# Antiviral medications for Herpes simplex

## Systemic and Topical

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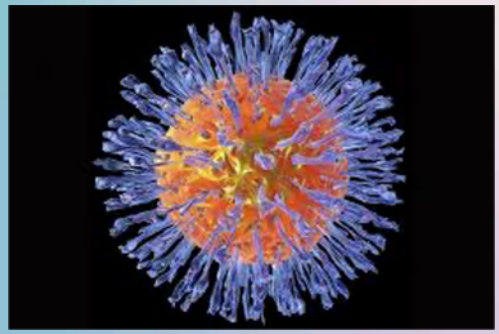
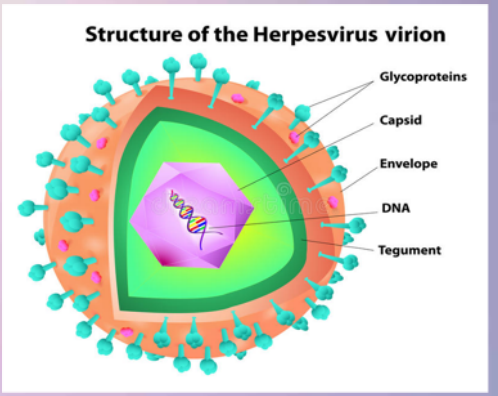




# Herpes Virus Therapy

Herpes simplex virus is a **highly contagious** disease. It is important as a dental professional to know the different types of medications that a person with this disease would need to help them with healing and prevent any further spreading of the infection.

According to CDC a patient with active herpes lesions must not be treated in the dental office until a few weeks after the initial outbreak.

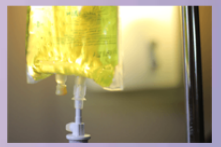
A clinician with a herpes outbreak should not treat patients and work for a minimum of two weeks while having an active outbreak.

Unfortunately no cure exists once infected with the virus only medications for treatment of herpes.

- Oral Antiviral Agents
  - Prescription capsules or tablets to take orally


- Topical Antiviral Agents
  - Over the counter external application comes in cream or tablet.

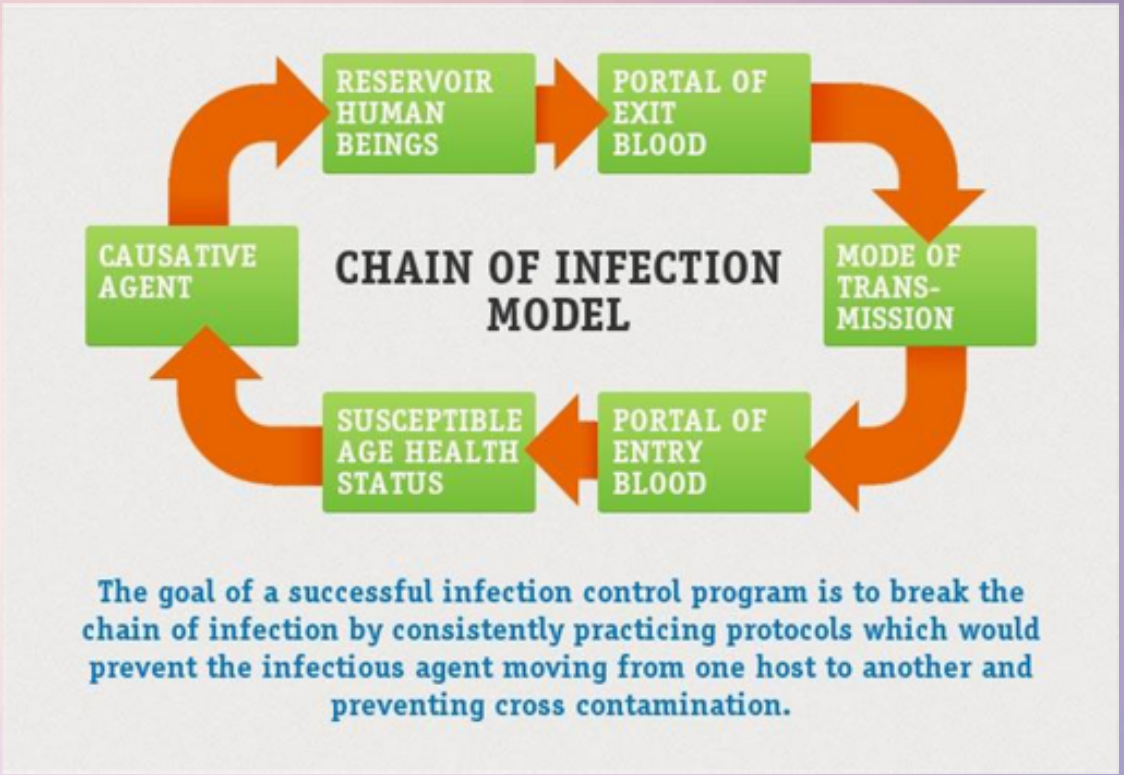

- Injections
  - IV acyclovir also an option for more severe cases or immunocompromised patients



# CHAIN OF INFECTION

Herpes is spread by:

- Examining a patient with active lesion and clinician spreading it to other areas of the person mouth.
- Dental clinician using a ultrasonic or handpiece and spreading by aerosol.
- Virus surviving on cloth, plastic and skin for several hours.
- Aerosol of the virus getting into clinician or patients eyes.
- Micro tears in gloves can occur during exam causing infection on clinicians hands.
- Virus continues shedding into saliva days after lesions have healed.

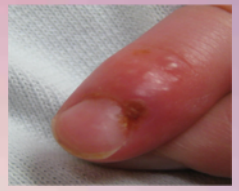



https://www.oshamanual.com/osha_dentistry.html

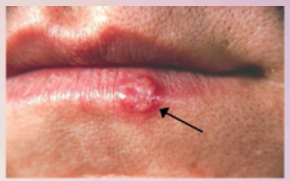
Sheela Alburquerque

# Clinical Infections in a Dental office

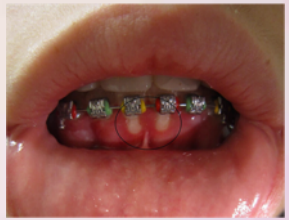
**Herpes Whitlow:** Can develop soon after direct contact with Herpes Simplex Virus causing infection and development of small painful fluid filled blister like lesions on finger called whitlow.

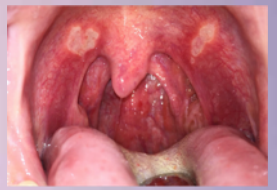


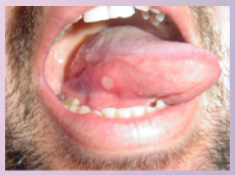
**Herpes Labialis:** Infection of the lips often called cold sores or fever blisters. Symptoms can occur with small fluid filled blisters, burning, itchy, painful



**Oral Herpes:** Develops small fluid filled blisters on different areas in the oral cavity like on the gingiva, ventral or lateral portion of tongue, palatine or other areas in the mouth.

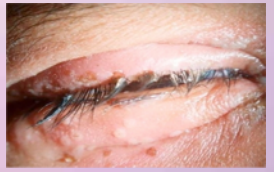


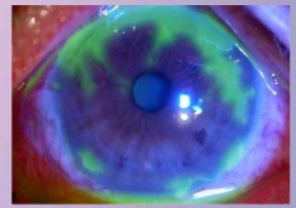




**Herpes in the eye:** Can cause scarring of the cornea, loss of vision, or blindness

- **Herpes Keratitis:** Corneal layer or epithelium
- **Stromal Keratitis:** Deeper layers of cornea
- **Irirdocyclittis:** Iris and surrounding tissues

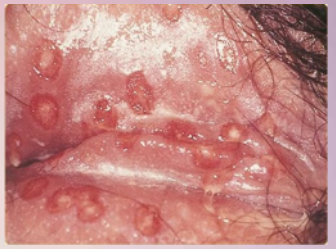




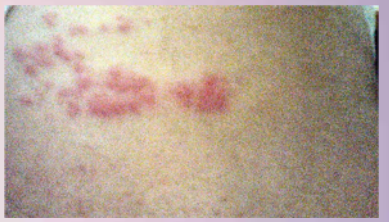
# Other Herpes Simplex Virus Conditions

The dental professional must be familiar with all diseases that the Herpes virus involves so we can better understand why a patient is taking certain medications

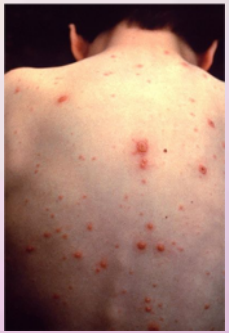
**Genital Herpes:** Herpes simplex can also affect the genital area. Usually sexually transmitted. Resulting in fluid-filled blister, itchy and painful.



**Herpes Zoster (shingles):** Can occur when a person has had chickenpox in the past and the virus lies latent then becomes reactivated in the body causing painful rash with blisters.



**Varicella (chickenpox):** Highly contagious viral infection causing itchy, blister-like rash on the skin. Now there exist a vaccine to prevent chickenpox so it can be rare for some who receive this vaccine to become infected with chickenpox.



Ying Liu

## Oral Herpes

- Palate
- Gum
- Tongue
- Lip
- Facial area
- Vermillion Borders

## Genital Herpes

- Labia majora
- Labia minora
- Vaginal mucosa
- Cervix
- Shaft of the penus in men

## Other Areas

- Herpetic whitlow
- Herpes gladiatorum
- Herpetic keratoconjunctivitis
- Temporal lobe resulting in meningitis and encephalitis

https://en.wikipedia.org/wiki/Herpes_simplex_virus

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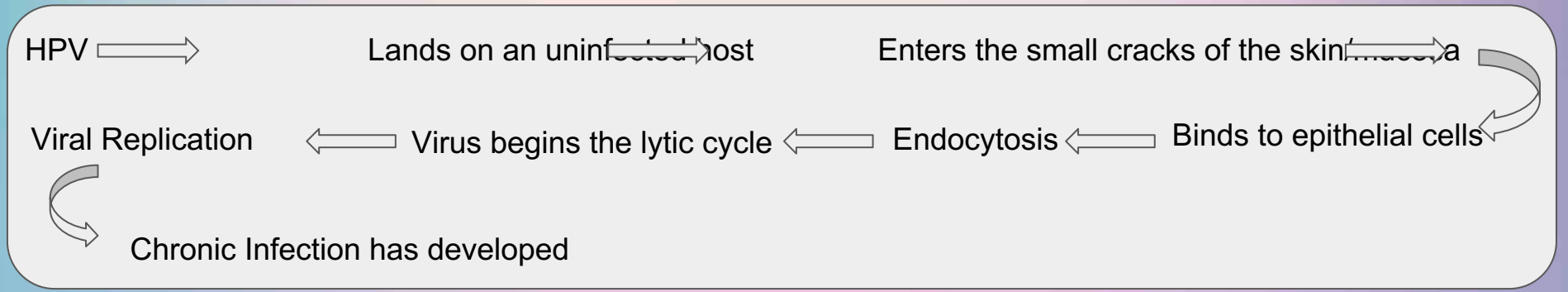
# Mode of Transmission

## Asymptomatic

- Shedding: Virus present in the bodily fluid such as the saliva and genital secretions can easily spread to another person.

## Symptomatic

- Lesions in the skin and mucous membranes are more contagious, and the most common mode of transmission.



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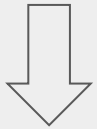
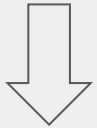
## Latency Cycle

Chronic condition has developed



Retrograde transportation to sensory ganglia



**Latent infection established**

## Recurrent Cycle

Unknown trigger causes reactivation of HSV

Active Replication of HSV

Anterograde Transportation

**Formation of Lesions on epithelial cells**

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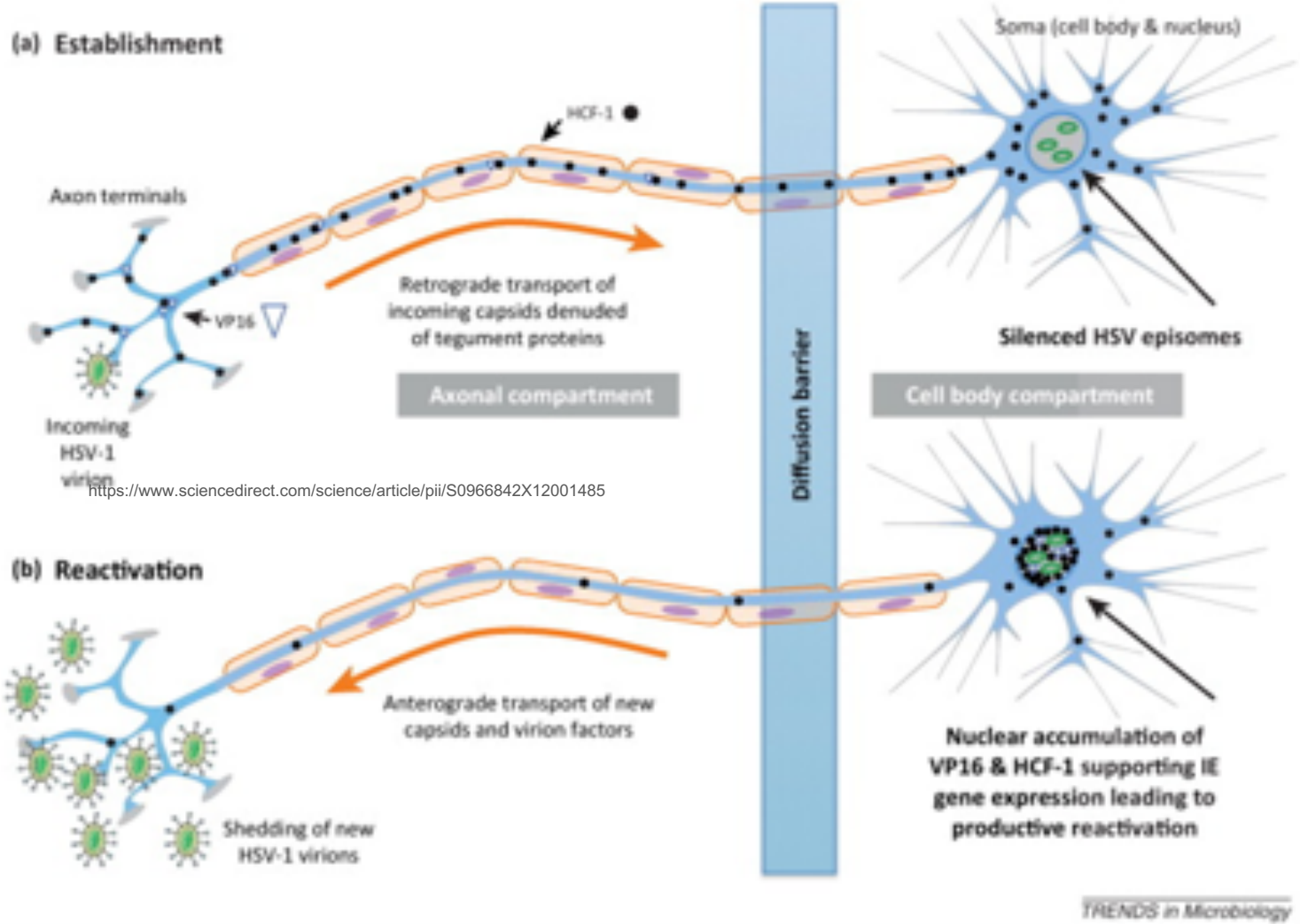


https://www.sciencedirect.com/science/article/pii/S0966842X12001485

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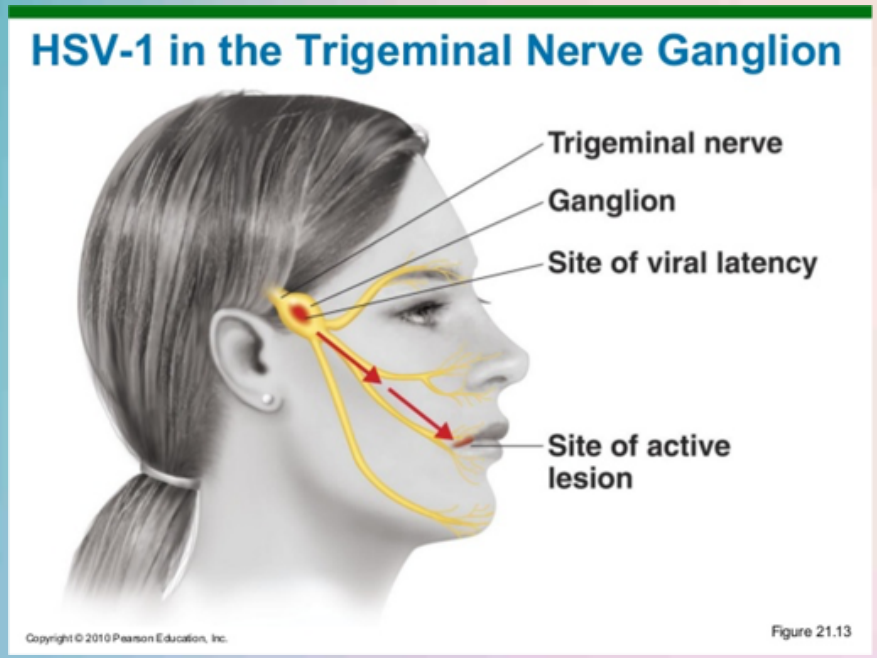
## Trigeminal Ganglia: The place that house dormant HSV-1.

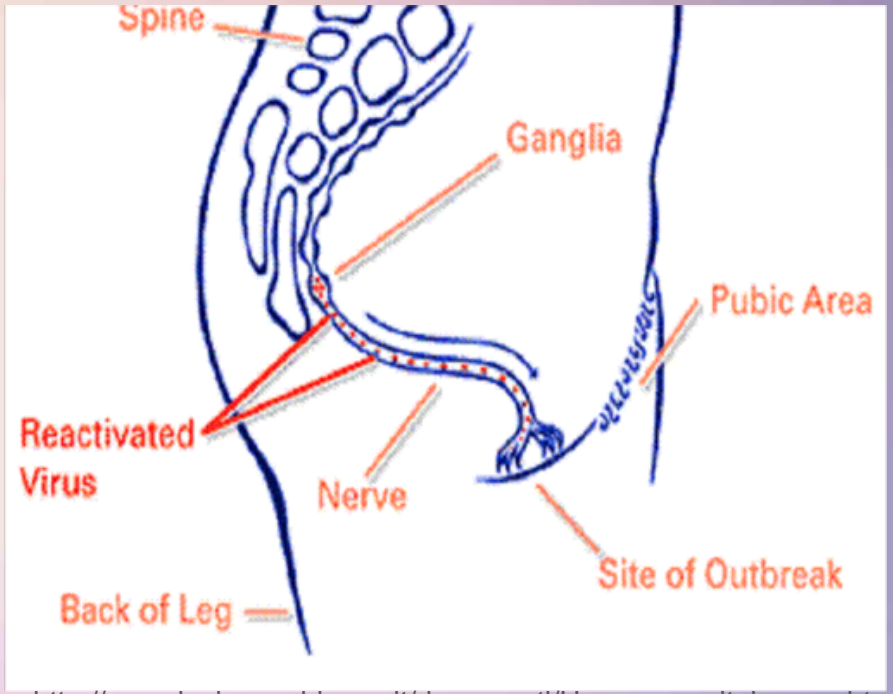
- Commonly responsible for the outbreak of lesions in the facial area by HSV-1.




https://www.slideshare.net/Prezi22/pp-5734834

## Sacral Ganglia: The place that house dormant HSV-2.

Commonly responsible for the outbreak of lesions in the genital area by HSV-2.




http://www.lucianoschiazza.it/documenti/Herpes_genitale_eng.html

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# Antiherpetic Agents

Goals:

- Minimize outbreaks of sores/ulcers.
- Minimize discomfort
- Minimize the duration of the outbreaks.
- Minimize transmission

**The antivirals are only used to control/alleviate symptoms, but not to cure the condition.**

Drugs:

- acyclovir; *Zovirax* (drug of choice) :Poor oral bioavailability of 15-30%
- penciclovir; *Denavir*
- ganciclovir; *Zirgan*

Prodrugs: inactive compounds that are metabolized in the body to produce active drugs

- valacyclovir; *Valtrex*---> acyclovir
- famciclovir; *Famvir*---->penciclovir
- valganciclovir; *Valcyte* ---> ganciclovir

# Viral DNA Polymerase Inhibitors

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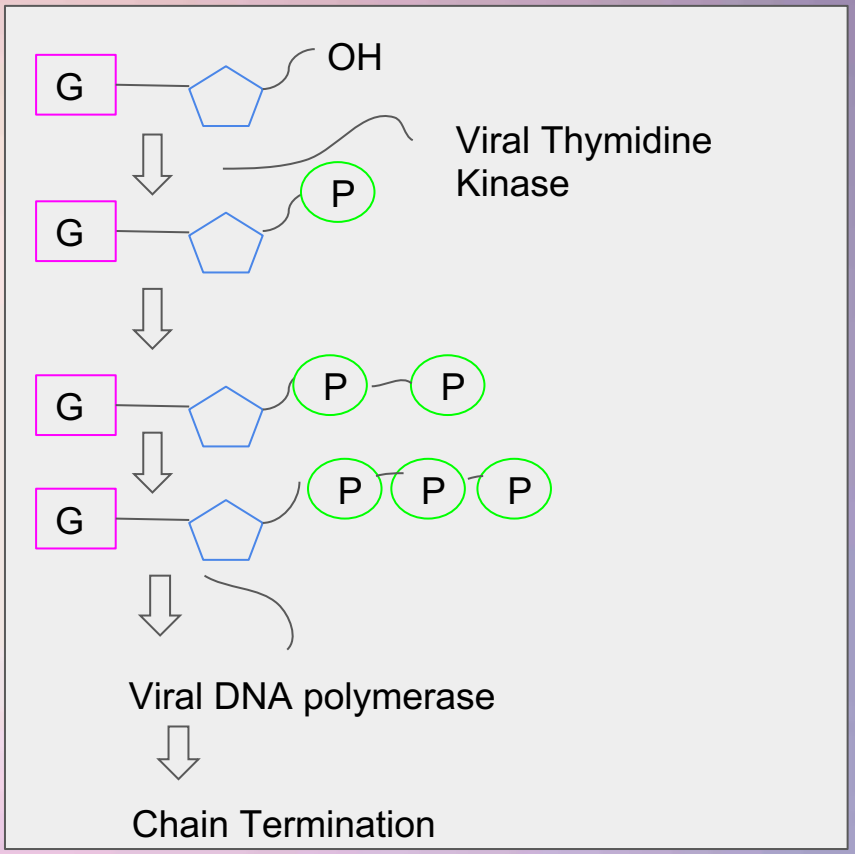
- Most anti-herpetic agents work in similar concept

- The drug gets phosphorylated by Viral Thymidine Kinase into Acyclovir monophosphate.
- Other enzymes then further turn acyclovir monophosphate into acyclovir diphosphate and acyclovir triphosphate.
- Viral DNA would then add acyclovir triphosphate into their DNA chain.
- Resulted in the termination of the viral DNA chain.



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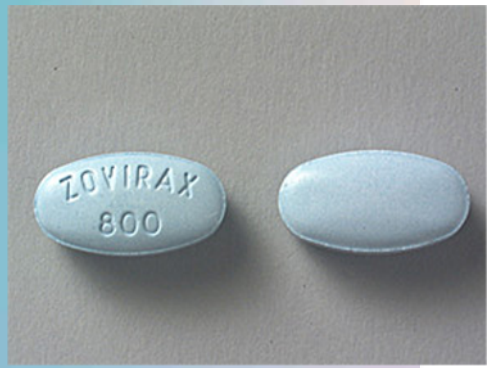


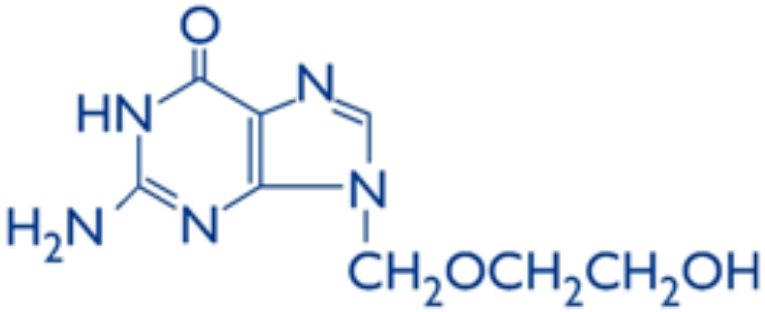

https://www.drugs.com/cdi/zovirax-acyclovir-capsules-and-tablets.html

Acyclovir + ATP —(HSV / Thymidine kinase)→ Acyclovir phosphate

Acyclovir phosphate —(Human enzymes)→ Acyclovir triphosphate

Acyclovir triphosphate —(HSV DNA polymerase)→ Acyclovir triphosphate incorporated into viral DNA

Acyclovir triphosphate incorporated into viral DNA → Viral DNA synthesis inhibited




Acyclovir

https://www.slideshare.net/abhijitch/antiviral-agents-and-sensitivity-tests

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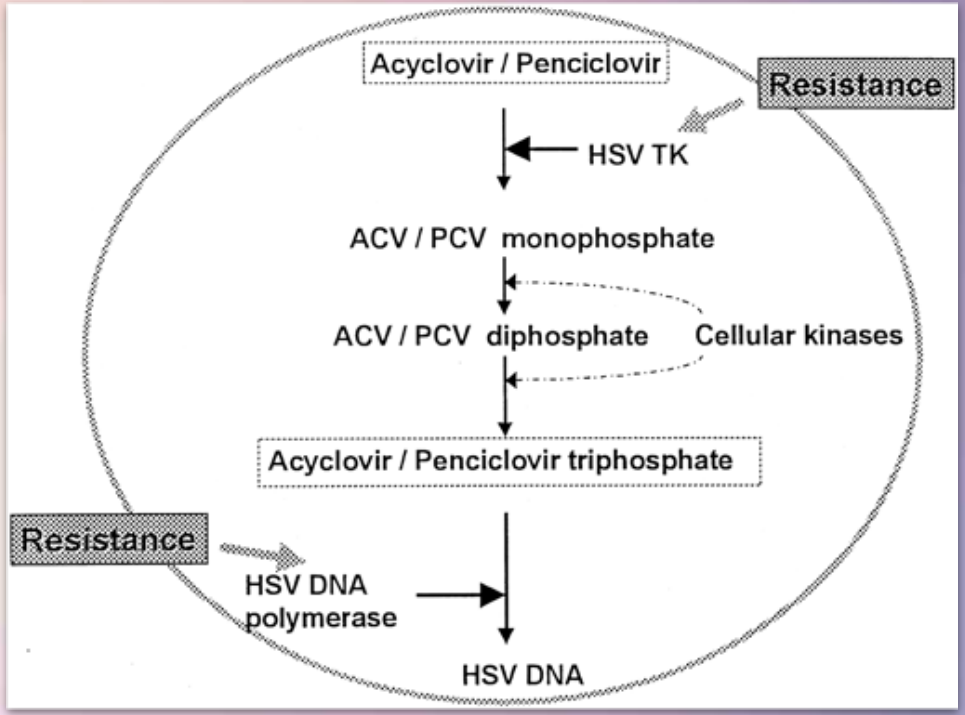
# Nucleoside Analogue Resistance

-Sometimes cross-resistance can happen between nucleoside analogues. As an alternative, pyrophosphate and nucleotide analogues would be used as an alternatives.

- foscarnet (Foscavir)

- cidofovir (Vistide)

- Directly inhibits viral DNA polymerase without the need of phosphorylation.

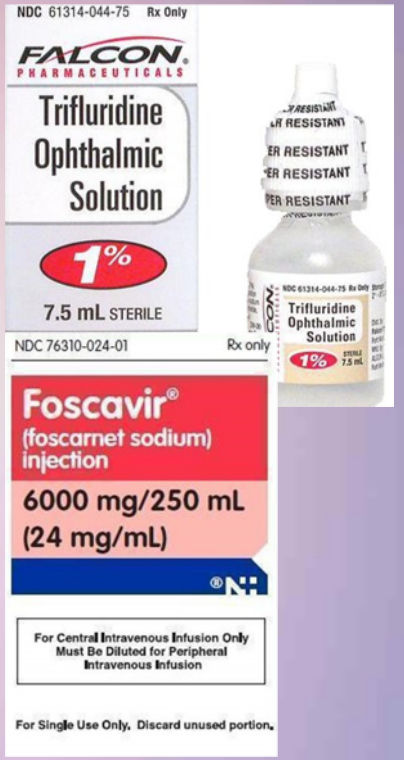



http://cmr.asm.org/content/16/1/114.figures-only

# Antiviral medications for Herpes simplex (systemic and topical)

| Generic name | Brand name |
|---|---|
| Acyclovir(Systemic) | Zovirax® |
| Acyclovir (Topical) | Sitavig®, Zovirax® |
| Cidofovir | Vistide® |
| Famciclovir | Famvir® |
| Foscarnet | Foscavir® |
| Penciclovir | Denavir® |
| Trifluridine | Viroptic® |
| Valacyclovir | Valtrex® |






Veronika Kropotova

# Drug: Acyclovir (Systemic) - *Zovirax®*

| *Dosage forms* | *Uses for Treatment of Disease* | *Dental Use* | *MOA (Mechanism of Action)* | *Adverse Effects and Reactions* |
|---|---|---|---|---|
| Capsule, Oral: 200 mg<br>Solution, Intravenous: 50 mg/mL<br>Suspension, Oral: 200 mg/5mL<br>Tablet, Oral: 400 mg, 800mg | • Herpes zoster (shingles)<br>• HSV, genital infection<br>• Varicella (chickenpox)<br>• Herpes simplex encephalitis<br>• HSV, neonatal<br>• HSV, mucocutaneous infection<br>• HSV gingivostomatitis<br>• Cytomegalovirus (CMV) infection off-label use; | Treatment of initial and prophylaxis of recurrent mucosal and cutaneous herpes simplex (HSV-1 and HSV-2) infections in immunocompro-mised patients | Acyclovir is converted to acyclovir monophosphate by virus-specific thymidine kinase then further converted to acyclovir triphosphate by other cellular enzymes. Acyclovir triphosphate prevents viral DNA synthesis by inhibiting the viral DNA polymerase. | ***CNS:*** Malaise, Headache, Lightheadedness<br>***Gastrointestinal:*** Nausea, Vomiting, Diarrhea, Abdominal pain<br>***Dermatologic***: Hives, Itching, Rash<br>***Hepatic***: Liver function tests increased<br>***Local***: Inflammation at injection site or phlebitis |

# Drug: Acyclovir (Topical) - *Sitavig®, Zovirax®*

| *Dosage forms* | *Uses for Treatment of Disease* | *Dental Use* | *MOA (Mechanism of Action)* | *Adverse Effects and Reactions* |
|---|---|---|---|---|
| Cream, External: 5%, 5g<br>Ointment, External: 5%, 5g, 15g, 30g<br>Tablet, Buccal: 50mg (Sitavig®) | • Genital HSV<br>• Herpes labialis (cold sores)<br>• Mucocutaneous HSV (non-life-threatening, immunocompromised) | Treatment of initial and prophylaxis of recurrent mucosal and cutaneous herpes simplex (HSV-1 and HSV-2) infections in immunocompromised patients | Acyclovir is converted to acyclovir monophosphate by virus-specific thymidine kinase then further converted to acyclovir triphosphate by other cellular enzymes. Acyclovir triphosphate prevents viral DNA synthesis by inhibiting the viral DNA polymerase. | ***Dermatologic***: Local pain, Erythema, Skin rash<br>***CNS:*** Lethargy<br>***Gastrointestinal:*** Aphthous stomatitis, gingival pain<br>***Local:*** Application site reaction including dry lips, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, stinging on skin; |

# Drug: Cidofovir - *Vistide®*

| *Dosage forms* | *Uses for Treatment of Disease* | *Dental Use* | *MOA (Mechanism of Action)* | *Adverse Effects and Reactions* |
|---|---|---|---|---|
| Solution, intravenous: 75 mg/mL (5 mL) | • Cidofovir is indicated only for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).<br>• Herpes simplex virus (HSV) infection, acyclovir-resistant (off-label use) | None | Cidofovir is converted to cidofovir diphosphate (the active intracellular metabolite); cidofovir diphosphate suppresses CMV replication by selective inhibition of viral DNA synthesis. Incorporation of cidofovir diphosphate into growing viral DNA chain results in viral DNA synthesis rate reduction. | ***Cardiovascular:*** cardiac failure, cardiomyopathy, edema, orthostatic hypotension, shock, syncope, tachycardia ***CNS:*** agitation, amnesia, anxiety, confusion,convulsions, dizziness,hallucination , insomnia, malaise ***Dermatologic:*** skin discoloration, skin photosensitivity, urticaria |

# Drug: Famciclovir – *Famvir®*

| *Dosage forms* | *Uses for Treatment of Disease* | *Dental Use* | *MOA (Mechanism of Action)* | *Adverse Effects and Reactions* |
|---|---|---|---|---|
| Tablet, Oral: 125mg, 250mg, 500mg | • Genital herpes simplex virus (HSV) infection<br>• Herpes labialis/orolabial (cold sores)<br>• Herpes zoster (shingles):<br>• Varicella infection (chickenpox) in HIV-infected patients (uncomplicated cases) (off-label use) | Management of acute herpes zoster (shingles); treatment of recurrent herpes labialis in immunocompetent patients | It is prodrug of penciclovir, which is phosphorylated by viral thymidine kinase in HSV-1, HSV-2, and VZV-infected cells to a monophosphate form; this is then converted to penciclovir triphosphate and competes with deoxyguanosine triphosphate to inhibit HSV-2 polymerase, therefore, herpes viral DNA synthesis/replication is selectively inhibited. | ***CNS:*** Headache, Fatigue, Migraine, Peresthesia<br>***Gastrointestinal:*** Nausea, Diarrhea, Vomiting, Flatulence<br>***Local:*** Application site reaction including dry lips, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin; application site irritation. |

# Drug: Foscarnet - *Foscavir®*

| *Dosage forms* | *Uses for Treatment of Disease* | *Dental Use* | *MOA (Mechanism of Action)* | *Adverse Effects and Reactions* |
|---|---|---|---|---|
| Solution, intravenous: 24 mg/mL | • Cytomegalovirus (CMV) retinitis<br>• CMV infection (preemptive therapy), (off-label use; second-line therapy)<br>• Herpes simplex infections (acyclovir-resistant)<br>• CMV neurological disease in HIV-infected patients (off-label use)<br>• CMV esophagitis or colitis in HIV-infected patients | Treatment of acyclovir-resistant mucocutaneous herpes simplex virus (HSV) infections in immunocompromised persons (eg, with advanced AIDS) | Pyrophosphate analogue which acts as a noncompetitive inhibitor of many viral RNA and DNA polymerases as well as HIV reverse transcriptase. Similar to ganciclovir, foscarnet is a virostatic agent. Foscarnet does not require activation by thymidine kinase. | ***CNS:*** Headache<br>***Endocrine & metabolic:*** Hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia<br>***Gastrointestinal:*** Nausea, diarrhea, vomiting<br>***Hematologic & oncologic:*** Anemia, granulocytopenia<br>***Renal:*** Renal insufficiency |

# Drug: Penciclovir - *Denavir®*

| *Dosage forms* | *Uses for Treatment of Disease* | *Dental Use* | *MOA (Mechanism of Action)* | *Adverse Effects and Reactions* |
|---|---|---|---|---|
| Cream, External: 1%, 5g | Topical treatment of recurrent herpes simplex labialis (cold sores) | Topical treatment of recurrent herpes simplex labialis (cold sores) | In cells infected with HSV-1 or HSV-2, viral thymidine kinase phosphorylates penciclovir to a monophosphate form which, in turn, is converted to penciclovir triphosphate by cellular kinases. Penciclovir triphosphate inhibits HSV polymerase competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and, therefore, replication are selectively inhibited. | *Dermatologic:* Erythema (50%; mild)<br>*CNS*: Headache (5%)<br>*Local*: Application site reaction (1%) |

# Drug: Trifluridine - *Viroptic®*

| *Dosage forms* | *Uses for Treatment of Disease* | *Dental Use* | *MOA (Mechanism of Action)* | *Adverse Effects and Reactions* |
|---|---|---|---|---|
| Ophthalmic; eye drops | • Herpes keratoconjunctivitis, keratitis: Treatment of primary keratoconjunctivitis and recurrent epithelial keratitis due to herpes simplex virus, types 1 and 2 | None | Interferes with viral replication by inhibiting thymidylate synthetase and incorporating into viral DNA in place of thymidine (Carmine 1982). | ***Ophthalmic:*** Burning sensation of eyes, stinging of eyes, eyelid edema ***Hypersensitivity:*** Local ocular hypersensitivity reaction |

# Drug: Valacyclovir - *Valtrex®*

| *Dosage forms* | *Uses for Treatment of Disease* | *Dental Use* | *MOA (Mechanism of Action)* | *Adverse Effects and Reactions* |
|---|---|---|---|---|
| Tablet, Oral: 500mg, 1g | • Herpes zoster (shingles)<br>• Herpes simplex virus (HSV), genital infection<br>• B virus, postexposure prophylaxis (off-label use)<br>• HSV keratitis (off-label use) | Treatment of herpes labialis (cold sores) | Valacyclovir is rapidly and completely converted to acyclovir. Acyclovir is converted to acyclovir monophosphate by virus-specific thymidine kinase then converted to acyclovir triphosphate by other cellular enzymes. Acyclovir triphosphate inhibits DNA synthesis and viral replication by competing with deoxyguanosine triphosphate for viral DNA polymerase and being incorporated into viral DNA. | ***CNS:*** Headache, Fatigue, depression, dizziness<br>***Gastrointestinal:*** Nausea, abdominal pain<br>***Hepatic:*** Increased serum AST, increased serum ALT<br>***Respiratory:*** Nasopharyngitis<br>***Dermatologic:*** Skin rash<br>**Endocrine & metabolic:** Dehydration |

| Drugs | Oral/dental side effects and effects on dental treatment |
|---|---|
| ***Acyclovir (Systemic) - Zovirax®*** | Dental treatment may be a risk factor for asymptomatic viral shedding of herpes simplex virus type-1 (HSV-1) into human saliva in patients with previous exposure to the virus.<br>It is recommended to reappoint the patient if an active lesion is present. If the lesion is already "crusted" over. Treatment will not induce spread of the virus. |
| ***Acyclovir (Topical) - Sitavig®, Zovirax®*** | |
| ***Cidofovir - Vistide®*** | Key adverse events) related to dental treatment: Stomatitis and abnormal taste. |
| ***Famciclovir – Famvir®*** | No significant effects or complications reported. |
| ***Foscarnet - Foscavir®*** | Xerostomia (normal salivary flow resumes upon discontinuation), taste perversion, and ulcerative stomatitis. |
| ***Penciclovir - Denavir®*** | No significant effects or complications reported. |
| ***Trifluridine - Viroptic®*** | No significant effects or complications reported |
| ***Valacyclovir - Valtrex®*** | Dental treatment may be a risk factor for asymptomatic viral shedding of herpes simplex virus type-1 (HSV-1) into human saliva in patients with previous exposure to the virus. |

# References


A&B:

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