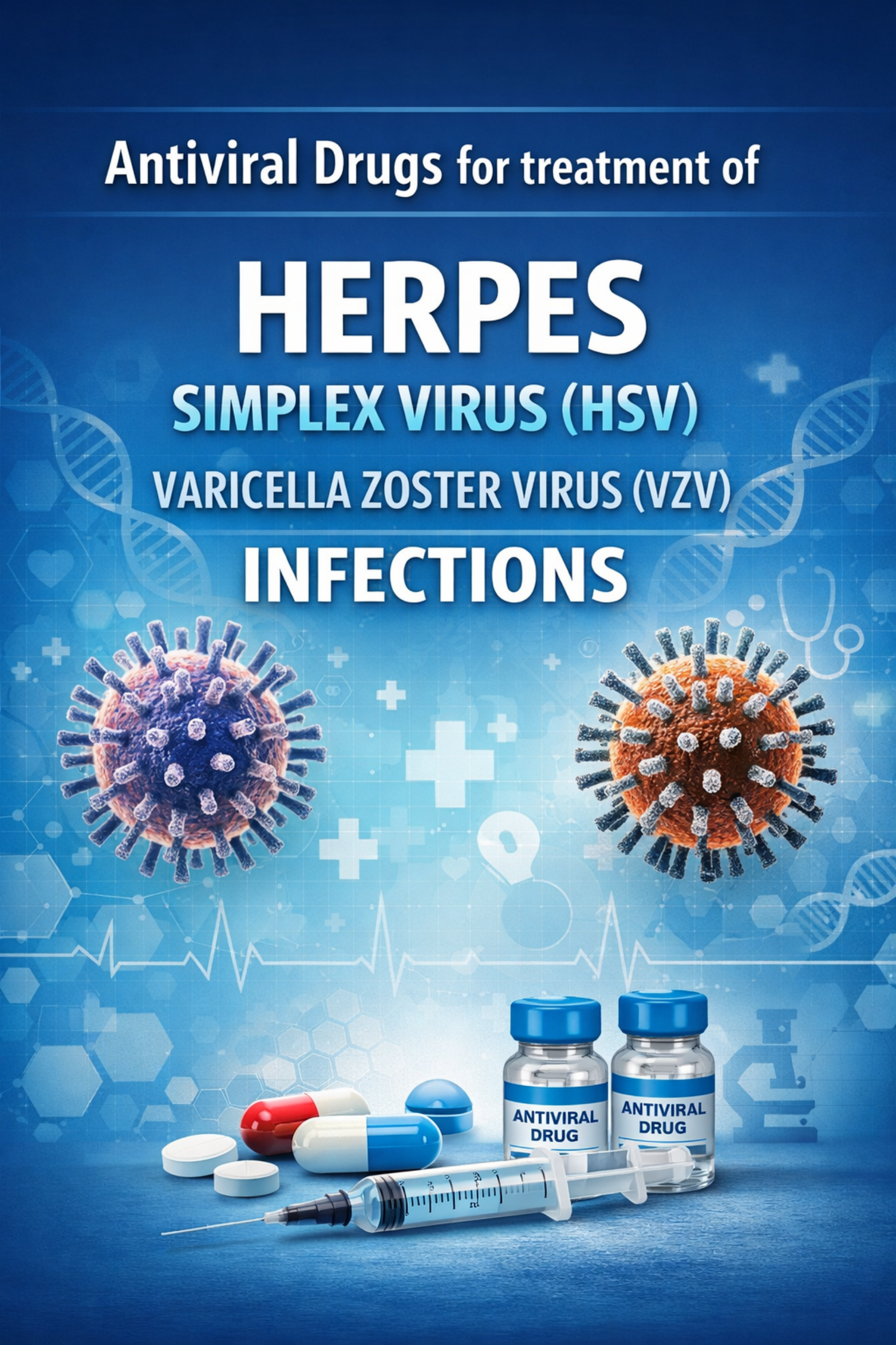
Antiviral Drugs for treatment of

HERPES

SIMPLEX VIRUS (HSV)

VARICELLA ZOSTER VIRUS (VZV)

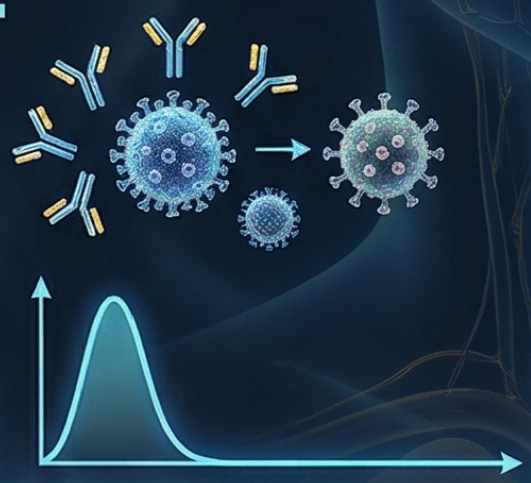
INFECTIONS



1. Patterns of Viral Infection

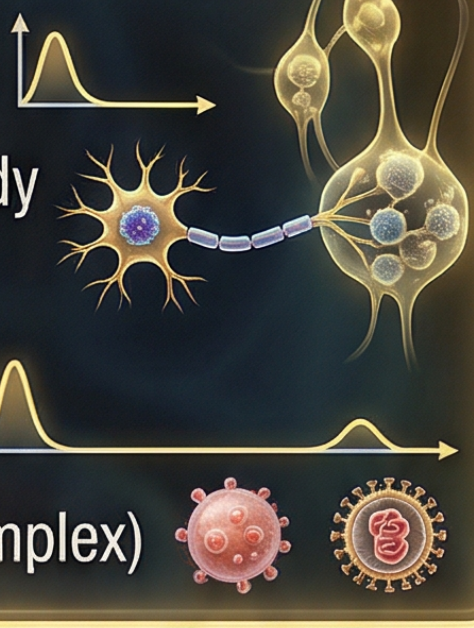
ACUTE INFECTION:

- The virus is completely cleared by the body's immune response
- (e.g., Influenza, Rubella)



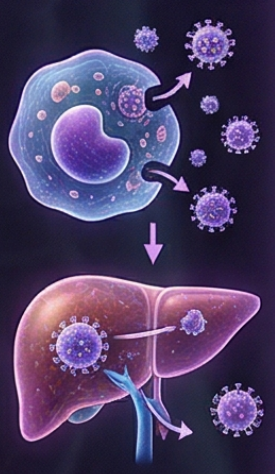
LATENT INFECTION:

- Starts as an acute infection
- but the virus stays in the body in a non-infectious form
- It reactivates periodically, causing viral shedding
- (e.g., Chickenpox, Herpes simplex)



CHRONIC INFECTION:

- The acute infection is not cleared
- and the virus is continuously present or shed in tissues
- (e.g., HIV, Hepatitis C)



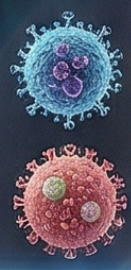
1. Patterns of Viral Infection

- **Acute infection:** The virus is completely cleared by the body's immune response (e.g., Influenza, Rubella).
- **Latent infection:** Starts as an acute infection, but the virus stays in the body in a non-infectious form. It reactivates periodically, causing viral shedding (e.g., Chickenpox, Herpes simplex).
- **Chronic infection:** The acute infection is not cleared, and the virus is continuously present or shed in tissues (e.g., HIV, Hepatitis C).

2. Oral Nucleoside Analogs (General Overview)

GENERAL OVERVIEW & USES

- Acyclovir, Valacyclovir, and Famciclovir are oral drugs.



- Used to treat Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV).

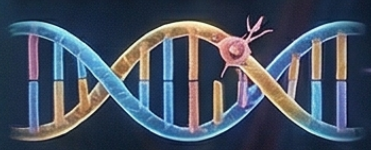
TOLERANCE & ROUTE

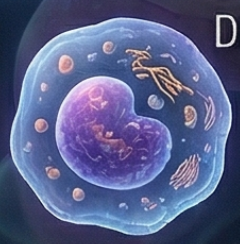
- These drugs are generally well tolerated.
- Acyclovir is the only drug among the three available for intravenous (IV) use in the US.

EFFICACY COMPARISON

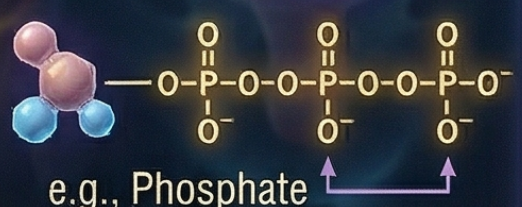
- Similar efficacy for treating HSV.
- But famciclovir and valacyclovir are slightly better for treating herpes zoster.

MECHANISM OF ACTION





- Act as ‘false’ DNA building blocks.
- To become active, they must undergo bio-activation by attaching three phosphate residues.



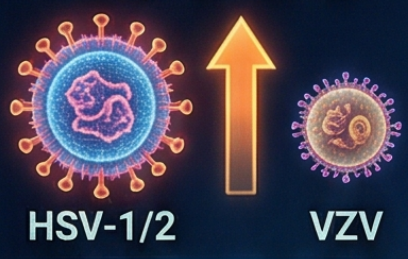
2. Oral Nucleoside Analogs (General Overview)

- Acyclovir, Valacyclovir, and Famciclovir are oral drugs used to treat Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV).
- These drugs are generally well tolerated.
- Acyclovir is the only drug among the three available for intravenous (IV) use in the US.
- They have similar efficacy for treating HSV, but famciclovir and valacyclovir are slightly better for treating herpes zoster.
- **Mechanism:** They act as "false" DNA building blocks. To become active, they must undergo bio-activation by attaching three phosphate residues.

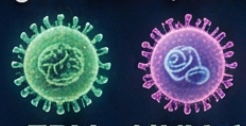
3. ACYCLOVIR

EFFECTIVENESS

10x MORE POTENT against **HSV-1 & HSV-2** compared to **VZV**.

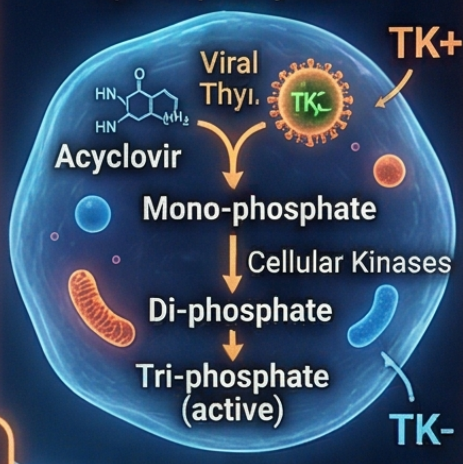


WEAKER ACTIVITY against **EBV, CMV, and HHV-6.**



ACTIVATION

Requires **THREE STEPS** of phosphorylation.



SELECTIVELY ACTIVATED only inside **INFECTED CELLS.**

MECHANISM OF ACTION

IRREVERSIBLY BINDS to viral **DNA POLYMERASE.**

TERMINATES viral **DNA CHAIN,** stopping synthesis.

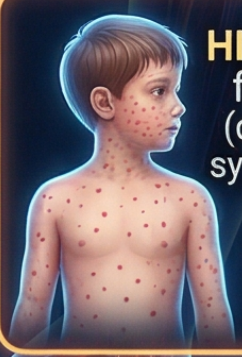
PHARMACOKINETICS

ORAL BIOAVAILABILITY VERY LOW (15-20%) & unaffected by food.

CLEARED by **KIDNEYS. HALF-LIFE 2.5-3 HOURS.**

TOPICAL CREAMS: high local concentrations; do **NOT** enter **SYSTEMIC BLOODSTREAM.**

CLINICAL USE



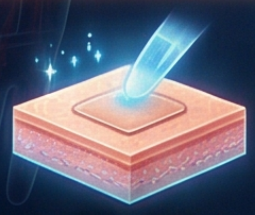
HIGHLY EFFECTIVE for **VARICELLA** (decreases lesions, symptoms, shedding).

REQUIRES HIGHER DOSES for **VZV** than for HSV.

Modestly beneficial for recurrent **COLD SORES** (herpes labialis).

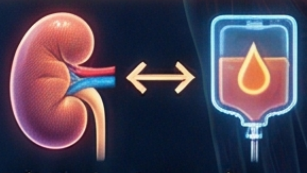
MODESTLY BENEFICIAL for recurrent **COLD SORES**

SIDE EFFECTS



TOPICAL: Local irritation.

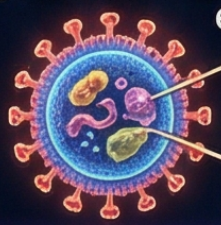
ORAL: Headaches, nausea, vomiting, diarrhea.



IV (High doses) or **DEHYDRATION:** Transient kidney dysfunction.

RESISTANCE

VIRUSES RESIST by **ALTERING/LOSING** Thymidine Kinase or DNA Polymerase enzymes.



MOSTLY SEEN in **IMMUNOCOMPROMISED PATIENTS.**

Causes **CROSS-RESISTANCE** to similar drugs.

3. Acyclovir

- **Effectiveness:** It is 10 times more potent against HSV-1 and HSV-2 compared to VZV. It has weaker activity against EBV, CMV, and HHV-6.

- **Activation:** It requires three steps of phosphorylation. The first step relies on a *viral* enzyme (thymidine kinase). Because of this, the drug is selectively activated only inside infected cells.

- **Mechanism of Action:** Once fully activated, it irreversibly binds to the viral DNA polymerase and terminates the viral DNA chain, stopping synthesis.

- **Pharmacokinetics:** Oral bioavailability is very low (15-20%) and is not affected by food. It is cleared by the kidneys and has a half-life of 2.5-3 hours. Topical creams have high local concentrations but do not enter the systemic bloodstream.

- **Clinical Use:** It is highly effective for varicella (decreases lesions, symptoms, and shedding) but requires higher doses for VZV than for HSV. It is only modestly beneficial for recurrent cold sores (herpes labialis).

- **Side Effects:** Topical forms can cause local irritation. Oral forms can cause headaches, nausea, vomiting, and diarrhea. High IV doses or dehydration can cause transient kidney dysfunction.

- **Resistance:** Viruses become resistant by altering or losing their thymidine kinase or DNA polymerase enzymes, mostly seen in immunocompromised patients. This causes cross-resistance to similar drugs.

4. VALACYCLOVIR

PRO-DRUG & CONVERSION

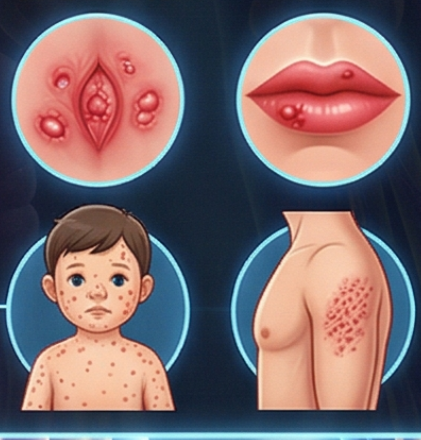
- It is a pro-drug (an ester) of Acyclovir.
- When taken orally, enzymes in the liver and intestines rapidly convert it into Acyclovir.

MAJOR ADVANTAGE

- This conversion results in blood serum levels that are 3 to 5 times higher than oral Acyclovir, making it nearly as effective as IV Acyclovir.

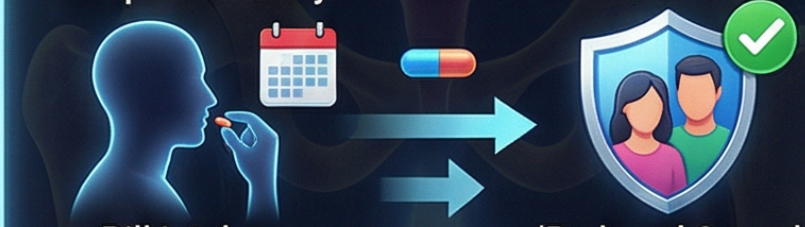
INDICATIONS

- Used for genital herpes, orolabial herpes, varicella, and zoster.



CHRONIC SUPPRESSION

- Taking it once daily for chronic suppression greatly reduces the risk of transmitting genital herpes sexually.



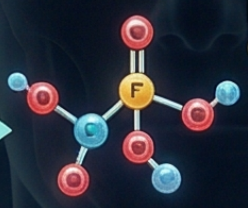
4. Valacyclovir

- It is a pro-drug (an ester) of Acyclovir.
- When taken orally, enzymes in the liver and intestines rapidly convert it into Acyclovir.
- **Major Advantage:** This conversion results in blood serum levels that are 3 to 5 times higher than oral Acyclovir, making it nearly as effective as IV Acyclovir.
- **Uses:** Used for genital herpes, orolabial herpes, varicella, and zoster. Taking it once daily for chronic suppression greatly reduces the risk of transmitting genital herpes sexually.

5. FOSCARNET

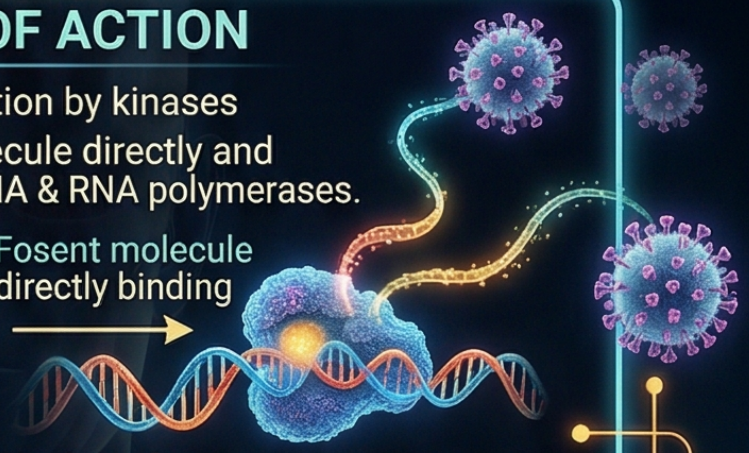
MECHANISM OF ACTION

- Does NOT require activation by kinases
- Phosphonoformate molecule directly and reversibly inhibits viral DNA & RNA polymerases.



Foscarnet

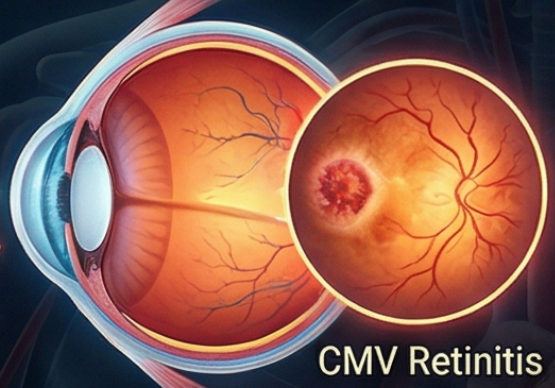
Fosent molecule directly binding



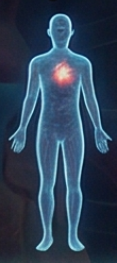
Blocks polymerase enzyme complex, stopping glowy replication strands

APPROVED USES

- CMV Retinitis in immunocompromised patients
- HSV infections resistant to Acyclovir



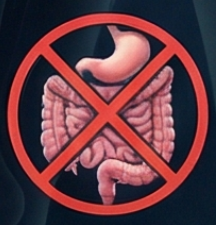
CMV Retinitis

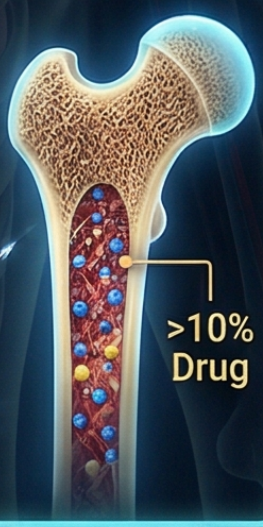


Acyclovir-resistant HSV

PHARMACOKINETICS

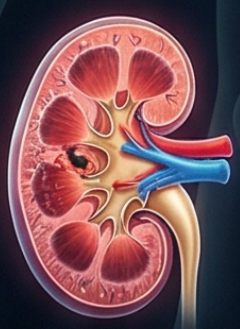
- Poorly absorbed orally
- Must be given via frequent IV injection
- >10% Drug in Bone Matrix



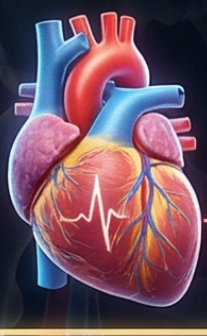


SIDE EFFECTS & TOXICITY

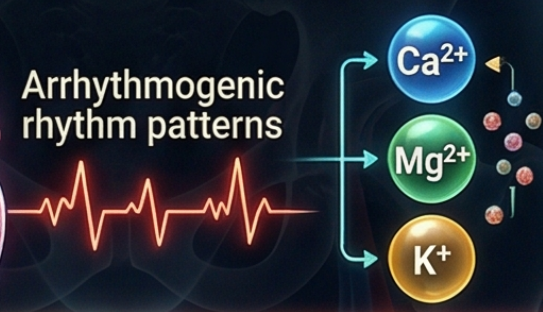
- Highly toxic
- Nephrotoxicity (25% patients)
- Chelates with minerals causing dangerous drops in calcium, magnesium, potassium, leading to seizures and arrhythmias.



Nephrotoxicity 25%



Arrhythmogenic rhythm patterns



HIGHLY TOXIC

5. Foscarnet

- **Mechanism:** Unlike Acyclovir, Foscarnet is a phosphonoformate and does *not* require activation by viral or cellular kinases. It directly and reversibly inhibits viral DNA and RNA polymerases.

- **Uses:** Approved for Cytomegalovirus (CMV) retinitis in immunocompromised patients and for HSV infections that are resistant to Acyclovir.

- **Pharmacokinetics:** It is poorly absorbed orally and must be given through IV injection frequently. More than 10% of the drug enters the bone matrix.

- **Side Effects:** Highly toxic. Nephrotoxicity (kidney damage) occurs in 25% of patients. It chelates with minerals, causing dangerous drops in calcium, magnesium, and potassium, which can lead to seizures and arrhythmias.

6. VIDARABINE & GANCICLOVIR: COMPARATIVE OVERVIEW

VIDARABINE: MECHANISM

- Selective inhibitor of viral DNA polymerase.

- Selective activity.

VIDARABINE: USES

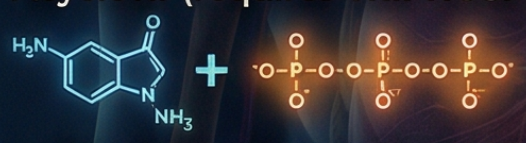
- **HISTORICAL** (Pre-Acyclovir): **HSV ENCEPHALITIS.**

- **CURRENT:** Mostly limited to **TOPICAL TREATMENTS** for **SEVERE HSV** or **EYE INFECTIONS (KERATITIS).**

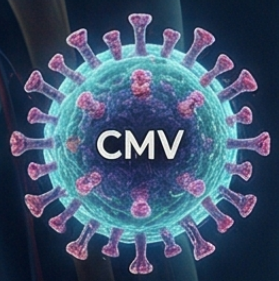
- In immunocompromised patients.

GANCICLOVIR: ACTIVATION & POTENCY

- Exact same activation mechanism as Acyclovir (requires **TRIPHOSPHORYLATION).**



- **100 TIMES MORE ACTIVE AGAINST CMV THAN ACYCLOVIR.**



CMV virus

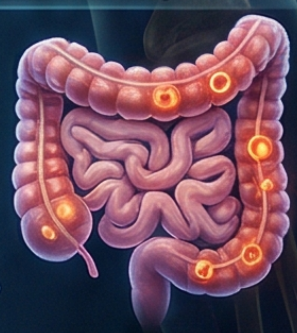
- Drug of choice for severe CMV.

GANCICLOVIR: PRIMARY INDICATIONS (Severe CMV)

RETINITIS

PNEUMONIA

Drug of choice

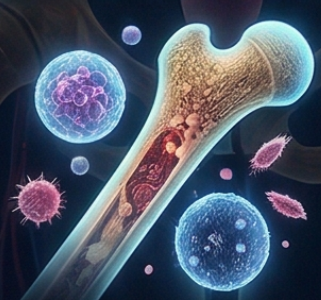


COLITIS

GANCICLOVIR: SEVERE SIDE EFFECTS

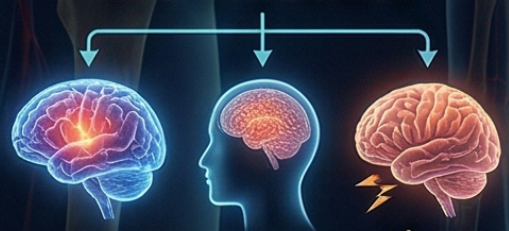
VERY SEVERE SIDE EFFECTS

VERY MARROW SUPPRESSION (causes 1/3 of patients to stop treatment).



BONE MARROW SUPPRESSION (low white blood cells and platelets).

CENTRAL NERVOUS SYSTEM EFFECTS like psychosis, coma, and convulsions.



6. Vidarabine & Ganciclovir

- **Vidarabine:** A chain terminator that selectively inhibits viral DNA polymerase. Before Acyclovir, it was used for HSV encephalitis. Today, its use is mostly limited to topical treatments for severe HSV or eye infections (keratitis) in immunocompromised patients.

- **Ganciclovir:** Has the exact same activation mechanism as Acyclovir (requires triphosphorylation).

- **Ganciclovir Uses:** It is 100 times more active against CMV than Acyclovir and is the drug of choice for severe CMV infections (retinitis, pneumonia, colitis).

- **Ganciclovir Side Effects:** Very severe side effects causing 1/3 of patients to stop treatment. It causes bone marrow suppression (low white blood cells and platelets) and central nervous system effects like psychosis, coma, and convulsions.
