

# Antiherpes antivirals

A family of nucleoside (and one pyrophosphate) analogues whose selectivity for herpesviruses depends on being switched on by a viral enzyme first - thymidine kinase for HSV and VZV, UL97 kinase for CMV - which is exactly the step each virus's resistance mutations most often disable.

Online guide: <https://www.medguideglobal.com/pharmacology/antivirals-antifungals-antiparasitics/antiherpes-antivirals>

Content updated: 2026-09-15

## Quick revision

One Liner: Acyclovir, valacyclovir, famciclovir, ganciclovir and valganciclovir are all prodrugs or direct agents that need a viral enzyme to convert them to their active triphosphate form before they can block viral DNA polymerase - which is exactly the activation step HSV, VZV and CMV most commonly mutate to become resistant.

1. Acyclovir is monophosphorylated by viral thymidine kinase roughly a million-fold more efficiently than by host cell thymidine kinase, which is the basis of its selectivity for HSV/VZV-infected cells over uninfected cells. [8]
2. Valacyclovir and famciclovir are oral prodrugs of acyclovir and penciclovir respectively, developed mainly to improve oral bioavailability over the parent drugs. [2]
3. The most common mechanism of acyclovir resistance in HSV is a mutation or deficiency in viral thymidine kinase itself, which removes the activation step the drug depends on. [8]
4. Ganciclovir and valganciclovir are activated first by the CMV-encoded UL97 kinase; mutations in UL97 are the most common cause of ganciclovir resistance, and additional mutations in the UL54 DNA polymerase gene confer high-level resistance with cross-resistance to cidofovir and/or foscarnet. [9]
5. Ganciclovir's dose-limiting toxicity is myelosuppression - neutropenia, anemia and thrombocytopenia - monitored with defined blood-count thresholds below which the drug is withheld. [4]
6. Foscarnet and cidofovir are second-line agents used mainly for ganciclovir-resistant CMV or acyclovir-resistant HSV/VZV, and both carry nephrotoxicity as their defining, dose-limiting toxicity rather than myelosuppression. [6][7]
7. Cidofovir's nephrotoxicity is severe enough that its own label contraindicates it with other nephrotoxic drugs and requires mandatory prehydration and probenecid with every infusion. [7]
8. CDC treatment guidelines list acyclovir, valacyclovir and famciclovir as the three FDA-approved options with clinical benefit for genital herpes, used for the first clinical episode, for episodic treatment of recurrences, and for daily suppressive therapy. [10]

## Overview

1. The antiherpes antivirals share a design logic that is worth understanding as a single idea rather than memorising drug by drug: each is a nucleoside analogue (or, for foscarnet, a pyrophosphate analogue) that only becomes an active DNA polymerase inhibitor after a phosphorylation step, and for most of this class that first phosphorylation step is carried out by a viral enzyme, not a host one. This is what gives the class its selectivity - a herpesvirus-infected cell activates the drug far more efficiently than an uninfected cell does - and it is also exactly the step viral resistance most commonly targets. [8]
2. For acyclovir specifically, the numbers behind that selectivity are concrete: viral thymidine kinase converts acyclovir to its monophosphate roughly a million times more efficiently than host cell thymidine kinase does. Host cellular enzymes then complete the second and third phosphorylation steps, producing an acyclovir triphosphate concentration 40 to 100 times higher inside an HSV-infected cell than an uninfected one. The resulting triphosphate is incorporated into viral DNA by the viral DNA polymerase, terminates the growing chain because it lacks the 3'-hydroxyl group needed to continue, and also directly inactivates the viral polymerase. [8]
3. Valacyclovir and famciclovir exist mainly to solve a bioavailability problem rather than a mechanism problem:

valacyclovir is the L-valyl ester prodrug of acyclovir, and famciclovir is the prodrug of penciclovir, both converted to their active parent drug after absorption, giving materially higher oral bioavailability and less frequent dosing than the parent compounds achieved on their own. [2]

4. Cytomegalovirus (CMV) does not encode a thymidine kinase, so ganciclovir and its oral prodrug valganciclovir are instead activated by the CMV-encoded UL97 phosphotransferase before host enzymes complete the remaining phosphorylation steps. This substitutes one viral-enzyme dependency for another, and it is why CMV resistance to ganciclovir most often arises from a UL97 mutation: the virus disables its own activating enzyme, exactly as HSV does with thymidine kinase, before host enzymes ever get a chance to finish the job. [9]

5. Foscarnet and cidofovir occupy a different niche entirely. Foscarnet is a pyrophosphate analogue that inhibits viral DNA polymerase directly, without requiring any activation by a viral kinase at all - which is precisely why it remains active against thymidine-kinase-deficient, acyclovir-resistant HSV/VZV and against UL97-mutant, ganciclovir-resistant CMV. Cidofovir, a nucleotide analogue, is already monophosphorylated on administration and needs only host-cell enzymes for further activation, giving it the same kinase-independent advantage. Both drugs trade that resistance-bypassing advantage for a shared, defining cost: nephrotoxicity severe enough to dictate how each drug is actually administered. [9][7]

## Classification and drug examples

Intro: This class divides naturally by which herpesvirus family member each drug reaches and by whether the drug needs viral-enzyme activation at all.

1. Name: HSV/VZV agents (thymidine-kinase-dependent)

1. Note: Activated first by viral thymidine kinase; the class most students encounter first because of its use for cold sores, genital herpes and shingles.

1. Name: Acyclovir

Zovirax

1. Route: Oral, intravenous, topical

1. Note: Requires renal dose adjustment; associated with reversible nephrotoxicity from crystalluria, especially with rapid IV infusion or dehydration. [1]

2. Name: Valacyclovir

Valtrex

2. Route: Oral

2. Note: L-valyl ester prodrug of acyclovir; substantially higher oral bioavailability, allowing less frequent dosing. [2]

3. Name: Famciclovir

Famvir

3. Route: Oral

3. Note: Prodrug of penciclovir; used for herpes labialis and genital herpes, including suppressive therapy. [3]

4. Name: Penciclovir

Denavir

4. Route: Topical

4. Note: The active drug famciclovir is converted to; topical formulation used for recurrent herpes labialis. [3] [8]

2. Name: CMV agents (UL97-kinase-dependent)

2. Note: Activated first by the CMV-encoded UL97 phosphotransferase rather than a thymidine kinase.

1. Name: Ganciclovir

Cytovene

1. Route: Intravenous

1. Note: Dose-limiting myelosuppression; avoided when absolute neutrophil count, hemoglobin or platelet count fall below labelled thresholds. [4]

2. Name: Valganciclovir

Valcyte

2. Route: Oral

2. Note: L-valyl ester prodrug of ganciclovir, giving oral bioavailability comparable to intravenous ganciclovir exposure. [5] [9]

3. Name: Kinase-independent second-line agents

3. Note: Do not require viral thymidine kinase or UL97 activation, which is why both remain active against resistant strains - at the cost of dose-limiting nephrotoxicity.

1. Name: Foscarnet

Foscavir

1. Route: Intravenous

1. Note: Pyrophosphate analogue inhibiting viral DNA polymerase directly; used for acyclovir-resistant HSV/VZV and ganciclovir-resistant CMV. [6]

2. Name: Cidofovir

Vistide

2. Route: Intravenous

2. Note: Nucleotide analogue requiring only host-cell phosphorylation; reserved for CMV retinitis and, off-label, resistant HSV/VZV, always given with mandatory prehydration and probenecid. [7] [9]

## Mechanism of action

Summary: Every drug in this class ultimately works the same way once activated: an analogue triphosphate (or, for foscarnet, foscarnet itself) competes with the natural nucleotide substrate for the viral DNA polymerase, gets incorporated (except foscarnet, which does not require incorporation), and halts viral DNA synthesis. What differs across the class is how each drug gets activated, and that difference is also the class's central resistance story.

Target: Herpesvirus DNA polymerase, reached via nucleoside/nucleotide analogue triphosphates or, for foscarnet, via direct pyrophosphate-binding-site inhibition

Cidal Static: Virustatic - halts viral DNA replication in actively replicating, infected cells rather than eliminating latent virus in neurons (HSV/VZV) or other reservoirs (CMV)

Kill Kinetics: Clinical response (lesion healing, viral load decline) typically over days; latency is not affected, so recurrence after stopping treatment is expected biology, not treatment failure

1. Step: 1

1. Title: Viral thymidine kinase (HSV/VZV) or UL97 kinase (CMV) performs the first phosphorylation

1. Detail: Acyclovir is converted to its monophosphate by viral thymidine kinase roughly a million-fold more efficiently than by host thymidine kinase; ganciclovir is instead activated first by the CMV-encoded UL97 phosphotransferase, since CMV does not encode a thymidine kinase. [8][9]

2. Step: 2

2. Title: Host cellular kinases complete the second and third phosphorylation steps

2. Detail: Cellular guanylate kinase and other cellular kinases convert the monophosphate to the diphosphate and then the active triphosphate form. [8]

3. Step: 3

3. Title: The resulting triphosphate accumulates selectively in infected cells

3. Detail: Because the first activation step depends on a viral enzyme, triphosphate concentrations end up far higher in infected cells than uninfected ones - 40 to 100-fold higher for acyclovir in HSV-infected cells. [8]

4. Step: 4

4. Title: The triphosphate is incorporated into viral DNA and terminates the chain

4. Detail: Viral DNA polymerase incorporates the analogue triphosphate preferentially over the host's own polymerase; because the analogue lacks the 3'-hydroxyl group needed for further chain extension, DNA synthesis stops. [8]

5. Step: 5

5. Title: Foscarnet skips activation entirely and binds the polymerase's pyrophosphate-binding site
5. Detail: Foscarnet requires no intracellular phosphorylation; it directly inhibits viral DNA polymerase (and reverse transcriptase, in other viral families) at the pyrophosphate-binding site, which is why kinase-deficient resistant strains remain susceptible to it. [6]

## Spectrum of activity

Intro: Coverage within this class tracks activation dependence closely: thymidine-kinase-dependent drugs reach HSV-1, HSV-2 and VZV; UL97-dependent drugs reach CMV; and the two kinase-independent agents reach across both groups, including resistant strains of either.

1. Subclass: Acyclovir, valacyclovir, famciclovir/penciclovir
1. Coverage: HSV-1, HSV-2 and varicella-zoster virus (VZV); acyclovir and valacyclovir also have activity against Epstein-Barr virus in vitro, though this is not a primary indication. [8]
2. Subclass: Ganciclovir, valganciclovir
2. Coverage: Cytomegalovirus (CMV) specifically; ganciclovir also has activity against HSV and VZV but is not first-line for those given its greater toxicity relative to acyclovir. [9]
3. Subclass: Foscarnet
3. Coverage: HSV, VZV and CMV, including thymidine-kinase-deficient acyclovir-resistant strains and UL97-mutant ganciclovir-resistant CMV. [6]
4. Subclass: Cidofovir
4. Coverage: CMV primarily (labelled for CMV retinitis); used off-label for acyclovir- and foscarnet-resistant HSV/VZV given its kinase-independent activation. [7]

## Major clinical uses

1. Drug: Acyclovir
1. Organism: HSV-1, HSV-2, VZV
1. Indication: Genital herpes (initial and recurrent), herpes zoster (shingles), varicella (chickenpox); IV form for herpes encephalitis and neonatal HSV
1. Line: first-line for HSV/VZV in immunocompetent and many immunocompromised patients
1. Note: Renal dose adjustment required; adequate hydration reduces the risk of crystalline nephropathy with IV use. [1]
2. Drug: Valacyclovir
2. Organism: HSV-1, HSV-2, VZV
2. Indication: Cold sores (herpes labialis), genital herpes (initial, recurrent and suppressive), herpes zoster
2. Line: first-line oral alternative to acyclovir, with simpler dosing
2. Note: Higher doses have been associated with thrombotic microangiopathy in advanced HIV or transplant patients in prior clinical experience. [2]
3. Drug: Famciclovir
3. Organism: HSV-1, HSV-2, VZV
3. Indication: Herpes zoster; recurrent genital herpes, including suppressive therapy; recurrent herpes labialis
3. Line: first-line oral alternative to acyclovir/valacyclovir
3. Note: Prodrug of penciclovir, converted to active drug after absorption. [3]
4. Drug: Ganciclovir
4. Organism: Cytomegalovirus
4. Indication: CMV retinitis in immunocompromised patients; CMV prophylaxis in transplant recipients
4. Line: first-line for CMV disease requiring systemic treatment
4. Note: Myelosuppression is dose-limiting; blood counts monitored frequently. [4]
5. Drug: Valganciclovir

- 5. Organism: Cytomegalovirus
- 5. Indication: CMV retinitis in AIDS patients; CMV prophylaxis in high-risk transplant recipients
- 5. Line: first-line oral alternative to intravenous ganciclovir
- 5. Note: Prodrug giving oral bioavailability approaching that of IV ganciclovir, enabling outpatient therapy. [5]
- 6. Drug: Foscarnet
- 6. Organism: CMV, acyclovir-resistant HSV/VZV
- 6. Indication: Ganciclovir-resistant or refractory CMV retinitis; acyclovir-resistant mucocutaneous HSV infections
- 6. Line: second-line, for resistant or refractory disease
- 6. Note: Renal impairment is the major dose-limiting toxicity; hydration is used to reduce nephrotoxicity risk. [6]
- 7. Drug: Cidofovir
- 7. Organism: Cytomegalovirus
- 7. Indication: CMV retinitis in AIDS patients
- 7. Line: second-line, when ganciclovir cannot be used or CMV is resistant
- 7. Note: Mandatory prehydration and probenecid required with every infusion to reduce nephrotoxicity. [7]

## Pharmacokinetics

- 1. Drug: Acyclovir
- 1. Route: Oral, IV, topical
- 1. Absorption: Oral bioavailability roughly 10-20%, unaffected by food
- 1. Csf Penetration: See prescribing reference
- 1. Metabolism: Minimal hepatic metabolism
- 1. Elimination: Predominantly renal, largely unchanged
- 1. Dose Adjust: Renal impairment is the principal dose-adjustment driver; adequate hydration reduces crystalline nephropathy risk with IV dosing [1]
- 2. Drug: Valacyclovir
- 2. Route: Oral
- 2. Absorption: Well absorbed and rapidly converted to acyclovir, giving 3-5 times the oral bioavailability of acyclovir itself
- 2. Csf Penetration: See prescribing reference
- 2. Metabolism: Rapidly hydrolysed to acyclovir and L-valine after absorption
- 2. Elimination: As acyclovir, predominantly renal
- 2. Dose Adjust: Renal impairment [2]
- 3. Drug: Ganciclovir
- 3. Route: Intravenous
- 3. Absorption: Not applicable (IV administration); poor oral bioavailability of ganciclovir itself was the reason valganciclovir was developed
- 3. Csf Penetration: See prescribing reference
- 3. Metabolism: Minimal metabolism
- 3. Elimination: Predominantly renal, largely unchanged
- 3. Dose Adjust: Renal impairment; myelosuppression thresholds also govern dose interruption [4]
- 4. Drug: Foscarnet
- 4. Route: Intravenous
- 4. Absorption: Not applicable (IV administration)
- 4. Csf Penetration: See prescribing reference
- 4. Metabolism: No significant metabolism
- 4. Elimination: Renal, largely unchanged
- 4. Dose Adjust: Dose is calculated from renal function (creatinine clearance) at baseline and adjusted as it changes

during therapy [6]

5. Drug: Cidofovir

5. Route: Intravenous

5. Absorption: Not applicable (IV administration)

5. Csf Penetration: See prescribing reference

5. Metabolism: Minimal metabolism; already a monophosphate, requiring only further host-cell phosphorylation

5. Elimination: Renal, largely unchanged; actively secreted by renal tubules, which is central to its nephrotoxicity

5. Dose Adjust: Contraindicated with significant baseline renal impairment; requires prehydration and probenecid with every dose [7]

1. This page gives no dose regimens by design. Dose, route and duration for any drug in this class depend on the specific herpesvirus, the indication, renal function and the immune status of the patient, and belong in a current prescribing reference used by the treating clinician.

2. Renal elimination, largely as unchanged drug, is the pharmacokinetic property shared across almost the entire class, which is why renal function dominates dose adjustment for every agent here except the topical formulations.

[1][6][7]

## Adverse effects

1. Effect: Nausea, vomiting, diarrhea and headache

1. Detail: Common with oral acyclovir, valacyclovir and famciclovir. [2]

2. Effect: Diarrhea and abdominal pain

2. Detail: Reported as among the most common adverse reactions with valacyclovir specifically. [2]

1. Effect: Renal impairment with acyclovir

1. Detail: Renal failure, in some cases resulting in death, has been reported with acyclovir therapy, and thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), sometimes fatal, has occurred in immunocompromised patients.

1. Action: Adequate hydration is maintained, especially with IV administration, and renal function guides dose adjustment. [1]

2. Effect: Neurotoxicity with acyclovir

2. Detail: Encephalopathy, hallucinations, confusion and seizure have been reported, particularly at higher exposures or with renal impairment.

2. Action: Neurological status is monitored, especially in patients with reduced renal clearance. [1]

3. Effect: Myelosuppression with ganciclovir

3. Detail: Granulocytopenia, anemia, thrombocytopenia and pancytopenia have been reported; neutropenia usually occurs in the first one to two weeks of treatment.

3. Action: Ganciclovir is avoided if absolute neutrophil count is below 500/ L, hemoglobin below 8 g/dL, or platelet count below 25,000/ L; frequent complete blood counts are used during treatment. [4]

4. Effect: Nephrotoxicity with foscarnet

4. Detail: Renal impairment is foscarnet's major toxicity, most likely to become clinically evident during the second week of induction therapy, though it can occur at any time.

4. Action: Renal function is monitored carefully during induction and maintenance, with dose adjusted to serum creatinine; hydration reduces the risk. [6]

5. Effect: Severe, dose-dependent nephrotoxicity with cidofovir

5. Detail: Acute renal failure resulting in dialysis and/or contributing to death has occurred with as few as one or two doses of cidofovir.

5. Action: Mandatory intravenous prehydration with normal saline and administration of probenecid are required with every infusion; renal function is checked within 48 hours before each dose. [7]

1. Drug: Acyclovir

1. Effect: Crystalline nephropathy from precipitation in renal tubules is a mechanism relatively specific to acyclovir among this class, linked to rapid IV infusion and dehydration. [1]
2. Drug: Ganciclovir/valganciclovir
2. Effect: The only agents in this class whose dose-limiting toxicity is hematologic rather than renal, a genuine point of contrast with every other drug on this page. [4]
3. Drug: Cidofovir
3. Effect: Requires mandatory co-administration of probenecid and IV prehydration with every single dose specifically to blunt its nephrotoxicity, a requirement unique to this drug within the class. [7]

## Contraindications, precautions and interactions

Cidofovir: known hypersensitivity to cidofovir; concomitant administration with other nephrotoxic agents (e.g. IV aminoglycosides, amphotericin B, foscarnet, IV pentamidine, vancomycin, NSAIDs) unless discontinued at least seven days beforehand. [7]

1. Pre-existing renal impairment is a caution across almost every drug in this class, given predominantly renal elimination. [1][6][7]
2. Pre-existing cytopenias, or concurrent myelosuppressive drugs or irradiation, are a caution for ganciclovir given its own myelosuppressive effect. [4]
3. Adequate hydration is required with IV acyclovir, foscarnet and cidofovir to reduce nephrotoxicity risk. [1][6][7]
1. With: Other nephrotoxic drugs (aminoglycosides, amphotericin B, cyclosporine, tacrolimus, IV pentamidine, NSAIDs)
1. Effect: Additive nephrotoxicity risk with acyclovir, foscarnet or cidofovir; foscarnet's own label specifically advises avoiding this combination unless benefit outweighs risk, and cidofovir's label contraindicates it outright. [6][7]
2. With: Other myelosuppressive drugs or irradiation
2. Effect: Additive bone marrow suppression risk with ganciclovir/valganciclovir. [4]

## Resistance mechanisms

Intro: Resistance in this class is a direct consequence of how each drug is activated: lose the activating viral enzyme, and the drug that depends on it loses most of its effect - which is exactly why the two kinase-independent agents exist as a fallback.

1. Mechanism: Thymidine kinase mutation or deficiency (HSV/VZV)
1. Detail: The most common mechanism of acyclovir resistance is a mutation in, or loss of, viral thymidine kinase, which removes the first and most selective activation step the drug depends on; TK-deficient strains are cross-resistant to valacyclovir and famciclovir/penciclovir for the same reason, but remain susceptible to foscarnet, which needs no viral kinase. [8]
2. Mechanism: UL97 kinase mutation (CMV)
2. Detail: Mutations in the CMV UL97 gene are the most common cause of ganciclovir resistance, arising because UL97 normally performs the first phosphorylation step ganciclovir requires. [9]
3. Mechanism: UL54 DNA polymerase mutation (CMV)
3. Detail: Mutations in the UL54 DNA polymerase gene are typically associated with high-level ganciclovir resistance and confer cross-resistance to cidofovir and, to varying degrees, foscarnet, since all three ultimately act on the same viral polymerase. [9]

## Comparison tables

Title: Activation dependence is the organising idea of this class

Caption: Kinase-dependent agents are selective and generally well tolerated; kinase-independent agents bypass resistance at the cost of nephrotoxicity.

1. Key: drug

1. Label: Drug
2. Key: activation
2. Label: Activation step
3. Key: target\_virus
3. Label: Primary target virus
4. Key: dose\_limiting\_toxicity
4. Label: Dose-limiting toxicity
1. Drug: Acyclovir / valacyclovir
1. Activation: Viral thymidine kinase, then host kinases
1. Target Virus: HSV-1, HSV-2, VZV
1. Dose Limiting Toxicity: Renal (crystalline nephropathy with IV use, especially if dehydrated) [1]
2. Drug: Ganciclovir / valganciclovir
2. Activation: CMV UL97 kinase, then host kinases
2. Target Virus: Cytomegalovirus
2. Dose Limiting Toxicity: Myelosuppression (neutropenia, anemia, thrombocytopenia) [4]
3. Drug: Foscarnet
3. Activation: None required - direct pyrophosphate-analogue inhibition
3. Target Virus: Resistant HSV/VZV and CMV
3. Dose Limiting Toxicity: Nephrotoxicity [6]
4. Drug: Cidofovir
4. Activation: Already monophosphorylated; only host-cell activation needed
4. Target Virus: Cytomegalovirus (and off-label resistant HSV/VZV)
4. Dose Limiting Toxicity: Severe, dose-dependent nephrotoxicity [7]

## High-yield exam pearls

1. Pearl: Acyclovir's selectivity comes from a numbers game, not an absolute one: host thymidine kinase can still activate it, just about a million times less efficiently than viral thymidine kinase.
1. Why: This is why acyclovir is well tolerated in uninfected cells despite not being perfectly virus-specific at the molecular level. [8]
2. Pearl: The most common cause of acyclovir resistance is loss or mutation of viral thymidine kinase - the exact enzyme that makes the drug selective in the first place.
2. Why: It is a clean example of a drug's selectivity mechanism and its principal resistance mechanism being the same molecular step. [8]
3. Pearl: Foscarnet needs no viral kinase at all, which is exactly why it still works against thymidine-kinase-deficient HSV/VZV and UL97-mutant CMV.
3. Why: It is the single fact that explains foscarnet's clinical niche as a second-line agent for resistant herpesvirus disease. [6]
4. Pearl: Ganciclovir is the one drug in this class whose dose-limiting toxicity is hematologic, not renal.
4. Why: Every other agent covered here - acyclovir, foscarnet, cidofovir - is primarily renal-toxicity-limited, making ganciclovir/valganciclovir the exception worth remembering by contrast. [4]
5. Pearl: Cidofovir is never given without mandatory prehydration and probenecid.
5. Why: It is one of very few antivirals whose label makes specific concomitant supportive measures a requirement of every single dose, not an optional precaution. [7]

## Common exam traps

1. Trap: Assuming valacyclovir and famciclovir have a different mechanism from acyclovir because they are different drug names.

1. Correction: Both are prodrugs converted after absorption to acyclovir or penciclovir respectively; the underlying mechanism (viral-thymidine-kinase-dependent activation and DNA chain termination) is the same. [2][3]
2. Trap: Assuming ganciclovir resistance works the same way as acyclovir resistance because both are nucleoside analogues.
2. Correction: CMV does not encode a thymidine kinase; ganciclovir resistance arises from mutations in the CMV UL97 kinase gene (and, for high-level resistance, UL54), not from a thymidine kinase mutation. [9]
3. Trap: Treating foscarnet and cidofovir as interchangeable second-line options with the same safety profile.
3. Correction: Both are nephrotoxic, but cidofovir's nephrotoxicity is severe enough to require mandatory prehydration and probenecid with every dose and outright contraindicates concurrent nephrotoxic drugs, a stricter requirement than foscarnet's label imposes. [7][6]
4. Trap: Assuming this class eliminates latent herpesvirus infection.
4. Correction: These drugs halt active viral DNA replication; none of them clears HSV/VZV latency in sensory ganglia or the CMV reservoir, which is why recurrence after stopping treatment is expected biology rather than treatment failure. [8]

## Self-test questions

1. Question: What is the basis of acyclovir's selectivity for HSV/VZV-infected cells?
  1. It only binds receptors present on infected cells
  2. Viral thymidine kinase phosphorylates it far more efficiently than host thymidine kinase does, concentrating the active triphosphate in infected cells
  3. It is inactive in uninfected cells entirely
  4. It requires host RNA polymerase to be activated
1. Explanation: Viral thymidine kinase converts acyclovir to its monophosphate roughly a million-fold more efficiently than host thymidine kinase, leading to much higher active triphosphate concentrations in infected cells. [8]
2. Question: What is the most common mechanism of acyclovir resistance in HSV?
  1. Efflux pump overexpression
  2. Mutation or deficiency of viral thymidine kinase
  3. A mutation in host cell DNA polymerase
  4. Increased viral entry receptors
2. Explanation: Loss or mutation of viral thymidine kinase removes the first, most selective activation step acyclovir depends on, making this the most common resistance mechanism. [8]
3. Question: Why does ganciclovir require a different activating enzyme than acyclovir?
  1. Ganciclovir does not need activation
  2. CMV does not encode a thymidine kinase, so ganciclovir is instead activated by the CMV UL97 phosphotransferase
  3. Ganciclovir is activated by host thymidine kinase only
  4. There is no difference in activation between the two drugs
3. Explanation: CMV lacks a thymidine kinase gene, so ganciclovir and valganciclovir depend on the viral UL97 kinase for their first phosphorylation step instead. [9]
4. Question: Which toxicity is dose-limiting for ganciclovir, distinguishing it from acyclovir and foscarnet?
  1. Nephrotoxicity
  2. Myelosuppression (neutropenia, anemia, thrombocytopenia)
  3. Hepatotoxicity
  4. Ototoxicity
4. Explanation: Ganciclovir's defining, dose-limiting toxicity is hematologic - neutropenia, anemia and thrombocytopenia - monitored with specific blood-count thresholds, unlike the predominantly renal toxicities of acyclovir, foscarnet and cidofovir. [4]
5. Question: Why does foscarnet remain active against thymidine-kinase-deficient, acyclovir-resistant HSV?

1. Foscarnet is metabolised by a completely different pathway inside human cells
2. Foscarnet requires no viral kinase activation at all, acting directly on viral DNA polymerase
3. Foscarnet targets a different virus entirely
4. Foscarnet is a prodrug of acyclovir
5. Explanation: Foscarnet is a pyrophosphate analogue that inhibits viral DNA polymerase directly without needing any kinase-mediated activation, so thymidine-kinase-deficient resistant strains remain susceptible to it. [6]
6. Question: What specific supportive measures does cidofovir's label require with every dose?
  1. No special measures are required
  2. Mandatory intravenous prehydration with normal saline and administration of probenecid
  3. Co-administration of a diuretic only
  4. Fasting for 12 hours before infusion
6. Explanation: Cidofovir's severe, dose-dependent nephrotoxicity means every infusion requires prehydration and probenecid, plus renal function testing within 48 hours beforehand. [7]

## Frequently asked questions

1. Question: Why are there so many different "-ciclovir" drugs if they all work the same way?
  1. Answer: Most exist to solve a practical problem with the original compound rather than to offer a different mechanism. Valacyclovir and famciclovir are prodrugs developed to improve oral bioavailability over acyclovir and penciclovir; valganciclovir does the same for ganciclovir. All are converted to the same active parent compound after absorption, and the underlying mechanism - viral-kinase-dependent activation followed by DNA chain termination - is shared. [2][5]
  2. Question: Why does CMV need a different drug (ganciclovir) than HSV and VZV (acyclovir)?
    2. Answer: CMV does not encode a thymidine kinase, the enzyme acyclovir depends on for its first activation step, so acyclovir is not effective against CMV. Ganciclovir is instead activated by the CMV-encoded UL97 kinase, and its structure lets it be incorporated into viral DNA once activated by that different enzyme. [9]
  3. Question: Are foscarnet and cidofovir ever used as first-line treatment?
    3. Answer: Generally no. Both are reserved for situations where first-line therapy has failed or cannot be used - ganciclovir-resistant or refractory CMV, or acyclovir-resistant HSV/VZV - because both carry significant nephrotoxicity that makes them less attractive as an initial choice when a better-tolerated option is available. [6][7]
  4. Question: Does treatment with these drugs cure herpes infections?
    4. Answer: No. These drugs suppress active viral DNA replication and speed healing of lesions or control CMV disease, but none of them eliminates latent HSV or VZV in sensory ganglia, or fully clears the CMV reservoir. Recurrence after treatment stops reflects the biology of viral latency, not a failure of the drug. [8]

## References

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