Antiviral chemotherapy

Dr.Fawziah Ali

PRINCIPLES OF ANTIVIRAL THERAPY

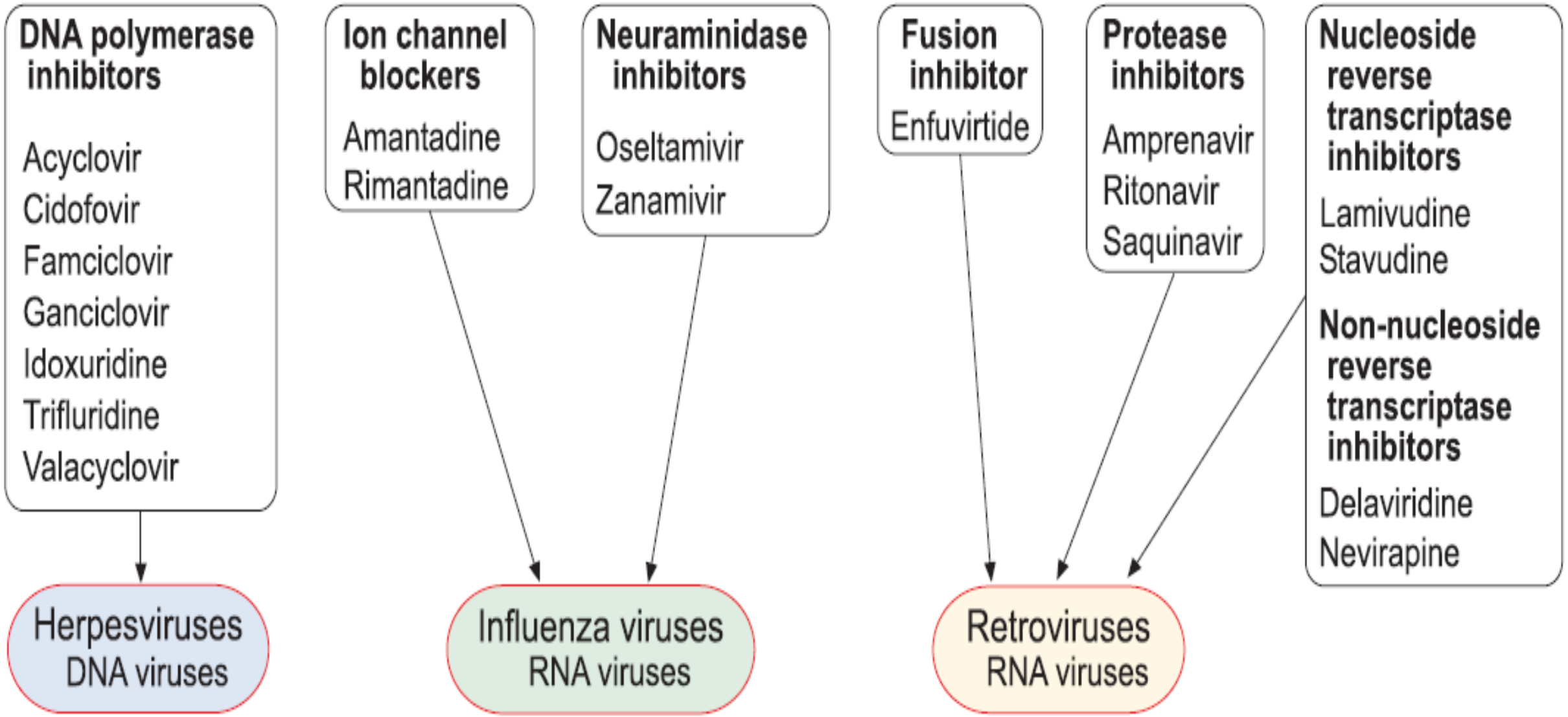
Compared with the number of drugs available to treat bacterial infections,the number of antiviral drugs is **very small**.

The major reason for this difference is the **difficulty in obtaining selective toxicity** against viruses; their replication is very well complicated with the normal synthetic processes of the cell.However several virus-specific replication steps have been identified that are the site of action of effective antiviral drugs(Table 35–1).

Another limitation of antiviral drugs is that they are relatively ineffective because many cycles of viral replication occur during the incubation period when the patient is well. By the time the patient has a recognizable systemic viral disease, the virus has spread throughout the body and it is too late to interdict it. Furthermore, some viruses (e.g.,herpesviruses) become latent within cells, and no current antiviral drug can eradicate them.

Another limiting factor is the emergence of drug-resistant viral mutants.

The modes of action and therapeutic spectrum of antiviral drugs



Antiviral drugs are employed to inhibit virus-specific events related to virus replication rather than host cell synthetic activities.

Most antiviral drugs interfere with viral-encoded enzymes or viral structures essential for replication.

Many antiviral drugs are nucleic acid analogues which interfere with DNA and RNA synthesis.

Other mechanisms of action include interference with virus–cell binding, interruption of virus uncoating and interference with virus progeny release from infected host cells.

Some antiviral substances such as interferons possess immunomodulatory activity

Categories of drugs or immune components with antiviral activity	Stage of replication where antiviral drugs or immune components act
Peptide analogues of attachment proteins; fusion protein inhibitors; neutralizing antibodies	Attachment to host cell
Ion channel blockers	Uncoating
Inhibitors of viral DNA polymerase, RNA polymerase, reverse transcriptase	Transcription of viral genome
Nucleoside analogues	Replication of viral genome
Interferons, antisense oligonucleotides	Translation of viral proteins
Protease inhibitors	Post-translational changes in proteins
Interferons	Assembly of virion components
Neuraminidase inhibitors; specific antibodies plus complement; cytotoxic T cells and NK cells	Release of virions by budding or cell lysis

Interferons

A number of immunomodulatory drugs induce interferon production and promote immune responses to viral pathogens.

Interferons are proteins produced by virus-infected cells or by sentinel immune cells which act on adjacent cells, inhibiting virus replication

These protective molecules bind to specific cell surface receptors and initiate intracellular events, including the induction of particular enzymes, which render cells resistant to viral invasion.

Interferons produced by recombinant technology and also by chemical synthesis are available for treating a number of viral infections in humans and animals

Table 53.2 Chemical nature, mode of action and antiviral spectrum of selected antiviral drugs.

Antiviral drug	Chemical nature / Mode of action	Antiviral spectrum	Comments
Acyclovir	Acyclic guanine nucleoside / Inhibits viral DNA polymerase	Herpesviruses	Used for treating herpesvirus infections in avian species and cats; ineffective against latent viral infections
Amprenavir	Aminosulphonamide non-peptide protease inhibitor / Active site inhibitor of HIV protease	HIV	The therapeutic role of protease inhibitors in viral diseases of animals is not well defined
Cidofovir	Cytidine nucleotide analogue / Inhibits viral DNA synthesis	Herpesviruses, poxviruses, papillomaviruses, adenoviruses	Long tissue half-life allows infrequent dosing
Delaviridine	Bis-heteroarylpiperazine compound / Disrupts the catalytic activity of HIV-1 reverse transcriptase	HIV-1	Cross-resistance to other drugs in this class usually applies
Enfuvirtide	Synthetic peptide / Prevents fusion of HIV-1 with host cell membrane	HIV-1	Retains activity against viruses which have become resistant to other classes of antiviral drugs

Famciclovir and penciclovir	Nucleotide analogues / Inhibit viral DNA polymerase	Herpesviruses	Development of resistance during clinical use is reported to be low
Ganciclovir	Acyclic guanine nucleoside analogue / Inhibits viral DNA synthesis and preferentially inhibits viral rather than host cellular DNA polymerases	Herpesviruses	This drug is especially active against cytomegalovirus
Idoxuridine	Iodinated thymidine analogue / Incorporated into viral DNA with interference in nucleic acid synthesis and viral gene expression	Herpesviruses and poxviruses	Because of its toxic effects if given systemically, it is used for topical treatment only; ophthalmic solutions containing idoxuridine are used for treating herpesvirus keratitis in animals
Immunomodulators including interferons	Proteins, other novel compounds / Promote protective antiviral immune responses	Most RNA viruses are inhibited by interferons; many DNA viruses are insensitive to their antiviral effects	Interferons produced by recombinant technology and also by chemical synthesis are available for treating viral infections in humans and animals
Lamivudine	Cytosine analogue / Inhibits reverse transcriptase activity of retroviruses and also inhibits the DNA polymerase of hepatitis B virus	Retroviruses and hepatitis B virus	Resistance to lamivudine develops rapidly in patients with HIV; when combined with zidovudine, a marked synergistic effect results
Oseltamivir	Analogue of sialic acid / Potent selective inhibitor of neuraminidase	Influenza A virus and influenza B virus	Can be used prophylactically and therapeutically

Rimantadine	Tricyclic amine / Ion channel blocker which interferes with virus uncoating	Influenza A virus	Primary drug resistance is uncommon but has been reported in some avian and swine influenza viruses
Trifluridine	Fluorinated analogue of thymidine / Competitive inhibitor of the incorporation of thymidine into DNA	Used topically for keratoconjunctivitis in humans and ocular herpesvirus infections in animals	Because of its toxicity, unsuitable for systemic use
Valacyclovir	L-Valyl ester of acyclovir, a nucleoside analogue / Inhibits viral DNA synthesis	Herpesviruses	Enhanced oral bioavailability offers many advantages over acyclovir

Antiviral drugs

1.Ion channel blocking compounds

Ion channel blocking compounds inhibit acid-mediated dissociation of the ribonucleoprotein complex early in the replication of influenza viruses, a process essential for uncoating of the single-stranded RNA genome.

2.Neuraminidase inhibitors

When influenza viruses complete their replicative cycle, they bud from the cell's membrane

Release of newly formed virions from infected cells requires neuraminidase for cleavage of sialic acid residues from the cell membrane envelope present on the budding virions.

If this does not take place, the binding of haemagglutinin protruding from the virion surface with persisting sialic acid residues on newly released adjacent virions causes agglutination of the virions on the cell surface.

Neuraminidase inhibitors are sialic acid analogues which specifically inhibit influenza A virus and influenza B virus neuraminidase activity.

3.Inhibition of viral genome replication

Many antiviral drugs which inhibit viral genome replication are nucleoside analogues. These compounds inhibit viral polymerases, especially DNA polymerases.

Before these drugs can exert their antiviral effect, they must undergo intracellular phosphorylation to the active triphosphate form. Phosphorylated nucleoside analogues inhibit polymerases by competing with natural substrates and they are usually incorporated into the growing DNA chain where they often terminate elongation.

Nucleoside analogues are widely used for treating infections caused by herpesviruses in humans and also in animals

4. Prevention of fusion of the virus envelope with host cell plasma membrane

The activity of antiretroviral drugs includes prevention of fusion of the virus envelope with receptors on the host cell plasma membrane, interference with the activity of reverse transcriptase and inhibition of viral protease activity.

Antiretroviral fusion inhibitors are drugs which interfere with virus attachment and entry into host cells, thereby preventing the subsequent stages of virus infection from proceeding. Such drugs also provide an opportunity for components of the immune system to clear viruses from body fluids and host tissues

5.Non-nucleoside reverse transcriptase inhibitors

induce conformational changes in reverse transcriptase which disrupt its catalytic activity.

Nucleoside reverse transcriptase inhibitors are activated intracellularly by phosphorylation with cellular kinases and their triphosphate forms competitively inhibit reverse transcriptase.

The triphosphate form of these antiviral agents terminates elongation of the proviral DNA chain.Together with genome replication, production of viral proteins is an essential part of the replicative cycle of all viruses. For a number of viruses, including human immunodeficiency virus(HIV)-1, assembly of proteins and nucleic acid into viral particles does not produce an infectious virion.

6.Virus-specific protease inhibitors

Maturation of virus require cleavage of new virus proteins by virus-specific proteases to become fully functional. When **protease inhibitors** introduced into an infected cell before virion budding begins, protease inhibitors prevent polyprotein cleavage and result in the production of non-infectious particles.

Resistance to antiviral drugs

All forms of microorganisms, including viruses, are capable of becoming resistant to inhibitory drugs and the development of resistance to antiviral compounds is an expected consequence of antiviral chemotherapy.

As current antiviral drugs inhibit active replication, viral replication is expected to restart when treatment completes. Effective antiviral host immune responses are essential, therefore, for clinical recovery from infection.

Failure of antiviral therapy may relate to the host's immunological competence or to the emergence of drug-resistant variants.

Of the many strategies that can be applied to the control of viral diseases in humans and animals, vaccination is the preferred option.

In the absence of effective vaccination,antiviral chemotherapy offers the possibility of prophylactic and therapeutic treatment for a defined number of viral pathogens.