**ANTIVIRAL AGENTS (NONRETROVIRAL)**

**ANTIVIRAL AGENTS (NONRETROVIRAL): INTRODUCTION**

Viruses are obligate intracellular parasites that consist of either double- or single-stranded DNA or RNA enclosed in a protein coat called a *capsid.* Some viruses also possess a lipid envelope that, like the capsid, may contain antigenic glycoproteins. Most viruses contain enzymes essential for viral replication inside a host cell. Effective antiviral agents inhibit virus-specific replicative events or preferentially inhibit virus-directed rather than host cell-directed nucleic acid or protein synthesis.

DNA viruses (and the diseases they cause) include poxviruses (smallpox), herpesviruses (chickenpox, shingles, oral and genital herpes), adenoviruses (conjunctivitis, sore throat), hepadnaviruses [hepatitis B (HBV)], and papillomaviruses (warts).

Examples of RNA viruses (and the diseases they cause) include rubella virus (German measles), rhabdoviruses (rabies), picornaviruses (poliomyelitis, meningitis, colds, hepatitis A), arenaviruses (meningitis, Lassa fever), flaviviruses (West Nile meningoencephalitis, yellow fever, hepatitis C), orthomyxoviruses (influenza), paramyxoviruses (measles, mumps), and coronaviruses [colds, severe acute respiratory syndrome (SARS)].

One group of RNA viruses that deserves special mention is retroviruses, responsible for diseases such as acquired immunodeficiency syndrome (AIDS).
Current agents inhibit active replication, so viral replication may resume following drug removal. Effective host immune responses remain essential for recovery from infection. Clinical failures of antiviral therapy may occur with drug-sensitive virus in highly immunocompromised patients or following emergence of drug-resistant variants.

Most drug-resistant viruses are recovered from immunocompromised patients with high viral replicative loads and repeated or prolonged courses of antiviral treatment. (Influenza A virus is an exception.)

**ANTIHERPESVIRUS AGENTS**

**Introduction**

Infection with herpes simplex virus type 1 (HSV-1) typically causes diseases of the mouth, face, skin, esophagus, or brain. Herpes simplex virus type 2 (HSV-2) usually causes infections of the genitals, rectum, skin, hands, or meninges.

***vidarabine,***.

Was the first antiviral agent for treatment of herpes but is no longer in use because of its fatal toxicities.

**Acyclovir and Valacyclovir**

they are acyclic guanine nucleoside analog

**Mechanisms of Action and Resistance.**

Acyclovir inhibits viral DNA synthesis *.*

**Absorption, Distribution, and Elimination.**

The oral bioavailability of acyclovir ranges from 10% to 30% and decreases with increasing dose .

Valacyclovir is converted rapidly and virtually completely to acyclovir after oral administration in healthy adults.

Acyclovir distributes widely in body fluids, including vesicular fluid, aqueous humor, and cerebrospinal fluid. Compared with plasma, salivary concentrations are low, and vaginal secretion concentrations vary widely. Acyclovir is concentrated in breast milk, amniotic fluid, and placenta. Newborn plasma levels are similar to maternal ones. Percutaneous absorption of acyclovir after topical administration is low.

The mean plasma *t*1/2 of elimination of acyclovir is about 2.5 hours.Renal excretion of unmetabolized acyclovir by glomerular filtration and tubular secretion is the principal route of elimination).

**Untoward Effects.** Acyclovir generally is well tolerated. may cause mucosal irritation and transient burning when applied to genital lesions.

Oral acyclovir has been associated infrequently with nausea, diarrhea, rash, or headache and very rarely with renal insufficiency or neurotoxicity.

 Valacyclovir also may be associated with headache, nausea, diarrhea, nephrotoxicity, and central nervous system (CNS) symptoms. High doses of valacyclovir have been associated with confusion and hallucinations, nephrotoxicity, and uncommonly, severe thrombocytopenic syndromes, sometimes fatal, in immunocompromised patients.

**Therapeutic Uses.** In immunocompetent persons, the clinical benefits of acyclovir and valacyclovir are greater in initial HSV infections than in recurrent ones.
***Herpes Simplex Virus Infections.*** In initial genital HSV infections, oral acyclovir (200 mg five times daily or 400 mg three times daily for 7 to 10 days) and valacyclovir (1000 mg twice daily for 7 to 10 days). Intravenous acyclovir (5 mg/kg every 8 hours).
Systemic acyclovir prophylaxis is highly effective in preventing mucocutaneous HSV infections in seropositive patients undergoing immunosuppression.
***Varicella-Zoster Virus Infections.*** If begun within 24 hours of rash onset, oral acyclovir has therapeutic effects in varicella of children and adults. In children weighing up to 40 kg, acyclovir (20 mg/kg, up to 800 mg per dose, four times daily for 5 days) reduces fever and new lesion formation by about one day. **Cidofovir**
is a cytidine nucleotide analog with inhibitory activity against human herpes, papilloma, polyoma, pox, and adenoviruses.

**Mechanisms of Action and Resistance.**

 Cidofovir inhibits viral DNA synthesis by slowing and eventually terminating chain elongation. Cidofovir is metabolized to its active diphosphate form by cellular enzymes.
Cidofovir resistance in CMV is due to mutations in viral DNA polymerase.
**Absorption, Distribution, and Elimination.**

has very low oral bioavailability.

The plasma levels after intravenous administration half-life that averages about 2.6 hours.

Cidofovir is cleared by the kidney *via* glomerular filtration and tubular secretion. Over 90% of the dose is recovered unchanged in the urine without significant metabolism in human beings.
**Untoward Effects.**

 Nephrotoxicity is the principal dose-limiting side effect of intravenous cidofovir.

 Topical application of cidofovir is associated with dose-related application-site reactions (*e.g.,* burning, pain, and pruritus.

**Therapeutic Uses.** Intravenous cidofovir is approved for the treatment of CMV retinitis in HIV-infected patients. Intravenous cidofovir (5 mg/kg once a week for 2 weeks .
**Famciclovir and Penciclovir**
**Mechanisms of Action and Resistance.**

 Penciclovir is an inhibitor of viral DNA synthesis.
**Absorption, Distribution, and Elimination.** Oral penciclovir has low (5%) bioavailability. Food slows absorption but does not reduce overall bioavailability.. The plasma *t*1/2 of elimination of penciclovir averages about 2 hours, and over 90% is excreted unchanged in the urine, probably by both filtration and active tubular secretion.
**Untoward Effects.** Oral famciclovir is well tolerated but may be associated with headache, diarrhea, and nausea. Urticaria, rash, and hallucinations or confusional states (predominantly in the elderly

**Therapeutic Uses.**

Herpes Simplex Virus and Varicella Zooster Virus

**Ganciclovir and Valganciclovir**

**Mechanisms of Action and Resistance.** Ganciclovir inhibits viral DNA synthesis.

**Absorption, Distribution, and Elimination.**

The plasma half-life is about 2 to 4 hours in patients with normal renal function. Over 90% of ganciclovir is eliminated unchanged by renal excretion through glomerular filtration and tubular secretion.
**Untoward Effects.** Myelosuppression is the principal dose-limiting toxicity of ganciclovir. Neutropenia and thrombocytopenia

CNS side effects like headache to behavioral changes to convulsions and coma.
**Therapeutic Uses.** Ganciclovir is effective for treatment and chronic suppression of CMV retinitis in immunocompromised patients and for prevention of CMV disease in transplant patients.

**Trifluridine**

Trifluridine (5-trifluoromethyl-2-deoxyuridine) is a fluorinated pyrimidine nucleoside that has *in vitro* inhibitory activity against HSV types 1 and 2, CMV.
Trifluridine also inhibits cellular DNA synthesis at relatively low concentrations.
Trifluridine currently is used for treatment of primary keratoconjunctivitis and recurrent epithelial keratitis owing to HSV types 1 and 2, HSV ocular infections.

 **Adverse reactions** include discomfort on instillation and edema. Hypersensitivity reactions, irritation,

**ANTI-INFLUENZA AGENTS**

**Amantadine and Rimantadine**

**Chemistry and Antiviral Activity.** *Amantadine* and rimantadine are tricyclic amines.
**Mechanisms of Action and Resistance.** They inhibit viral replication.
**Absorption, Distribution, and Elimination.** Amantadine and rimantadine are well absorbed after oral administration. Both drugs have very large volumes of distribution. Nasal secretion and salivary levels of amantadine approximate those found in the serum. Amantadine is excreted in breast milk.
Amantadine is excreted largely unmetabolized in the urine through glomerular filtration and probably tubular secretion. The plasma *t*1/2 of elimination is about 12 to 18 hours in young adults. Because amantadine's elimination is highly dependent on renal function, the elimination *t*1/2 increases up to twofold in the elderly and even more in those with renal impairment. Dose adjustments are advisable in those with mild decrements in renal function

**Untoward Effects.** The most common side effects related to amantadine and rimantadine are minor dose-related gastrointestinal and CNS complaints . These include nervousness, light-headedness, difficulty concentrating, insomnia, and loss of appetite or nausea

**Therapeutic Uses.** Amantadine and rimantadine are effective for the prevention and treatment of influenza A virus infections.
 uncomplicated influenza A illness of adults, early amantadine or rimantadine treatment (200 mg/day for 5 days.

**Oseltamivir**

It inhibits amantadine- and rimantadine-resistant influenza A viruses and some zanamivir-resistant variants.

**Absorption, Distribution, and Elimination.** Oral oseltamivir phosphate is absorbed rapidly and cleaved by esterases in the gastrointestinal tract and liver to the active carboxylate. Low blood levels of the phosphate are detectable.The time to maximum plasma concentrations of the carboxylate is about 2.5 to 5 hours. Food does not decrease bioavailability but reduces the risk of gastrointestinal intolerance. Following oral administration, the plasma half-life of oseltamivir phosphate is 1 to 3 hours and that of the carboxylate ranges from 6 to 10 hours. Both the prodrug and active metabolite are eliminated primarily unchanged through the kidney. Probenecid doubles the plasma half-life of the carboxylate, which indicates tubular secretion by the anionic pathway.

**Untoward Effects.** Oral oseltamivir is associated with nausea, abdominal discomfort, and, less often, emesis, probably owing to local irritation. Gastrointestinal complaints usually are mild-to-moderate in intensity, typically resolve in 1 to 2 days despite continued dosing, and are preventable by administration with food.
Very high doses have been associated with increased mortality, perhaps related to increased brain concentrations, and oseltamivir is not approved for use in children younger than 1 year of age.

**Therapeutic Uses.** Oral oseltamivir is effective in the treatment and prevention of influenza A and B virus infections. Treatment of previously healthy adults (75 mg twice daily for 5 days)

 used for prophylaxis during the influenza season, oseltamivir (75 mg once daily) is effective (approximately 70% to 90%) in reducing the likelihood of influenza illness in both unimmunized working adults and in immunized nursing home residents short-term use (7 to 10 days) protects against influenza in household contacts .

**Zanamivir**

is a sialic acid analog that potently and specifically inhibits the neuraminidases of influenza A and B viruses.

Zanamivir inhibits replication of influenza A and B viruses, including amantadine- and rimantadineresistant strains and several oseltamivir-resistant variants. It is active after topical administration

**Mechanisms of Action and Resistance.** Like oseltamivir, zanamivir inhibits viral neuraminidase and thus causes viral aggregation at the cell surface and reduced spread of virus within the respiratory tract

**Absorption, Distribution, and Elimination.** The oral bioavailability of zanamivir is low (5%).

The plasma half-life of zanamivir averages 2.5 to 5 hours after oral inhalation but only 1.7 hours following intravenous dosing. Over 90% is eliminated in the urine without recognized metabolism.

**Untoward Effects.** Topically applied zanamivir generally is well tolerated in ambulatory adults and children with influenza. Wheezing and bronchospasm have been reported in some influenza-infected patients without known airway disease, and acute deteriorations in lung function, including fatal outcomes, have occurred in those with underlying asthma or chronic obstructive airway disease. Zanamivir is not generally recommended for treatment of patients with underlying airway disease (*e.g.,* asthma or chronic obstructive pulmonary disease) because of the risk of serious adverse events.

**Therapeutic Uses.** Inhaled zanamivir is effective for the prevention and treatment of influenza A and B virus infections. Early zanamivir treatment (10 mg twice daily for 5 days) of febrile influenza in ambulatory adults and children aged 5 years and older shortens the time to illness resolution by 1 to 3 days and in adults reduces by 40% the risk of lower respiratory tract complications leading to antibiotic use. Once-daily inhaled, but not intranasal, zanamivir is highly protective against community-acquired influenza illness and when given for 10 days, it protects against household transmission .
**ANTIHEPATITIS AGENTS**

**Introduction**

A number of agents are available for treatment of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Several agents (*e.g.,* interferons and *ribavirin*) have other uses as well.

**Adefovir**
an acyclic phosphonate nucleotide analog of adenosine monophosphate.
**Mechanisms of Action and Resistance.** Adefovir dipivoxil enters cells and is deesterified to adefovir. Adefovir is converted by cellular enzymes to the diphosphate, which acts as a competitive inhibitor of viral DNA polymerases and reverse transcriptases with respect to deoxyadenosine triphosphate and also serves as a chain terminator of viral DNA synthesis.

The intracellular *t*1/2 of the diphosphate is prolonged, ranging from 5 to 18 hours, so once-daily dosing is feasible. Adefovir resistance has been detected in a small proportion (~4%) of chronically infected HBV patients during 3 years of treatment.
**Absorption, Distribution, and Elimination.**

 Food does not affect bioavailability.

Adefovir is eliminated unchanged by renal excretion through a combination of glomerular filtration and tubular secretion, the serum *t*1/2 of elimination ranges from 5 to 7.5 hours.

**Untoward Effects.** Adefovir dipivoxil causes dose-related nephrotoxicity and tubular dysfunction, manifested by azotemia and hypophosphatemia, acidosis, glycosuria, and proteinuria that usually are reversible months after discontinuation. The lower dose (10 mg/day) used in chronic HBV infection patients has been associated with few adverse events (*e.g.,* headache, abdominal discomfort, diarrhea,.

Adefovir is genotoxic, and high doses cause renal tubular nephropathy, hepatotoxicity, and toxicity to lymphoid tissues in animals. Adefovir dipivoxil is not associated with reproductive toxicity, although high intravenous doses of adefovir cause maternal and embryotoxicity with fetal malformations .

**Therapeutic Uses.** Adefovir dipivoxil is approved for treatment of chronic HBV infections.

Regression of cirrhosis may occur in some patients.
**Interferons**

**Classification and Antiviral Activity.** Interferons (IFNs) are potent cytokines that possess antiviral, immunomodulating, and antiproliferative activities.These proteins are synthesized by host cells in response to various inducers and, in turn, cause biochemical changes leading to an antiviral state in cells.

**Absorption, Distribution, and Elimination.**

With subcutaneous or intramuscular dosing, the plasma *t*1/2 of elimination of IFN- ranges from approximately 3 to 8 hours. Elimination from the blood relates to distribution to the tissues, cellular uptake, and catabolism primarily in the kidney and liver. Negligible amounts are excreted in the urine.
**Untoward Effects.** Injection of IFN doses of 1 to 2 million units (MU) or greater usually is associated with an acute influenzalike syndrome beginning several hours after injection. Symptoms include fever, chills, headache, myalgia, arthralgia, nausea, vomiting, and diarrhea . Fever usually resolves within 12 hours. Tolerance develops gradually in most patients. Febrile responses can be moderated by pretreatment with various antipyretics.

Others; neurotoxicity manifested by somnolence, confusion, behavioral disturbance, and rarely, seizures; debilitating neurasthenia and depression; autoimmune disorders including thyroiditis; and uncommonly, cardiovascular effects with hypotension and tachycardia. The risk of depression appears to be higher in chronically infected HCV than in HBV patients. Elevations in hepatic enzymes and triglycerides, alopecia, proteinuria and azotemia, interstitial nephritis, autoantibody formation, pneumonia, and hepatotoxicity may occur. Alopecia and personality change are common in IFN-treated children . contraindicated in pregnancy.
**Therapeutic Uses**

for treatment of condyloma acuminatum9genital warts), chronic HCV infection, chronic HBV infection, Kaposi's sarcoma in HIV-infected patients, other malignancies, and multiple sclerosis.

***Hepatitis B Virus.*** In patients with chronic HBV infection, parenteral administration of various IFNs is associated with loss of HBV DNA. (typically 5 MU/day or 10 MU in adults and 6 MU/m2 in children three times per week for 4 to 6 months). Plasma HBV DNA and polymerase activity decline promptly in most patients, but complete disappearance is sustained in only about one-third of patients or less

. High-dose IFN can cause myelosuppression and clinical deterioration in those with decompensated liver disease.

***Hepatitis C Virus.*** In chronic HCV infection

***Papillomavirus.*** In refractory condylomata acuminata (genital warts), intralesional injection of various natural and recombinant IFNs is associated with complete clearance of injected warts .Intramuscular or subcutaneous administration is associated with some regression in wart size but greater toxicity. Systemic IFN may provide adjunctive benefit in recurrent juvenile laryngeal papillomatosis and in treating laryngeal disease in older patients.

***Other Viruses.*** IFNs have been shown to have virologic and clinical effects in various herpesvirus infections including genital HSV infections, localized herpes-zoster infection of cancer patients or of older adults, and CMV infections of renal transplant patients.

In HIV-infected persons, IFNs have been associated with antiretroviral effects. In advanced infection, however, the combination of zidovudine and IFN is associated with only transient benefit and excessive hematological toxicity.

 IFN- (3 MU three times weekly) is effective for treatment of HIV-related thrombocytopenia resistant to zidovudine therapy.

Except for adenovirus, IFN has broad-spectrum antiviral activity against respiratory viruses *.*

**Lamivudine**

**Chemistry and Antiviral Activity.** Lamivudine, is a nucleoside analog that inhibits HIV reverse transcriptase and HBV DNA polymerase.
**Mechanisms of Action and Resistance.** Lamivudine triphosphate is a potent inhibitor of the DNA polymerase/reverse transcriptase of HBV.Lamivudine shows enhanced antiviral activity in combination with adefovir . Lamivudine resistance confers cross-resistance to related agents such as *emtricitabine* and *clevudine*

**Absorption, Distribution, and Elimination.** Following oral administration, lamivudine is absorbed rapidly with a bioavailability of about 80% in adults . Peak plasma levels average approximately 1000 ng/ml after 100-mg doses. The plasma *t*1/2 of elimination averages about 9 hours, and approximately 70% of the dose is excreted unchanged in the urine. Dose reductions are indicated for moderate renal insufficiency (creatinine clearance  50 ml/min). *Trimethoprim* decreases the renal clearance of lamivudine.

**Untoward Effects.** At the doses used for chronic HBV infection, lamivudine generally has been well tolerated.
**Therapeutic Uses.** Lamivudine is approved for the treatment of chronic HBV hepatitis in adults and children. In adults, doses of 100 mg/day for 1 year cause suppression of HBV DNA levels. In children aged 2 to 17 years, lamivudine (3 mg/kg per day to a maximum of 100 mg for 1 year

In HIV and HBV coinfections, higher lamivudine doses are associated with antiviral effects and uncommonly anti-HBe seroconversion.Administration of lamivudine before and after liver transplantation may suppress recurrent HBV infection.

**Ribavirin**

**Chemistry and Antiviral Activity.** Ribavirin (1--D-ribofur-anosyl-1*H*-1,2,4-triazole-3-carboxamide) is a purine nucleoside analog .

Ribavirin inhibits the replication of a wide range of RNA and DNA viruses, Similar concentrations may reversibly inhibit macromolecular synthesis and proliferation of uninfected cells, suppress lymphocyte responses, and alter cytokine profiles*.*

**Mechanisms of Action and Resistance.** The antiviral mechanism of ribavirin is incompletely understood but relates to alteration of cellular nucleotide pools and inhibition of viral messenger RNA synthesis .
**Absorption, Distribution, and Elimination.** Ribavirin is actively taken up by nucleoside transporters in the proximal small bowel; oral bioavailability averages approximately 50% . Extensive accumulation occurs in plasma, and steady state is reached by about 4 weeks. Food increases plasma levels .

Plasma protein binding is negligible. The elimination of ribavirin is complex., with a *t*1/2 of approximately 40 days. Hepatic metabolism and renal excretion of ribavirin and its metabolites are the principal routes of elimination
**Untoward Effects.** Aerosolized ribavirin may cause conjunctival irritation, rash, transient wheezing, and occasional reversible deterioration in pulmonary function. When used in conjunction with mechanical ventilation, equipment modifications and frequent monitoring are required to prevent plugging of ventilator valves and tubing with ribavirin.

Systemic ribavirin causes dose-related reversible anemia owing to extravascular hemolysis and suppression of bone marrow. Associated increases occur in reticulocyte counts and in serum bilirubin, iron, and uric acid concentrations.

Bolus intravenous infusion may cause rigors. About 20% of chronic HCV infection patients receiving combination IFN-ribavirin therapy discontinue treatment early because of side effects. In addition to IFN toxicities, oral ribavirin increases the risk of fatigue, cough, rash, pruritus, nausea, insomnia, dyspnea, depression, and particularly, anemia. Preclinical studies indicate that ribavirin is teratogenic.
Ribavirin inhibits the phosphorylation and antiviral activity of pyrimidine nucleoside HIV reverse-transcriptase inhibitors such as zidovudine and stavudine but increases the activity of purine nucleoside reverse-transcriptase inhibitors (*e.g.,* didanosine) *.* It increases the risk of mitochondrial toxicity from didanosine.

**Therapeutic Uses.** Oral ribavirin in combination with injected IFN has become standard treatment for chronic HCV infection .The combination is superior to IFN monotherapy .

 Ribavirin aerosol is approved in the United States for treatment of RSV bronchiolitis and pneumonia in hospitalized children.

Intravenous and/or aerosol ribavirin has been used occasionally in treating severe influenza virus infection and in the treatment of immunosuppressed patients with adenovirus, vaccinia, parainfluenza, or measles virus infections. Aerosolized ribavirin is associated with reduced duration of fever but no other clinical or antiviral effects in influenza infections in hospitalized children. Intravenous ribavirin decreases mortality in Lassa fever and has been used in treating other arenavirus-related hemorrhagic fevers. Intravenous ribavirin is beneficial in hemorrhagic fever with renal syndrome owing to hantavirus infection but appears ineffective in hantavirus-associated cardiopulmonary syndrome or SARS.
**OTHER AGENTS**

**Imiquimod**

is effective for topical treatment of condylomata acuminata and certain other dermatologic conditions ), imiquimod cream is associated with complete clearance of treated genital and perianal warts in about 50% of patients, with response rates being higher in women than in men .The median time to clearance is 8 to 10 weeks; relapses are not uncommon. Application is associated with local erythema,excoriation/flaking ,itching ,burning and less often, erosions or ulcerations.