Antiviral Drugs

I. OVERVIEW

- Viruses are obligate intracellular parasites.
- They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes.
- Viruses use much of the host's metabolic machinery, and few drugs are selective enough to prevent viral replication without injury to the infected host cells.
- Therapy for viral diseases is further complicated by the fact that the clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated.
- At this stage of viral infection, administration of drugs that block viral replication has limited effectiveness.

II. TREATMENT OF RESPIRATORY VIRAL INFECTIONS

- Viral respiratory tract infections for which treatments exist include influenza A and B and respiratory syncytial virus (RSV).

- [Note: Immunization against influenza is the preferred approach. However, antiviral agents are used when patients are allergic to the vaccine or outbreaks occur.]

A. Neuraminidase inhibitors

- The neuraminidase inhibitors *oseltamivir* and *zanamivir* are effective against both type A and type B influenza viruses.

- They do not interfere with the immune response to influenza vaccine.

- Administered prior to exposure, neuraminidase inhibitors prevent infection and, when administered within 24 to 48 hours after the onset of symptoms, they modestly
  - decrease the intensity and
  - duration of symptoms.

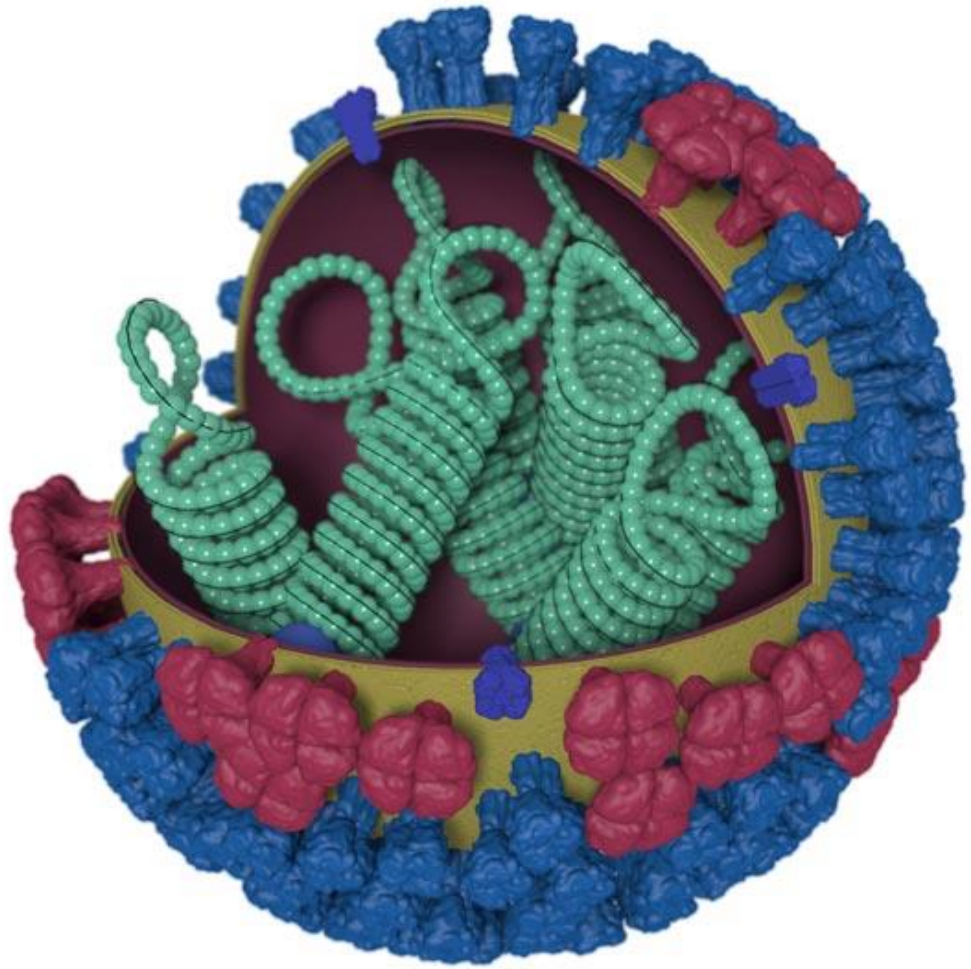
1. Mechanism of action:

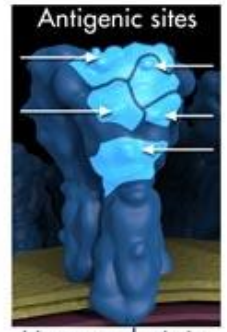
- Influenza viruses employ a specific neuraminidase that is inserted into the host cell membrane for the purpose of releasing newly formed virions.

- This enzyme is essential for the virus life cycle.

- *Oseltamivir* and *zanamivir* selectively inhibit neuraminidase, thereby preventing the release of new virions and their spread from cell to cell.

AN INFLUENZA VIRUS





Hemagglutinin

Neuraminidase

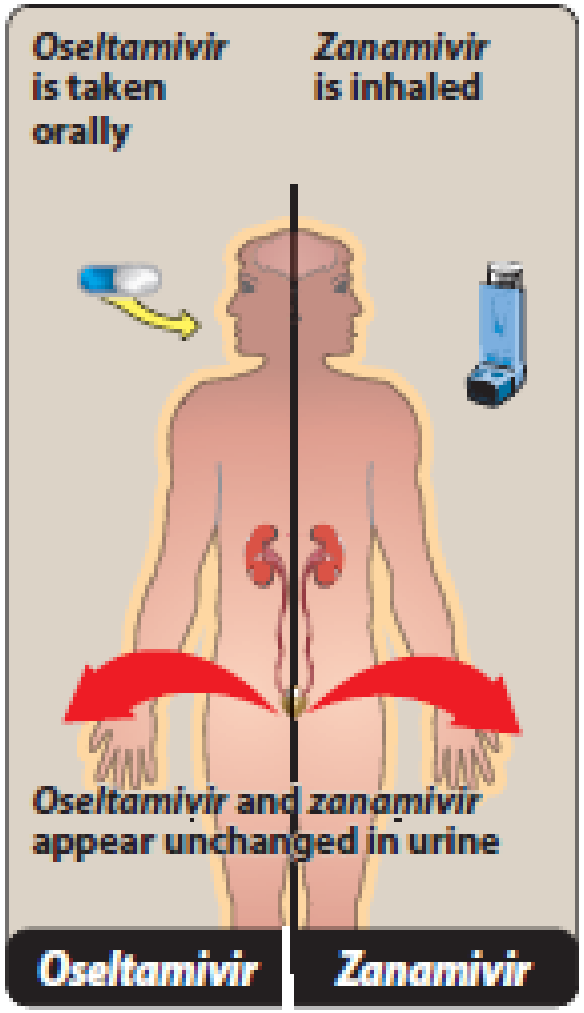
M2 ion channel

Ribonucleoprotein

2. Pharmacokinetics:

- *Oseltamivir* is an orally active prodrug that is rapidly hydrolyzed by the liver to its active form.

- *Zanamivir* is not active orally and is administered via inhalation. Both drugs are
- eliminated unchanged in the urine.



3. Adverse effects:

- The most common adverse effects of *oseltamivir* are gastrointestinal (GI) discomfort and nausea, which can be alleviated by taking the drug with food.

- Irritation of the respiratory tract occurs with *zanamivir*.

- It should be used with caution in individuals with asthma or chronic obstructive pulmonary disease, because bronchospasm may occur.

4. Resistance:

- Mutations of the neuraminidase enzyme have been identified in adults treated with either of the neuraminidase inhibitors.

- These mutants, however, are often less infective and virulent than the wild type.

B. Adamantane antivirals

- The therapeutic spectrum of the adamantane derivatives, *amantadine* and *rimantadine* , is limited to influenza A infections.

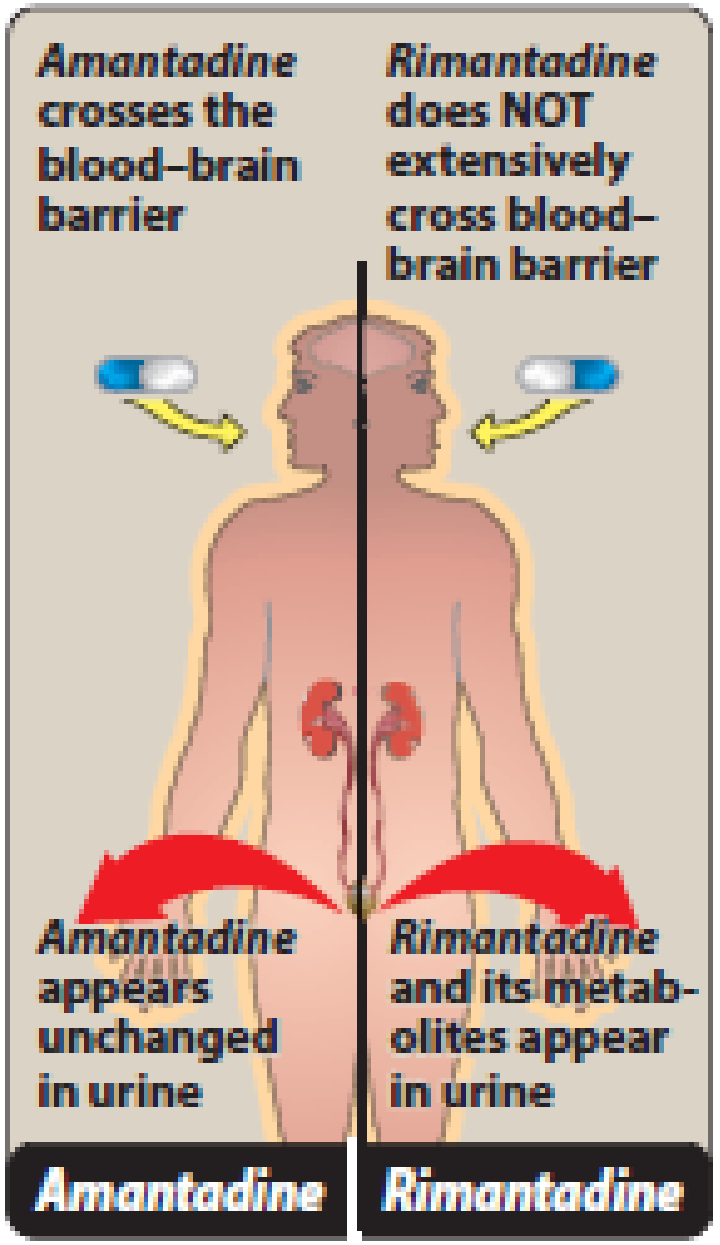
- Due to widespread resistance, the adamantanes are not recommended in the United States for the treatment or prophylaxis of influenza A.

Mechanism of action:

- ***Amantadine and rimantadine interfere with*** the function of the viral M2 protein, possibly blocking uncoating of the virus particle and preventing viral release within infected cells.

2. Pharmacokinetics:

- **Both drugs are well absorbed after oral administration.**
- *Amantadine distributes throughout the body and readily* penetrates into the central nervous system (CNS), whereas *rimantadine* does not cross the blood–brain barrier to the same extent.
- *Amantadine is primarily excreted unchanged in the urine, and dosage* reductions are needed in renal dysfunction.
- *Rimantadine is* extensively metabolized by the liver, and both the metabolites and the parent drug are eliminated by the kidney


Amantadine crosses the blood–brain barrier
Rimantadine does NOT extensively cross blood–brain barrier
Amantadine appears unchanged in urine
Rimantadine and its metab-olites appear in urine
Amantadine
Rimantadine

3. Adverse effects:

- ***Amantadine is mainly associated with CNS*** adverse effects, such as insomnia, dizziness, and ataxia.
- More serious adverse effects may include hallucinations and seizures.
- *Amantadine should be employed cautiously in patients with psychiatric* problems, cerebral atherosclerosis, renal impairment, or epilepsy.
- *Rimantadine causes fewer CNS reactions. Both drugs* cause GI intolerance.
- They should be used with caution in pregnant and nursing mothers.

4. Resistance:

- **Resistance can develop rapidly, and resistant strains** can be readily transmitted to close contacts.

- Resistance has been shown to result from a change in one amino acid of the M2 matrix protein.

- Cross-resistance occurs between the two drugs.

C. Ribavirin

- *Ribavirin , a synthetic guanosine analog, is effective* against a broad spectrum of RNA and DNA viruses.

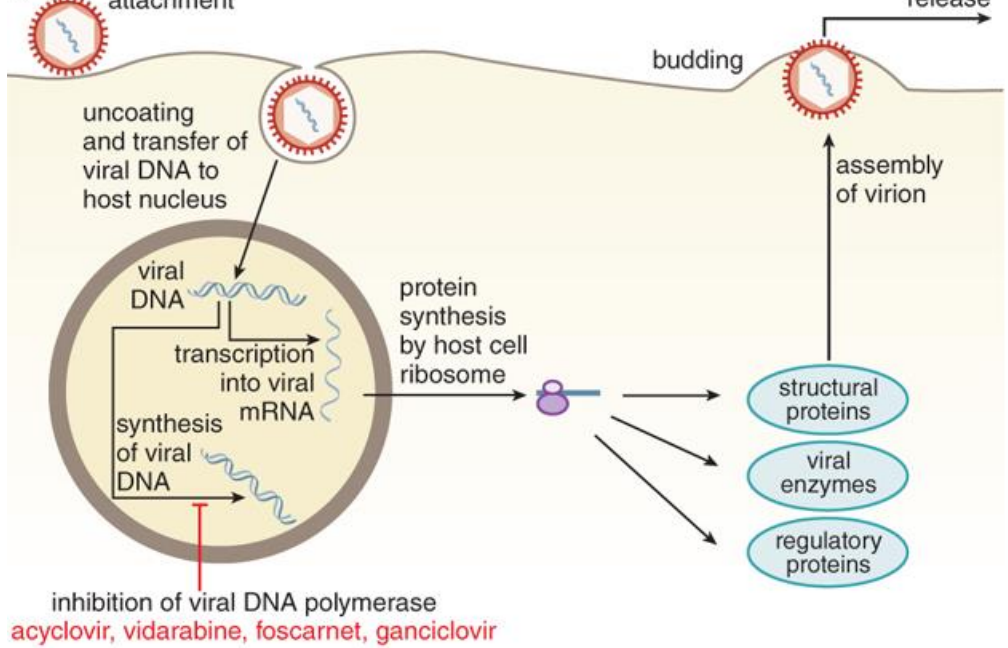
- For example, *ribavirin* is used in treating immunosuppressed infants and young children with severe RSV infections.

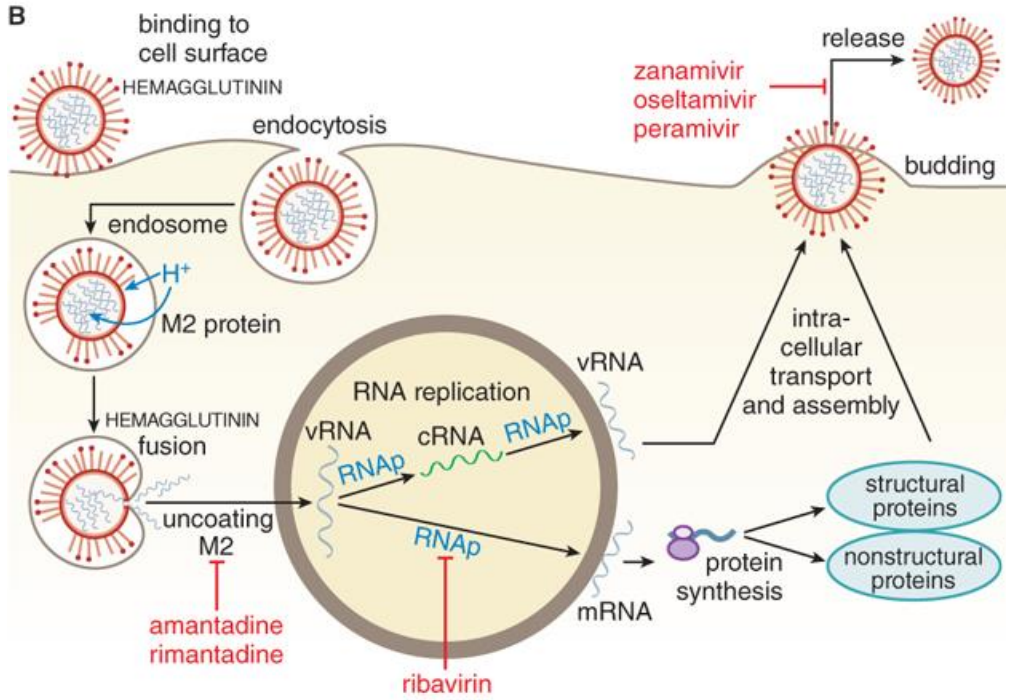
- *Ribavirin is also effective in chronic hepatitis* C infections when used in combination with other direct acting antivirals (DAAs)

1. Mechanism of action:

- ***Ribavirin*** *inhibits replication* ***of RNA and*** DNA viruses.

- The drug is first phosphorylated to the 5’**-phosphate** derivatives, the major product being the compound ribavirin triphosphate, which exerts its antiviral action by inhibiting guanosine triphosphate formation, preventing viral messenger RNA (mRNA) capping, and blocking RNA-dependent RNA polymerase.

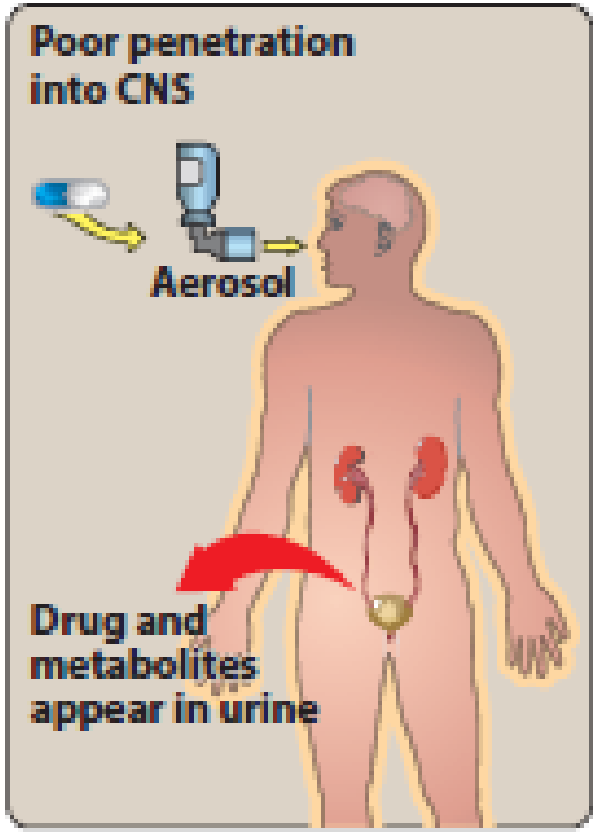




Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann:

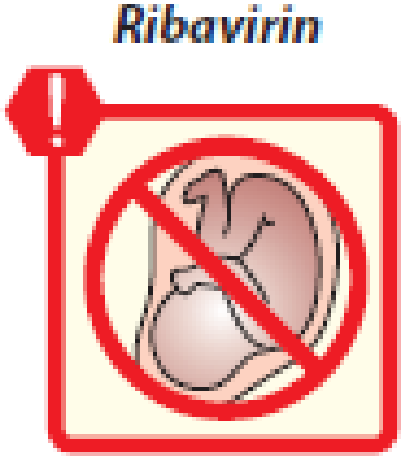
2. Pharmacokinetics:

- ***Ribavirin is effective orally and by inhalation.***
- Absorption is increased if the drug is taken with a fatty meal.
- The drug and its metabolites are eliminated in urine.



3. Adverse effects:

- **Side effects of *ribavirin include dose-dependent*** transient anemia.
- Elevated bilirubin has also been reported.
- The aerosol may be safer, although respiratory function in infants can deteriorate quickly after initiation of aerosol treatment.
- Therefore, monitoring is essential.
- *Ribavirin is contraindicated in pregnancy*



III. TREATMENT OF HEPATIC VIRAL INFECTIONS

- The hepatitis viruses thus far identified (A, B, C, D, and E) each have a pathogenesis specifically involving replication in and destruction of hepatocytes.

- Of this group, hepatitis B (a DNA virus) and hepatitis C (an RNA virus) are the most common causes of
  - chronic hepatitis,
  - cirrhosis, and
  - hepatocellular carcinoma and
  - are the only hepatic viral infections for which therapy is currently available.

- [Note: Hepatitis A is a commonly encountered infection caused by oral ingestion of the virus, but it is not a chronic disease.]

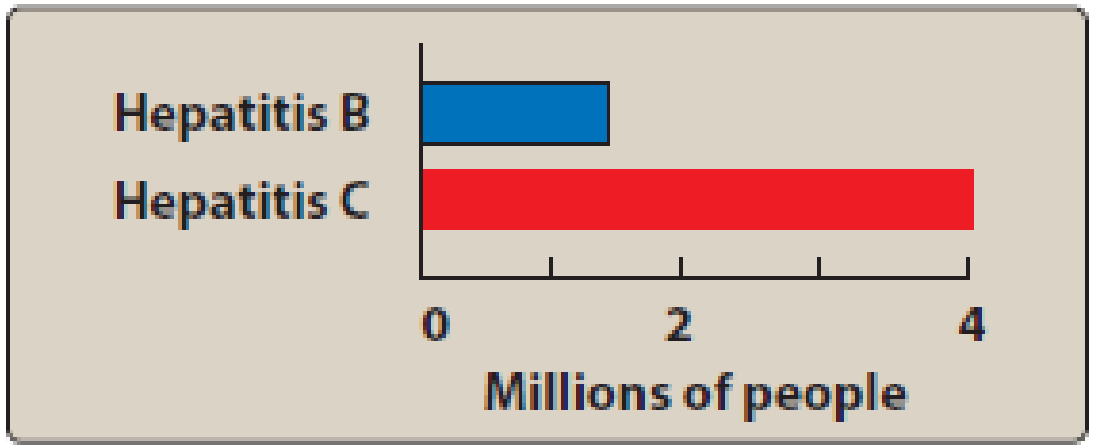


Figure 45.6

The prevalence of chronic hepatitis B and C in the United States.

- Chronic hepatitis B may be treated with *peginterferon-α-2a*, which is injected subcutaneously once weekly.

- [Note: *Interferon-α-2b* injected intramuscularly or subcutaneously three times weekly is also useful in the treatment of hepatitis B, but *peginterferon-α-2a* has similar or slightly better efficacy with improved tolerability.]

- Oral therapy for chronic hepatitis B includes *lamivudine, adefovir, entecavir, or tenofovir*.

- The preferred treatment for chronic hepatitis C is a combination of DAAs (selection is based on hepatitis C genotype)

- In certain cases Ribavirin is added a DAA regimen to enhance response.

- Pegylated interferon-alpha is no longer recommended due to inferior efficacy and poor tolerability.

A. Interferons

- Interferons are a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells.
- The interferons are synthesized by recombinant DNA technology.
- At least three types of interferons exist—α, β, and γ.

- In “pegylated” formulations, bis-monomethoxy polyethylene glycol has been covalently attached to either *interferon-α-2a* or *-α-2b* to increase the size of the molecule.

- The larger molecular size delays absorption from the injection site, lengthens the duration of action of the drug, and also decreases its clearance.

Interferon-α	*Interferon-β*	*Interferon-γ*
Chronic hepatitis B and C	Relapsing-remitting multiple sclerosis	Chronic granulo-matous disease
Genital warts caused by papilloma-virus		
Leukemia, hairy-cell Leukemia, chronic myelogenous		
Kaposi sarcoma		

Figure 45.7
Some approved indications for *interferon*.

1. Mechanism of action:

- The antiviral mechanism is incompletely understood.

- It appears to involve the induction of host cell enzymes that inhibit viral RNA translation, ultimately leading to the degradation of viral mRNA and tRNA.

2. Pharmacokinetics:

- *Interferon* is not active orally, but it may be administered intralesionally, subcutaneously, or intravenously.

- Very little active compound is found in the plasma, and its presence is not correlated with clinical responses.

- Cellular uptake and metabolism by the liver and kidney account for the disappearance of *interferon* from the plasma.

- Negligible renal elimination occurs.

3. Adverse effects:

- Adverse effects include flu-like symptoms, such as fever, chills, myalgias, arthralgias, and GI disturbances.
- Fatigue and mental depression are common.
- These symptoms subside with continued administration.
- The principal dose-limiting toxicities are
  - bone marrow suppression,
  - severe fatigue and weight loss,
  - neurotoxicity characterized by somnolence and behavioral disturbances,
  - autoimmune disorders such as thyroiditis and,
  - rarely, cardiovascular problems such as heart failure.

B. Lamivudine

- This cytosine analog is an inhibitor of both hepatitis B virus (HBV) and human immunodeficiency virus (HIV) reverse transcriptases (RTs).
- *Lamivudine* must be phosphorylated by host cellular enzymes to the triphosphate (active) form.
- This compound competitively inhibits HBV RNA-dependent DNA polymerase.
- As with many nucleotide analogs, the intracellular half-life of the triphosphate is many hours longer than its plasma half-life.

- The rate of resistance is high following long-term therapy with *lamivudine*.

- *Lamivudine* is well absorbed orally and is widely distributed.

- High HBV resistance

C. Adefovir

- *Adefovir dipivoxil* is a nucleotide analog that is phosphorylated by cellular kinases to adefovir diphosphate, which is then incorporated into viral DNA.

- This leads to termination of chain elongation and prevents replication of HBV.

- *Adefovir* is administered once a day and is renally excreted via glomerular filtration and tubular secretion.

- As with other agents, discontinuation of *adefovir* may result in severe exacerbation of hepatitis.

- Nephrotoxicity may occur with chronic use, and the drug should be used cautiously in patients with existing renal dysfunction.

- *Adefovir* may raise levels of *tenofovir* through competition for tubular secretion, and concurrent use should be avoided.

D. Entecavir

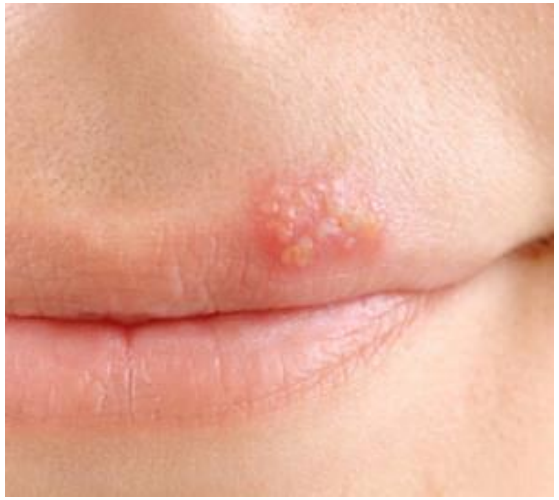
- *Entecavir* is a guanosine nucleoside analog for the treatment of HBV infections.
- *Entecavir* is effective against *lamivudine*-resistant strains of HBV and is dosed once daily.
- The drug is primarily excreted unchanged in the urine and dosage adjustments are needed in renal dysfunction.
- Concomitant use of drugs with renal toxicity should be avoided.

Hepatitis C treatments

- NS3/NS4A protease inhibitors
- NS5B Polymerase inhibitors
- NS5A replication complex inhibitors
- Ribavirin

IV. TREATMENT OF HERPESVIRUS INFECTIONS

- Herpes viruses are associated with a broad spectrum of diseases, for example,
  - cold sores,
  - viral encephalitis, and
  - genital infections.



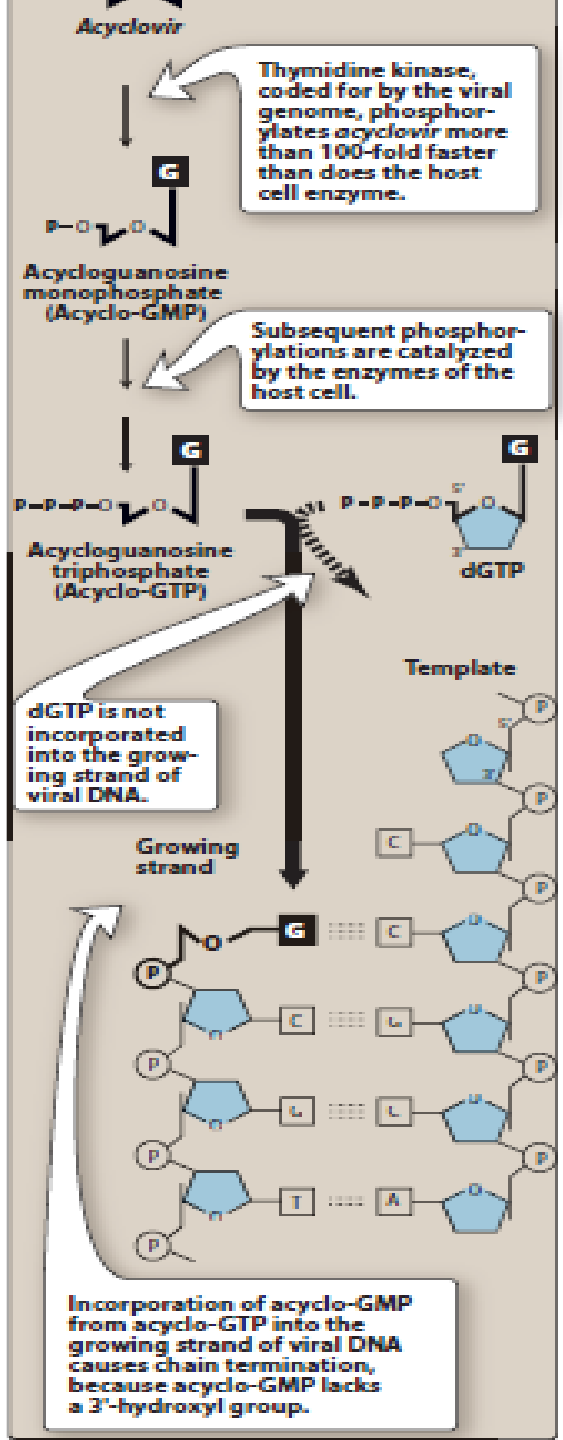
The drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase.

A. Acyclovir

- *Acyclovir* (*acycloguanosine*) is the prototypic antiherpetic therapeutic agent.
- Herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus (VZV), and some Epstein-Barr virus–mediated infections are sensitive to *acyclovir*.
- It is the treatment of choice in HSV encephalitis.
- The most common use of *acyclovir* is in therapy for genital herpes infections.
- It is also given prophylactically to seropositive patients before bone marrow transplant and post–heart transplant to protect such individuals from herpetic infections.

1. Mechanism of action:

- *Acyclovir*, a guanosine analog, is monophosphorylated in the cell by the herpesvirus-encoded enzyme thymidine kinase.
- Therefore, virus-infected cells are most susceptible.
- The monophosphate analog is converted to the di- and triphosphate forms by the host cell kinases.
- Acyclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorporated into the viral DNA, causing premature DNA chain termination.


Acyclovir
Thymidine kinase, coded for by the viral genome, phosphorylates acyclovir more than 100-fold faster than does the host cell enzyme.
Acycloguanosine monophosphate (Acyclo-GMP)
Subsequent phosphorylations are catalyzed by the enzymes of the host cell.
Acycloguanosine triphosphate (Acyclo-GTP)
dGTP
Template
dGTP is not incorporated into the growing strand of viral DNA.
Growing strand
Incorporation of acyclo-GMP from acyclo-GTP into the growing strand of viral DNA causes chain termination, because acyclo-GMP lacks a 3'-hydroxyl group.

2. Pharmacokinetics:

- *Acyclovir* is administered by intravenous (IV), oral, or topical routes.

- [Note: The efficacy of topical applications is questionable.]

- The drug distributes well throughout the body, including the cerebrospinal fluid (CSF).

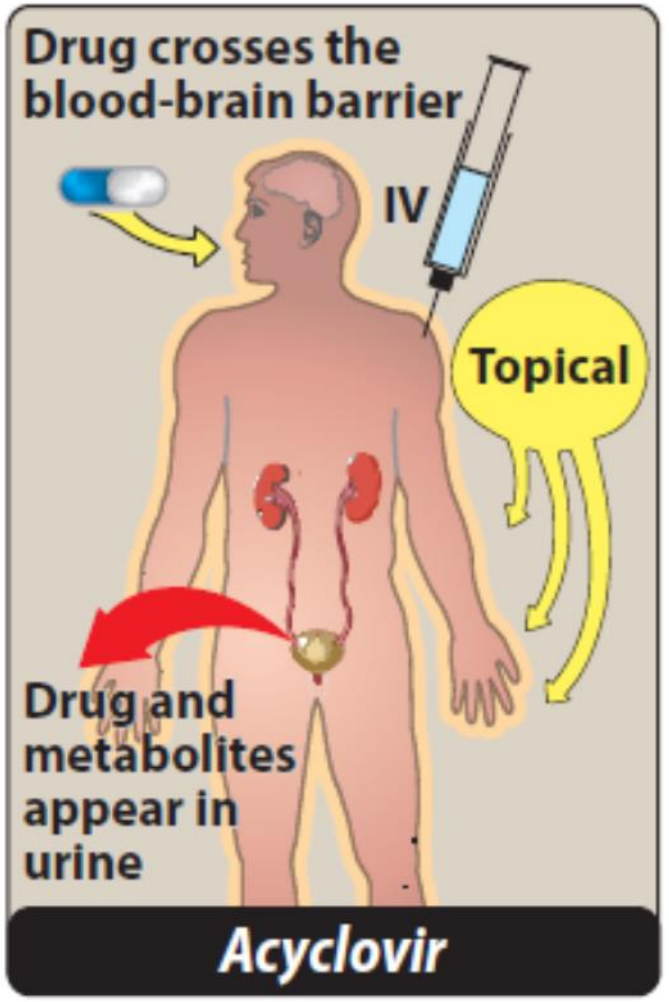


Figure 45.9
Administration and fate of *acyclovir*. IV = intravenous.

- Excretion into the urine occurs both by glomerular filtration and tubular secretion

- *Acyclovir* accumulates in patients with renal failure.

3. Adverse effects:

- Side effects of *acyclovir* treatment depend on the route of administration.
- For example, local irritation may occur from topical application;
- headache, diarrhea, nausea, and vomiting may result after oral administration.
- Transient renal dysfunction may occur at high doses or in a dehydrated patient receiving the drug intravenously.

4. Resistance:

- Altered or deficient thymidine kinase and DNA polymerases have been found in some resistant viral strains and are most commonly isolated from immunocompromised patients.

- Crossresistance to the other agents in this family occurs.

B. Cidofovir

- *Cidofovir* is approved for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. [Note: CMV is a member of the herpesvirus family.]
- It inhibits viral DNA synthesis.
- Slow elimination of the active intracellular metabolite permits prolonged dosage intervals and eliminates the permanent venous access needed for *ganciclovir* therapy.
- *Cidofovir* is administered intravenously.
- Intravitreal injection (injection into the vitreous humor between the lens and the retina) of *cidofovir* is associated with risk of hypotony and uveitis and is reserved for extraordinary cases.

- *Cidofovir* produces significant renal toxicity, and it is
- contraindicated in patients with preexisting renal impairment and in those taking nephrotoxic drugs.
- Oral probenecid and IV normal saline are coadministered with cidofovir to reduce the risk of nephrotoxicity.

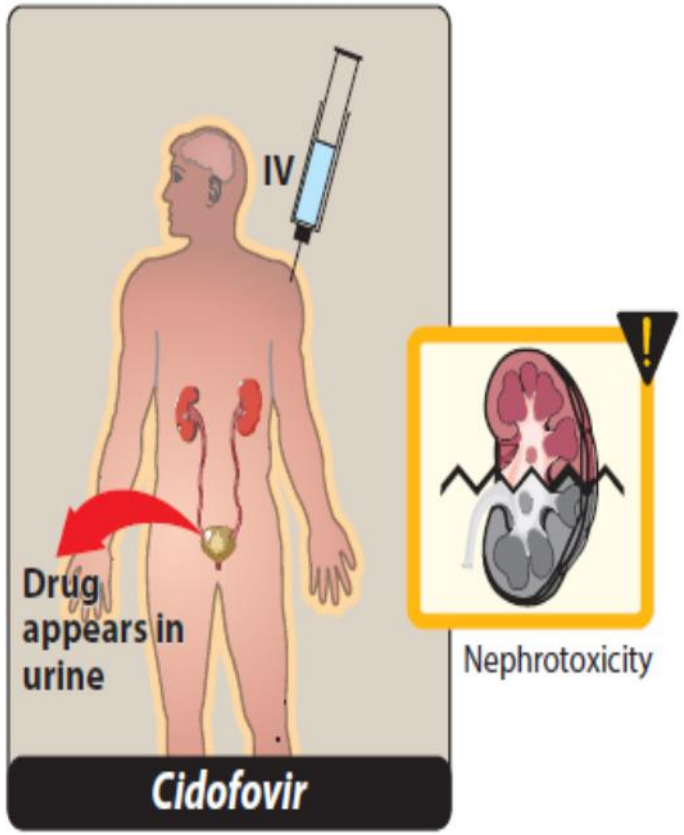


Figure 45.10
Administration, fate, and toxicity of *cidofovir*. IV = intravenous.

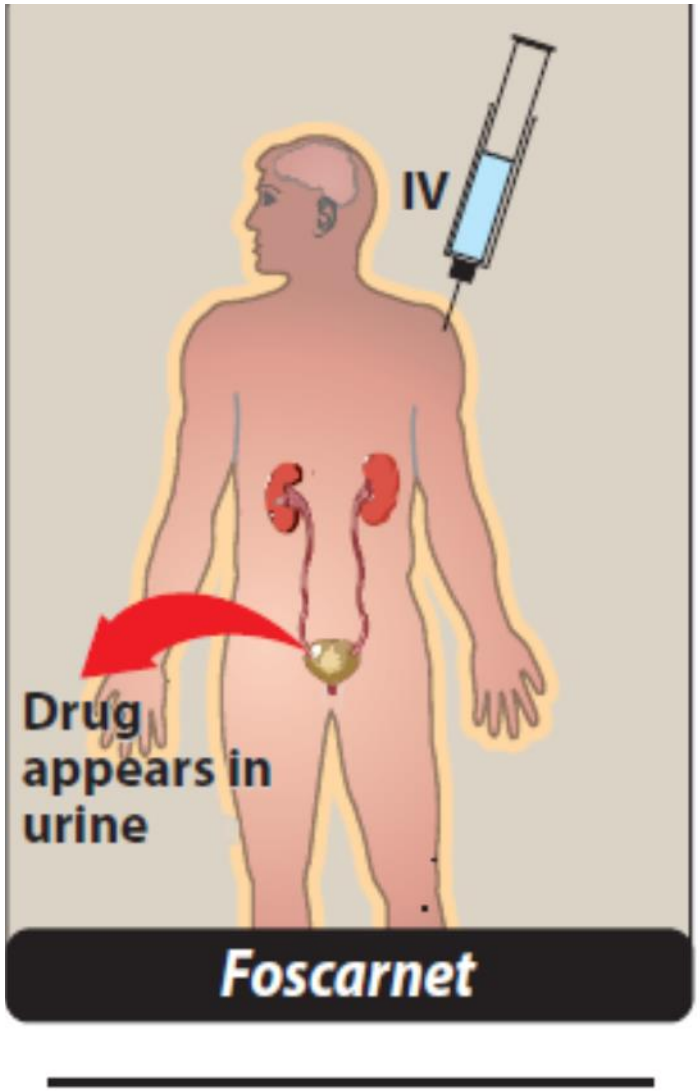
C. Foscarnet

- *Foscarnet* is approved for CMV retinitis in immunocompromised hosts and for *acyclovir*-resistant HSV infections.

Foscarnet works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis.

- Mutation of the polymerase structure is responsible for resistant viruses.

- *Foscarnet* is poorly absorbed orally and must be injected intravenously.
- It must also be given frequently to avoid relapse when plasma levels fall.
- It is dispersed throughout the body, and greater than 10% enters the bone matrix, from which it slowly leaves.
- The parent drug is eliminated by glomerular filtration and tubular secretion.



- Adverse effects include nephrotoxicity, anemia, nausea, and fever.
- Due to chelation with divalent cations, hypocalcemia and hypomagnesemia are also seen.
- In addition, hypokalemia, hypo- and hyperphosphatemia, seizures, and arrhythmias have been reported.

D. Ganciclovir

- *Ganciclovir* is an analog of *acyclovir* that has greater activity against CMV.
- It is used for the treatment of CMV retinitis in immunocompromised patients
- and for CMV prophylaxis in transplant patients.

1. Mechanism of action:

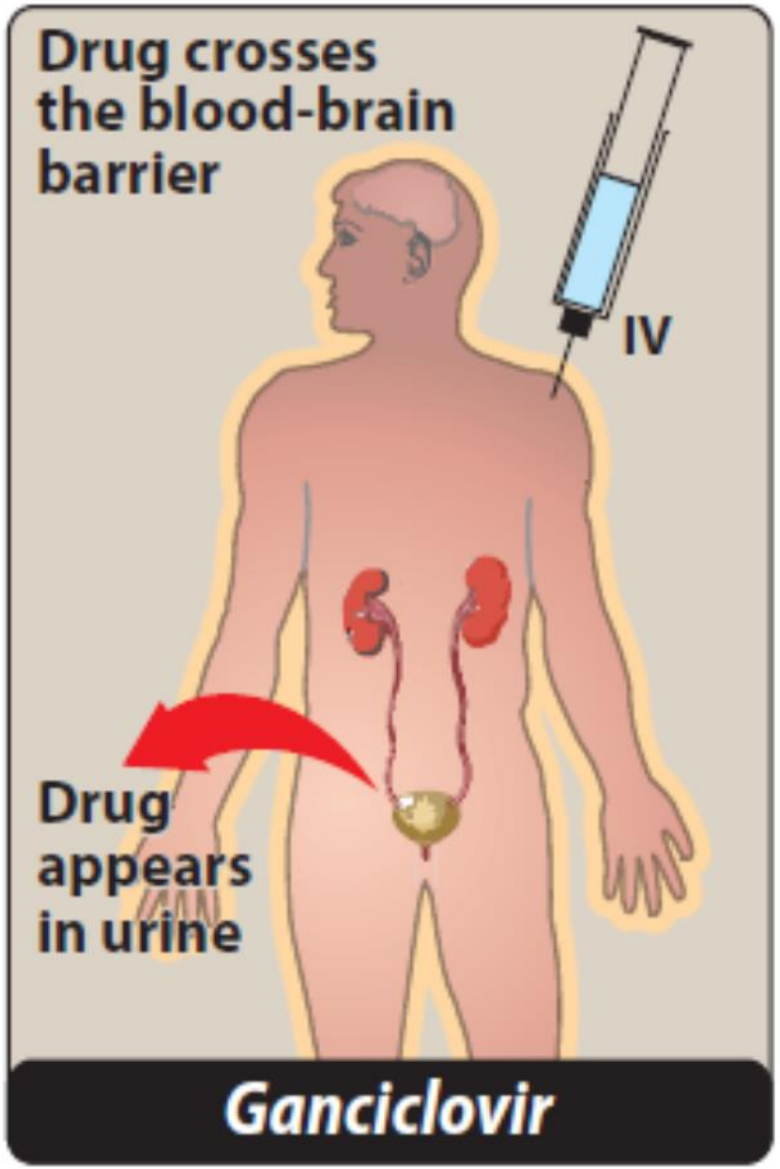
- Like *acyclovir*, *ganciclovir* is activated through conversion to the nucleoside triphosphate by viral and cellular enzymes.

- The nucleotide inhibits viral DNA polymerase and can be incorporated into the DNA resulting in chain termination.

2. Pharmacokinetics:

- *Ganciclovir* is administered IV and distributes throughout the body, including the CSF.

- Excretion into the urine occurs through glomerular filtration and tubular secretion



- Like *acyclovir*, *ganciclovir* accumulates in patients with renal failure.

- *Valganciclovir* , an oral drug, is the valyl ester of *ganciclovir*.

- Like *valacyclovir*, *valganciclovir* has high oral bioavailability, because rapid hydrolysis in the intestine and liver after oral administration leads to high levels of *ganciclovir*.

3. Adverse effects:

- Adverse effects include severe, dose-dependent neutropenia.

- *Ganciclovir* is carcinogenic as well as embryotoxic and teratogenic in experimental animals.

- **4. Resistance:** Resistant CMV strains have been detected that have lower levels of ganciclovir triphosphate

E. Penciclovir and famciclovir

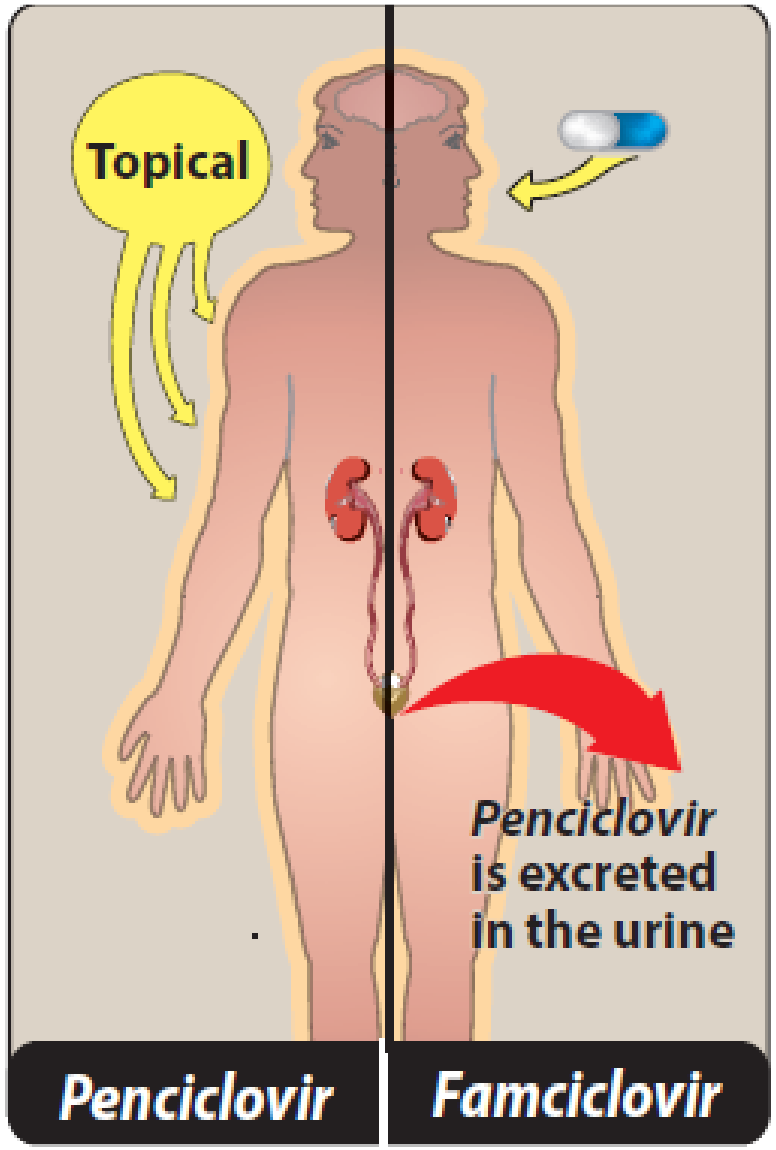
- *Penciclovir* is an acyclic guanosine nucleoside derivative that is active against HSV-1, HSV-2, and VZV.
- *Penciclovir* is only administered topically. It is monophosphorylated by viral thymidine kinase, and cellular enzymes form the nucleoside triphosphate, which inhibits HSV DNA polymerase.
- Penciclovir triphosphate has an intracellular half-life much longer than acyclovir triphosphate.
- *Penciclovir* is negligibly absorbed upon topical application and is well tolerated.

- *Famciclovir*, another acyclic analog of 2′-deoxyguanosine, is a prodrug that is metabolized to the active *penciclovir*.

- The antiviral spectrum is similar to that of *ganciclovir*, and it is approved for treatment of
    - acute herpes zoster,
    - genital HSV infection, and
    - recurrent herpes labialis.

- The drug is effective orally.

- Adverse effects include headache and nausea.


Topical
Penciclovir
is excreted
in the urine
Penciclovir
Famciclovir

F. Trifluridine

- *Trifluridine* is a fluorinated pyrimidine nucleoside analog that is structurally similar to thymidine.

- Once converted to the triphosphate, the agent is believed to inhibit the incorporation of thymidine triphosphate into viral DNA and, to a lesser extent, lead to the synthesis of defective DNA that renders the virus unable to replicate.

- *Trifluridine* is active against HSV-1, HSV-2, and vaccinia virus.

- It is indicated for treatment of HSV keratoconjunctivitis and recurrent epithelial keratitis.
- Because the triphosphate form of *trifluridine* can also incorporate to some degree into cellular DNA, the drug is considered to be too toxic for systemic use.
- Therefore, the use of *trifluridine* is restricted to a topical ophthalmic preparation.
- Adverse effects include a transient irritation of the eye and palpebral (eyelid) edema.

Antiviral drug	Mechanism of action	Viruses or diseases affected
Acyclovir	Metabolized to acyclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex, varicella-zoster, cytomegalovirus
Amantadine	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A
Cidofovir	Inhibition of viral DNA polymerase	Cytomegalovirus; indicated only for virus-induced retinitis
Famciclovir	Same as *penciclovir*	Herpes simplex, varicella-zoster
Foscarnet	Inhibition of viral DNA polymerase and reverse transcriptase at the pyrophosphate-binding site	Cytomegalovirus, *acyclovir*-resistant herpes simplex, *acyclovir*-resistant varicella-zoster
Ganciclovir	Inhibits viral DNA polymerase	Cytomegalovirus
Interferon-α	Induction of cellular enzymes that interfere with viral protein synthesis	Hepatitis B and C, human herpesvirus 8, papilloma virus, Kaposi sarcoma, hairy cell leukemia, chronic myelogenous leukemia
Lamivudine	Inhibition of viral DNA polymerase and reverse transcriptase	Hepatitis B (chronic cases), human immunodeficiency virus type 1
Oseltamivir	Inhibition of viral neuraminidase	Influenza A
Penciclovir	Metabolized to penciclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex
Ribavirin	Interference with viral messenger RNA	Lassa fever, hantavirus (hemorrhagic fever renal syndrome), hepatitis C (in chronic cases in combination with *interferon-α* and in combination both with *interferon-α* and HCV protease inhibitor for HCV genotype I), RSV in children and infants
Rimantadine	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A
Valacyclovir	Same as *acyclovir*	Herpes simplex, varicella-zoster, cytomegalovirus
Zanamivir	Inhibition of viral neuraminidase	Influenza A