Antiviral Drugs for treatment ofHERPES SIMPLEX VIRUS (HSV& (VARICELLA ZOSTER VIRUS (VZV(INFECTIONS

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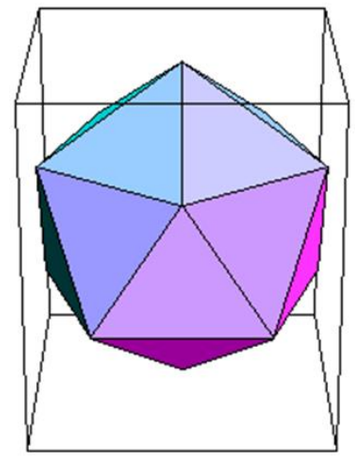


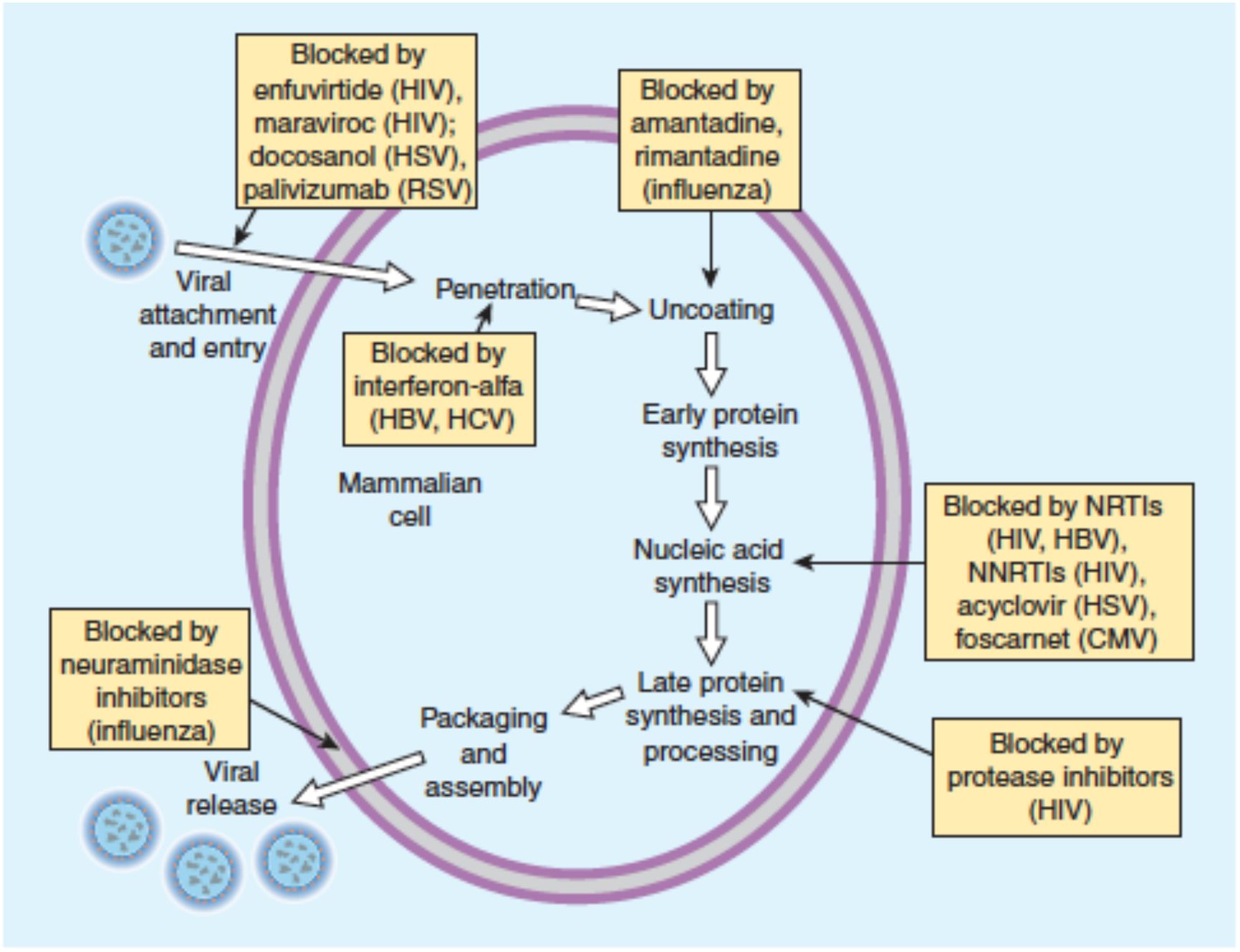


FIGURE 49–1 The major sites of antiviral drug action. Note: Interferon alfas are speculated to have multiple sites of action. (Modified and reproduced, with permission, from Trevor AJ, Katzung BG, Masters SB: *Pharmacology: Examination & Board Review*, 9th ed. McGraw-Hill, 2010.)

Patterns of Viral Infection

Acute infection:

- Complete viral clearance mediated by immune response
- E.g. Influenza, Rubella.

Latent infection :

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

Chronic infection (progressive or persistent :(

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

HSV and VZV infections

Oral nucleoside analogs licensed
.1acyclovir
.2valacyclovir
.3famciclovir.

All are well tolerated .
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

Nucleoside Analogs

- **Result in** “False” DNA building blocks **or nucleosides**(a nucleoside consists of a nucleobase and the sugar deoxyribose .(

- This abnormal nucleoside undergoes bio-activation by attachment of three phosphate residues

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

Acyclovir

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

- 10times 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.

Acyclovir

- Acyclovir requires three phosphorylation steps for activation .

- 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

- 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 :

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

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

Acyclovir

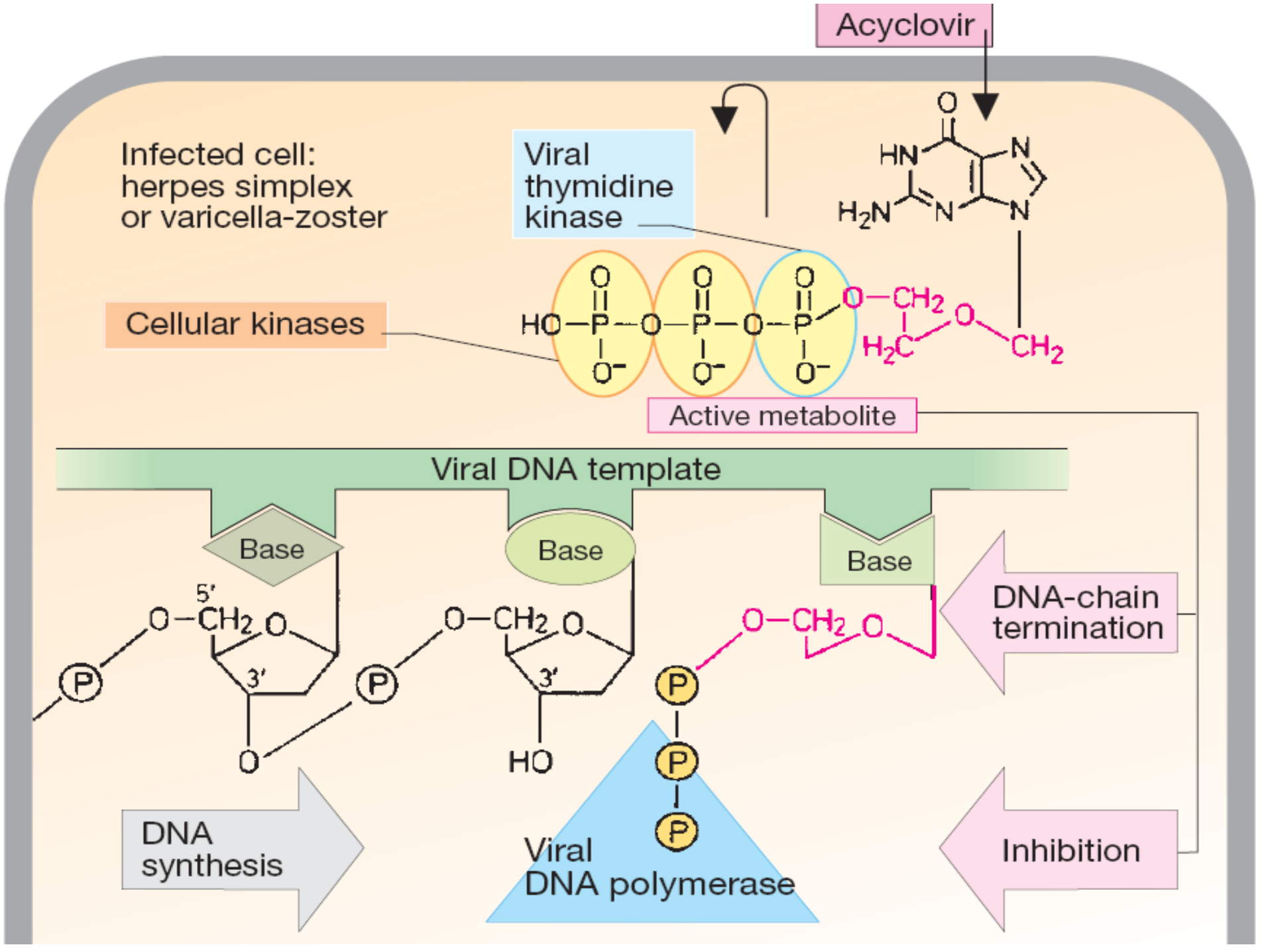
A Guanine analogue with activity against Herpes viruses.

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

Thymidine kinase — **Cellular kinases**

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

Resistance:
↓ .1activity of thymidine kinase
.2Altered DNA polymerase


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

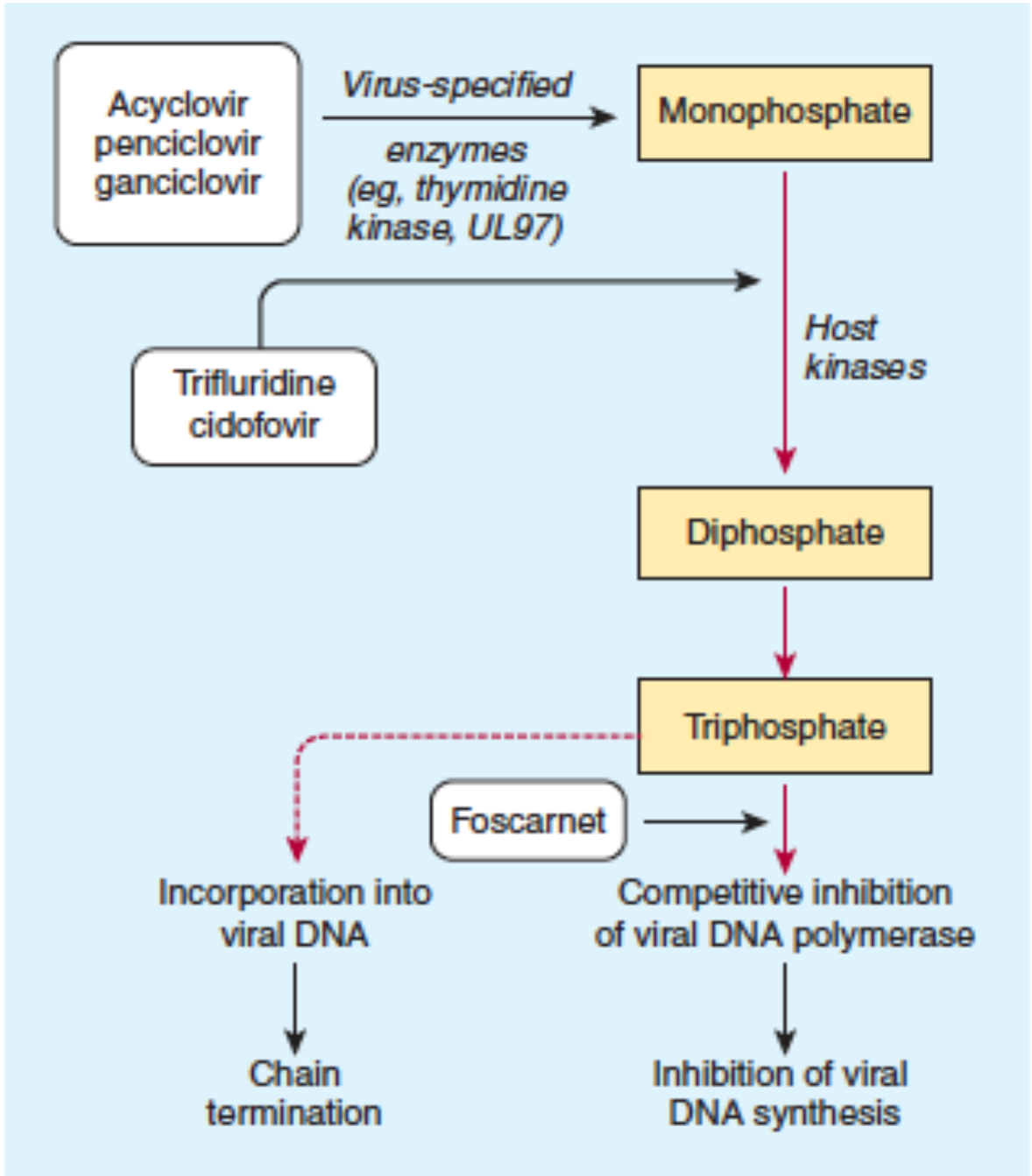


FIGURE 49–3 Mechanism of action of antiherpes agents.

Pharmacokinetics

- The bioavailability of oral acyclovir is low (15–20%) and is unaffected by food .

- An intravenous formulation is available.

- 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

Uses

- Oral acyclovir is used in first episodes of genital herpes oral acyclovir shortens the duration of symptoms by approximately 2 days, the time to lesion healing by 4 days, and the duration of viral shedding by 7 days .

- In recurrent genital herpes, the time course is shortened by 1–2 days .

- Treatment of first episode genital herpes does not alter the frequency or severity of recurrent outbreaks.

Clinical Use

- Oral acyclovir is only modestly beneficial in recurrent herpes labialis .

- In contrast, acyclovir therapy significantly decreases the total number of lesions, duration of symptoms, and viral shedding in patients with varicella .

- However, because VZV is less susceptible to acyclovir than HSV, higher doses are required.

Adverse effects:

Side effects of *acyclovir* treatment depend on the route of administration.
For example, local irritation may occur from topical applicatio

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.

Oral bioavailability is 54–70%, and cerebrospinal fluid levels are about 50% of those in serum.
Elimination half-life is 2.5–3.3 hours

Clinical uses

Approved uses of valacyclovir include treatment of first or recurrent genital herpes, suppression of frequently recurring genital herpes, as a 1-day treatment for orolabial herpes, and as treatment for varicella and herpes zoster (Table 49–1). 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

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

	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 × 3–5 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

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

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 .

- 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.

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 .

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.