

Drugs for Influenza and Cytomegalovirus Retinitis

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Antiviral agents are chemotherapeutic drugs that are effective against different viruses. Influenza is a common infection; anti-influenza agents are useful for both prophylaxis and the treatment of influenza. CMV retinitis is a common opportunistic infection in immunocompromised patients; there are several antiviral drugs effective against CMV. Pharmacology of all the drugs will be discussed briefly.



Anti-Influenza Drugs

Influenza is a respiratory infection caused mainly by influenza viruses A and B, which are orthomyxoviruses RNA viruses. Influenza presents with high fever, chills, dry cough, headache, arthralgia, myalgia, fatigue, and malaise. In severe cases, influenza may lead to secondary bacterial infection of the respiratory tract, sinuses, and middle ear, or viral infection of the lung parenchyma (pneumonia), brain (encephalitis), or heart (myocarditis).

Management of influenza includes supportive therapy (eg, rehydration, antipyretics, analgesia, and antitussives) and antiviral therapy. Antiviral therapy is usually reserved for

patients with severe disease or those who are at risk of developing complications.

Amantadine and Rimantadine

Tricyclic amines are effective against **influenza A, but not influenza B**. They act by **blocking M2 proton ion channels** within the viral membrane to prevent acidification of the virus core; prevent uncoating, an early step in replication; and prevent activation of the **RNA transcriptase** of the virus (see image).

Amantadine is excreted unchanged in the urine; therefore, a dose reduction is required in elderly patients and those with renal insufficiency.

Rimantadine is an α -methyl derivative of amantadine with 4–10 times more anti-influenza activity in vitro, a longer half-life, and **hepatic metabolism**; dose reduction is required in patients with hepatic insufficiency, but not in those with **renal failure**.

As 100% of seasonal H3N2 and 2009 pandemic influenza samples tested showed resistance to rimantadine, it is no longer used as treatment for influenza. If initiated before exposure to influenza A, however, these drugs are very effective in preventing infection (if no resistance), and if initiated within 1–2 days after the onset of illness, they reduce the duration of symptoms by 1–2 days.

Common adverse effects include nausea, anorexia, insomnia, nervousness, light-headedness, difficulty in concentration, slurred speech, dizziness, ataxia, and **teratogenicity**.

Serious neurological adverse effects (hallucinations, agitation, behavioral changes, seizures, and delirium) can occur due to altered dopamine neurotransmission. These effects are more common with **amantadine** than with rimantadine in elderly patients, those with renal insufficiency or **seizure disorders**, and with the co-administration of certain drugs (antihistamines, anticholinergics, hydrochlorothiazide, trimethoprim-sulfamethoxazole). Acute amantadine overdose can present with **anticholinergic symptoms**.

The M2 protein is a mutation-prone site; resistance to both drugs develops rapidly in up to 50% of treated persons.

Neuraminidase Inhibitors (Oseltamivir and Zanamivir)

Oseltamivir and zanamivir are sialic acid analogs that are active against both influenza A and influenza B viruses. These drugs reversibly and competitively inhibit **viral neuraminidase and prevent the cleavage of sialic acid residues**, causing the clumping of newly released virions to each other and to the membrane of infected cells. They prevent the spread of infection within the respiratory tract by interfering with the release of influenza virus **progeny** within mucosal secretions and reducing viral infectivity.

Oseltamivir (Food and Drug Administration [FDA]-approved for patients aged ≥ 1 year) is an orally administered prodrug. It is activated by **hepatic esterases** and excreted through filtration and tubular secretion in the kidneys; dose reduction is required in patients with **renal insufficiency**.

Important adverse effects include nausea, vomiting, abdominal pain, and (rarely) rash; diarrhea, headache, and fatigue are more common when taken prophylactically.

Transient neuropsychiatric events, such as **self-injury or delirium**, have been

reported in patients in Japan.

Zanamivir (FDA-approved for patients aged ≥ 7 years) is administered intranasally, with approximately 10%–20% of the drug reaching the lungs and the remainder being deposited in the oropharynx. About 5%–15% of the dose undergoes **systemic absorption**, followed by **excretion in urine** with minimal metabolism.

Important adverse effects of zanamivir include coughing, bronchospasm, transient discomfort in nose and throat, and a reversible decrease in lung function; the drug should not be administered in patients with underlying airway disease.

If initiated before exposure to the influenza virus, these drugs are very effective in preventing infection; if initiated within 36–48 hours after the onset of illness, they reduce the duration of illness by 1–2 days, reduce the severity of symptoms, and decrease secondary complications.

Resistance to neuraminidase inhibitors can develop due to **point mutations** in viral hemagglutinin or neuraminidase genes, but worldwide resistance is rare at present.

Peramivir

Peramivir is a cyclopentane analog, a neuraminidase inhibitor with activity against both influenza A and influenza B viruses. It received temporary FDA authorization due to the **H1N1 pandemic** in 2009, although it is currently not licensed for use in the United States.

Peramivir is available for **intravenous administration**. Important adverse effects include nausea, vomiting, diarrhea, and neutropenia.

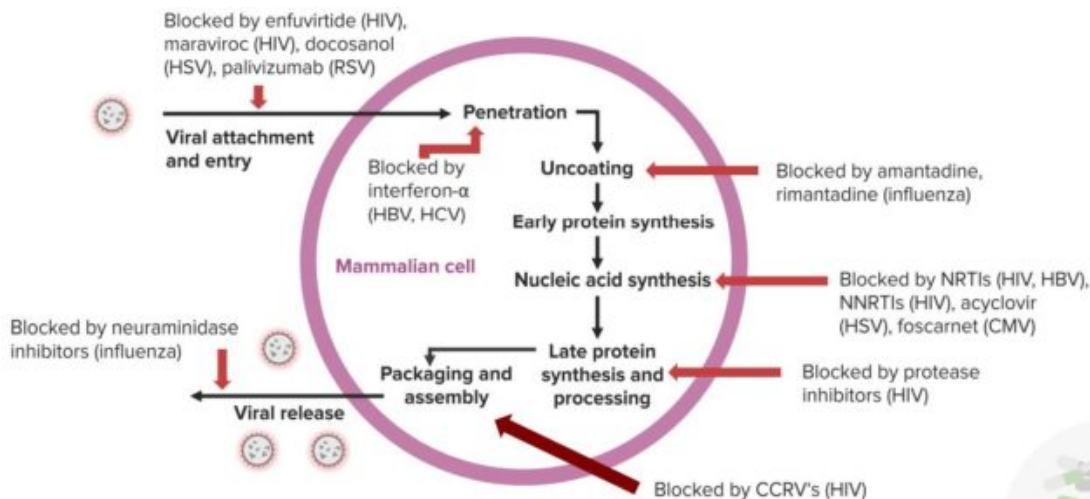


Image: Overview of antiviral activity. By: Lecturio.

Cytomegalovirus Retinitis Drugs

Cytomegalovirus (CMV) is a **DNA virus** that causes asymptomatic infection or a **mononucleosis-like syndrome** in immunocompetent hosts, but that also causes opportunistic infection of multiple organ systems, including necrotizing retinitis, in immunocompromised hosts. CMV retinitis is usually seen in patients with AIDS or who have undergone organ transplants, or those on immunosuppressive treatments.

Treatment of **sight-threatening lesions** (adjacent to the **optic nerve** or **fovea**) requires intravitreal injections of ganciclovir or foscarnet for 7–10 days, plus systemic therapy with valganciclovir (preferred) or ganciclovir (alternative). Peripheral lesions are treated by systemic therapy with 1 of the effective agents.

Ganciclovir

Ganciclovir is a **guanosine analog** that, after activation by phosphorylation, **inhibits viral DNA polymerase** and causes a chain termination of CMV. It also has in vitro activity against the **herpes simplex virus** (HSV), **varicella-zoster virus** (VZV), **Epstein-Barr virus** (EBV), **human herpesvirus 6** (HHV-6), and HHV-8.

Oral bioavailability is approximately 10% and renal elimination is directly proportionate to creatinine clearance.

Intravenous ganciclovir is used to delay the progression of **CMV retinitis** in patients with AIDS; combination therapy with foscarnet is more effective. Induction therapy is followed by maintenance therapy with oral ganciclovir.

Intraocular administration via intravitreal injection or **intraocular implant** is possible; intraocular implant delays the progression of CMV retinitis to a greater degree than systemic ganciclovir. The implant needs to be replaced at intervals of 5–8 months.

The most common adverse effect of intravenous ganciclovir is myelosuppression (this occurs less often with the oral form), which causes leukopenia and **thrombocytopenia**; other important adverse effects include fever, rash, **mucositis**, headache, nausea, diarrhea, **hepatic dysfunction**, seizures, and peripheral neuropathy.

Resistance can develop due to **UL97 mutation** (resistance to ganciclovir only) or **UL54 mutation** (associated with cross-resistance with cidofovir and foscarnet).

Valganciclovir

Valganciclovir is a prodrug that is rapidly hydrolyzed by **esterases** in the intestinal wall and liver into ganciclovir after oral administration. Oral bioavailability is approximately 60%. The drug is taken with food, and elimination is mainly by the kidneys.

Valganciclovir is used in the treatment of **CMV retinitis** in patients with AIDS.

Adverse effects and resistance patterns are similar to those of ganciclovir.

Foscarnet

Foscarnet is a pyrophosphate analog that does not require activation (phosphorylation). It inhibits **herpesvirus DNA polymerase**, **RNA polymerase**, and **HIV reverse transcriptase** by blocking pyrophosphate-binding sites of these enzymes.

The drug is available for intravenous administration only; a large volume of fluid is required because of its poor solubility. Clearance is primarily **renal**, and approximately 30% of the drug is deposited in the bones.

Foscarnet is effective in the treatment of **CMV retinitis**, **CMV colitis**, **CMV esophagitis**, acyclovir-resistant HSV infection, and acyclovir-resistant VZV infection. It can be administered intravitreally in patients who have CMV retinitis with AIDS.

Important adverse effects include **nephrotoxicity** (reduced by preloading with saline

and avoidance of other nephrotoxic drugs), electrolyte disturbances (hypocalcemia > **hypercalcemia**, hypo-/hyperphosphatemia, **hypokalemia**, and **hypomagnesemia**), genital ulcerations (due to high levels of ionized drug in the urine), neurotoxicity (headache, seizures, hallucinations), nausea, vomiting, elevation of **hepatic transaminases**, anemia, and fatigue.

The risk of **hypocalcemia**, **anemia**, and **seizures** is increased by the co-administration of pentamidine, zidovudine, and imipenem, respectively.

Resistance can develop with prolonged use; foscarnet-resistant CMV isolates show cross-resistance to ganciclovir. However, the drug is effective against ganciclovir-resistant and cidofovir-resistant CMV isolates.

Cidofovir

Cidofovir is a cytosine nucleotide analog that, after phosphorylation by host kinases (not viral enzymes), competitively inhibits **viral DNA polymerase** and becomes incorporated into the viral DNA chain. It is active against CMV, HSV, adenovirus, and the human papillomavirus.

Cidofovir has 2 active metabolites—cidofovir diphosphate and cidofovir phosphocholine—with prolonged intracellular half-lives. Elimination is mainly renal by active tubular secretion.

The drug is used intravenously in the treatment of **CMV retinitis**, along with probenecid to reduce its active tubular secretion.

An important adverse effect is **proximal tubular nephrotoxicity** (reduced by probenecid, dose-adjustment based on creatinine clearance or urinary protein, prehydration with normal saline, and avoidance of other nephrotoxic drugs), including **proteinuria**, **azotemia**, metabolic acidosis, and **Fanconi's syndrome**; other adverse effects include **neutropenia** and **ocular toxicity** (uveitis, **ocular hypotension**). Cidofovir is contraindicated in **renal insufficiency**.

Cidofovir-resistant isolates show cross-resistance to ganciclovir, but not to foscarnet.

Fomivirsen

Fomivirsen is a **phosphorothioate oligonucleotide**, an antisense agent that interferes with viral **gene expression**, causing inhibition of **viral replication**. It is approved for intravitreal administration for the treatment of CMV retinitis in patients with AIDS and is used when other anti-CMV agents are ineffective.

Important adverse effects include **iritis**, **vitritis**, **cataract formation**, and increased **intraocular pressure**.

References

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[CMV Retinitis](#) via emedicine.medscape.com

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