بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 5

# Antivirals - Herpes


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# REMEMBER FROM GENERAL PHARMACOLOGY

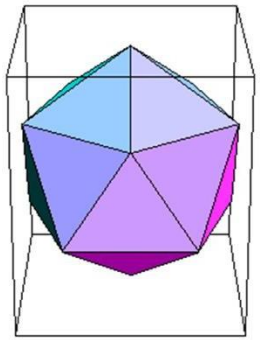
- **Prodrug:** An inactive compound that undergoes metabolic conversion in the body to release the active drug, improving its bioavailability, targeting, or tolerability – slide 7.

- **Bioavailability:** is the fraction of an administered dose that reaches systemic circulation unchanged and becomes available to exert its pharmacological effect – slide 13.

# Antiviral Drugs for treatment of

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

Alia Shatanawi



# Patterns of Viral Infection

- Each of these are characterized by a different interaction between the virus and the host immune system.

❖ **Acute infection** (most common):

- Complete viral clearance mediated by immune response. -> the virus won't stay in our body

  E.g. Influenza, Rubella.

❖ **Latent infection:**

- Initially, Acute infection but followed by virus persistence in non- infectious form. doesn't leave the body rather it stays in the body as dormant.
- Periodic reactivation of infection with viral shedding. (no active replicate but can reactivate at any time → with existence of some triggers or conditions (weakening of immune system, stress,etc) reactivating → shedding → symptoms).

E.g.

1- Chickenpox: can remain latent in the body and later reactivate in the form of shingles (herpes zoster).

2- Herpes simplex: remains dormant in the body and can reactivate intermittently, causing. herpes labialis (cold sores) or genital herpes.

# Patterns of Viral Infection

**Chronic infection (progressive or persistent):**

- Acute infection followed by lack of viral clearance → stays in the body and replicates continuously or it stays in the tissue.

- Virus continuously shed or present in tissues and cause symptoms or progressive damage of organs (long term health complications.

  **E .g. HIV, Hepatitis C.**

Check a quick comparison in the next slide ☺

# Patterns of Viral Infection - Con.



| | Acute infection | Latent infection | Chronic infection |
|---|---|---|---|
| Clearence | YES | NO | NO |
| Replicating continuously | NO | NO | YES |
| Reactivating | NO | YES | NO |
| Examples | Influenza, Rubella | Chickenpox, Herpes simplex | HIV, Hepatitis C |

Both latent and Chronic infections start as acute infection, the difference is that:

- Chronic infection: symptoms and replicating of the virus persist longer.
- Latent infection: express virus persistence in non- infectious form followed by periodic reactivation of infection with viral shedding.

# HSV and VZV infections

- Oral nucleoside analogs licensed

1. Acyclovir
2. Valacyclovir
3. famciclovir.

- All are well tolerated = 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, used for more severe or complicated infections; such as infections in immunocompromised patients or in cases of disseminated Herpes infection or in pateints who can't tolerate or can't take it orally* [1A].

- 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 with less frequent dosing compared to Acyclovir (Easier to adhere to)

# Nucleoside Analogs



- **Mechanism of action** (Interfere with the viral replication by) :

- **Result in** "False" DNA building blocks **or nucleosides** (a nucleoside consists of a nucleobase and the sugar deoxyribose).
- Structural modification of nucleosides-> abnormal nucleosides-> nucleosides are no longer proper as DNA component -> disruption of viral DNA synthesis.

- This abnormal nucleoside undergoes bio-activation by attachment of three phosphate residues
- **Acyclovir.**
- **Valacyclovir**(**a pro-drug** -needs to be activated in the body- **with better availability)**
- **Foscarnet**

# 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 drugs activated?

# Acyclovir



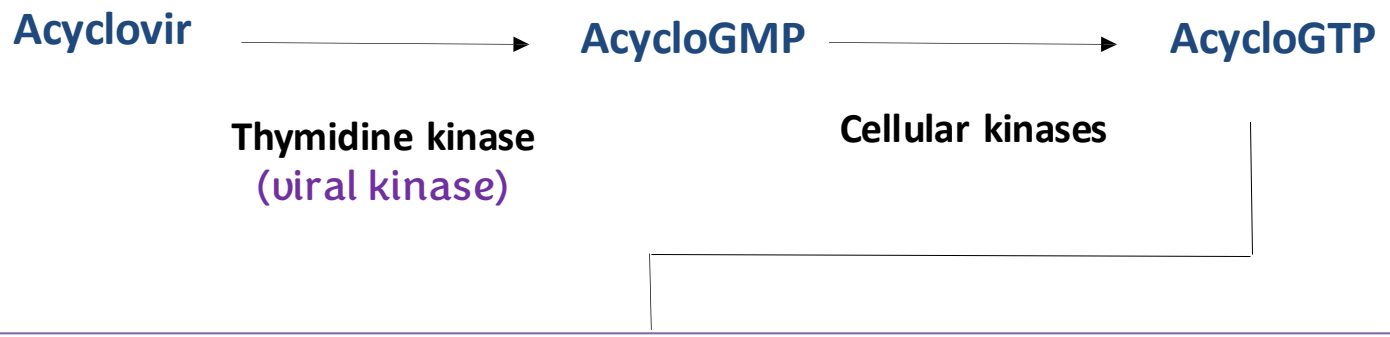
- Acyclovir requires three phosphorylation steps for activation (More clarification in the next slide)
- It is converted first to the monophosphate derivative by the virus specified thymidine kinase and then to the di- and triphosphate compounds by host cell enzymes → allow the drug to be incorporated into the viral DNA.
- 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 deoxy GTP 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.



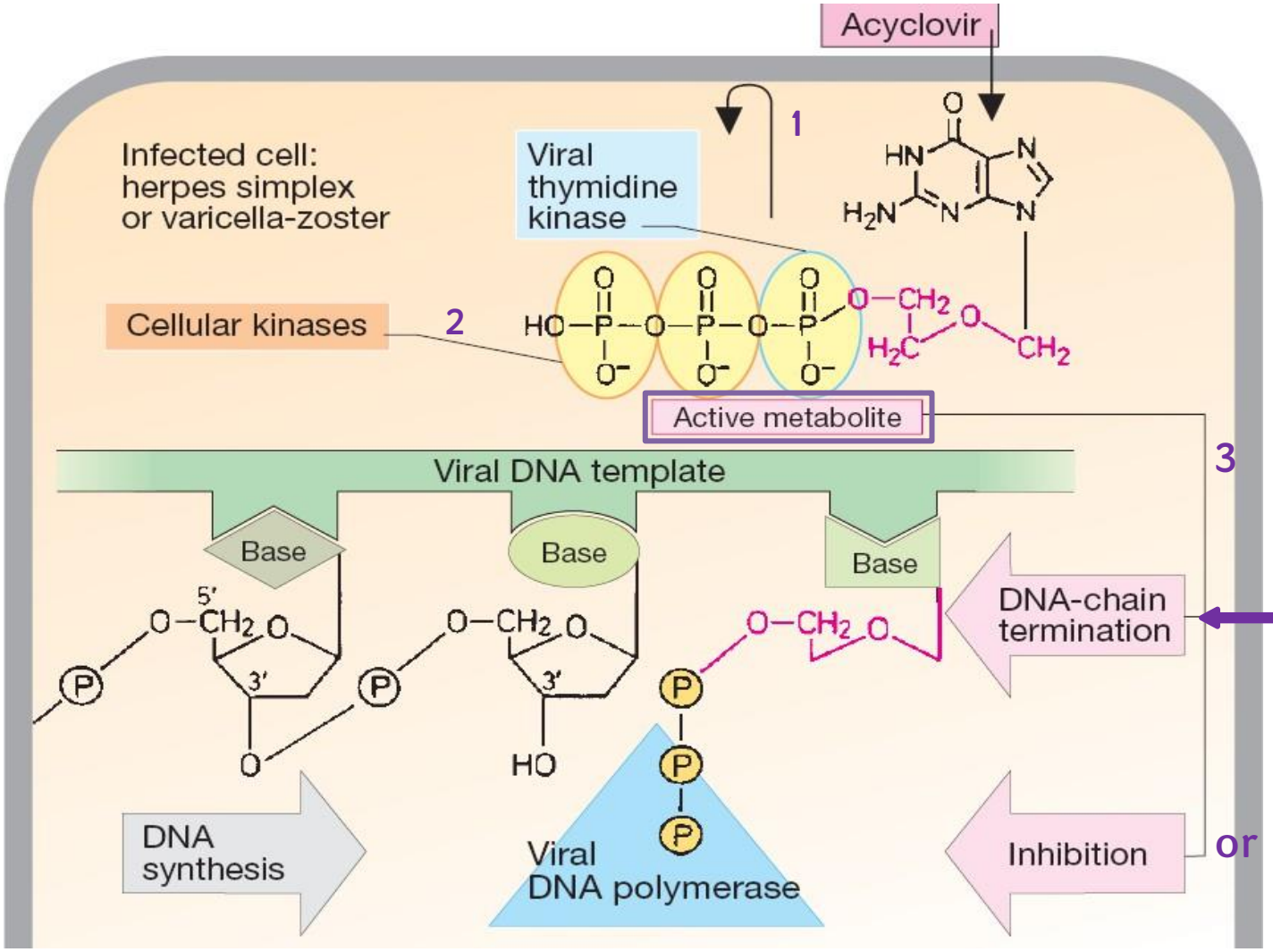

After activation Acyclovir can work in two mechanisms:

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

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

# Acyclovir activation & action






Incorporating in the elongation of DNA chain leading to:

**All are nucleoside analogs**

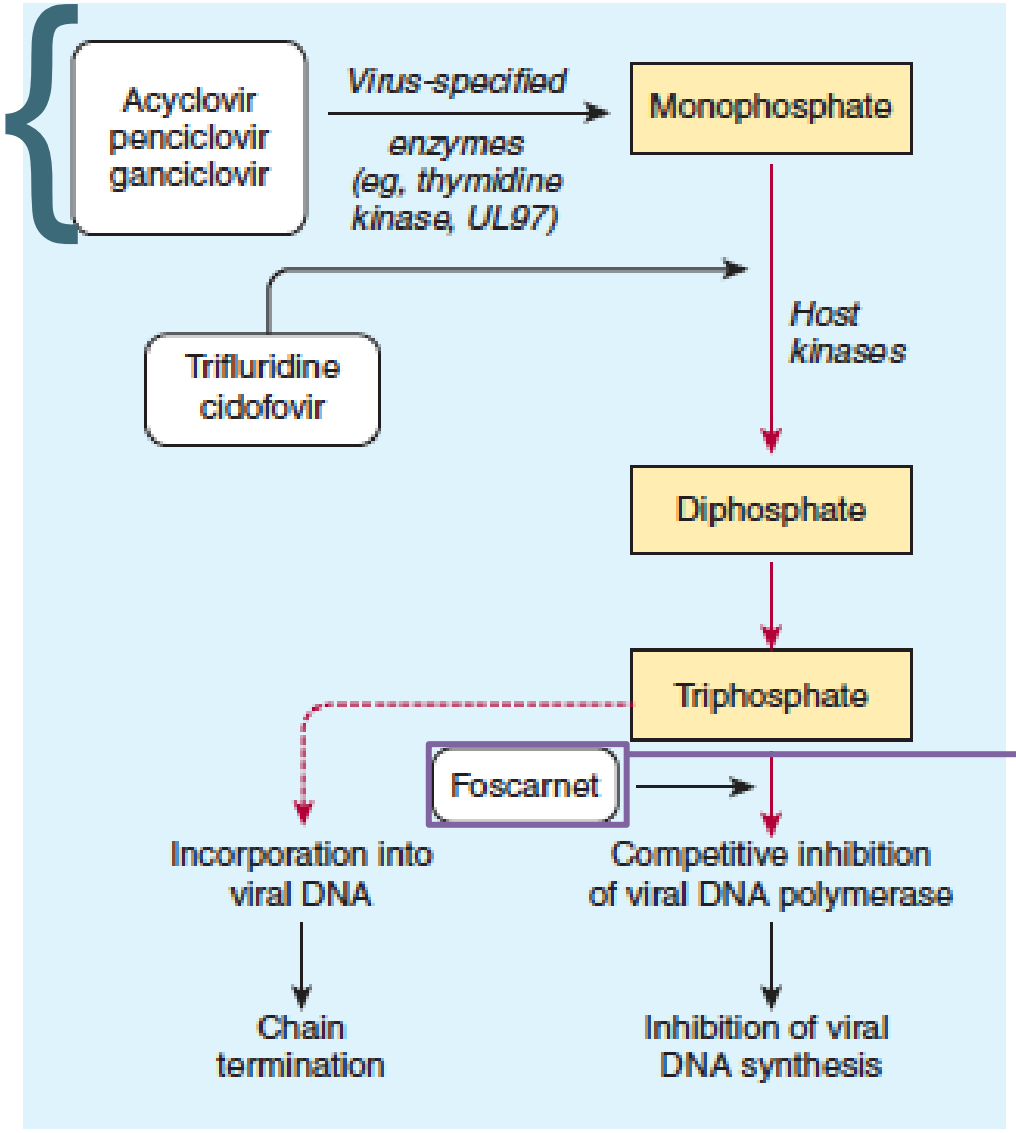



**FIGURE 49–3** Mechanism of action of antiherpes agents.

- Foscarnet:

  - Unlike Acyclovir and Valacyclovir (which are nucleoside analogs) Foscarnet is a **non- nucleoside antiviral.**

  - It directly inhibits the viral DNA, it causes competitive inhibition of viral DNA polymerase (the enzyme responsible for DNA synthesis of the virus).

  - It does so by interfering with the enzyme function preventing the addition of new nucleosides to the growing DNA chain.

# Pharmacokinetics

حسبي الله لا إله إلا هو عليه توكلت
و هو رب العرش العظيم

- The bioavailability of oral acyclovir is low (15–20%) and is unaffected by food.
- An intravenous formulation is available check slide 6(*1A).
- Topical formulations (Direct application) produce high local 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 = quickly elimination of it multiple doses of the drug administered for the patient whether oral or IV formulation.

· This slide compares the effectiveness of oral acyclovir in treating recurrent herpes labialis versus varicella infection.

# Clinical Use

- Oral acyclovir is **only <u>modestly beneficial</u>** in recurrent herpes labialis (cold sores) .
  = not a definitive treatment

- This is maybe because the virus can have a predictable course. While acyclovir can shorten the duration and reduce the number of outbreak, its effects are limited compared to other treatment options for HSV.

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

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

Due to the variation in effectiveness, we need to tailor the antiviral therapy based on: the type of infection, the virus involved and the patient's condition.

This is the first part of the table.
(Go to slide 26 for the second part).

Focus on the different uses

The Dr. mentioned all the uses during the lecture.

**No need to memorize the doses!**

- Just notice the differences between the doses for the different drugs.

**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 |
| | can lead to | * 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 |

- Also, notice that the half-life of this drug is short, so it has to be administered multiple times a day.
- This can be a drawback because multiple dosing will lower the adherence of the patient to take proper doses of the drug.

## 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

- **Mechanisms of resistance:**

1) **Altered or deficient thymidine kinase** (the enzyme that's needed for the first phosphorylation for the activation of these nucleotide analogues)

2) **Altered** (mutated) **or deficient DNA polymerases** (Which can hinder the binding between the drug and the DNA polymerase; Thus less inhibition of the DNA polymerase).

- **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

  - The low dose increases the patient's compliance.

- 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.**

Important!

➢ Main use/recommendation:-

*Like HIV patients*

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

# Foscarnet

➢ Mechanism of action:

- **Works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis.**
  → So it's a competitive inhibitor of these DNA polymerases.

- **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** (Fall below the minimum effective concentration).

- **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.** (this is regarding the clearance of the drug).

# Foscarnet

## Adverse effects :

- **Nephrotoxicity (25%) is the most common side effect**
- **Less commonly: 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

## ➢ Mechanism of action:

- **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 more effective in the treatment of CMV than acyclovir).**

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

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

# Ganciclovir

This drug has a Blackbox warning!

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

- It's also a potential human carcinogen, mutagen (can lead to mutations that increase risk of cancer) and teratogen (contraindicated in pregnancy).

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

Important!

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

**Continuation of the table in slide 15.**

The Dr. Mentioned all the uses during the lecture.

| | | | |
|---|---|---|---|
| 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.

**"The last 3 drugs, we didn't talk about , they're mainly used topically for the treatment of herpes labialis or herpes genitalis".**

**Dr.Alia said.**

# رسالة من الفريق العلمي:


"You don't need a perfect plan—you just need a first step."

# For any feedback, scan the code or click on it.

Corrections from previous versions:

| Versions | Slide # and Place of Error | Before Correction | After Correction |
|---|---|---|---|
| V0 → V1 | | | |
| V1 → V2 | | | |