Antiviral Drugs for treatment of

HERPES
SIMPLEX VIRUS (HSV)
VARICELLA ZOSTER VIRUS (VZV)
INFECTIONS

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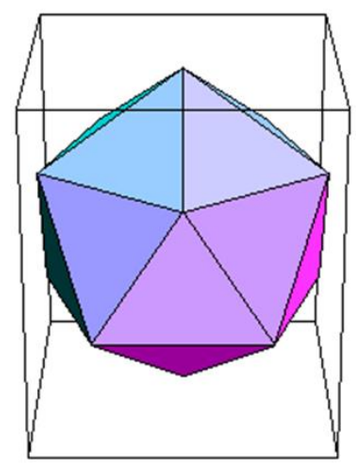


Patterns of Viral Infection

Acute infection: (the disease is going to be cleared out completely by our Immune system)

- Complete viral clearance mediated by immune response
- E.g. Influenza, Rubella. Recovers fully without any long-term viral persistence so the virus doesnt stay in our Body !!

خامن

Latent infection: (Acute infection but will stay in our Body so it persists in the body in Non-infectant dormant form)

- Acute infection but followed by virus persistence in non- infectious form.
- Periodic reactivation of infection with viral shedding
- E.g. Chickenpox, Herpes simplex

↳ Reactivate in the form of shingles

Chronic infection (progressive or persistent): (the virus isnot Cleared by immune system , it stays in the body for long period of time)

- Acute infection followed by lack of viral clearance
- Virus continuously shed or present in tissues
- e.g. HIV, Hepatitis C

* long-term health complications.

HSV and VZV infections

(varicella zoster viruses)

All drugs have the same efficacy to treat herbs but why we prefere Vacyclovir and famicyclovir

① Because the have modest superiority in herpes zoster.

② more convenient dozing

Oral nucleoside analogs licensed

1. Acyclovir
2. Valacyclovir
3. famciclovir.

They show superiority so they are better in the zoster

All are well tolerated. (they have good safety profile with minimal adverse effects on most of the cases)

Acyclovir was licensed first and is the only one of the three that is available for intravenous use in the United States.

Comparative trials have demonstrated similar efficacies of these three agents for the treatment of HSV but modest superiority of famciclovir and valacyclovir for the treatment of herpes zoster infections (patient who have immuno compromised or Generalized herpes infection)

Nucleoside Analogs

++ phoscarnates

- **Result in** "False" DNA building blocks **or nucleosides**(a nucleoside consists of a nucleobase and the sugar deoxyribose). A chemical (They Resemble the normal building Block of the DNA with a slight structure modification) cause disruption of the viral DNA synthesis
- This abnormal nucleoside undergoes bio-activation by attachment of three phosphate residues

- **Acyclovir.**
- **Valacyclovir(a pro-drug with better availability)**
- **.Foscarnet**

↳ needs to be activated in the body

DNA consist of a Deoxiribose when the drug is used it mimics the structure but it has a flaw in it structure that prevents it from functional normally in the DNA.

Acyclovir

- Acyclovir is an acyclic guanosine derivative with clinical activity against HSV-1, HSV-2, and VZV,

- 10 times more potent against HSV-1 and HSV-2 than against VZV.

- In vitro activity against Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus-6 (HHV-6) is present but weaker.

How are these drug activated :

Acyclovir

→ ++ cellular enzyme transforming the drug into its active form

- Acyclovir requires three phosphorylation steps for activation.

→ They Allow the drug to be incorporated into the viral DNA.

- It is converted first to the monophosphate derivative by the virus specified thymidine kinase and then to the di- and triphosphate compounds by host cell enzymes

→ selectively activated

- Because it requires the viral kinase for initial phosphorylation, acyclovir is selectively activated—and the active metabolite accumulates— only in infected cells.

- Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms:

1. competition with deoxyGTP for the viral DNA polymerase, resulting in binding to the DNA template as an irreversible complex;

2. and chain termination following incorporation into the viral DNA.

Acyclovir

A Guanine analogue with activity against Herpes viruses.

Acyclovir → **AcycloGMP** → **AcycloGTP**

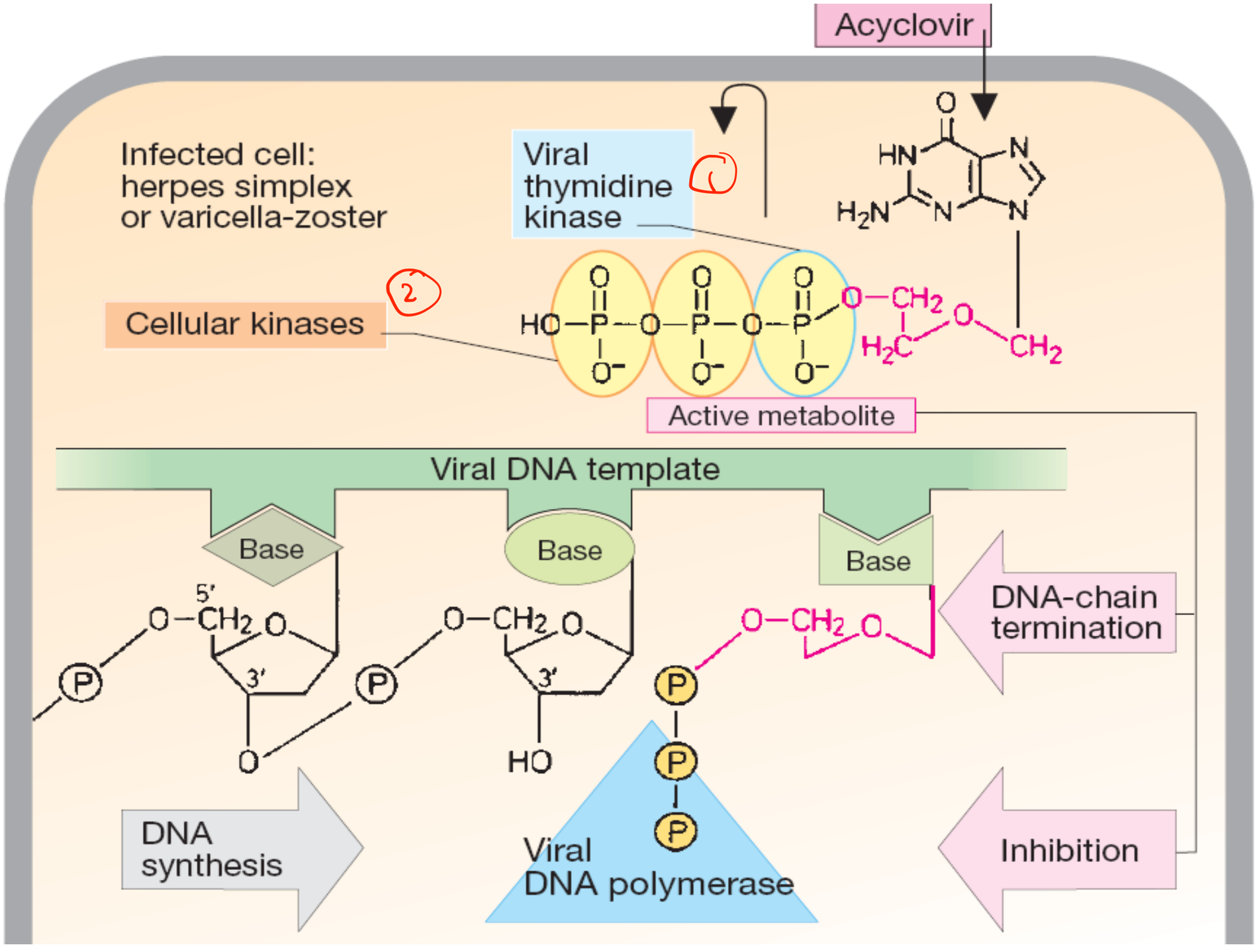
Thymidine kinase — **Cellular kinases**

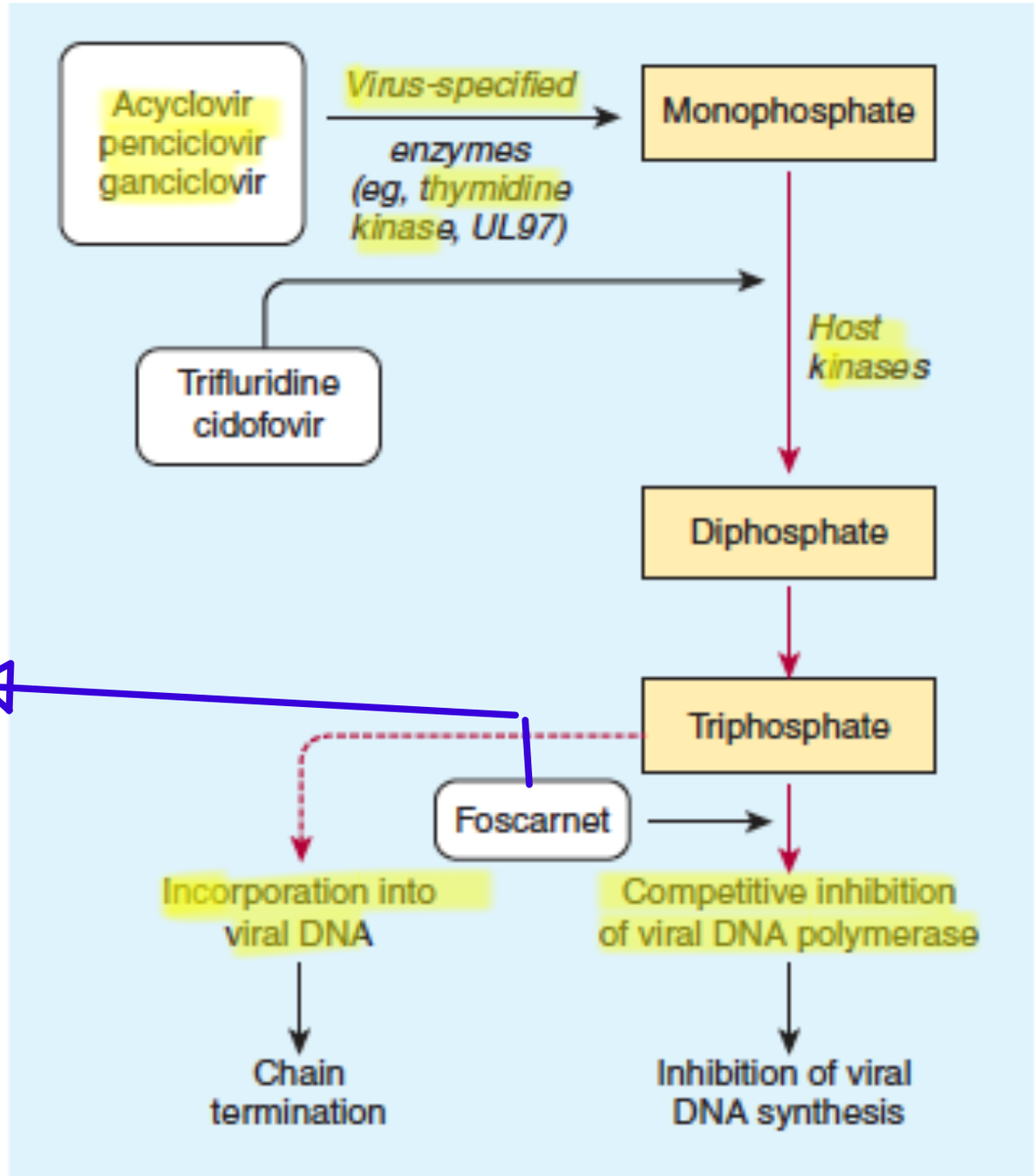
1. **Selectively inhibits viral DNA polymerase.**
2. **Incorporated into DNA and terminates synthesis**

Resistance:

1. ↓ activity of thymidine kinase

2. Altered DNA polymerase


Acyclovir
Infected cell:
herpes simplex
or varicella-zoster
Viral
thymidine
kinase
1
Cellular kinases
2
Active metabolite
Viral DNA template
Base
Base
Base
DNA-chain
termination
DNA
synthesis
Viral
DNA polymerase
Inhibition



non-nucleioside anti-viral
Directly inhibits the
viral DNA polymerase

FIGURE 49–3 Mechanism of action of antiherpes agents.

Pharmacokinetics

- The bioavailability of oral acyclovir is low (15–20%) and is unaffected by food. (small fraction of the drug gets to the bloodstream and its utilized by the body)
- An intravenous formulation is available. ① immunocompromised patient ② patient who can't tolerate or it cannot take it orally.
- Topical formulations produce high concentrations in herpetic lesions, but systemic concentrations are undetectable by this route.
- Acyclovir is cleared primarily by glomerular filtration and tubular secretion. The half-life is 2.5–3 hours in patients with normal renal function

↳ short half-life (Eliminated from the body quickly which can Result in multiple dosings of the drug administered for the patient whether we are talking about oral or IV formulation.

Clinical Use

for herpes labialis (cold oral) oral cyclovir is moderately helpful but not a definitive treatment.

for versilla or chickenpox oral cyclovir significantly improve the outcome it Reduces the symptoms the lesion but we can need a higher doses due to the lower susceptibility of versilla virus to the drug

- Oral acyclovir is only modestly beneficial in recurrent herpes labialis. (These are the cold sores that are caused by herpes simplex virus)
- In contrast, oral acyclovir therapy significantly decreases (1) the total number of lesions, (2) duration of symptoms, and viral shedding in patients with varicella.
- However, because VZV is less susceptible to acyclovir than HSV, higher doses are required.

TABLE 49–1 Agents to treat or prevent herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections.

given multiple time a day.

	Route of Administration	Use	Recommended Adult Dosage and Regimen
Acyclovir[1]	Oral	First episode genital herpes treatment	400 mg tid or 200 mg 5 times daily × 7–10 days
		Recurrent genital herpes treatment	400 mg tid or 200 mg 5 times daily or 800 mg bid × 2–5 days or 800 mg tid × 2 days
		Genital herpes in the HIV-infected host treatment	400 mg 3–5 times daily × 5–10 days
		Genital herpes suppression in the HIV-infected host	400–800 mg bid–tid
		Herpes proctitis treatment	400 mg 5 times daily until healed
		Orolabial herpes treatment	400 mg 5 times daily × 5 days
		Varicella treatment (age ≥ 2 years)	800 mg qid × 5 days
		Zoster treatment	800 mg 5 times daily × 7–10 days
	Intravenous	Severe HSV treatment	5 mg/kg q8h × 7–10 days
		Mucocutaneous herpes in the immunocompromised host treatment	10 mg/kg q8h × 7–14 days
		Herpes encephalitis treatment	10–15 mg/kg q8h × 14–21 days
		Neonatal HSV infection treatment	10–20 mg/kg q8h × 14–21 days
		Varicella or zoster in the immunosuppressed host treatment	10 mg/kg q8h × 7 days
	Topical (5% cream)	Herpes labialis treatment	Thin film covering lesion 5 times daily × 4 days

Adverse effects:

Side effects of *acyclovir* treatment depend on the route of administration.

For example, local irritation may occur from topical application

Oral Administration: headache, diarrhea, nausea, and vomiting

Transient renal dysfunction may occur at high doses or in a dehydrated patient receiving the drug intravenously.

Resistance

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

Cross resistance to the other agents in this family occurs.

Valacyclovir

Valacyclovir is the L-valyl ester of acyclovir. It is rapidly converted to acyclovir after oral administration via first pass enzymatic hydrolysis in the liver and intestine, resulting in serum levels that are three to five times greater than those achieved with oral acyclovir and approximate those achieved with intravenous acyclovir.

Clinical uses

Approved uses of valacyclovir include treatment of

1. first or recurrent genital herpes
2. suppression of frequently recurring genital herpes
3. orolabial herpes
4. treatment for varicella and herpes zoster

→ this increase the compliance and the adherence of the patient to the drug.

Once-daily dosing of valacyclovir for chronic suppression in persons with recurrent genital herpes has been shown to markedly decrease the risk of sexual transmission

Foscarnet

Unlike most antiviral agents, *foscarnet* [fos-KAR-net] is not a purine or pyrimidine analog. Instead, it is a phosphonoformate (a pyrophosphate derivative) and does not require activation by viral (or cellular) kinases.

- Uses: CMV (retinitis and other CMV infections),Herpes simplex, and HIV.

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

Foscarnet

competitive inhibitors

works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis.
Mutation of the polymerase structure is responsible for resistant viruses.

***Foscarnet* is poorly absorbed orally and must be injected intravenously.**

It must also be given frequently to avoid relapse when plasma levels fall.
It is dispersed throughout the body, and greater than 10% enters the bone matrix, from which it slowly leaves.

The parent drug is eliminated by glomerular filtration and tubular secretion.

Foscarnet

Adverse effects :

- Nephrotoxicity (25%) is the most common side effect
- anemia, nausea, and fever

Due to chelation with divalent cations, hypocalcemia and hypomagnesemia are also seen.
In addition, hypokalemia, hypo- and hyperphosphatemia, seizures, and arrhythmias have been reported

Vidarabine

- **Selectively inhibits virally induced DNA polymerase more than the endogenous enzyme.**
  ↳ (human DNA polymerase)
- **Vidarabine is a chain terminator and is active against herpes simplex, varicella zoster, and vaccinia.**
- **Use is limited to topical treatment of severe herpes simplex infection.**
- **Before the introduction of acyclovir, it was used in the treatment of herpes simplex encephalitis**
- **Used in treatment of immunocompromised patients with herpetic and vaccinia keratitis and in keratoconjunctivitis**.

Ganciclovir

- **Same mechanism of action of Acyclovir, requires activation by triphosphorylation before inhibiting viral DNA polymerase causing termination of viral DNA elongation.**

- **Active against all Herpes viruses including CMV (100 times than acyclovir)**

- **Low oral bioavailability so, usually given I.V.**

- **Gel formulation is available for herpetic keratitis.**

Black Box warning

Ganciclovir

- **Most common adverse effects: bone marrow suppression (leukopenia 40%, thrombocytopenia 20%), and CNS effects (headache, behavioral, psychosis, coma, convulsions).**

- **1/3rd of patients have to stop treatment because of adverse effects.**

- **Drug of choice for CMV infections: retinitis, pneumonia, colitis.**

* it is a potential human carcinogen

* it is a teratogenecity X pregnancy

Famciclovir[1]	Oral	First episode genital herpes treatment	500 mg tid × 5–10 days
		Recurrent genital herpes treatment	1000 mg bid × 1 day
		Genital herpes in the HIV-infected host treatment	500 mg bid × 5–10 days
		Genital herpes suppression	250 mg bid
		Genital herpes suppression in the HIV-infected host	500 mg bid
		Orolabial herpes treatment	1500 mg once
		Orolabial or genital herpes suppression	250-500 mg bid
		Zoster	500 mg tid × 7 days
Valacyclovir[1]	Oral	First episode genital herpes treatment	1000 mg bid × 10 days
		Recurrent genital herpes treatment	500 mg bid × 3 days
		Genital herpes in the HIV-infected host treatment	500–1000 mg bid × 5–10 days
		Genital herpes suppression	500–1000 mg once daily
		Genital herpes suppression in the HIV-infected host	500 mg bid
		Orolabial herpes	2000 mg bid × 1 day
		Varicella (age ≥ 12 years)	20 mg/d tid × 5 days (maximum, 1 g tid)
		Zoster	1 g tid × 7 days
Foscarnet[1]	Intravenous	Acyclovir-resistant HSV and VZV infections	40 mg/kg q8h until healed
Docosanol	Topical (10% cream)	Recurrent herpes labialis	Thin film covering lesion q2h × 4 days
Penciclovir	Topical (1% cream)	Herpes labialis or herpes genitalis	Thin film covering lesions q2h × 4 days
Trifluridine	Topical (1% solution)	Acyclovir-resistant HSV infection	Thin film covering lesion 5 times daily until healed

[1]Dosage must be reduced in patients with renal insufficiency.

HSV, herpes simplex virus; VZV, varicella-zoster virus.