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following the real infection pathway. In addition, clinical preparations of viruses used for vaccines, vaccine vectors, gene therapy vectors, and oncolytic viruses need to be defined precisely and specifically in terms of particles versus infectious units for accurate and safe dosing. As an example, a recent adenovirus-based COVID vaccine was quantified on the basis of spectrophotometric measurement of purified virions. After the trial was initiated, lower than expected immune responses led to a reexamination of the vaccine dose. An excipient discovered in the vaccine was found to cause errors in spectrophotometric measure ment that led to an overestimate of the virus concentration. Parallel measurements of viral genomes with RT-PCR allowed a more accurate measurement of the vaccine vector batches, and the dose was revised to one-half of the original level. This example illustrates the importance of precise measurements of viral particles and infectious particles in preparations of viruses for clinical use. DETECTION OF VIRUS-SPECIFIC ANTIBODIES The presence of virus-specific antibodies provides evidence of prior infection with a virus or prior exposure to viral antigens through immunization; thus, antibody tests are extremely important clinically. The most common tests for antibodies are the enzyme-linked immuno sorbent assay (ELISA) and the Western blot or immunoblot assay. An ELISA involves the immobilization of viral antigen on a substrate such as a microtiter well, its incubation with the patient’s serum, and further incubation with an antibody to human IgG coupled to an enzyme. The amount of bound antibody is measured by detection of a colored product made by the bound enzyme. The Western blot assay involves the resolution of viral proteins in a polyacrylamide gel, their transfer to a membrane, incubation with the patient’s serum, and further incuba tion with antibody to human IgG coupled to an enzyme. Proteins with bound antibodies are detected as a colored product made by the bound antibody. The Western blot detects antigen of a specific size and there fore is more specific than ELISA. For example, HIV serologic testing involves high-throughput ELISA screening followed by a Western blot assay to confirm the specificity of any positive ELISA result.

PART 5 Infectious Diseases In a hemagglutination inhibition assay, antibodies specific for viral surface proteins are detected by their ability to block hemagglutination. IMMUNIZATION AGAINST VIRAL DISEASES Viral vaccines are among the most effective biomedical and public health measures that have been implemented: millions of deaths have been pre vented by their use. These vaccines are safe because extensive protocols have been developed for monitoring vaccine safety both before and after licensure. Historically, viral vaccines were based on either inactivated virus or live attenuated viruses, as exemplified by the Salk polio vaccine and the Sabin live attenuated polio vaccine, respectively. Both of these vaccines were quite successful, offering individual advantages. Further vaccine types have been developed, including those based on recombi nant proteins, viral vectors, and, most recently, mRNA. For each virus, the optimal antigen and immunization strategy must be developed on the basis of the virus-specific immune correlates, antibodies, or T cells needed for immunologic protection against infection and disease. These concepts are discussed in greater detail in Chap. 129. ANTIVIRAL THERAPEUTICS ■ ■ANTIVIRAL DRUGS Viruses replicate in human cells and use much of the host cell's machin ery. Therefore, antiviral drugs must target virus-specific events to optimize safety. Viral targets for drugs have been identified in studies of the mechanisms of viral infection and replication (Chap. 196). Many of the most successful antiviral drugs target viral enzymes; examples include the anti-HSV drugs that target the virus DNA polymerases and thymidine kinase (Chap. 196) and the HIV drugs that target the virus reverse transcriptase, protease, and integrase (Chap. 208). ■ ■VIRUSES AS THERAPEUTICS Viruses have been engineered for a number of medical purposes, including gene delivery and tumor cell killing. As described above,

viruses have been developed as vaccines and vaccine vectors. For exam ple, vesicular stomatitis virus–based vectors have been employed as Ebola vaccines. Adenovirus-based vectors have been used as AIDS vac cine vectors and have been used as COVID-19 vaccine vectors. Viral recombinants, including those of retroviruses and adeno-associated viruses, have been approved as vectors for delivery of genes to cells for treatment of single-gene defects. Retroviruses integrate into the cell's chromosomes and are maintained with stable expression of the trans gene, although some concerns have arisen about possible activation of neighboring promoters and adverse effects due to that activation. Adeno-associated viruses are not integrated but are stably maintained and capable of durable expression of the transgene. Adenoviruses and herpesviruses are also being tested as gene therapy vectors. Finally, an attenuated strain of HSV expressing granulocyte-macrophage colonystimulating factor has been approved for treatment of melanoma because of its oncolytic and immunotherapeutic properties. Many additional studies are assessing viruses for use as vectors and for immu notherapeutic and oncolytic applications. SUMMARY As obligate intracellular parasites, viruses enter host cells, replicate, and spread in the form of progeny viruses. Injury to the host cell resulting from viral entry may lead to tissue and organ damage. Basic knowledge of the mechanisms underlying infection by and replication of viruses that infect humans is the foundation for medical studies of viral pathogenesis, viral vaccines, antiviral drugs, and the use of viruses as therapeutics. There are many interactions between different viruses; thus, a broad knowledge of all viruses is essential to our preparedness for the next viral epidemic or pandemic. ■ ■FURTHER READING Choutka J et al: Unexplained post-acute infection syndromes. Nat Med 28:911, 2022. Howley PM et al (eds): Fields Virology: Vol. 4: Fundamentals, 7th ed. Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins Health, 2023. Knipe DM et al: Ensuring vaccine safety. Science 370:1274, 2020. Ksiazek TG et al: A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 348:1953, 2003. Sodroski CN, Knipe DM: Nuclear

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Drugs Most antiviral drugs inhibit viral DNA or RNA replication, but other activities, such as virus entry, viral RNA transcription, cleavage of pro teins by the viral protease, virus uncoating after infection, and virus release from cells, are all targeted by different licensed antiviral agents. Inhibition of viral replication does not eliminate the virus in the cell; host cell immune responses are important for viral clearance. Antiviral

drugs usually do not eradicate latent viral infections but instead inhibit viral replication; thus, when treatment is stopped, the virus can reac tivate and replicate again. Resistance to antiviral agents due to muta tions in viral proteins is not uncommon and is more common for RNA viruses with a higher mutation rate than for DNA viruses. This differ ence may explain the observation that drug-resistant DNA viruses are a greater problem in immunocompromised patients, whereas drugresistant RNA viruses can be found in healthy persons as well. Patients may harbor a mixture of drug-resistant and drug-sensitive viruses that is dynamic and changes under pressure from the drug. Combina tion therapy with more than one antiviral agent, each with a differ ent mechanism of action, may be more effective than monotherapy, particularly against RNA viruses, which may be present as mixtures with different resistance patterns. Antiviral testing can be performed in patients who do not respond to antiviral drugs or whose response diminishes. For some viruses, such testing involves the sequencing of selected viral genes; however, in many cases, it involves the growth of virus in the presence of different concentrations of the drug, which is a laborious, time-consuming process. Response to antiviral therapy has traditionally been assessed clinically, but quantitative PCR has been useful in monitoring the response to therapy for viruses that circulate in the blood (e.g., cytomegalovirus [CMV], hepatitis B and C viruses [HBV and HCV, respectively]). Systemic therapy with antivirals is usu ally more effective than topical therapy but is more commonly associ ated with side effects. ANTIVIRAL DRUGS FOR HERPESVIRUS INFECTIONS ■ ■ACYCLOVIR, VALACYCLOVIR, FAMCICLOVIR, AND PENCICLOVIR Acyclovir is an analogue of deoxyguanosine and is phosphorylated to the monophosphate form by viral thymidine kinase in cells infected with herpes simplex virus (HSV) or varicella-zoster virus (VZV). Cellular protein kinases further phosphorylate the drug to the active triphosphate form, which inhibits viral DNA polymerase; the drug is incorporated into viral DNA to terminate its replication. Valacyclovir, a valine ester of acyclovir, is absorbed much better than acyclovir; its rapid conversion to acyclovir in the liver and intestine results in plasma acyclovir levels approximately four times higher than are attained with oral acyclovir. Acyclovir and valacyclovir are approved by the U.S. Food and Drug Administration (FDA) for treatment of initial episodes of genital herpes, recurrent genital herpes, varicella, and zoster (Table 196-1). Valacyclovir is also approved for treatment of herpes labialis (cold sores), for suppres sion of recurrences of genital herpes, and for reduction of transmission of genital HSV. The doses of acyclovir and valacyclovir used for treating VZV infections are higher than those used for HSV infections since VZV is less susceptible to inhibition by these drugs. Both

drugs exhibit poor activity against CMV. Intravenous acyclovir is used for severe dis ease requiring hospitalization; oral acyclovir or valacyclovir is used for outpatient therapy; and topical acyclovir, penciclovir, and docosanol are approved for treatment of orolabial herpes but are much less effective than the oral drugs. Acyclovir is excreted by the kidneys. Thus the dose of acyclovir or valacyclovir needs to be reduced with renal insufficiency. Central nervous system (CNS) side effects that occur with IV acyclovir or oral valacyclovir are more common with the higher drug levels seen in persons with renal insufficiency. Reversible renal insufficiency due to crystallization of the drug in renal tubules can occur with IV acyclovir, especially in persons who are dehydrated. Headache, nausea, rash, and diarrhea have been reported with acyclovir. Mutations in the HSV or VZV thymidine kinase or, less commonly, in viral DNA polymerase can result in resistance to acyclovir or valacyclovir. Viruses lacking thymidine kinase activity are also resistant to famciclovir and ganci clovir. Acyclovir- and valacyclovir-resistant HSV and VZV are rare in immunocompetent persons. Resistant virus is treated with foscarnet or, less commonly, cidofovir. Mucosal disease due to resistant virus in immunocompromised persons is sometimes treated with topical foscarnet, trifluridine, or cidofovir.

Famciclovir is a diacetyl ester of penciclovir that is converted to penciclovir in the intestine and liver. Penciclovir is a guanosine analogue that is less potent than acyclovir, but, because of its longer intracellular half-life, its activity is similar to that of acyclovir. Pen ciclovir is phosphorylated by HSV and VZV thymidine and cellular kinases and has activity similar to that of acyclovir for HSV and VZV infections. Famciclovir is approved for treatment of zoster, suppres sion of genital herpes, and treatment of recurrent mucocutaneous herpes in patients with HIV infection. Famciclovir is excreted by the kidneys, and the dose is adjusted for renal insufficiency. Side effects are uncommon and can include headache, nausea, and diar rhea. Resistance due to mutations in viral thymidine kinase or DNA polymerase can occur.

Oral acyclovir reduces the duration of pain and other symptoms, time to healing, and shedding in patients with their first episode of genital herpes when treatment is begun within 6 days of infection. Acyclovir, valacyclovir, and famciclovir are all effective for treatment of primary and recurrent genital and orolabial herpes as well as for sup pressive therapy for these conditions. Topical acyclovir cream reduces shedding and time to healing by 1–2 days if given within 1 day of symp tom onset in persons with recurrent genital or orolabial herpes. Oral acyclovir or valacyclovir reduces the severity of varicella when given within 1 day of onset of the rash. Oral acyclovir, famciclovir, or vala cyclovir shortens the duration of pain and rash associated with zoster if given within 3 days of onset. Oral valacyclovir is more effective than oral acyclovir and is generally preferred since it has better oral bioavail ability and does not need to be given as frequently. Suppressive vala cyclovir therapy for genital herpes reduces transmission to uninfected partners by 50%. Intravenous acyclovir is used for herpes encephalitis and disseminated HSV or VZV disease. CHAPTER 196 ■ ■GANCICLOVIR AND VALGANCICLOVIR Ganciclovir is a deoxyguanosine analog that is phosphorylated by UL97 protein kinase in cells infected with CMV and converted to its active form, ganciclovir triphosphate, by cellular protein kinases. Ganciclovir triphosphate inhibits both viral DNA polymerase and incorporation of guanosine triphosphate into viral DNA. Valganciclovir is a valine ester of ganciclovir and is converted to ganciclovir in the liver and intestine. Valganciclovir has much better oral bioavailability than ganciclovir; plasma levels of oral valganciclovir and IV ganciclovir are similar. Ganciclovir and valganciclovir are used for treatment and prevention of CMV disease in immunocompromised patients and are approved for prevention of CMV infection in

transplant recipients and for treatment of CMV retinitis. Ganciclovir is effective against HSV, VZV, human herpesvirus type 6 (HHV-6), and herpes B virus. This drug is excreted by the kidneys, and dose adjustment is required in renal insufficiency. Ganciclovir therapy often results in neutropenia and thrombocytope nia after 1 week. Less commonly, ganciclovir has been associated with CNS symptoms, particularly at high plasma drug levels. Mutations in CMV UL97 protein kinase or, less commonly, UL54 viral DNA poly merase can result in resistance to ganciclovir or valganciclovir. CMV with mutations in protein kinase is usually sensitive to foscarnet and cidofovir, while CMV with mutations in both protein kinase and DNA polymerase is usually sensitive only to foscarnet. Mutations are more common among persons who are highly immunocompromised and who have been taking the drug for a long time. Resistant virus is treated with foscarnet or cidofovir. Antiviral Chemotherapy, Excluding Antiretroviral Drugs Ganciclovir and valganciclovir are used for treating severe CMV infections in immunocompromised patients, including colitis, pneu monitis, retinitis, and encephalitis. Induction therapy, given two or three times daily, is usually followed by less frequently administered maintenance therapy. Oral valganciclovir has activity similar to that of intravenous ganciclovir. Ganciclovir and valganciclovir are used for prevention of CMV infection in transplant recipients when given either preemptively (on the basis of viremia) or prophylactically. Ganciclovir reduces developmental delay in infants with congenital CMV disease involving the CNS and reduces hearing loss in infants with asymptom atic congenital CMV infection. Ganciclovir and valganciclovir are used for treatment of HHV-6 encephalitis, HHV-8–associated Castleman

TABLE 196-1 Antiviral Drugs for Herpesvirus Treatment and Prophylaxis in Adults DISEASE DRUG ROUTE ADULT DOSE COMMENTS Orolabial herpes, primary episode Acyclovir Valacyclovir Famciclovir Oral Oral Oral 400 mg tid × 7–10 d 1 g bid × 7–10 d 500 mg bid or 250 mg tid × 7–10 d Orolabial herpes, recurrence Acyclovir Valacyclovir Famciclovir Oral Oral Oral 400 mg 5 times daily × 5 d 2 g bid × 1 d 1500 mg × 1 d Orolabial herpes, suppression Acyclovir Valacyclovir Famciclovir Oral Oral Oral 400 mg bid 500 mg or 1 g once daily 500 mg bid Genital herpes, primary episode Acyclovir Valacyclovir Famciclovir Oral Oral Oral 400 mg tid or 200 mg 5 times daily × 7–10 d 1 g bid × 7–10 d 250 mg tid × 7–10 d Genital herpes, recurrence Acyclovir Valacyclovir Famciclovir Oral Oral Oral 800 mg tid × 2 d or 400 mg tid × 5 d 500 mg bid × 3 d or 1 g daily × 5 d 500 mg once, then 250 mg bid × 2 d Genital herpes suppression Acyclovir Valacyclovir Famciclovir Oral Oral Oral 400 mg bid 250 mg bid 500 mg to 1 g daily HSV encephalitis Acyclovir IV 10–15 mg/kg q8h × 14–21 d Reduces mortality and sequelae HSV keratitis Acyclovir Trifluridine Vidarabine Topical Topical Topical 3% ophthalmic ointment, 5 times daily 1% ophthalmic solution, 1 drop q2h when awake

(9 drops daily max) 3% ointment, 0.5-inch ribbon 5 times daily Mucocutaneous herpes in immunocompromised patient Acyclovir Valacyclovir Famciclovir IV Oral Oral 5 mg/kg q8h × 7–14 d 500 mg to 1 g bid × 7–10 d 500 mg bid × 7–10 d PART 5 Infectious Diseases Varicella Acyclovir Valacyclovir Oral Oral 20 mg/kg (800 mg max) 5 times daily × 5 d 20 mg/kg (1 g max) tid × 5 d Zoster Acyclovir Valacyclovir Famciclovir Oral Oral Oral 800 mg 5 times daily × 7 d 1 g tid × 7 d 500 mg tid × 7 d Varicella or zoster, disseminated Acyclovir IV 10 mg/kg q8h × 7 d Reduces time for last new lesion formation and virus shedding; reduces cutaneous dissemination Cytomegalovirus disease Ganciclovir IV 5 mg/kg q12h × 14–21 d, then 5 mg/kg daily (maintenance dose) 900 mg bid × 14–21 d, then 90 mg daily (maintenance dose) 60 mg/kg q8h × 14–21 d, then 90–120 mg daily (maintenance dose) 5 mg/kg once weekly twice, then every other week 400 mg bid Valganciclovir Oral Foscarnet IV Cidofovir Maribavir IV Oral Cytomegalovirus prophylaxis

Letermovir Oral IV 480 mg qd 480 mg qd disease in patients with poorly controlled HIV infection, and severe HSV or VZV disease when acyclovir is unavailable. ■ ■FOSCARNET Foscarnet is a pyrophosphate analogue that directly inhibits herpesvi rus DNA polymerases by blocking the pyrophosphate binding site in the enzyme. Foscarnet does not require additional phosphorylation (unlike acyclovir, cidofovir, or ganciclovir) in virus-infected cells for its activity. This drug is approved for treatment of CMV retinitis and mucocutaneous acyclovir-resistant HSV disease. It is also used to treat ganciclovir-resistant CMV and acyclovir-resistant VZV. Foscarnet is given intravenously and is excreted by the kidneys; dose adjustment is required in renal insufficiency. Up to one-third of patients receiving foscarnet develop nephrotoxicity with elevated levels of creatinine and

Reduces duration of fever, lesions, and virus shedding Reduces duration of lesions by 1–2 d if given during prodrome In patients with >6 recurrences per year, reduces number of recurrences by ~50% and increases time to first recurrence Reduces duration of symptoms, genital lesions, and virus shedding by 2, 4, and 7 d, respectively Reduces duration of symptoms, genital lesions, and virus shedding by 1–2 d In patients with >6 recurrences per year, reduces recurrence rates from 80–85% to 25–30%, reduces virus shedding and transmission Shortens duration of disease; acyclovir better tolerated, especially with prolonged treatment IV acyclovir reduces time to healing, duration of pain, and duration of virus shedding Has modest effect on symptoms, reduces fever duration by 1 day Reduces time for last new lesion formation, virus shedding, and pain duration Neutropenia and thrombocytopenia common after 1 week Levels and side effects similar to ganciclovir Nephrotoxicity, electrolyte abnormalities; give with additional saline Nephrotoxicity; give with probenecid and saline Used for disease refractory to ganciclovir, foscarnet, or cidofovir Antagonizes activity of ganciclovir Numerous drug interactions Numerous drug interactions Given 100 days after stem cell transplant, 200 days after kidney transplant blood urea nitrogen, and proteinuria. Renal tubular acidosis and inter stitial nephritis also have been reported. Renal insufficiency is more common among persons who are dehydrated, given other nephrotoxic drugs, or given high doses or rapid infusions of foscarnet. Administer ing IV saline before and after each foscarnet dose and giving the drug over an adequate period can reduce nephrotoxicity. Renal insufficiency is often reversible after treatment when the drug is stopped. Other side effects include hypomagnesemia and hypocalcemia, which can be asso ciated with arrhythmias, paresthesias, and seizures. Other metabolic abnormalities include hypokalemia, hypophosphatemia, or hyper phosphatemia. Foscarnet can also cause headache, fever, rash, diar rhea, acute dystonia, tremors, hemorrhagic cystitis, genital ulcerations, anemia, and abnormal liver function values. Mutations in CMV DNA polymerase (UL54) or in HSV or VZV DNA polymerase can result

in resistance to foscarnet. CMV, HSV, and VZV can become resistant to foscarnet; some strains of CMV are resistant to foscarnet, ganci clovir, and cidofovir; and HSV can become resistant to acyclovir and foscarnet. Foscarnet is typically used to treat CMV retinitis, HHV-6 encephalitis, or drug-resistant severe CMV, HSV, or VZV infections in immunocompromised patients. Topical foscarnet has been used to treat acyclovir-resistant mucosal infections due to HSV. ■ ■CIDOFOVIR Cidofovir is an analogue of deoxycytidine monophosphate and is phos phorylated in cells to its active diphosphate form. The diphosphate form of cidofovir competes with deoxycytidine triphosphate for incorpora tion into herpesvirus DNA. The drug inhibits replication of all human herpesviruses as well as poxviruses, papillomaviruses, polyomaviruses, and adenoviruses. Cidofovir

is approved for treatment of CMV retinitis in patients with AIDS; it is also used for treatment of infections caused by CMV exhibiting ganciclovir resistance due to mutations in UL97 protein kinase and those caused by HSV or VZV displaying mutations in thymidine kinase. Because cidofovir is excreted by the kidneys, dose adjustment is required in renal insufficiency. About one-fifth of patients receiving cidofovir develop nephrotoxicity, and the drug is associated with metabolic acidosis and glucosuria. Cidofovir therapy is preceded by at least 1 L of saline, and probenecid is given 3 h before, 2 h after, and 8 h after each dose to reduce nephrotoxicity. An addi tional 1 L of saline is recommended during treatment or immediately thereafter. About one-fourth of patients receiving cidofovir develop neutropenia; additional side effects include ocular hypotony, uveitis, iritis, headache, nausea, vomiting, diarrhea, and rash. Mutations in CMV DNA polymerase (UL54) or HSV DNA polymerase can result in resistance to cidofovir. Some strains of CMV exhibiting ganciclovir resistance due to mutations in viral DNA polymerase are resistant to cidofovir, whereas many CMV and HSV strains exhibiting foscarnet resistance due to mutations in DNA polymerase may retain sensitiv ity to cidofovir. Cidofovir is typically used to treat ganciclovir- and/or foscarnet-resistant severe CMV disease or acyclovir- and/or foscarnetresistant HSV disease in immunocompromised patients. Cidofovir has been used as preemptive therapy against CMV infection in transplant recipients. It has also been used to treat severe adenovirus infections, adenovirus or BK virus hemorrhagic cystitis, BK nephropathy, and severe molluscum contagiosum, although controlled studies have not been performed. Topical cidofovir has been used to treat acyclovirresistant HSV mucosal infections and anogenital warts. ■ ■LETERMOVIR Letermovir is a dihydroquinazolin that inhibits the CMV DNA ter minase complex (UL51, UL59), which is required for cleavage and packaging of CMV into nucleocapsids. The drug has no activity against other human herpesviruses. Letermovir is approved for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant or donor CMV-positive, recipient CMV-negative kidney transplant recipients. Letermovir is metabolized by the liver and excreted in the feces; dose adjustment is not required if the creatinine clearance rate (CrCl) is >10 mL/min. The dose of letermovir must be decreased in persons taking cyclospo rine. Letermovir therapy results in reduced levels of voriconazole and increased levels of sirolimus, tacrolimus, cyclosporine, and other drugs metabolized by CYP2C8 or transported by OAT1B1/3. Side effects of letermovir include headache, nausea, diarrhea, and peripheral edema. Letermovir does not cause nephrotoxicity and is not myelosuppressive. Resistance to letermovir occurs more frequently in vitro than resistance to ganciclovir or foscarnet, and clinically significant letermovir resis tance due to mutations in UL56 in patients with CMV disease has been reported; resistance may be less common when the drug is used for pro phylaxis in patients with low or undetectable CMV levels. When given to CMV-seropositive patients, starting a median of 8 days after hemato poietic stem cell transplantation and continuing for 14 weeks, letermo vir reduced the incidence of clinically significant CMV infection by 38% compared with placebo. While anecdotes describe the use of letermovir for treatment of CMV disease, resistance may develop quickly.

■ ■MARIBAVIR Maribavir is a benzimidazole that inhibits the CMV UL97 protein kinase and CMV replication, and reduces the egress of viral particles from the nucleus. Maribavir is approved for treating adults and chil dren with posttransplant CMV infection/disease that is refractory to treatment (with or without proven genotype resistance) with ganciclo vir, cidofovir, or foscarnet. Since maribavir inhibits the UL97 protein kinase, it can antagonize ganciclovir and should not be given with the latter drug. Resistance to maribavir has been reported, and such CMV strains are also resistant to ganciclovir. Maribavir can increase concen trations of several drugs including

tacrolimus, sirolimus, everolimus, and cyclosporine. The most common side effect of maribavir is taste disturbance.

■ ■TRIFLURIDINE AND VIDARABINE Trifluridine is a thymidine analogue that is incorporated into viral DNA and inhibits its synthesis. Vidarabine is approved for topical therapy of herpes keratitis and has also been used topically to treat acyclovir-resistant mucosal HSV infections. Trifluridine is active against acyclovir-resistant HSV, CMV, and vaccinia virus. Vidarabine is an adenosine analogue that is incorporated into viral DNA and inhibits viral DNA polymerase. Both trifluridine and vidarabine are used for topical therapy only. ■ ■INVESTIGATIONAL AND OTHER AGENTS Brincidofovir is a phospholipid conjugate of cidofovir that is rapidly taken up by cells and converted into cidofovir. It is active against herpesviruses (including most strains of ganciclovir-resistant CMV), poxviruses, adenovirus, and polyomaviruses. It does not cause neph rotoxicity and is not myelosuppressive. Diarrhea is the most common side effect. The drug has been associated with intestinal toxicity and acute graft-versus-host disease of the gastrointestinal tract. The drug did not meet its primary endpoints in trials for adenovirus disease or CMV prophylaxis. At the time of this writing, it is not available as part of an expanded access program. An intravenous formulation that, it is hoped, will cause less gastrointestinal toxicity is being tested for adenovirus viremia. CHAPTER 196 Antiviral Chemotherapy, Excluding Antiretroviral Drugs Pritelivir inhibits the helicase–primase complex required for repli cation of HSV. This drug has reduced viral shedding in patients with recurrent genital herpes and is being tested for use against acyclovirresistant HSV mucocutaneous infection. Pritelivir is available as an expanded access drug for acyclovir-resistant HSV infection. Amenamevir is a helicase–primase inhibitor under development for HSV and VZV infections. ANTIVIRAL DRUGS FOR RESPIRATORY VIRUS INFECTIONS ■ ■INFLUENZA Neuraminidase Inhibitors Oseltamivir, zanamivir, and perami vir are neuraminidase inhibitors that inhibit cleavage of sialic acid, which is required for the release of influenza virus from infected cells and its spread to other cells. Oseltamivir phosphate is an oral prodrug that is cleaved by esterases in the liver, gastrointestinal tract, and blood to oseltamivir carboxyl ate, the more active form. It is approved for treatment of uncompli cated influenza A or B disease when given ≤48 h after symptom onset and for prophylaxis of influenza A and B in persons ≥1 year of age (Table 196-2). Oseltamivir is much less active against influenza B

than against influenza A. The drug is excreted by the kidneys, and the dose is adjusted in renal insufficiency. The most common side effects are nausea, abdominal pain, and vomiting. Although CNS side effects have been reported, particularly in children, it is unclear whether they are due to the drug or to influenza virus infection itself. Resis tance to oseltamivir can develop as a result of mutations in the viral neuraminidase or in the hemagglutinin. Oseltamivir-resistant virus has been transmitted from person to person. Resistance has been reported in ~15% of healthy children and ~1% of adults; resistance is more common among immunocompromised persons.

TABLE 196-2 Antiviral Drugs for Respiratory Virus Treatment and Prophylaxis in Adults DISEASE DRUG ROUTE ADULT DOSE COMMENTS Influenza A, B Oseltamivir Oral Treatment: 75 mg bid × 5 d Prophylaxis: 75 mg/d Influenza A, B Zanamivir Inhaled Treatment: 10 mg bid × 5 d Prophylaxis: 10 mg/d Influenza A, B Peramivir IV 600 mg once Shortens duration of symptoms by 1–2 d when given within 2 d of onset Influenza A, B Baloxavir Oral Treatment or postexposure prophylaxis: 40 mg once; if

> 80 kg, 80 mg once Influenza A Amantadine Oral Treatment: 100 mg bid × 5 d Prophylaxis: 200 mg/d Influenza A Rimantadine Oral Treatment: 100 mg bid × 5 d Prophylaxis: 200 mg/d Respiratory syncytial virus Ribavirin Inhaled Aerosol from reservoir containing 20 mg/mL for

12–18 h/d × 3–7 d SARS-CoV-2 Nirmatrelvir/ ritonavir Oral 300 mg/100 mg bid × 5 days Reduces rate of hospitalization by 50% within 30 days after diagnosis SARS-CoV-2 Remdesivir IV 200 mg on day 1, then 100 mg qd × 2 d for outpatients, × 4 days for inpatients SARS-CoV-2 Molnupiravir Oral 800 mg q12h × 5 days Recommended for patients when nirmatrelvir or remdesvir are not available, unable to be used, or not appropriate. Approved under EUA. Abbreviation: EUA, emergency use authorization by the U.S. Food and Drug Administration (FDA). PART 5 Infectious Diseases Zanamivir is approved for treatment of uncomplicated influenza A and B in adults and children ≥7 years of age who have had symptoms for ≤2 days and for prophylaxis in persons ≥5 years of age. Because zanamivir has poor oral bioavailability, it is given as a powder through an inhaler. Thus, use of the drug can be difficult for young children and some elderly patients. Inhalation of zanamivir may cause bron chospasm, particularly in persons with underlying lung disease; it is not recommended for persons with asthma, chronic obstructive pul monary disease, or other airway disease. Zanamivir is more active than oseltamivir against influenza B. It is also active against some isolates of influenza virus that are resistant to oseltamivir; resistance to zanamivir is less common than that to oseltamivir. Peramivir is approved for treating uncomplicated influenza in patients ≥2 years of age who have had symptoms for ≤2 days. Because of its long half-life, it is given as a single IV dose. Peramivir is highly active against both influenza A and B. The drug is excreted by the kid neys, and the dose is adjusted in renal insufficiency. The most common side effect is diarrhea. While peramivir-resistant virus is rare in healthy persons, peramivir-resistant virus has been isolated from immuno compromised persons. Oseltamivir, zanamivir, and peramivir are effective for treatment of uncomplicated influenza A and B, including disease caused by avian influenza viruses (e.g., H5N1, H7N9, and H9N2). None of the neuraminidase inhibitors is approved by the FDA for complicated influenza or for persons requiring hospitalization for the disease. While not licensed for the treatment of persons with complicated disease, inpatients, and pregnant women, oseltamivir is considered the drug of choice in these settings. The efficacy of zanamivir is similar to that of oseltamivir in hospitalized patients. Treatment is most effective when begun within 2 days of symptom onset and should be started as early as possible; such early treatment reduces symptoms by ~1 day in per sons with uncomplicated disease. For persons with influenza requiring hospitalization and with pneumonia, treatment with oseltamivir or zanamivir is recommended even later. Treatment may reduce the risk of complications and death in hospitalized patients with influenza. Oseltamivir and zanamivir (but not peramivir) are approved for prophylaxis of influenza, especially in institutions where outbreaks can be severe, and for prophylaxis in persons who have been exposed to the virus, are at high risk for disease complications, and have not recently been vaccinated. The efficacy of oseltamivir and zanamivir for

Shortens duration of symptoms by 1 d when given within 2 d of onset; reduces complications; considered drug of choice for patients with complications of influenza Shortens duration of symptoms by 1–2 d when given within 2 d of onset; requires patient training for use; can cause

bronchospasm; not recommended for persons with asthma or chronic obstructive pulmonary disease Shortens duration of symptoms by 1 d when given within 2 d of onset; active against virus resistant to neuraminidase inhibitors Most influenza virus strains are resistant; use only if virus is known to be sensitive. Most influenza virus strains are resistant; use only if virus is known to be sensitive. Reduces severity of symptoms in hospitalized infants with lower respiratory tract disease; anecdotal reports of reduced progression to lower respiratory tract disease and mortality in stem cell transplant patients Reduces duration of hospitalization in some studies. Duration of treatment extended up to 10 days if no improvement. prophylaxis is estimated to be ~70–90%. For persons at institutions, prophylaxis is given for at least 2 weeks and for up to 1 week after out breaks resolve. For other high-risk persons, prophylaxis is given within 2 days of exposure and continued for 1 week after exposure. Since neuraminidase inhibitors reduce virus release from cells, they should not be given 2 days before or within 2 weeks after receipt of live, attenu ated influenza vaccine. Resistance has been reported during treatment with oseltamivir or peramivir, especially in immunocompromised persons; oseltamivir-resistant viruses are usually sensitive to zanamivir. Baloxavir Baloxavir inhibits the cap-dependent endonuclease that is important in initiating synthesis of influenza virus mRNA. This drug is approved by the FDA as a single oral dose for postexposure pro phylaxis of influenza and for treatment of uncomplicated influenza in persons ≥12 years of age who have had symptoms for ≤48 h. Baloxavir inhibits influenza A and B viruses, including avian strains and strains that are resistant to neuraminidase inhibitors. The drug’s efficacy is similar to that of the neuraminidase inhibitors in persons with uncom plicated influenza and reduces symptoms by ~1 day. In addition, baloxa vir exhibits efficacy similar to that of oseltamivir for reducing symptoms in high-risk patients. However, its effectiveness in patients hospitalized with complications of influenza is unknown. Reduced sensitivity of influenza virus to baloxavir has been associated with mutations in the viral polymerase acidic protein after one dose. The incidences of nausea and vomiting are lower with baloxavir than with oseltamivir. Levels of the drug are lower if it is taken with dairy products, polyvalent cation–containing laxatives or antacids, or oral supplements containing calcium, iron, magnesium, selenium, or zinc. Since baloxavir reduces virus replication, it should not be given 2 days before or within 2 weeks after receipt of live, attenuated influenza vaccine. Adamantanes Amantadine and rimantadine inhibit the influenza virus’s M2 protein and its uncoating and membrane fusion. While these drugs are active against influenza A, resistance is widespread and can develop rapidly; thus, the adamantanes are not recommended as treatment or prophylaxis for influenza unless the virus is known to be sensitive. ■ ■RESPIRATORY SYNCYTIAL VIRUS Ribavirin Ribavirin is an analogue of guanosine and inhibits replication of numerous RNA and DNA viruses. The drug inhibits

viral RNA synthesis and capping of viral mRNA and in some cases increases the viral RNA mutation rate to lethal levels for some viruses. Ribavirin inhibits replication of respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, and many other RNA viruses in vitro. While the drug has been used to treat numerous viral infections, including Lassa fever and hepatitis E, it is approved by the FDA only for use against RSV and as a component of combination therapy for hepatitis C. Aerosolized ribavirin is approved for treatment of hospi talized infants and young children with severe lower respiratory tract infections due to RSV; it is given for 12–18 h per day and is most effec tive when used early in the course of these severe infections. Ribavirin is given in a generator that yields an aerosol of particles small enough to reach the lower respiratory tract; the level of systemic absorption is low. The aerosolized form of the drug can induce bronchospasm, sud den deterioration of respiratory function (especially in infants), and rash and can precipitate in

ventilators, interfering with their function. Ribavirin is mutagenic and teratogenic in animals; accordingly, it is not recommended for use in pregnant women, and the exposure of health care workers should be minimized with personal protective equipment. In early studies, ribavirin reduced the shedding of RSV and the severity of symptoms in hospitalized infants with lower respiratory tract disease who were not on mechanical ventilation, the duration of oxygen sup plementation, and the duration of time on mechanical ventilation in infants. More recent analyses of the literature suggest that the efficacy of the drug in these settings is much less certain, and the drug is not recommended for routine use by the American Academy of Pediatrics. In retrospective studies, ribavirin has been reported to reduce the risk of progression of RSV from upper to lower respiratory tract disease in stem cell transplant recipients and to reduce mortality rates in these patients. In a retrospective study, the outcome of treatment with oral ribavirin was similar to that obtained with the aerosolized drug in hematopoietic stem cell transplant recipients with RSV disease. Riba virin has not been shown to affect the clinical course of patients with parainfluenza and is not recommended for their treatment. Aerosol ized ribavirin costs more than $25,000 per day. Nirsevimab-alip Nirsevimab-alip, a human monoclonal antibody that targets the prefusion form of the RSV F protein, is approved for prevention of RSV lower respiratory tract disease in neonates and infants born during or entering their first RSV season, and for children up to 24 months who are vulnerable to severe RSV disease through their second RSV season. Palivizumab Palivizumab, a humanized monoclonal antibody to RSV F protein, is approved for prevention of lower respiratory tract dis ease due to RSV in pediatric patients at high risk of RSV disease, includ ing premature infants and children with bronchopulmonary dysplasia. ■ ■SARS-COV-2 (SEE CHAP. 204) Remdesivir is converted in cells to an adenosine triphosphate analogue that inhibits the RNA-dependent RNA polymerase of several viruses. The drug is approved by the FDA for treatment of persons ≥12 years of age with SARS-CoV-2 requiring hospitalization; it shortens the dura tion of hospitalization in persons with lower respiratory tract disease. While the results of studies with the drug vary, it is recommended by the National Institutes of Health (NIH) for patients with SARS-CoV-2 who require supplemental oxygen while hospitalized. The drug is given intravenously and is not recommended in persons with a glomerular filtration rate (GFR) <30 mL/min. Serum transaminase elevations have been reported in healthy persons receiving remdesivir, and liver enzymes should be monitored before and during treatment. Chloro quine inhibits the activity of remdesivir in vitro; hydroxychloroquine or chloroquine phosphate should not be given with remdesivir. Nirmatrelvir, a SARS-CoV-2 main protease inhibitor, boosted with ritonavir, a CYP3 and HIV protease inhibitor, is approved for treatment of mild to moderate COVID-19 in adults at high risk for progression to severe COVID-19. The drug should be given as soon as possible after infection and within 5 days of onset of symptoms. The dose should not be given with drugs highly dependent on CYP3A in which elevated lev els can be associated with severe reactions, such as statins, sirolomus,

tacrolimus, colchicine, and many other drugs. Use of the drug with medications that induce CYP3A can reduce the levels of nirmatrelivir or ritonavir with loss of effectiveness. The dose should be reduced for renal impairment.

Molnupiravir is an oral ribonucleoside analogue that inhibits rep lication of SARS-CoV-2. The drug reduced the risk of hospitalization or death in patients with mild to moderate COVID-19 by ~50% in a phase 3 clinical trial. AT-527 is an oral nucleotide prodrug that reduced SARS-CoV-2 viral loads in patients hospitalized with COVID-19 in a phase 2 clinical trial. PF-07321332 is an oral SARS-CoV-2 protease inhibitor that is being tested in combination with low-dose ritonavir in a phase 2/3 clinical

trial for prevention of COVID-19 infection. Remdesivir and nirmatrelvir boosted with ritonavir are approved by the FDA and recommended as first-line therapy for COVID-19 by the NIH guidelines; molnupiravir is approved under an emergency use authorization by the FDA and is considered second-line therapy. At the time of this writing, Pemgarda, a monoclonal antibody to SARSCoV-2, can be given under emergency use authorization to prevent COVID-19 in immunocompromised persons age 12 and older. ■ ■INVESTIGATIONAL AGENTS FOR RESPIRATORY VIRUS INFECTIONS Favipiravir (T705) inhibits viral RNA polymerases and is active against influenza and other RNA viruses. It is approved for treatment of emerg ing influenza viruses in Japan. Presatovir is an RSV fusion inhibitor that was ineffective in two trials of RSV disease. DAS181 (Fludase) is a siali dase that cleaves sialic acid, a receptor for influenza A and B and parain fluenza viruses; it did not improve the clinical outcomes of patients with influenza, but in case reports transplant recipients with parainfluenza have improved clinically with the drug. Laninamivir octanoate inhibits the neuraminidase of influenza A and B viruses and is approved for treat ing influenza in Japan. RSV604 interacts with the RSV nucleocapsid and is undergoing phase 2 studies in transplant recipients. CHAPTER 196 Antiviral Chemotherapy, Excluding Antiretroviral Drugs ANTIVIRAL DRUGS FOR HUMAN PAPILLOMAVIRUS AND POXVIRUS INFECTIONS Interferon α (IFN-α) inhibits replication of many RNA and DNA viruses in vitro. IFN-α is approved by the FDA for intralesional treat ment of external anogenital warts caused by human papillomavirus (HPV). It is effective in resolving lesions in ~50% of cases, with a recur rence rate of ~25%. Imiquimod is a toll-like receptor 7 agonist that induces production of IFN-α and other cytokines. It is approved as a topical cream for treatment of external genital and perianal warts caused by HPV in persons ≥12 years of age. This drug is effective in resolving lesions in ~40% of cases. Tecovirimat is approved by the FDA for treatment of smallpox and inhibits replication of mpox and vaccinia viruses. Resistance to teco virimat developed in a person treated with the drug for progressive vaccinia and has been reported in persons with mpox. INVESTIGATIONAL ANTIVIRAL DRUGS

FOR PICORNAVIRUS Pocapavir inhibits picornaviruses by inhibiting virus uncoating and is being developed to reduce poliovirus shedding; resistance to the drug develops rapidly. ANTIVIRAL DRUGS FOR HEPATITIS B

VIRUS INFECTION Eight drugs representing two classes are approved for the treatment of chronic HBV infection in the United States. One class, the nucleos(t)ide

analogues, act as chain terminators of nascently replicating DNA thereby competitively inhibiting HBV reverse transcriptase; the other class, exogenous IFNs, mimic and augment the role of endogenous interferons (Table 196-3). The goal of therapy for chronic hepatitis B is to prevent progression to cirrhosis, liver failure, and hepatocellular carcinoma. This can be achieved through long-term inhibition of viral replication with reduction in hepatic inflammation, the driver of liver

TABLE 196-3 Antiviral Drugs for Chronic Hepatitis B Treatment in Adults DEVELOPMENT OF RESISTANCE COMMON SIDE EFFECTSa TREATMENT MONITORING COMMENTS DRUG ROUTE AND DOSE Interferons SC injection; 180 μg/week for 48 weeks SC injection;

1.5 μg/kg per week for 48 weeks Not described in longterm studies. Side effects are common and include fevers, chills, myalgia, fatigue, neurotoxicity, and leukopenia. Autoantibodies can develop, particularly antithyroid antibodies. Pegylated a2a Pegylated a2b Nucelos(t)ide Analogues

Lamivudine Oral; 100 mg daily 30% after 1 year; 70% after 5 years Malaise or fatigue, GI symptoms (nausea/ vomiting, abdominal pain, diarrhea), headache, upper respiratory tract infection Adefovir Oral; 10 mg daily 20–29% after 5 years Adefovir is usually active against lamivudine-resistant HBV strains. Headache, asthenia, GI symptoms (abdominal pain, nausea) Telbivudine Oral; 600 mg daily 11–25% after 2 years Cross-resistance is common between lamivudine- and telbivudine-resistant HBV strains. Headache, fatigue, GI symptoms (abdominal pain) PART 5 Infectious Diseases Entecavir Oral; 0.5–1 mg daily 1–2% after 5 years in nucleos(t)ide-naïve patients; 50% after 5 years in lamivudine-resistant patients Headache, fatigue, elevated alanine aminotransferase level Tenofovir disoproxil Oral; 300 mg daily No resistance after up to 10 years of treatment Headache, fatigue, nasopharyngitis, upper respiratory tract infection, nausea Tenofovir alafenamide Oral; 25 mg daily No resistance after up to 3 years of treatment Headache, fatigue, nasopharyngitis, upper respiratory tract infection Emtricitabine Oral; 200 mg daily Not defined Headache, GI symptoms (nausea, diarrhea, abdominal pain), fatigue, depression, insomnia, abnormal dreams, rash, asthenia, increased cough, rhinitis aFor emtricitabine, side effects were assessed only in combination with antiretroviral therapy. Abbreviation: GI, gastrointestinal. fibrosis. Virologic responses (defined by suppression of HBV replica tion), biochemical responses (improvement or normalization of liver function values), and histologic responses (reduction in inflammation and fibrosis on liver biopsy) are often achievable with current treat ments. However, loss of hepatitis B e antigen (HBeAg) (an intermedi ate treatment endpoint), viral clearance with loss of hepatitis B surface antigen (HBsAg), and immune control (defined by a hepatitis B surface

Complete blood counts should be performed biweekly for the first month and then monthly, renal and liver function testing monthly, thyroid function testing every 3 months. Recommended as first-line therapy. Best treatment response seen among patients with HBV genotype A and B infections. Contraindicated in clinically significant portal hypertension and pregnancy. Renal and liver function testing every 3–6 months Assessment of lactic acid level HBV DNA and serologic testing every 3–6 months Monotherapy recommended if duration of therapy is to be <1 year, as in prophylaxis against HBV reactivation with immunosuppression or chemotherapy. Renal and liver function testing every 6 months Assessment of lactic acid level HBV DNA and serologic testing every 3–6 months — Measurement of creatine kinase level if there is concern about myopathy Renal and liver function testing every 3–6 months Assessment of lactic acid level HBV DNA and serologic testing every 3–6 months — Renal and liver function testing every 3–6 months Assessment of lactic acid level HBV DNA and serologic testing every 3–6 months Recommended as first-line therapy. Dose of 0.5 mg daily in treatment-naïve patients, 1 mg daily in treatment-experienced patients. Dose adjusted in renal dysfunction. Renal and liver function testing every 3–6 months Phosphorus assessment in patients with chronic kidney disease Assessment of lactic acid level HBV DNA and serologic testing every 3–6 months Recommended as first-line therapy. Dosing frequency— but not dose—reduced in chronic kidney disease. May be used during pregnancy; possible risk of low birth weight. Renal and liver function testing every 3–6 months Phosphorus assessment in patients with chronic kidney disease Assessment of lactic acid level HBV DNA and serologic testing every 3–6 months Recommended as first-line therapy. May be used during pregnancy; possible risk of low birth weight. Renal and liver function testing every 3–6 months Assessment of lactic acid level HBV DNA and serologic testing every 3–6 months While not approved for treatment of chronic HBV infection, used interchangeably with lamivudine. Dosing frequency adjusted in chronic kidney disease. antibody [HBsAb] level of >10 IU/mL) are uncommon with current therapies. Treatment with a nucleos(t)ide analogue is considered first-line ther apy for

chronic HBV infection because of its antiviral potency, favor able side-effect profile, and ease of administration. All drugs in this class are given by mouth once daily. While all nucleos(t)ide analogues carry a black box warning for lactic acidosis and severe hepatomegaly,

these adverse events were observed in patients taking older nucleoside analogues (such as stavudine and didanosine for the treatment of HIV) and have not occurred in clinical trials of newer nucleos(t)ides for chronic HBV infection. Once initiated, nucleos(t)ide therapy must be continued for a long duration because of the risk of virus rebound and subsequent hepatitis flare if treatment is stopped. This can occur in up to 40–50% of patients and rarely may lead to hepatic decompensation. Viral rebound occurs because nucleos(t)ides analogues do not target the covalently closed circular DNA—an episomal form of viral DNA. Comparative studies of nucleos(t)ide analogues have demonstrated that newer drugs (entecavir, tenofovir, disoproxil, and tenofovir alaf enamide) are associated with lower rates of viral resistance than older agents (lamivudine, telbivudine, and adefovir), but, if viral replication is effectively suppressed, histologic and biochemical improvement will occur in ~60–75% of patients without significant differences between antiviral agents or combinations. However, rates of HBsAg clearance remain extremely low (<1–5%). Pegylated IFN-α2a also is considered a first-line therapy for chronic hepatitis B infection. Pegylated IFN-α2a has certain advantages over nucleos(t)ide analogues—including a finite dosing period of 48 weeks, absence of viral resistance, and higher rates of serologic response—but it has lower rates of biochemical and virologic responses (<40% for both). Downsides to pegylated IFN-α2a include its poor tolerability because of numerous side effects; it is contraindicated in patients with clinically significant portal hypertension and pregnancy. Response rates are higher when pegylated IFN-α2a is combined with nucleos(t)ide therapy in treatment-naïve patients: overall rates of HBsAg loss after 48 weeks of combination therapy with pegylated IFN-α2a and tenofovir disoproxil fumarate (TDF) were low but signifi cantly higher than when either was given alone: 9.1% versus 0% with TDF alone ($p<.001$) and 2.8% with IFN alone ($p<.005$). Combination therapy is not recommended because long-term nucleos(t)ide analogue monotherapy can achieve similar rates of HBsAg loss as 1 year of combination therapy and greater viral suppression. There is minimum benefit to adding pegylated IFN-α2a to ongoing nucleos(t)ide therapy. The choice of a class of agent is dependent on the presence of comorbid conditions that prevent the use of one agent over another and patient preference. ■ ■LAMIVUDINE Lamivudine is an oral cytidine analogue that competitively inhibits the viral reverse transcriptase activity of both HIV and HBV, prevent ing viral replication. Lamivudine was the first oral agent approved for therapy of chronic hepatitis B. Its long-term use was limited by high rates of viral resistance, approaching 30% among patients treated for 1 year and ~70% after 5 years of therapy. Its use in chronic hepatitis B has been superseded by agents with better resistance profiles. While not approved for the treatment of chronic HBV infection, emtricitabine is a cytosine analogue similar in structure, activity, and resistance to lamivudine. Used alone, it offers no advantage over lami vudine, but in combination with tenofovir (both TDF and tenofovir alafenamide fumarate [TAF]) it is used as part of an antiretroviral regi men to treat patients with HIV/HBV co-infection requiring lifelong antiviral therapy and off-label in selected cases of established nucleo side resistance. ■ ■ADEFOVIR Adefovir dipivoxil is the oral prodrug of adefovir—a monophosphate nucleotide analogue of adenosine. This drug is active against HBV, HIV, some herpesviruses (HSV and CMV), and poxviruses. Adefovir is effective for the management of HBV in treatment-naïve patients and those infected with lamivudine-resistant HBV. Viral resistance to adefovir is slower to emerge than resistance to lamivudine but still develops in 20–30% of patients after 5 years of treatment.

Adefovir has been replaced with nucleos(t)ide analogues with higher barriers to resistance as first-line treatment for chronic hepatitis B. ■ ■TELBIVUDINE Telbivudine, a β-L enantiomer of thymidine, was approved by the FDA in 2006 for the treatment of chronic HBV infection. It has little or no

activity against HIV replication. Telbivudine is generally well tolerated and effective against HBV replication, but the risk of viral resistance (25% in HBeAg-positive and 11% in HBeAg-negative patients after 2 years of use), myopathy, peripheral neuropathy, and fatigue limited its use. Telbivudine was withdrawn from the U.S. market primarily for economic reasons.

■ ■ENTECAVIR Entecavir is a cyclopentyl guanosine analogue that, once triphosphory lated, blocks HBV polymerase in multiple ways, inhibiting priming and reverse transcription of the HBV negative strand and positive-strand synthesis. Entecavir effectively inhibits HBV replication, with resulting biochemical and histologic improvement. This drug is active against some lamivudine-resistant HBV strains, but only at concentrations 20- to 30-fold higher than those obtained with the standard 0.5-mg dose; thus, a higher dose (1 mg daily) of entecavir is recommended for patients with previous lamivudine exposure. Entecavir resistance leading to viral rebound and clinical hepatitis is uncommon among previously untreated patients but may occur in up to 50% of patients with prior lamivudine resistance after 5 years of entecavir treatment. Entecavir-resistant strains retain susceptibility to tenofovir and occa sionally adefovir. Entecavir is generally well tolerated and highly bioavailable but should be taken on an empty stomach because food interferes with its absorption. The drug is renally cleared, and dosing should be adjusted for a CrCl of <50 mL/min. ■ ■TENOFOVIR Tenofovir is a nucleotide analogue of adenosine monophosphate with activity against both retroviruses and hepadnaviruses. Two prodrug forms, TDF and TAF, are approved by the FDA for the treatment of both HIV infection and HBV infection. Tenofovir potently inhib its HBV replication. Rates of viral suppression are similar between TDF and TAF at 3 years. After 10 years of continuous use, 96–98% of patients receiving TDF achieve complete viral suppression. TAF is associated with higher biochemical response compared with TDF. Clinical resistance to tenofovir has not been observed with up to 8 years of therapy. Both formulations are renally eliminated, and renal toxicity—including acute renal failure, Fanconi syndrome, and diabetes insipidus—has been reported. The risk is higher with TDF compared to TAF. In clinical trials of TAF, there have been no reported cases of Fanconi syndrome or proximal renal tubulopathy. Small declines in bone mineral density (~2.3% at 5 years with TDF and <1% at 3 years with TAF) have been observed. Routine monitoring of renal func tion during therapy with both agents is indicated, and dose frequency should be reduced in patients with GFR <50 mL/min. CHAPTER 196 Antiviral Chemotherapy, Excluding Antiretroviral Drugs ■ ■INTERFERONS IFNs have a broad spectrum of antiviral activity in addition to modu lating the immune system. Recombinant α, β, γ, and λ IFNs have been evaluated in a variety of viral infections. Standard IFN- α2b was the first drug approved for treatment of chronic hepatitis B, but it has been largely replaced by pegylated IFN-α2a. Pegylation of IFN, through linkage of IFN to polyethylene glycol, results in slower absorption, decreased clearance, and more sustained serum IFN concentrations, thereby permitting a more convenient once-weekly dosing schedule. Consequently, pegylated IFN has supplanted standard IFN. IFNs are associated with numerous adverse effects including fever, myalgia, fatigue, somnolence, depression, confusion, leukopenia, and develop ment of autoantibodies, including antithyroid antibodies, that limit its tolerability and patient acceptance. Pegylated IFN-α2a is approved by the FDA for therapy in patients with chronic hepatitis B and C. Pegylated IFN-α2b is no longer avail able in the United

States. The administration of pegylated IFN-α2a for 48 weeks in patients with HBeAg-positive infection resulted in the loss of markers for HBV replication (e.g., HBeAg and HBV DNA in 29–36% and 8–14% of cases, respectively; 2–7% of patients also cleared HBsAg). In most patients who lose HBeAg and HBV DNA, serum aminotransferases return to normal levels, and the viral and biochemical responses are maintained

in the long term. Predictors of a favorable response to pegylated IFN-α2a therapy include low pretherapy levels of HBV DNA, high pretherapy serum levels of alanine aminotransferase (ALT), a short duration of chronic HBV infection, HBV genotypes A and B, and active liver inflammation on biopsy. Poor responses are seen in patients with HBeAg-negative and immunosuppressed patients, including those infected with HIV.

ANTIVIRAL DRUGS FOR HEPATITIS C INFECTION The goal of HCV treatment is long-term suppression of viral replica tion or a sustained virologic response (SVR). SVR is achieved when levels of HCV RNA in the serum remain undetectable 12 weeks after the end of treatment. SVR is considered synonymous with cure, as it is associated with durable suppression of HCV replication, lower allcause and liver-related mortality, and a reduced risk of hepatocellular carcinoma. These benefits have been confirmed in patients with and without advanced liver disease and cirrhosis who received IFN-based and IFN-sparing, combination direct-acting antiviral drugs (DAAs). Several targeted therapies with DAAs are effective against HCV (Table 196-4). Three classes of DAAs that target the NS5B RNAdependent RNA polymerase, the NS3/4 protease, and NS5A, a zincbinding phosphoprotein that is integral for HCV RNA replication, form the basis of curative regimens for chronic HCV infection. A combination of two or three DAAs is now the standard of care for the treatment of chronic HCV infection, regardless of genotype or fibro sis stage. Two pangenotypic regimens, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir administered for 8 to 12 weeks, respectively, are PART 5 Infectious Diseases TABLE 196-4 Antiviral Drugs for Hepatitis C Treatment in Adultsa MECHANISM(S) OF ACTION DRUG FORMULATION ROUTE, DOSE, DURATION Sofosbuvir Oral; 400 mg daily; duration varies (12–24 weeks) Nucleoside analogue Genotypes 1–6 Headache, fatigue Should be combined with at least one other DAA from a different class. Sofosbuvir/ledipasvir Oral; 400 mg/90 mg daily; 8, 12, or 24 weeks Nucleoside analogue/ NS5A inhibitor Sofosbuvir/velpatasvir Oral; 400 mg/100 mg daily; 12 weeks Nucleoside analogue/ NS5A inhibitor Sofosbuvir/velpatasvir/ voxilaprevir Oral; 400 mg/100 mg/100 mg once daily; 12 weeks Nucleoside analogue/ NS5A inhibitor/protease inhibitor Elbasvir/grazoprevir Oral; 50 mg/100 mg once daily; 12 or 16 weeks NS5A inhibitor/protease inhibitor Glecaprevir/ pibrentasvir Oral; 3 100-mg tablets/40 mg once daily; 8, 12, or 16 weeks NS5A inhibitor/protease inhibitor Daclatasvir Oral; 60-mg tablet once daily; 12 weeks Dose reduced to 30 mg once daily when taken with a strong CYP3A inhibitor Dose increased to 90 mg once daily when taken with moderate CYP3A inducers NS5A inhibitor Genotypes 1 and 3 Ribavirin Oral; 3–6 200-mg capsules once daily or in divided doses, based on weight, history of cardiovascular disease, and renal function Nucleoside analogue, also unknown mechanisms aWhile these drugs are approved by the FDA for chronic but not acute HCV, they have been recommended for acute HCV by both the Infectious Diseases Society of America and the American Association for the Study of Liver Diseases. Abbreviation: DAA, directly acting antiviral agent.

the most widely used regimens with SVR rates that exceed 95% for all HCV genotypes. Two pangenotypic regimens with high SVR rates are approved specifically for re-treatment of chronic

HCV infection after initial treatment failure: glecaprevir/pibrentasvir and sofosbuvir/velpatasvir/voxilaprevir. In the setting of unfavorable resistance-associated variants (RAVs) or cirrhosis, re-treatment efficacy can frequently be improved by extension of the treatment course or the addition of ribavirin. Review of the online joint American Association for the Study of Liver Diseases/Infectious Diseases Society of America's HCV Guidelines is useful for selecting the appropriate DAA regimen. In addition, for all DAA-based treatments, checking for drug–drug interactions before the initiation of therapy is recommended. Most regimens are well tolerated, but all DAAs carry a black-box warning about reactivation of HBV—mostly among HBsAg-positive persons and to a lesser extent patients with isolated anti-HBc following HCV suppression. In some cases, fulminant hepatitis, hepatic flare, and death have occurred in patients with untreated HBV infection who underwent treatment for chronic HCV infection. These risks are rare and can be safely managed with routine monitoring; treatment of HCV should not be deferred because of HBV co-infection. ■ ■NS5B POLYMERASE AND NS5A-CONTAINING REGIMENS Sofosbuvir Sofosbuvir is the prodrug of a uridine inhibitor of the HCV NS5B RNA-dependent RNA polymerase. The active uridine nucleoside triphosphate results in termination of viral RNA replica tion. Sofosbuvir is approved by the FDA for the treatment of HCV SPECTRUM OF ACTIVITY COMMON SIDE EFFECTS COMMENTS Genotypes 1, 4, 5, and 6 Headache, fatigue Avoid coadministration with antacid medications. Genotypes 1–6 Headache, fatigue Avoid coadministration with antacid medications. Genotypes 1–6 Headache, fatigue, diarrhea, nausea Approved for re-treatment of patients with previous DAA experience. Avoid coadministration with antacid medications. Genotypes 1 and 4 Fatigue, anemia, headache, nausea Pretreatment testing for resistanceassociated variants recommended in patients infected with genotype 1a. Monitor hepatic function panel at 8 weeks and again at 12 weeks if patient is receiving 16 weeks of treatment. Genotypes 1–6 Headache, fatigue — Headache, fatigue Use recommended only along with sofosbuvir—with or without ribavirin—for genotype 1 or 3 infection; no longer considered a first- or second-line regimen. Unknown, used for all genotypes Anemia, nausea, teratogenic in pregnancy Used only as combined therapy with DAAs or interferon. Complete blood counts should be monitored after 2 weeks of treatment and as clinically indicated thereafter. Dose may be adjusted based on anemia and renal function.

genotypes 1–4 and is active against genotypes 1–6. Resistance to sofos buvir is conferred by an S282T substitution in the NS5B protein, but clinically significant resistance to sofosbuvir treatment has rarely been encountered and virologic breakthrough during sofosbuvir treatment is exceedingly rare. Sofosbuvir is approved for use with other DAAs as part of three fixed-dose combination regimens: as two-drug regimens with the NS5A protein inhibitors ledipasvir and velpatasvir, and as a three-drug regimen with velpatasvir and the protease inhibitor voxi laprevir. Both sofosbuvir and its active metabolite are renally cleared, and while the FDA has approved this drug only for patients with an estimated GFR of ≥30 mL/min, several studies have demonstrated its safety and efficacy in end-stage renal disease and for patients undergo ing dialysis. Sofosbuvir has not been associated with significant toxicity or drug interactions with one notable exception: sofosbuvir potentiates amiodarone and may cause severe bradycardia, especially if coadmin istered with amiodarone and a beta blocker. Sofosbuvir/Ledipasvir Ledipasvir is an NS5A protein inhibitor that is available only in combination with sofosbuvir. The fixed-dose combination of ledipasvir and sofosbuvir is effective against genotypes 1, 4, 5, and 6 with SVR rates of 95–100%. The standard duration of treatment is 12 weeks for genotypes 1 (all subgenotypes), 4, 5, and 6; however, treatment duration may be reduced to 8 weeks in treatmentnaïve, genotype 1–infected

noncirrhotic patients with baseline HCV RNA levels below 6 million copies/mL. Treatment should be extended to 24 weeks or ribavirin should be added in patients who have decom pensated cirrhosis or previous DAA exposure. Ledipasvir is excreted via the biliary route, and no adjustment is needed for mild or moder ate renal impairment. Several studies have shown that sofosbuvir/

ledipasvir is safe in end-stage renal disease, but it remains FDA approved only for patients with a CrCl of >30 mL/min. No dose reduc tion is required for decompensated cirrhosis (Child–Turcotte–Pugh class B or C). Ledipasvir absorption is improved with food intake and is inhibited by antacids or proton pump inhibitors. Ledipasvir is an inhibitor of P-glycoprotein and may increase levels of tenofovir; renal function should be monitored in patients receiving both medications, although clinically significant interactions are unlikely during the relatively short period of treatment. Ledipasvir is generally well toler ated, and clinical trials have shown only a small increase in side effects, including headache and fatigue, over those occurring with placebo. Sofosbuvir/Velpatasvir While chemically similar to ledipas vir, velpatasvir has an expanded spectrum of activity and exhibits improved efficacy over ledipasvir against HCV genotypes 2 and 3. Velpatasvir is available only in combination with sofosbuvir for the treatment of naïve patients with genotype 1–6 infection and all stages of fibrosis, including decompensated cirrhosis. SVR rates for patients without cirrhosis were 96–100% for all HCV genotypes. In contrast to sofosbuvir/ledipasvir treatment, shortening of the duration of sofosbuvir/ velpatasvir therapy in these patients is not required. Similar to ledipas vir, velpatasvir should be taken with food, and coadministration with antacids or proton pump inhibitors should be avoided. Velpatasvir is in general well tolerated, and reported side effects are minimal. Sofosbuvir/Velpatasvir/Voxilaprevir Available in a triple-drug combination with sofosbuvir and velpatasvir, voxilaprevir is a NS3/ NS4A protease inhibitor that is active against HCV genotypes 1–6. The fixed-dose combination for 12 weeks is recommended for the re-treatment of patients with genotype 1–6 infection in whom SVR has not been attained after previous combination DAA treatment and for treatment-naïve genotype 3–infected patients with cirrhosis and the NS5A resistance-associated variant Y93H. Patients with genotype 3 infection who have failed an NS5A protein inhibitor–regimen have lower SVR rates to re-treatment with sofosbuvir/velpatasvir/voxilaprevir for 12 weeks; thus, it is recommended either to add ribavirin or, if riba virin cannot be tolerated, to extend the duration of therapy to 24 weeks. Voxilaprevir is not recommended for patients with decompensated cirrhosis (see “Protease Inhibitors and Protease Inhibitor–Containing Regimens,” below) or those with significant renal impairment and a CrCl of <30 mL/min. Voxilaprevir, like other protease inhibitors, is

metabolized by the CYP3A system, and the effect of voxilaprevir may be reduced in the presence of other CYP inducers.

Sofosbuvir/Daclatasvir The combination of sofosbuvir with daclatasvir—the only NS5A protein inhibitor available individually rather than coformulated with other DAAs—is approved for the treat ment of HCV genotypes 1 and 3. Daclatasvir binds the N terminus of the NS5A protein, both inhibiting viral RNA replication and blocking virion assembly. It is given in combination with sofosbuvir for 12 weeks and is safe for the treatment of patients with decompensated cirrhosis. Daclatasvir is a substrate of CYP3A, and the dose should be reduced if daclatasvir is given with a strong CYP3A inhibitor and increased if it is given with moderate CYP3A4 inducers. Daclatasvir absorption is not affected by food, and daclatasvir is highly protein bound. The dose does not need to be adjusted for renal impairment, and side effects are uncommon. ■ ■PROTEASE

INHIBITOR–CONTAINING REGIMENS Protease inhibitors are specifically designed to inhibit the HCV NS3/4A serine protease by mimicking the HCV polypeptide and, when bound by the viral protease, form a covalent bond with the catalytic NS3 serine residues, blocking further activity and preventing proteolytic cleavage of the HCV polyprotein into NS4A, NS4B, NS5A, and NS5B proteins. As a class, the protease inhibitors are hepatically metabolized and therefore should not be administered to patients with decompensated (Child–Turcotte–Pugh class B or C) cirrhosis. For patients receiving protease inhibitors, the current recommendation is that liver function tests should be monitored monthly. CHAPTER 196 Glecaprevir/Pibrentasvir Glecaprevir is a pangenotypic NS3/ NS4A protease inhibitor that is coformulated with pibrentasvir, a pangenotypic NS5A protein inhibitor. Each medication individually has a high genetic barrier to resistance and is active against HCV geno types 1–6. In patients infected with genotypes other than genotype 3, baseline resistance has no influence on glecaprevir treatment efficacy, and NS3/NS4A baseline polymorphisms have not been noted to cor relate with virologic failure. Treatment duration varies with fibrosis and treatment experience: an 8-week course of therapy is recommended for treatment-naïve patients who are infected with any genotype and have any degree of fibrosis up to compensated cirrhosis, including patients with genotype 3 infection. This results in SVR rates of 95–100% across all HCV genotypes. Treatment-experienced cirrhotic patients should receive 12 weeks of treatment, and patients with prior NS5A protein inhibitor exposure with or without compensated cirrhosis should receive 16 weeks of therapy. The combination of glecaprevir/pibrentasvir should be taken with food. Clearance is via biliary excretion; therefore, no dose adjustment is required in end-stage renal disease. Because of the protease component, the combination of glecaprevir/pibrentasvir is not appropriate for patients with decompensated cirrhosis. Glecaprevir and pibrentasvir are only weak CYP3A inducers, but they inhibit the P glycoprotein, breast cancer resistance protein (BCRP), and organic anion transporter P1 (OATP1) drug transporters. When taken with other drugs that are substrates for these transporters, concentrations of both drugs may be increased. The combination regimen is generally well tolerated; mild headache, fatigue, diarrhea, and nausea have been reported. Antiviral Chemotherapy, Excluding Antiretroviral Drugs Elbasvir/Grazoprevir The coformulation of elbasvir, an NS5A replication complex inhibitor, and grazoprevir, an NS3/NS4A protease inhibitor, is active against HCV genotypes 1 and 4. However, its effi cacy in the treatment of HCV genotype 1a is reduced in the presence of baseline RAVs in the NS5A protein at positions M28, Q30, L31, and Y93; thus, in patients infected with genotype 1a, baseline resistance testing should be performed and, if the result is positive, ribavirin should be added and therapy should be extended to improve response rates. Susceptibility to grazoprevir is reduced with NS5A protein D168 substitutions, but few resistant isolates have been noted in cases of virologic failure; thus, testing for these substitutions before therapy is not recommended. Treatment duration is 12 weeks (genotype 1b or genotype 1a without baseline RAVs) or 16 weeks (in combination with

ribavirin in patients with baseline NS5A protein polymorphisms and in genotype 4–infected patients with previous IFN exposure). Absorp tion of grazoprevir and elbasvir is unaffected by food, and the dose does not need to be adjusted in patients with chronic kidney disease or those who are undergoing dialysis. Elbasvir, like grazoprevir, is a sub strate of the CYP3A system; coadministration with moderate or strong CYP3A inducers or with strong inhibitors is not recommended. Both components are well tolerated, and few side effects have been reported. The use of this drug combination, as with all those containing protease inhibitors, is contraindicated in decompensated cirrhosis.

■ ■INTERFERONS Several IFN preparations have been studied and approved as therapeu tic options for chronic HCV infection. Approved regimens combined IFN/pegylated IFN with ribavirin, a nonspecific nucleoside analogue with the antiviral effects discussed below. The approval of direct acting antiviral agents in 2014 led to revised guidance, and IFN therapy is no longer recommended for the treatment of hepatitis C. ■ ■RIBAVIRIN Ribavirin, a synthetic oral triazole guanosine analogue, weakly inhibits both DNA and RNA polymerases, but its primary mechanism in HCV treatment is not well understood. It may promote infidelity of RNA viral replication, giving rise to unfit or less fit viral mutations, and also appears to stimulate IFN-response genes and modulate adaptive immune responses. The role of ribavirin in HCV therapy has changed over time. Ribavirin played an integral role in HCV treatment during the IFN era to prevent virologic relapse and, combined with sofosbuvir, was required as part of IFN-sparing regimens before other DAAs were available. However, adverse drug effects associated with higher doses (in heavier patients)—including hemolytic anemia, which is increased with renal failure—were frequently treatment-limiting. Other side effects include rash, myalgia, and fatigue. Ribavirin is teratogenic, and its use in women with child-bearing potential is therefore limited. PART 5 Infectious Diseases With the advent of several combination DAA-only, IFN-sparing regimens, there are often multiple ribavirin-free options for treatment. However, there are still several indications for ribavirin augmenta tion of combination DAA-based therapy. Most importantly, ribavirin improves the SVR rate by an average of 5% in treatment-naïve and treatment-experienced patients with genotype 1 infection, particularly that due to subgenotype 1a. The addition of ribavirin to treatment with paritaprevir/ritonavir/ombitasvir plus dasabuvir is recommended for patients with genotype 1a or 4 infection as well as for patients infected with genotype 1a who are receiving elbasvir/grazoprevir with baseline NS5A protein RAVs to overcome reduced susceptibility to elbasvir. Ribavirin is frequently included in regimens for re-treatment of geno type 1–infected, therapy-experienced patients with cirrhosis in order to preserve SVR rates while shortening re-treatment duration. SVR rates at 12 weeks were comparable in treatment-experienced cirrhotic patients receiving 24 weeks of ledipasvir/sofosbuvir and those receiv ing 12 weeks of ledipasvir/sofosbuvir plus ribavirin. Ribavirin also improves outcomes in treatment-experienced patients with genotype 3 infection—an ongoing therapeutic challenge even in the setting of cur rent pangenotypic regimens. Ribavirin improves treatment response in other clinical settings as well, specifically in patients with decompen sated cirrhosis for whom treatment protease inhibitors cannot be used and in patients with genotype 2 infection in resource-limited settings where ribavirin is more affordable than fixed-dose combination DAA regimens. Because of its broad antiviral effects, ribavirin is not known to select for any particular RAVs. Absorption of ribavirin is improved by administration with food, and the drug is excreted renally. Lowering the dose of the drug may reduce toxicity. While determining red blood cell counts and hemo globin levels after 2 weeks of therapy is recommended to monitor for hemolytic anemia, ribavirin can be administered safely to most patients for the relatively short period of DAA-based therapy. In patients with renal insufficiency and those with end-stage renal disease who are undergoing dialysis, the dose must be adjusted and the patient closely monitored for anemia.

In a recent large-scale study, ribavirin was effective in the treatment of chronic infection with hepatitis E virus, which can cause chronic inflammatory hepatitis in immunosuppressed patients, particularly solid-organ transplant recipients. ANTIVIRAL DRUGS FOR HEPATITIS D INFECTION ■ ■INTERFERONS At high doses, IFN-α and pegylated IFN-α are active against hepatitis D virus infection. In off-label use for hepatitis D, SVR was achieved in 25–35% of patients treated with IFN-

α and 17–43% of patients treated with pegylated IFN-α for 48 weeks. Virologic and biochemical relapse occur frequently after stopping IFN. Extending the duration is associated with maintenance of clinical response and HBsAg loss in a few cases. ■ ■ENTRY INHIBITORS Bulevirtide is a synthetic lipopeptide that mimics a region within pre-S1 of the large HBsAg and irreversibly binds to the sodium tauro cholate cotransporting polypeptide, the hepatocyte entry receptor for both HDV and HBV. Bulevirtide indirectly reduces HDV replication by blocking viral entry and new rounds of infection. Bulevirtide is approved by the European Medicines Agency (EMA) at a dose of 2 mg subcutaneously once daily for use in patients with compensated chronic HDV infection. In off-label use, bulevirtide was shown to be effective in patients with decompensated liver disease due to chronic hepatitis D infection. In a clinical trial, bulevirtide given 2 or 10 mg subcutaneously once daily was able to suppress HDV viremia by at least 100-fold and normalize alanine aminotransferase (ALT) levels in 45% and 48% of patients, respectively; undetectable viremia was achieved in 12.2% and 20% of patients, respectively. Combined bulevirtide and pegylated interferon was superior to bulevirtide alone to reduce HDV RNA to an undetectable level. No emergence of viral resistance has been observed to date. Asymptomatic elevation in bile acids and injectionsite reactions are the most common adverse reactions. Bulevirtide is not yet approved in the United States. Acknowledgment The authors gratefully acknowledge the contributions of Dr. Eleanor Wilson to this chapter in the previous edition. ■ ■FURTHER READING Acosta E et al: Advances in the development of therapeutics for cyto megalovirus infections. J Infect Dis 221:S32, 2020. American Association for the Study of Liver Diseases/Infectious Diseases Society of America: Recommendations for testing, man aging, and treating hepatitis C. Available at http://www.hcvguidelines

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