea were the most frequently reported adverse events in those taking both famciclovir and placebo. In an experimental study of Herpes simplex labialis, adverse events (diarrhea and nausea) occurred with similar frequency with famciclovir and placebo (44C). No laboratory abnormalities were consistently associated with famciclovir.

Sexual function Prolonged administration of high dosages of famciclovir has been associated with reversible dose-dependent adverse effects on testicular function in rats and dogs. However, in a double-blind placebo-controlled trial in which 34 men with recurrent genital herpes took famciclovir 250 mg bd for 18 weeks, there were no significant effects on sperm production or function (45C).

Valaciclovir

Valaciclovir, the L-valyl ester of aciclovir is an oral prodrug that is rapidly metabolized (first-pass effect) to yield aciclovir and valine. Compared with oral aciclovir, the systemic availability of aciclovir from oral valaciclovir is markedly improved. The drug is highly active against Herpes simplex and Herpes zoster. It is also effective in suppressing recurrent episodes of genital herpes (46C). Its adverse effects are generally mild and comparable to those of aciclovir. Nausea, vomiting, and abdominal pain were commonly reported in human volunteers, but only diarrhea remained significantly associated with exposure (47C). Prophylactic administration of high doses of valaciclovir to prevent CMV disease was effective in patients with AIDS and...
in liver transplant recipients (48c, 49c). However, with
the high doses administered (8 g/day), adverse effects
(hallucinations and confusions) were a significant con-
cern.

In a phase I clinical trial, valaciclovir administered
in the third trimester of pregnancy was well tolerated
(50c).

**DRUGS ACTIVE AGAINST HEPATITIS VIRUSES**

**Famciclovir**

Famciclovir, which is mainly used against infections
with HSV-1, HSV-2, HZV (see above), is also active
against hepatitis B virus.

**Ganciclovir**

Ganciclovir has excellent antiviral activity against
hepatitis B virus and studies are under way to evaluate
its usefulness in this infection. See under drugs active
against CMV.

**Lamivudine**

Lamivudine (3TC) has been widely used against HIV
infection but also has antiviral effects against hepatitis
B (51R). See under drugs active against HIV.

**Ribavirin**

The synthetic triazole nucleoside, ribavirin (1-ß-D-
ribofuranosyl-1,2,4-triazole-3-carboxamide, virazole),
has a broad spectrum of antiviral activity, including
data as well as RNA viruses (52R). Ribavirin closely
resembles guanosine and is converted intracellularly to
mono-, di- and triphosphate derivatives, which inhibit
the virally-induced enzymes involved in nucleic acid synthesis by different mechanisms that are not fully
understood (53R). Of the DNA viruses, ribavirin is active against *Herpes simplex* virus and hepatitis B
virus; among the RNA viruses, good activity has been
observed against hepatitis C virus, orthomyxoviruses,
paramyxoviruses, arenaviruses, and bunyaviruses. Al-
though active against HIV in vitro and in vivo (54c),
ribavirin is not widely used in the treatment of HIV
infection. So far, drug resistance has not been de-
scribed.

Ribavirin is well absorbed orally, but it can be given
in aerosol form for the treatment of respiratory syncy-
tial virus (RSV) infections in immunocompromised pa-
tients, and in those with cardiopulmonary abnormalities, or in infants receiving mechanical ventilation (55c,
56c).

Oral ribavirin has been successfully used in the treat-
ment of Lassa fever (57c) and Crimean Congo hemor-
raghic fever (58c), but its use has recently increased
owing to beneficial results in combination therapy with
interferon-alfa for hepatitis C infection (59c, 60c).

**Hematological** Ribavirin accumulates in erythro-
cytes, resulting in hemolysis. Time-dependent and
dose-dependent hemolytic anemia (eventually associ-
ated with hyperbilirubinemia and high reticulocyte
counts) is the only major toxicity associated with oral
or intravenous ribavirin and is reversible on withdrawal.
There was a fall in hemoglobin concentrations below
10.0 g/dl in 9% of patients with hepatitis C treated with
ribavirin and interferon-alfa (59c, 60c).

**Skin and appendages** A case of photosensitivity
after administration of ribavirin has been described
(61c).

**Second-generation effects** Ribavirin is teratogenic
and embryotoxic in laboratory animals and should not be
given to pregnant women. Concern has been expressed
about the safety of people in the same room as patients
being treated with ribavirin by aerosol, particularly
women of child-bearing age. However, no ribavirin
was detected in the urine, plasma, or erythrocytes of 19
nurses exposed to ribavirin administered via ventilator,
oxygen tent, or oxygen hood over 3 days (62c).

**Interferons** (see also Chapter 37)

Interferons are a group of host-cell proteins. Three
major classes are recognized: alfa-interferons (IFN-α),
derived from B lymphocytes, null lymphocytes, and
macrophages/dendritic cells; ß-interferons (IFN-ß),
produced by epithelial cells and fibroblasts; and γ-in-
terferons (IFN-γ) derived from T lymphocytes and
macrophages after antigenic or mitogenic stimulation.
Only IFN-α2b has been approved as an antiviral drug
for the treatment of chronic hepatitis C, hepatitis B,
Kaposi’s sarcoma, and condylomata acuminate (intra-
lesional). On binding to surface receptors, IFN-α
results in activation of cytoplasmic enzymes affecting
messenger RNA translation and protein synthesis
(63R). The antiviral state takes hours to develop but
may persist for days. Besides broad antiviral activity,
interferons are of major importance in regulating immu-
nological functions.

Subcutaneous IFN-α2b has successfully been used in
chronic hepatitis C and chronic hepatitis B, with rates of
treatment-associated remissions of 25% or more (64R).
Adverse effects have been extensively reviewed in this series (SEDA-17, 345). Contrary to earlier beliefs, the natural products seem to be less toxic than the pure synthetic compounds. The most common adverse effects, as observed in earlier clinical trials, include a flu-like syndrome with fever, chills, fatigue, myalgia, nausea, and general malaise, and hematological disorders. Adverse effects, however, may also include neurotoxicity (paresthesia, polyneuropathy), hepatic toxicity, renal toxicity, or an increase in eyelash growth (65°C)–(69°C).

The most common adverse effects reported in two large multicenter studies were fever (60%), leukopenia (43%), increase in serum aspartate aminotransferase activity (30%), anorexia (30%), thrombocytopenia (25%), fatigue (21%), nausea, and vomiting (17%) (70°C, 71°C). Compared with subcutaneous administration, intravenous interferon-alfa is associated with similar adverse effects of greater severity and frequency (72°C, 73°C).

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS

Strategies to treat infection with the human immunodeficiency virus (HIV) have undergone major changes within the past ten years. The great success and achievements in terms of survival benefit and reduction in perinatal transmission rates have been the result of a collaborative effort by numerous basic and clinical scientists in industry and academic departments. The precise characterization of the role of viral enzymes in the replication cycle of HIV has defined a number of important specific targets for antiretroviral therapy. Several drugs are now available that target either viral reverse transcriptase or viral protease. More drugs are in development that specifically target viral integrase or reverse transcriptase or viral protease. More drugs are recently introduced agents.

Two classes of drugs interfere with the viral life cycle at the step of the reverse transcription. The nucleoside analogues are reverse transcriptase inhibitors (NRTI). The non-nucleotide reverse transcriptase inhibitors (NNRTI) were developed to interfere specifically at the substrate binding site of the enzyme. A third class of antiretroviral drugs consists of the protease inhibitors, which interfere with the viral protease required for the post-transcriptional cleavage of the gag–pol polyprotein to mature viral structures.

Currently antiretroviral therapy is almost exclusively given as a combination of three or more drugs. Hence, the dissection of adverse events observed in clinical studies or in an individual patient and the causative correlation of an observed reaction with a single drug becomes more and more difficult. Many new compounds share adverse effect profiles with other compounds of the same class. In fact, some adverse effects (such as lipodystrophy) were exclusively attributed to one class of drug until it became evident that they may also occur with other classes of antiretroviral drugs. We shall therefore discuss major adverse event syndromes associated with classes of drugs and only briefly discuss the specific adverse effect profiles of single compounds.

Nucleoside analog reverse transcriptase inhibitors (NRTI)

To be converted into an active compound, all NRTIs have to be phosphorylated intracellularly to the triphosphate form. The triphosphates compete with cellular nucleotides and inhibit the reverse transcriptase by introducing a chain terminator into the growing complementary DNA strand during reverse transcription. However, this mechanism also occurs when human DNA is transcribed by the human DNA polymerase. In fact, the first NRTI in clinical use (zidovudine) was initially developed as an anticancer drug, targeting human DNA polymerase in cancer cells. However, all NRTIs have higher specificity for viral RT than for the human DNA polymerase.

Almost all NRTIs cause non-specific gastrointestinal and general adverse effects (nausea, sleep disturbances, headache) that are difficult to attribute to a single agent and usually disappear after the first 2–4 weeks of therapy.

Mitochondrial toxicity associated with NRTIs Initially, most of the adverse effects seen with zidovudine use (in particular hematological effects) were attributed to the interference with cellular DNA replication. However, DNA replication also occurs in mitochondria. Mitochondrial DNA encodes some of the enzymes used for oxidative phosphorylation. Only recently has it been hypothesized that inhibition of this pathway could lead to mitochondrial toxicity and be responsible for most of the toxicity seen with NRTIs, including polyneuropathy, myopathy, cardiomyopathy, steatosis, lactic acidosis, exocrine pancreas failure, bone-marrow failure, and proximal tubular dysfunction (74°C). These adverse effects are also a compilation of the clinical features seen in several genetic mitochondrial cytopathies.

In vitro, NRTIs reduce mitochondrial DNA, most
ovudine-induced pure red cell aplasia has recently been reported (85C).

**Pancreas** Pancreatitis has been observed in patients treated with zalcitabine, stavudine, lamivudine, and didanosine (86C), but its incidence is also increased in drug-naive patients with advanced HIV infection (87R).

**Musculoskeletal** Myopathy has been well described with long-term zidovudine and is reversible after withdrawal (88C). Phosphorus magnetic resonance spectroscopy has been used to study the changes in phosphorylated metabolites (ATP, phosphocreatine, and inorganic phosphate) during exercise in 19 healthy volunteers, six drug-naive patients, six untreated HIV-positive individuals, and nine zidovudine-treated patients with biopsy-proven myopathy (89C). Zidovudine altered the normal muscle energy metabolism in the patients with myopathy, suggesting that it reduces maximal work output, and thus the maximal rate of mitochondrial ATP synthesis, in human muscle. So far, the syndrome has not been associated with any other NRtIs and it has been suggested that other factors might contribute to the development of zidovudine-associated myopathy (91). Mitochondrial abnormalities have also been observed in biopsies from untreated patients infected with HIV-1, suggesting that the virus itself can also cause myopathy. To assess the contribution of zidovudine to the mitochondrial damage, the effects of zidovudine on non-infected co-cultures of spinal ganglia, spinal cord, and skeletal muscle in fetal rats have been studied (92). There were significant changes not only in the mitochondria but also in the nuclei of all cells tested. These changes depended less on the concentration of zidovudine than on the duration of exposure.

**Zidovudine**

**Nervous system** Various CNS adverse effects of zidovudine have been reported, which may or may not be related directly to the drug. These include seizures, confusion, and acute encephalopathy occurring after zidovudine dosage reduction (93C).

**Hematological** The main dose-limiting adverse reactions of zidovudine therapy in HIV-infected adults and children are hematological complications (94B). Almost uniformly, zidovudine treatment results in a progressive increase in the erythrocyte mean cell volume, which cannot be prevented by supplementation with vitamin B12 and folinic acid (95C). When zidovudine was introduced it was given in about twice the dosage used today. Consequently, dose-dependent hematological adverse effects occur at a much lower frequency than previously reported (96C, 97C). While recombinant erythropoietin is useful in correcting zidovudine-induced pure red cell aplasia has recently been reported (85C).
induced anemia, some cases of anemia are associated with high serum erythropoietin concentrations and normocytic cells, indicating bone-marrow unresponsiveness to erythropoietin (98R). Measuring baseline serum erythropoietin concentrations may help to predict the response to this very costly hormone supplementation.

Skin and appendages A fatal case of toxic epidermolysis (Lyell's syndrome) has been attributed to zidovudine (99R) as has a case of cutaneous hypersensitivity (100R).

Miscellaneous Other adverse effects include severe headache, insomnia, confusion, nausea, vomiting, abdominal discomfort, myalgia (myopathy), and nail pigmentation (101R).

Second-generation effects Zidovudine reduces maternal–infant transmission of HIV-1 (102C). It is relatively well tolerated in pregnancy, with anemia, neutropenia, or thrombocytopenia occurring in 10% and abnormalities of serum electrolytes and liver function in 5% (102C).

Oral zidovudine in a dosage of 200 mg every 4 hours for 42 days was used as prophylaxis in health-care workers after percutaneous exposure to blood or body fluids from HIV-infected patients. Adverse reactions occurred in 73%, the most frequent being nausea (47%), headache (35%), and fatigue (30%). Of selected hematological laboratory markers only platelet counts increased significantly over 4 weeks. Although adverse reactions were not very severe and none of the laboratory changes was considered clinically significant, treatment was poorly accepted and stopped prematurely by 30% (103C). Current guidelines for post-exposure prophylaxis recommend a much lower dosage (300 mg bd) with much better tolerance (104C).

Abacavir

Abacavir is a recently developed guanidine analog active against HIV. In vitro, its potency is similar to that of zidovudine and viral resistance is not rapidly selected for. Cross-resistance has been shown to the other analogs of cytosine and guanidine (DDI, 3TC, DDC). Abacavir does not interfere with drugs that are metabolized by liver microsomal cytochrome P450 (105). It has no other significant drug interactions and can be administered without food restrictions.

The adverse events most frequently observed in clinical trials were fatigue, nausea and vomiting, abdominal pain, diarrhea, headache, rash, and dyspepsia (106C, 107C).

Immunological and hypersensitivity reactions A hypersensitivity reaction occurs in about 2–3% of individuals within the first 28 days of therapy, and rarely thereafter. It is characterized by fever, rash, or nausea and vomiting. Resolution of the symptoms occurs within days of withdrawal. Severe and even fatal reactions to readministration have been observed; rechallenge is therefore strictly contraindicated in any patients who have experienced such a hypersensitivity reaction (108R).

Didanosine

Didanosine (2',3'-dideoxyinosine, ddi) is a purine analog. The major clinical adverse effects reported during the first years of use of this drug were acute pancreatitis and a painful neuropathic syndrome (peripheral neuropathy), which appeared to be related to both dosage and cumulative dose (SEDA-17, 340; 109R). However, the incidence of acute pancreatitis and peripheral neuropathy in these studies was lower than in earlier studies with didanosine (110C, 111C). This may be related to the fact that treatment was started earlier or to the use of lower dosages (200–400 mg/day) in these studies compared with earlier studies. In the latter studies, gastrointestinal symptoms, most notably nausea and vomiting, were the most commonly reported adverse effects in patients taking didanosine. Minor adverse effects include insomnia, headaches, anxiety, irritability, rash, increased plasma uric acid concentration, and increased hepatic transaminase activities combined with a rash (112R). Retinal depigmentation has been described in children (94).

There is no indication that didanosine contributes to the development of myopathy in cases where this adverse event occurs in patients taking didanosine and zidovudine (90R). No dose-related toxicity of didanosine was noted regarding hematological laboratory indices (113R).

Lamivudine

The safety and activity of lamivudine (300–600 mg/day) in combination with zidovudine (600 mg/day) in the treatment of antiretroviral-naive and zidovudine-experienced HIV-infected persons has been compared with zidovudine monotherapy in two placebo-controlled studies of 129 and 223 patients (114R, 115C). There were no significant differences in the incidence or severity of adverse effects between patients taking zidovudine alone or in combination with lamivudine. In both studies gastrointestinal symptoms, notably nausea, were the most commonly observed adverse reactions, occurring in 5–11% of zidovudine-experienced patients and 23–29% of antiretroviral drug-naive individuals. Al-
though one antiretroviral drug-naive patient taking combined therapy had an asymptomatic rise in pancreatic amylase activity, acute pancreatitis was not observed in either study. Grade 1 peripheral neuropathy was reported in one zidovudine-experienced patient taking low-dose lamivudine (150 mg bd) and zidovudine.

In a 24-week phase I/II study, 89 children aged 3 months to 17 years (median 7.3 years) were treated with lamivudine for 24 weeks in dosages of 1—20 mg/kg/day (116c). Dosages over 20 mg/kg/day were not tested because of reported neutropenia in adults at this dosage (117c). Lamivudine was generally well tolerated in these children. Ten children were withdrawn because of presumed adverse effects: three because of increased serum transaminase activities, three because of neutropenia, and two because of hyperactivity. One child became ataxic shortly after the start of therapy, and one developed pancreatitis during hospitalization for acute cryptosporidiosis. All of these events resolved with supportive care on withdrawal of lamivudine, except one case of hepatitis, which persisted up to ten months after withdrawal. Treatment was discontinued temporarily in other patients because of pancreatitis (2), rashes (2), neutropenia (1), anemia (1), and increased serum transaminase activities (1). On resolution of the presumed adverse reaction, the drug was reintroduced in all of these cases without further problems. There were no significant hematological or biochemical changes. Neither the incidence nor the severity of the observed adverse events was dose-related. The assignment of causality to lamivudine of most of the adverse events was complicated by intercurrent conditions and concomitant medications.

In a study of the efficacy of lamivudine (25, 100, or 300 mg/day for 12 weeks) in the treatment of chronic hepatitis B virus infections, lamivudine was similarly well tolerated in 32 patients (118c). Only minor non-specific non-dose-related adverse reactions were observed. In addition, there were mild asymptomatic increases in serum activities of amylase, lipase, and creatine kinase, which in most cases resolved despite continued therapy.

Stavudine

**Nervous system** The principal toxic effect of stavudine is peripheral neuropathy, with symptoms similar to the neuropathy associated with didanosine and zalcitabine (119c, 120c). The development of neuropathy seems to depend on the duration of treatment, with an increasing risk after 12 weeks of treatment. A prior history of neuropathy increases the risk of stavudine-induced neuropathy. After withdrawal, the symptoms usually resolve within two weeks, although they may persist for several months.

**Hematological** Modest dose-related macrocytosis without associated anemia can occur during treatment with stavudine (119c, 120c).

**Liver** Asymptomatic increases in hepatic transaminases, which are not clearly dose-related, can occur during treatment with stavudine, requiring dosage modification because of moderate or severe toxicity in about 10% of patients (119c, 120c).

Zalcitabine (dideoxycytidine, dDC)

The most important adverse effect of zalcitabine is a peripheral neuropathy. Several large-scale studies of the efficacy of combined antiretroviral treatment with zalcitabine and zidovudine in HIV-infected patients (compared with zidovudine monotherapy or a combination of zidovudine and didanosine) have not shown unexpected adverse effects (110c, 111c, 121c, 122c). The most common adverse effects in patients taking zalcitabine were peripheral neuropathy and aphthous mouth ulcers.

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

**Delavirdine**

Delavirdine is an NNRTI which is dosed three times daily. No food restrictions apply, but antacids and dideoxyinosine interfere with its absorption and may therefore not be given concomitantly. It is metabolized by the hepatic cytochrome system, and so interactions with other drugs that use this metabolic pathway have to be observed.

**Skin and appendages** The most frequent adverse event is a rash, which usually occurs during the first 3 months of therapy in up to 50% of individuals. It is usually mild and resolves spontaneously in most patients or can be treated successfully with a short course of antihistamines. Interruption of treatment is required in less than 4% of patients (123c, 124c).

Efavirenz

Efavirenz is an NNRTI with excellent inhibitory activity against HIV-1. The most frequent adverse effects involve the central nervous system and the skin (125c). At the start of therapy, dizziness, insomnia, or fatigue are observed in most patients, and headache and even
psychotic reactions have also been observed. A maculoapopular rash is seen in about 10%. These adverse events usually vanish within the first 2—4 weeks of therapy. About 1—2% of individuals discontinue efavirenz because of neurological or dermatological adverse events. Administration of efavirenz at bedtime reduces the incidence of severe adverse events, and the rash can be managed by short-term antihistamines or topical corticosteroids. Nausea and vomiting are less often observed than in patients treated with zidovudine, lamivudine, or indinavir.

Interactions Because efavirenz is metabolized by cytochrome P450, several clinically significant interactions have been described. Increased dosage of indinavir is recommended if efavirenz is co-administered. No significant interaction was noted with co-administration of nelfinavir, zidovudine, lamivudine, fluconazole, or azithromycin. Rifampicin induces the metabolism of efavirenz. Other drugs that induce or utilize CYP3A4 for their metabolism need to be co-administered with caution.

Nevirapine

Hematological The principal dose-limiting adverse effect of nevirapine in adults is skin rashes. In a multiple dose study, 21 children aged 3 months to 15 years were treated with nevirapine in dosages of 7.5—400 mg/m²/day for up to 168 days. At dosages over 240 mg/m²/day they were pretreated with a lower dosage (120 mg/m²/day) for 28 days to reduce the risk of rash. However, the only adverse effect that was thought to be related to nevirapine treatment was a rash, which developed in one child after 2 weeks of treatment with nevirapine at a dosage of 240 mg/m²/day, resolved on withdrawal, and recurred on rechallenge with a single dose of 120 mg/m².

Successful induction of tolerance to nevirapine in patients who develop rash has recently been described. Two patients developed grade 4 thrombocytopenia (under 25 x 10⁹/l) after 42 and 151 days of treatment. In the first patient, zidovudine and intravenous immunoglobulin were added to continued nevirapine, and the rash can be managed by short-term antihistamines or topical corticosteroids. In the second, nevirapine was discontinued and alternative antiretroviral therapy was started, whereupon the platelet count returned to normal within 22 days.

Protease inhibitors

All the recently developed protease inhibitors have in common a specific effect against the aspartic HIV protease that cleaves viral proteins to yield structural proteins. Competitive inhibition of this process by the protease inhibitors results in the production of immature, non-infectious viral particles. These drugs are also characterized by their high specificity, being more than a thousand-fold more active against viral than human aspartic proteases.

Combination therapy including a protease inhibitor resulted in the first breakthrough of antiviral treatment in the mid-nineties, since when several protease inhibitors have been developed. However, results from in vitro and clinical studies clearly showed that these drugs share a cross-resistance pattern, probably due to secondary conformational changes of the protease outside the active binding site of the protease inhibitor. Nevertheless, some patients may benefit from a second protease inhibitor if therapy is promptly switched before multiple mutations have accumulated.

Endocrine, metabolic Short after the introduction of highly active antiretroviral combination treatments, lipodystrophy was associated with the use of protease inhibitors. The syndrome is characterized by loss of subcutaneous fat tissue in the face and extremities, an increased abdominal girth ("Crix-belly" or "protease pouch"), and dorsocervical fat pad enlargement ("buffalo hump")

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Interaction Protease inhibitors are all metabolized by cytochrome P450 and interact with drugs and food components that interfere with this metabolic pathway. Of all the currently available protease inhibitors, ritonavir is the most potent inducer of the CYP3A isozyme. Drug—drug interactions with protease inhibitors have been comprehensively reviewed and an updated summary of known interactions is presented on the world wide web by the University of Liverpool.
Amprenavir (141W94, VX-478)

Amprenavir is the most recent protease inhibitor. It can be given twice daily without food restrictions and had high potency when given as monotherapy in dose-finding studies (134C).

Adverse events in patients treated with combination therapy included nausea, vomiting, diarrhea, epigastric pain, flatulence, paresthesia, headache, rash, and fatigue (135C), but the contribution of a single drug to the observed adverse effects is difficult to establish. In the above mentioned monotherapy trial (n = 37), adverse effects were frequent but generally mild, and included rash, diarrhea or loose stools, and headache. In general, these adverse effects tend to disappear or weaken in severity within the first 2—4 weeks of treatment.

Interactions with other drugs that are metabolized by CYP3A4 need to be observed. Amprenavir inhibits CYP3A4 to a greater extent than saquinavir, and to a much lesser extent than ritonavir (136). Co-administration with rifampicin and rifabutin should be avoided.

Indinavir

In addition to metabolic adverse effects, indinavir causes indirect hyperbilirubinemia (which has no clinical consequences) and nephrolithiasis. The latter is a result of precipitation of indinavir crystals in the urinary tract (137R). To a large extent indinavir-associated nephrolithiasis can be prevented by ensuring adequate fluid intake; if it occurs increased hydration often allows continuation of treatment.

Nelfinavir

Like amprenavir, nelfinavir is a non-peptidic inhibitor of the HIV protease. Its most prominent adverse effect is diarrhea, occurring in up to one-third of individuals. However, the diarrhea is usually mild and can be controlled, if necessary, by antidiarrheal agents (138C). Other adverse effects, including rash, nausea, headache, and weakness, are reported in under 5%.

Ritonavir

In early monotherapy studies, including 62 and 87 patients (139C, 140C), in which the potent antiretroviral effect of ritonavir was first demonstrated, the most common adverse events were nausea, diarrhea, headache, circumoral paresthesia, and altered taste sensation. Nausea, vomiting, and diarrhea are common during the start of therapy and usually disappear over the first few weeks of treatment. These adverse effects can be markedly reduced by using a step-up approach, increasing to the full dose over six days. General weakness, circumoral paresthesia, and taste disturbance occur in 5—10% of patients and are seldom dose-limiting.

Three patients developed reversible renal failure 10—12 days after starting treatment including ritonavir (141C).

Saquinavir

Of all protease inhibitors, saquinavir is the most potent in vitro. However, due to its poor systemic availability (less than 4%), it is the least potent of all protease inhibitors in clinical use, although a new formulation with increased availability has been marketed. However, when saquinavir is given together with ritonavir, the strong inhibitory effect on CYP3A4 of the latter results in high plasma concentrations of saquinavir. This interaction has been exploited, with favorable clinical results, both in first-line protease therapy and as salvage treatment in patients with virus resistant to a regimen containing a protease inhibitor.

Hitherto, no particular or frequent adverse effects attributable to saquinavir have been reported from trials in which saquinavir was used at the licensed dosage of 600 mg tds (142C). Diarrhea, usually of only moderate severity, occurring in 3—4% of patients, seems to be the most common single adverse effect (143C, 144C, 145C).

Interactions Saquinavir is a much less potent inhibitor of CYP3A4 than ritonavir. The chance of severe adverse effects when saquinavir is combined with other drugs that are metabolized by CYP3A4 is therefore much smaller. However, in view of the already poor systemic availability of saquinavir, reduced saquinavir blood concentrations resulting from the concomitant use of drugs, such as rifampicin, that induce CYP3A4 warrants careful consideration.
Neuraminidase inhibitors

The major drawbacks of older drugs for the treatment of influenza (amantadine and rimantadine) include lack of activity against influenza B, a considerable frequency of adverse effects, and probably a higher likelihood of resistance. With the recent development of inhibitors of the viral neuraminidase, a more specific class of drugs has been added to the antiviral armamentarium. After the description of the crystal structure of the viral neuraminidase, a surface glycoprotein, specific inhibitors were designed. Two derivatives of sialic acid, the natural substrate of the neuraminidase, are currently in use. These drugs were designed to bind strongly to a conserved region of the cleavage site, which resulted in a class of compounds with limited risk of viral resistance. In fact, resistance is rare during the use of these drugs (155a).

The two drugs that are currently in clinical use have very few adverse effects. Zanamivir is administered by inhalation and oseltamivir as an oral capsule.

Zanamivir

Zanamivir has poor oral systemic availability. Intranasal administration slightly increased the availability, but in mice strongly reduced viral replication (156). In vitro, zanamivir does not significantly inhibit human lysosomal neuraminidases, and so the potential for severe adverse effects is low (157).

Zanamivir does not interfere with cytochrome P450 and no interactions with commonly co-administered drugs have been observed in vivo (158a).

Zanamivir has been evaluated in the prevention and treatment of influenza A and B, and was effective against both viruses. In placebo-controlled trials, the adverse events profile, including local nasal irritation, did not differ significantly between zanamivir and placebo (159a)-(162a).

Oseltamivir, GS4104

GS4104, or oseltamivir is a prodrug with much higher systemic availability than its active form (GS4071) to which it is hydrolyzed after absorption. In animals oseltamivir had a wide safety margin, with no evidence of teratogenicity or adverse effects on fertility. Like zanamivir, oseltamivir has also been studied in the treatment and prevention of influenza A and B, but published results are sparse. To date it has been well tolerated. Headache was the most frequent complain
and mild to moderate gastrointestinal adverse effects (nausea, diarrhea) have been described (163R).

OLDER ANTIVIRAL DRUGS NO LONGER IN USE

Idoxuridine and trifluorothymidine, active against HSV and VZV, have only been used for topical antiherpetic solutions. Because they have major neurological adverse effects and inferior antitherpetic activity, these agents should not be used.

Vidarabine was only used as an intravenous drug but is no longer used because of unacceptable toxicity and inferior activity compared with newer drugs for HSV and VZV.

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