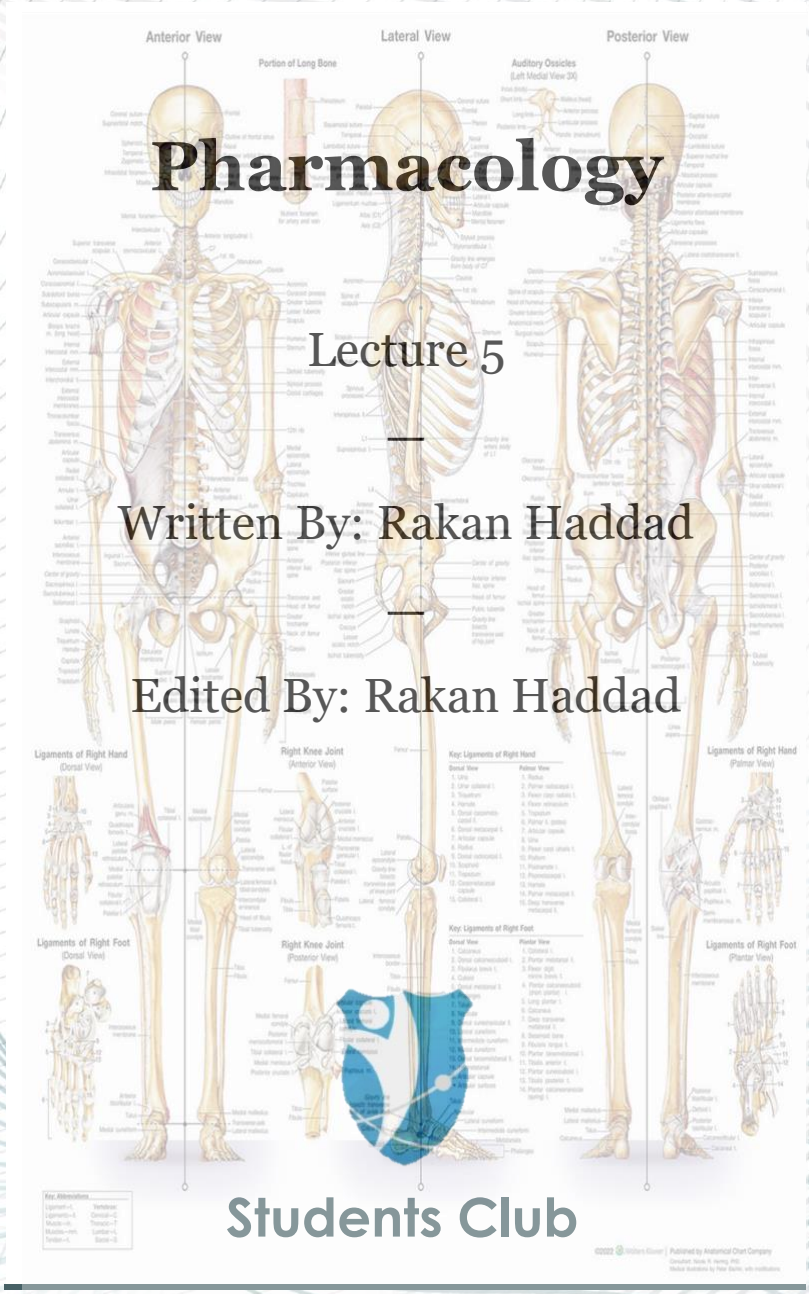
MUSCULOSKELETAL SYSTEM



Pharmacology

Lecture 5

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Students Club

- Helloooo… in this lecture we will discuss the anti-viral drugs that are used for the treatment of: Herpes Simplex Virus (HSV)/ Varicella Zoster Virus (VZV) Infections! This will be the last pharmacology lecture for this system and it isnt difficult so grab your chips and lets start!

- **Patterns of Viral Infection**

→ These patterns are characterized by a different interaction between the virus and the host immune system.

1) **Acute infection** (most common)**:**

- Complete viral clearance mediated by immune response & the virus wont stay in our bodies.
- E.g. Influenza, Rubella.

2) **Latent infection:**

- Initially Acute infection but followed by virus persistence in non- infectious form, here the virus doesn't leave the body but rather it stays in the body as dormant.
- Periodic reactivation of infection with viral shedding. (no active replication but can reactivate at any time due to the existence of some triggers or conditions such as the weakening of the immune system or stress which causes: reactivation→ shedding→ symptoms.
- E.g. 1- Chickenpox: may 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.

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

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

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

  →e.g. HIV, Hepatitis C.

- **HSV and VZV infections:**

→Oral nucleoside analogs licensed:

1. Acyclovir
2. Valacyclovir
3. famciclovir.

All are well tolerated which means they are of good safety profile with minimal adverse effects in 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, it is 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.

→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 in comparison to Acyclovir➔ Easier to adhere to. When there is multiple dosing the patient usually stops the medication (low adherence) in cases such as giving acyclovir.

- **Nucleoside Analogs:**

➔**Mechanism of action**➔Interference with viral replication:

- **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 ,which needs to be activated, with better availability)

• Foscarnet

1) 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.

- 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 which allows 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

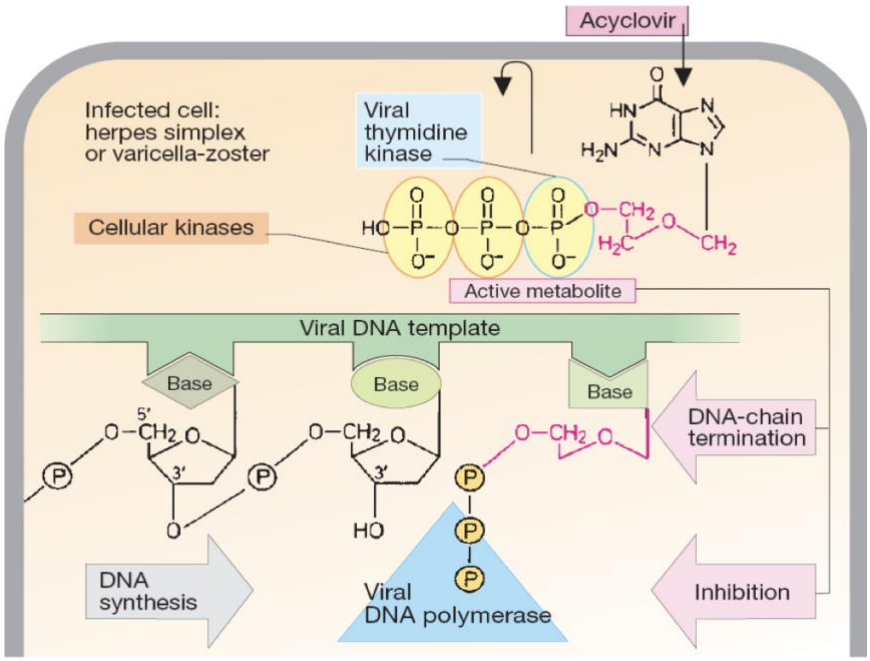
A Guanine analogue with activity against Herpes viruses.

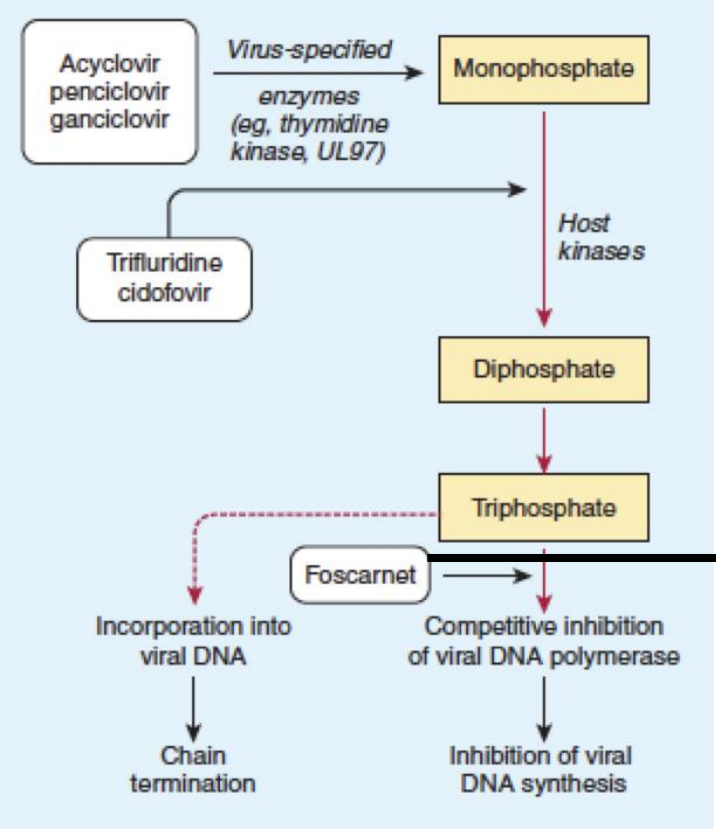
Acyclovir → AcycloGMP → AcycloGTP

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





→ Unlike Acyclovir and Valacyclovir (which are nucleoside analogs) Foscarnet is a non nucleoside antiviral.
→It directly inhibits the viral DNA, causing 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

- **<u>Pharmacokinetics:</u>**
  - The bioavailability of oral acyclovir is low (15–20%) and is unaffected by food.
  - An intravenous formulation is available
  - 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 means quick elimination of the drug→multiple doses of the drug administered for the patient whether oral or IV formulation.

- **Clinical Use:**

- Oral acyclovir is only modestly beneficial in recurrent herpes labialis (cold sores), so its not a definitive treatment.

  → This may be because the virus can have a predictable course. While acyclovir can shorten the duration and reduce the number of outbreaks, 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.

→ There is a variation in effectiveness, that's why we need to tailor the antiviral therapy based on:

1) the type of infection.
2) the virus involved.
3) the patient's condition.

	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

- **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 is needed for the first phosphorylation for the activation of these nucleotide analogues)

  2-Altered (mutated) or deficient DNA polymerases (Which can stop the binding between the drug and the DNA polymerase which means 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.

- **<u>Valacyclovir:</u>**

• 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

→ When a medication has a low dose it tends to increase 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.**
- Approved for CMV retinitis in immunocompromised hosts (Like HIV/ AIDS patients) and for acyclovir- resistant HSV infections.

- **Mechanism of action**:

• Works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis ➔ Acts as 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 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.

- **Foscarnet Adverse Effects:**
  - Nephrotoxicity (25%) is the most common side effect
  - Less common: 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

- **<u>Vidarabine: MOA:</u>**

- 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**: BLACKBOX WARNING

  • 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.

  • 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) it can lead to mutations that increase risk of cancer, and teratogenic (contraindicated in pregnancy).
  •Due to that, 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


Good Luck Drs!