# Rash decisions

**CLINID conference**
Hunter Ratliff
07/10/2025

*Ages, dates, and other identifying information may have been changed*
*I have no conflict of interest in relation to this presentation*

# HPI

A **71 y/o M** with PMH including T-cell PLL s/p alloSCT (-14 mo ago) c/b cutaneous GVHD (currently on pred & Jakafi) p/w **2 month history of...**

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# HPI at time of consult

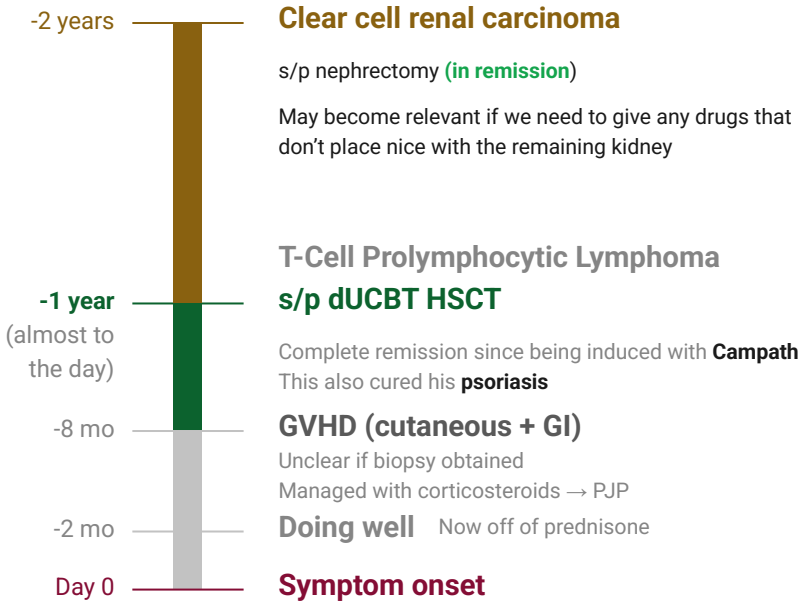
A **71 y/o M** with PMH including T-cell PLL s/p alloSCT (-14 mo ago) c/b cutaneous GVHD (currently on pred & Jakafi) p/w **2 month history of...**

- Often, but not always painful
- Has not improved with PO meds (which is why we are seeing him!)
- No other painful spots elsewhere
    - Has had another rash...

# The backstory

A **71 y/o M** with PMH including T-cell PLL s/p alloSCT (-1 yr ago), GVHD, Hx PJP, psoriasis, PMR, renal cancer s/p nephrectomy (-2 years)

**Convention/notation for timing**
Day "zero" = onset of symptoms
ID was consulted around day 65



# Week 1

PCP note says patient noted a **pruritic rash** “**everywhere**” for past **few months**. Has been applying **topical triamcinolone**.

**Med list**

- Budesonide 3mg TID
- Beclomethasone 2mg QID
- Acyclovir 400 BID
  - Topical acyclovir
- Isavuconazole 372 daily
- Letermovir 480 daily
- SMX/TMP SS qMWF

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Separately, has had a **cold sore** develop on the **upper lip** and has been applying **topical acyclovir**.  Area is getting **larger** and **scabbed**

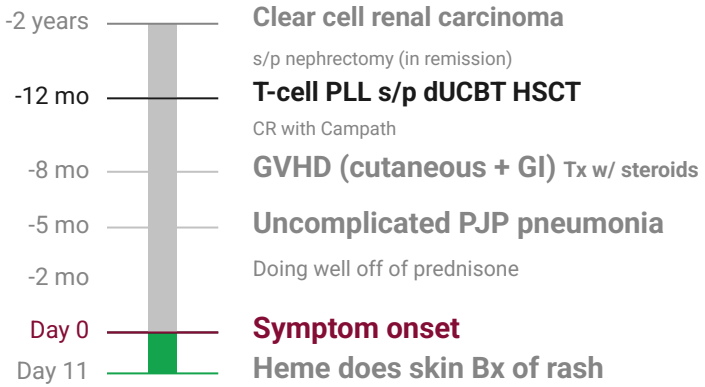
**Med list**

- Budesonide 3mg TID
- Acyclovir 400 BID
  - Topical acyclovir
- Isavuconazole 372 daily
- Letermovir 480 daily
- SMX/TMP SS qMWF

# Week 2 (day 11)

Heme onc clinic: **Skin biopsy** of arm to evaluate for cGVHD

No medication changes made

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# Week 2 (day 11)

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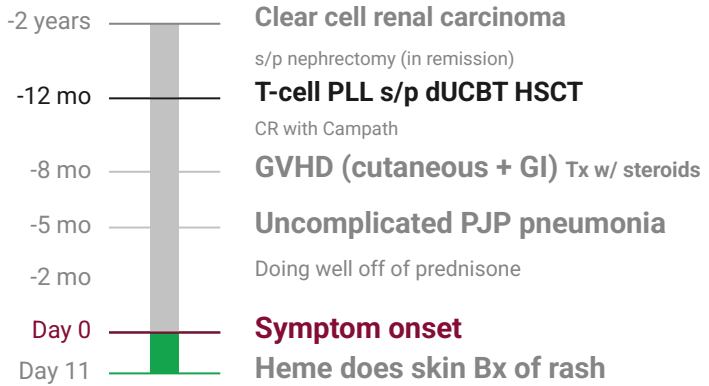
**Pathology report:** Mild **subacute spongiotic dermatitis** with **superficial lymphomononuclear cell infiltrates** with **occasional eosinophils**

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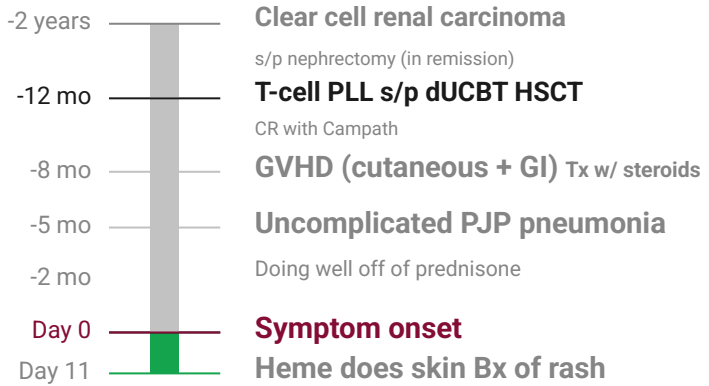


**Pathology report:** Mild **subacute spongiotic dermatitis** with **superficial lymphomononuclear cell infiltrates** with **occasional eosinophils**

The histologic profile shows irregular hyperkeratosis with serum protein exudates, irregular acanthosis, spongiosis, and superficial perivascular lymphocytic infiltrates with occasional eosinophils.

The **presence of occasional eosinophils** may indicate an **underlying hypersensitivity mechanism** and a **spongiotic drug eruption** may be considered. At least objectively certain viral exanthems, urticarial reaction patterns, or other unknown systemic allergen.

## Med list

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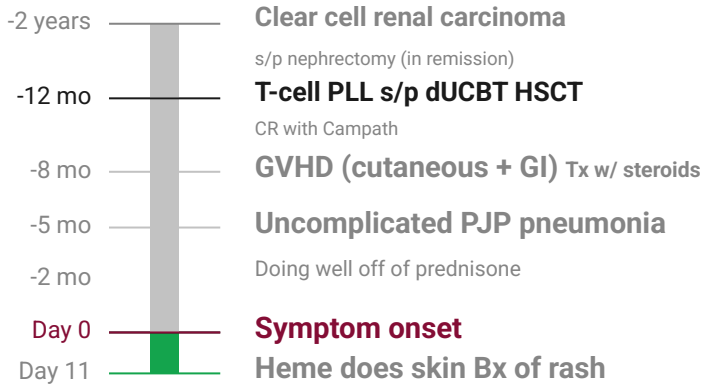


**Pathology report:** Mild **subacute spongiotic dermatitis** with **superficial lymphomononuclear cell infiltrates** with **occasional eosinophils**

The **lymphomononuclear cell infiltrate is particularly sparse** raising **significant doubt for the possibility of leukemia cutis**. Migration of lymphocytes into the epidermis is focal and minimal likely to be a feature of lymphocytic spongiosis rather than epidermotropism in the setting of erythrodermic mycosis fungoides at least objectively. However, this disease may initiate within the setting of a spongiotic or eczematous process. Additional biopsies may be needed in the future

## Med list

- Budesonide 3mg TID
- Acyclovir 400 BID
  - Topical acyclovir
- Isavuconazole 372 daily
- Letermovir 480 daily
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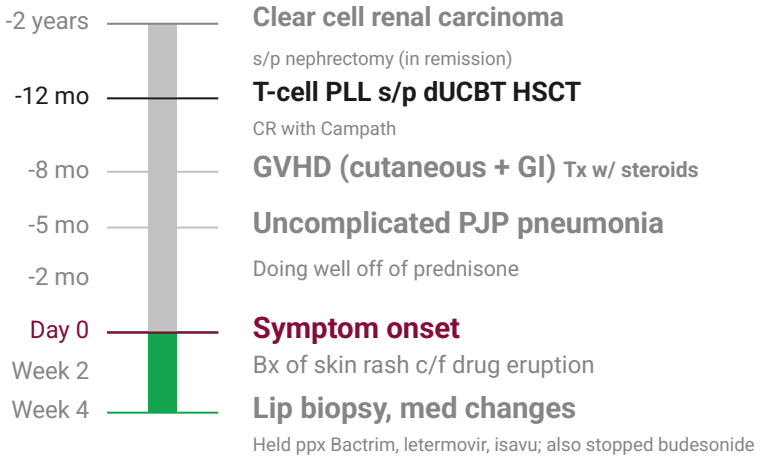
# Week 4 (day 25)

Heme onc clinic: Worried about **drug eruption** causing skin rash → **discontinued many of his meds**




**Med list**

- ~~Budesonide 3mg TID~~
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- ~~Isavuconazole 372 daily~~
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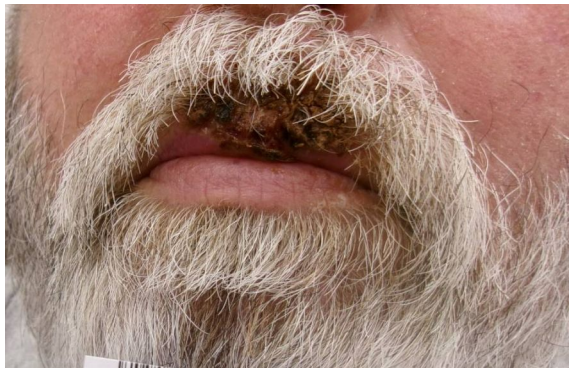
- ~~SMX/TMP SS qMWF~~

# Week 4 (day 25)

Heme onc clinic: c/f drug eruption → d/c many of his meds

Derm clinic:

- Worried about the chronicity of lip lesion
  - Did biopsy & PCR
  - No cultures sent
- Didn't talk much of the skin rash



-2 years — **Clear cell renal carcinoma**
s/p nephrectomy (in remission)

-12 mo — **T-cell PLL s/p dUCBT HSCT**
CR with Campath

-8 mo — **GVHD (cutaneous + GI)** Tx w/ steroids

-5 mo — **Uncomplicated PJP pneumonia**

-2 mo — Doing well off of prednisone

Day 0 — **Symptom onset**
Bx of skin rash c/f drug eruption

Week 2

Week 4 — **Lip biopsy, med changes**
Held ppx Bactrim, letermovir, isavu; also stopped budesonide

**Med list**

- ~~Budesonide 3mg TID~~
- Acyclovir 400 BID
  - Topical acyclovir
- ~~Isavuconazole 372 daily~~
- ~~Letermovir 480 daily~~
- ~~SMX/TMP SS qMWF~~

# Break 1

[Q1.1] DDx? Infectious or otherwise

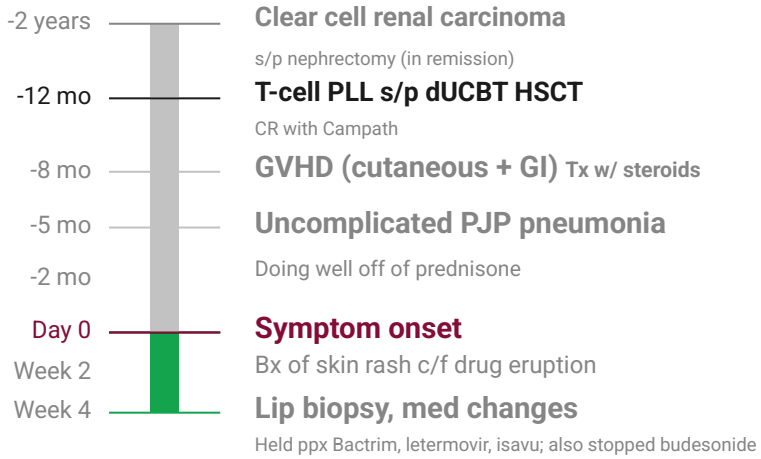
[Q1.2] Diagnostic w/up

[Q1.3] What to do for treatment?

# Week 4 (day 25)

Derm clinic: Worried about the chronicity of lip lesion so did lip biopsy w/ PCR

**Pathology report: HERPES VIRUS INFECTION**



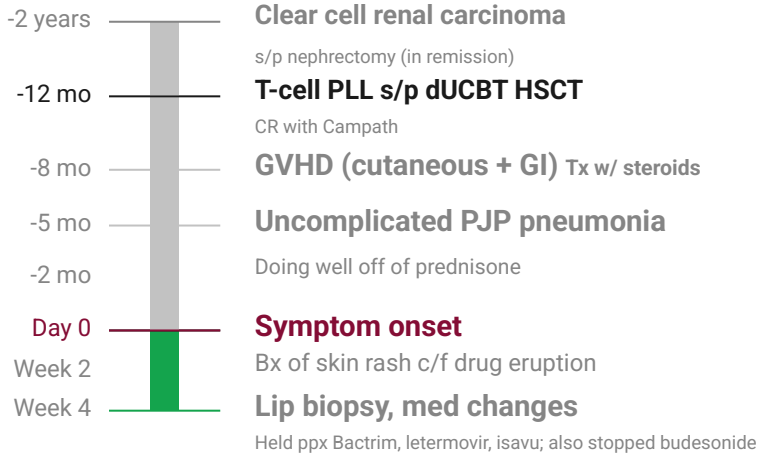

# Week 4 (day 25)

Derm clinic: Worried about the chronicity of lip lesion so did lip biopsy w/ PCR

**Pathology report: HERPES VIRUS INFECTION**

COMMENT: The **histopathologic findings** are consistent with infection by varicella zoster virus (VZV) or herpes simplex virus (HSV). Clinical correlation is essential.

MICROSCOPIC DESCRIPTION: The specimen displays areas of epidermal necrosis with ballooning degeneration of keratinocytes. Many keratinocytes display viral cytopathic changes including multinucleation, nuclear molding, margination of chromatin, and a glassy cytoplasm. Brisk mixed inflammation is present in the dermis

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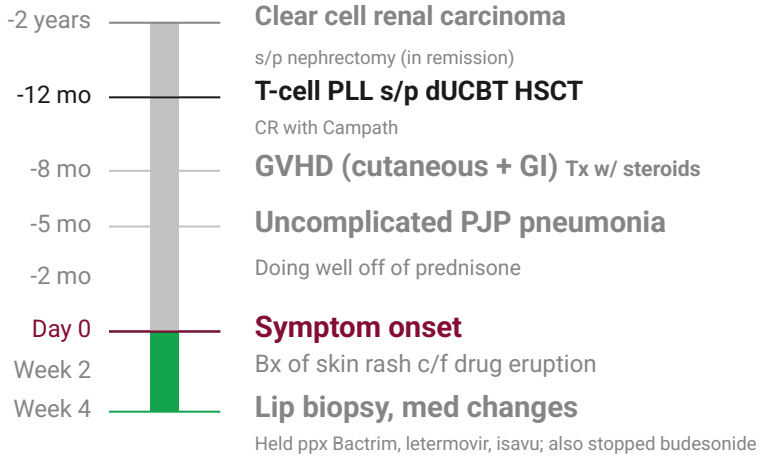
MICROSCOPIC DESCRIPTION: The specimen displays areas of epidermal necrosis with ballooning degeneration of keratinocytes. Many keratinocytes display viral cytopathic changes including multinucleation, nuclear molding, margination of chromatin, and a glassy cytoplasm. Brisk mixed inflammation is present in the dermis

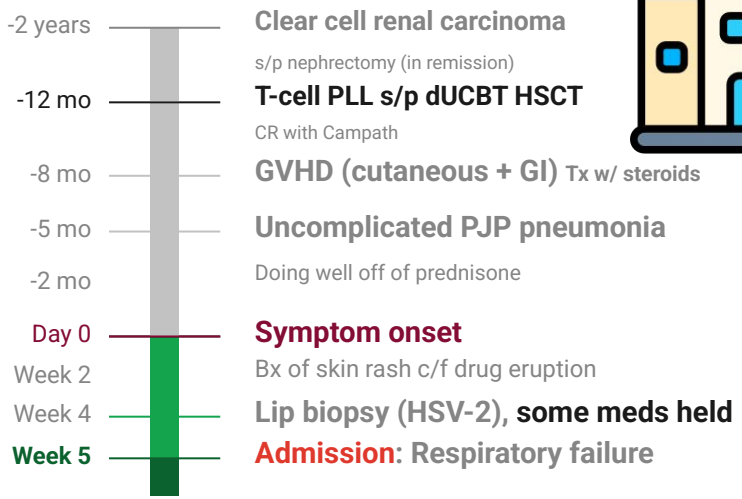
**PCR**: Positive for **HSV-2**
- Negative for VZV or HSV-1




# Week 5

Admitted with cough, subjective fevers, & diarrhea

- Tested positive for influenza A
- Tested negative for C diff but still treated anyways..?




## Med list

- ~~Budesonide 3mg TID~~
- Acyclovir 400 BID
  - Topical acyclovir
- ~~Isavuconazole 372 daily~~
- ~~Letermovir 480 daily~~
- ~~SMX/TMP SS qMWF~~

# Week 5 (day 35)

Admitted with cough, subjective fevers, & diarrhea

- Tested positive for influenza A
- Tested negative for C diff but still treated anyways..?

Hospitalist was concerned for **HSV** (biopsy wasn't back yet)

-2 years — **Clear cell renal carcinoma**
s/p nephrectomy (in remission)

-12 mo — **T-cell PLL s/p dUCBT HSCT**
CR with Campath

-8 mo — **GVHD (cutaneous + GI)** Tx w/ steroids

-5 mo — **Uncomplicated PJP pneumonia**

-2 mo — Doing well off of prednisone

Day 0 — **Symptom onset**
Bx of skin rash c/f drug eruption

Week 2

Week 4 — **Lip biopsy (HSV-2), some meds held**

**Week 5** — **Admission: Respiratory failure**

## Med list

- ~~Budesonide 3mg TID~~
- Acyclovir 400 BID
  - Topical acyclovir
- ~~Isavuconazole 372 daily~~
- ~~Letermovir 480 daily~~
- ~~SMX/TMP SS qMWF~~

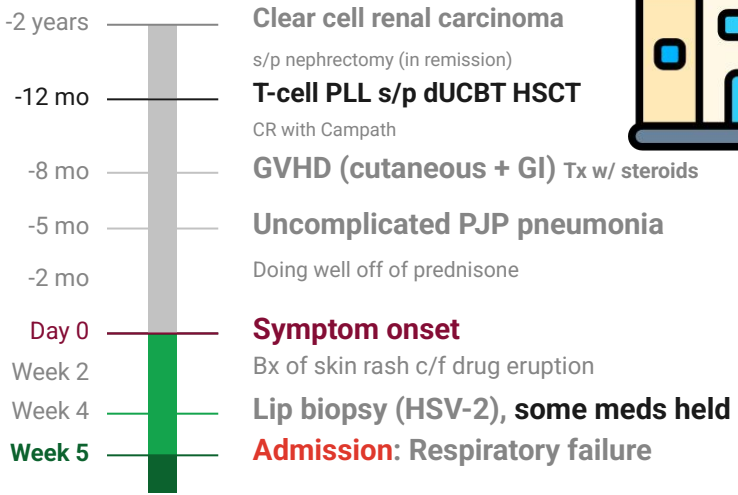
# Week 5

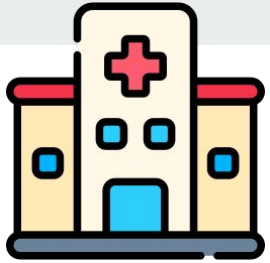
Admitted with cough, subjective fevers, & diarrhea

- Tested positive for influenza A
- Tested negative for C diff but still treated anyways..?

Hospitalist was concerned for **HSV**

- Switched acyclovir 400 BID → **valacyclovir 1g BID** x 10 days



**Med list**

- ~~Budesonide 3mg TID~~
- **Valacyclovir 1g BID**
- ~~Isavuconazole 372 daily~~
- ~~Letermovir 480 daily~~
- ~~SMX/TMP SS qMWF~~

# Week 6 (day 39)

Discharged from admission #1 but
**readmitted the next day**

# Week 6 (day 39)

Discharged from admission #1 but readmitted the next day for cGVHD

- Started on high dose steroids for presumed cGVHD

-2 years — **Clear cell renal carcinoma**

s/p nephrectomy (in remission)

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Week 2 — Bx of skin rash c/f drug eruption

Week 4 — **Lip biopsy (HSV-2), some meds held**

**Week 5** — **Admission #1: Respiratory failure**

**Week 6** — **Admission #2: GVHD**

# Week 6 (day 39)

**Pathology report:** Lichenoid and dyskeratotic **interface dermatitis with dense lymphoeosinophilic cell infiltrates** and features consistent with **acute graft-versus-host disease**, **grade 2**

-2 years — **Clear cell renal carcinoma**
s/p nephrectomy (in remission)

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Week 2

Week 4 — **Lip biopsy (HSV-2), some meds held**

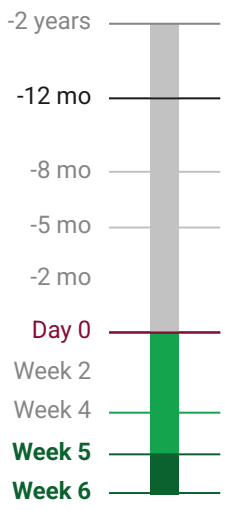
**Week 5** — **Admission #1: Respiratory failure**

**Week 6** — **Admission #2: GVHD**

# Week 6 (day 39)

**Pathology report:** Lichenoid and dyskeratotic **interface dermatitis with dense lymphoeosinophilic cell infiltrates** and features consistent with **acute graft-versus-host disease**, **grade 2**

Variable irregular acanthosis and atrophy of the epidermis with focal vacuolar alteration of basal cell layer associated with spongiosis and substantial dyskeratosis of epidermal cells, papillary dermal edema, lymphomononuclear cell infiltrate with numerous eosinophils in the papillary dermis are present with epidermal exocytosis of few lymphocytes. Mononuclear cells in close apposition to necrotic keratinocytes known as **"satellite cell necrosis"** are suggested. Vacuolar alteration of basal cells and dyskeratosis of follicular epithelium mostly in the infundibulum



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Week 4 — **Lip biopsy (HSV-2), some meds held**

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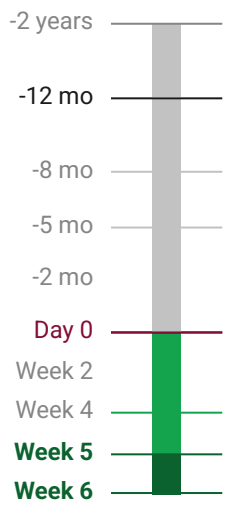
**Week 6** — **Admission #2: GVHD**

# Week 6 (day 39)

**Pathology report:** Lichenoid and dyskeratotic **interface dermatitis with dense lymphoeosinophilic cell infiltrates** and features consistent with **acute graft-versus-host disease**, **grade 2**

Variable irregular acanthosis and atrophy of the epidermis with focal vacuolar alteration of basal cell layer associated with spongiosis and substantial dyskeratosis of epidermal cells, papillary dermal edema, lymphomononuclear cell infiltrate with numerous eosinophils in the papillary dermis are present with epidermal exocytosis of few lymphocytes. Mononuclear cells in close apposition to necrotic keratinocytes known as **"satellite cell necrosis"** are suggested. Vacuolar alteration of basal cells and dyskeratosis of follicular epithelium mostly in the infundibulum

Comment: There are overwhelming histopathological features of an interface dermatitis with focal vacuolar changes at the dermo-epidermal junction associated with prominent dyskeratosis, features that would be appropriate for acute GVHD. However the presence of a **significant number of eosinophils within the infiltrate** may also suggest an **underlying hypersensitivity mechanism** and would not necessarily exclude this type of pathogenesis




Clear cell renal carcinoma

s/p nephrectomy (in remission)

**T-cell PLL s/p dUCBT HSCT**

CR with Campath

**GVHD (cutaneous + GI)** Tx w/ steroids

**Uncomplicated PJP pneumonia**

Doing well off of prednisone

**Symptom onset**

Bx of skin rash c/f drug eruption

**Lip biopsy (HSV-2), some meds held**

**Admission #1: Respiratory failure**

**Admission #2: GVHD**

# Week 6 (day 39)

Discharged from admission #1 but readmitted the next day for GVHD

- Started on **high dose steroids** for presumed cGVHD
  - Also atovaquone & fluconazole ppx

-2 years — **Clear cell renal carcinoma**
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Week 2

Week 4 — **Lip biopsy (HSV-2), some meds held**

**Week 5** — **Admission #1: Respiratory failure**

**Week 6** — **Admission #2: GVHD**

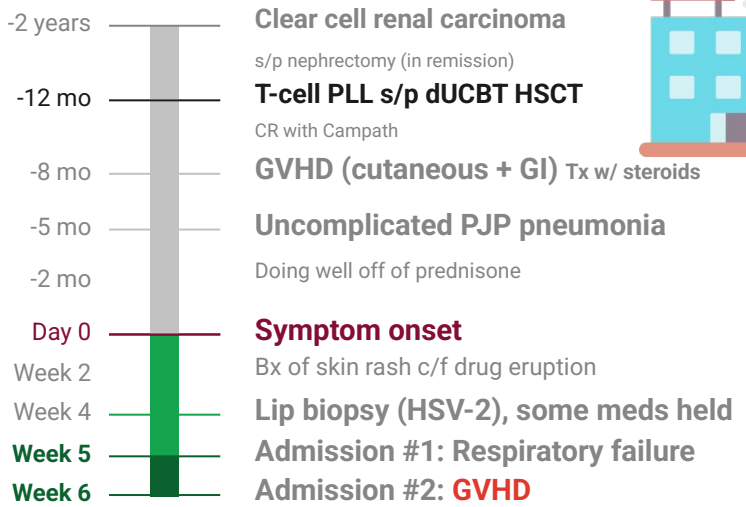
## Med list

- **Prednisone** 100
- **Atovaquone** 1500 daily
- **Fluconazole** 200 daily
- Valacyclovir 1g BID
- ~~Letermovir 480 daily~~

# Week 6

Discharged from admission #1 but readmitted the next day for GVHD

- Started on **high dose steroids** for presumed cGVHD
  - Also atovaquone & fluconazole ppx
- **Rash improved** with treatment (as did GI symptoms)




**Med list**

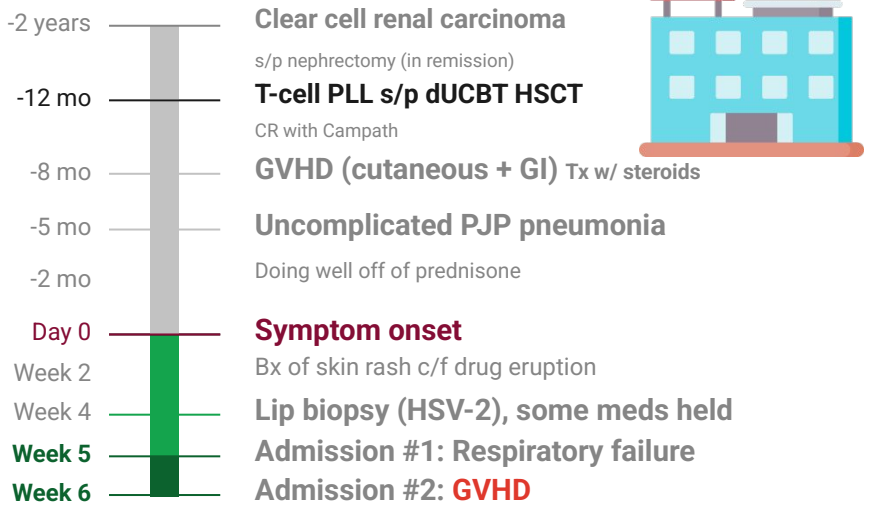
- Prednisone 100
- Atovaquone 1500 daily
- Fluconazole 200 daily
- Valacyclovir 1g BID
- ~~Letermovir 480 daily~~

# Week 6 (day 42)

Discharged from admission #1 but readmitted the next day for GVHD

- Started on **high dose steroids** for presumed cGVHD
  - Also atovaquone & fluconazole ppx
- **Rash improved** with treatment (as did GI symptoms)

After 10 days of valacyclovir 1g BID → **valacyclovir 500 BID**

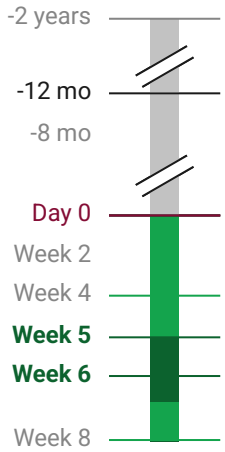



## Med list

- Prednisone 100
- Atovaquone 1500 daily
- Fluconazole 200 daily
- Valacyclovir **500** BID
- ~~Letermovir 480 daily~~

# Week 8 (day 50)

Dermatology: GHVD responding well (no comment on lip lesion)




**Clear cell renal carcinoma**

s/p nephrectomy (in remission)

**T-cell PLL s/p dUCBT HSCT**

**GVHD (cutaneous + GI)** Tx w/ steroids

**Symptom onset**

Bx of skin rash c/f drug eruption

**Lip biopsy (HSV-2), some meds held**

**Admission #1: Respiratory failure**

**Admission #2: GVHD**

Started on high dose prednisone

**Clinic**

# Week 8 (day 50)

Dermatology: GHVD responding well (no comment on lip lesion)

-2 years

-12 mo

-8 mo

Day 0

Week 2

Week 4

Week 5

Week 6

Week 8

**Clear cell renal carcinoma**

s/p nephrectomy (in remission)

**T-cell PLL s/p dUCBT HSCT**

**GVHD (cutaneous + GI)** Tx w/ steroids

**Symptom onset**

Bx of skin rash c/f drug eruption

**Lip biopsy (HSV-2), some meds held**

**Admission #1: Respiratory failure**

**Admission #2: GVHD**

Started on high dose prednisone

**Clinic**

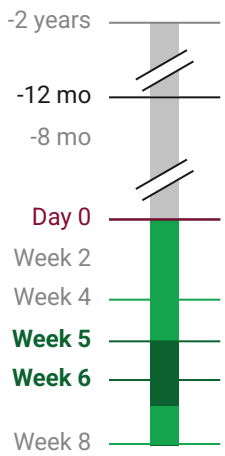
From day 35

# Week 8 (day 50)

Dermatology: GHVD responding well

Heme/Onc clinic:

- Doing well, start **tapering prednisone** by 10mg weekly




**Clear cell renal carcinoma**
s/p nephrectomy (in remission)
**T-cell PLL s/p dUCBT HSCT**
**GVHD (cutaneous + GI)** Tx w/ steroids

**Symptom onset**
Bx of skin rash c/f drug eruption
**Lip biopsy (HSV-2), some meds held**
**Admission #1: Respiratory failure**
**Admission #2: GVHD**
Started on high dose prednisone
**Clinic**

**Med list**

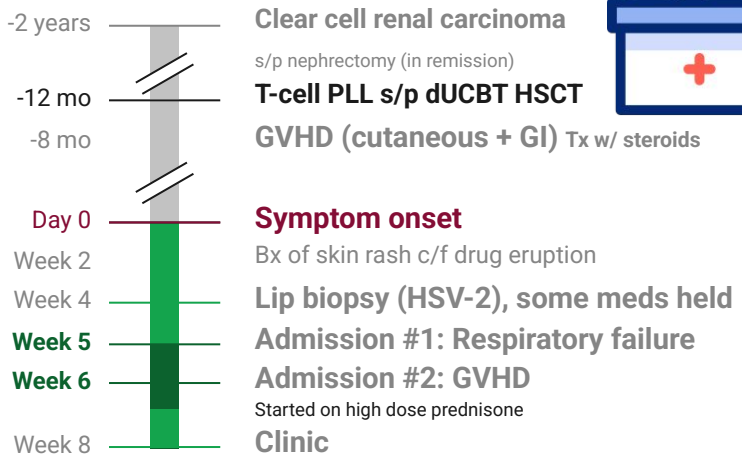
- Prednisone 100
- Atovaquone 1500 daily
- Fluconazole 200 daily
- Valacyclovir 500 BID
- ~~Letermovir 480 daily~~

# Week 8 (day 50)

Dermatology: GHVD responding well

Heme/Onc clinic:

- Doing well, start **tapering prednisone** by 10mg weekly
- Insurance approved **Jakafi** (Ruxolitinib, tyrosine kinase inhibitor)




**Med list**

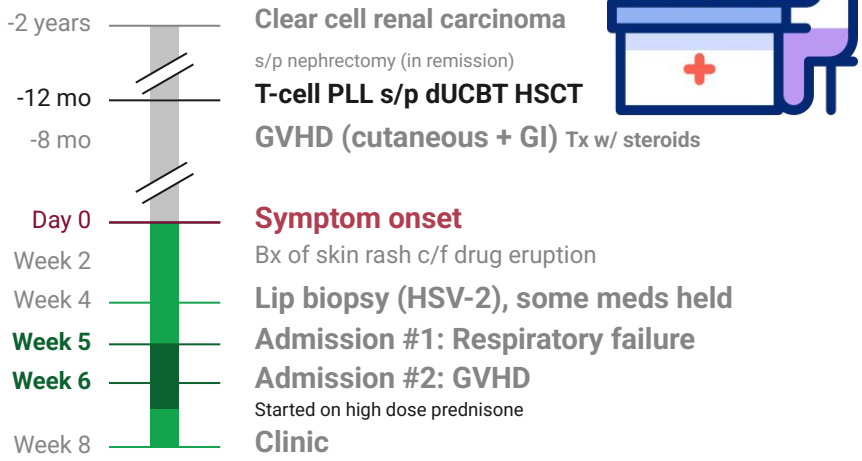
- Prednisone 100
- **Ruxolitinib** (Jakafi)
- Atovaquone 1500 daily
- Fluconazole 200 daily
- Valacyclovir 500 BID
- ~~Letermovir 480 daily~~

# Week 8 (day 50)

Dermatology: GHVD responding well

Heme/Onc clinic:

- Doing well, start **tapering prednisone** by 10mg weekly
- Insurance approved **Jakafi** (Ruxolitinib, tyrosine kinase inhibitor)
- **Posaconazole** approved (for PPx)




**Med list**

- Prednisone 100
- Ruxolitinib (Jakafi)
- Atovaquone 1500 daily
- **Posaconazole** 300 daily
- Valacyclovir 500 BID
- ~~Letermovir 480 daily~~

# Week 10 (day 64)

Heme/Onc clinic: Upper **lip lesion worsening** in past week. Now on pred 70 + Ruxolitinib

-2 years — **Clear cell renal carcinoma**

s/p nephrectomy (in remission)

-12 mo — **T-cell PLL s/p dUCBT HSCT**

-8 mo — **GVHD (cutaneous + GI)** Tx w/ steroids

Day 0 — **Symptom onset**

Bx of skin rash c/f drug eruption

Week 2

Week 4 — **Lip biopsy (HSV-2), some meds held**

**Week 5** — **Admission #1: Respiratory failure**

**Week 6** — **Admission #2: GVHD**

Started on high dose prednisone

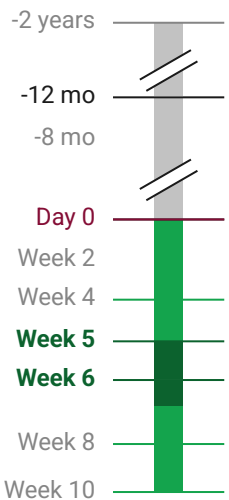
Week 8 — Clinic: Started Jakafi

Week 10 — **Clinic**

# Week 10 (day 64)

Heme/Onc clinic: Upper **lip lesion worsening** in past week. Now on pred 70 + Ruxolitinib

Derm: Feels this is consistent with HSV, but wants to get ID's input




**Clear cell renal carcinoma**

s/p nephrectomy (in remission)

**T-cell PLL s/p dUCBT HSCT**

**GVHD (cutaneous + GI)** Tx w/ steroids

**Symptom onset**

Bx of skin rash c/f drug eruption

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Started on high dose prednisone

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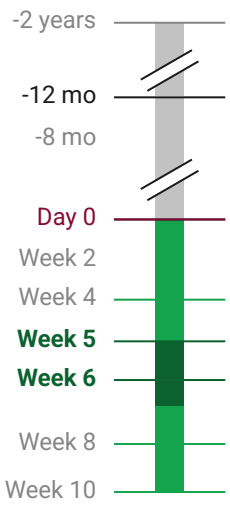
**Clinic**

# Week 10 (day 64)

Heme/Onc clinic: Upper **lip lesion worsening** in past week. Now on pred 70 + Ruxolitinib

Derm: Feels this is consistent with HSV, but wants to get ID's input

- Sends HSV & VZV PCR
- Starts therapeutic valacyclovir (1g BID)




**Clear cell renal carcinoma**

s/p nephrectomy (in remission)

**T-cell PLL s/p dUCBT HSCT**

**GVHD (cutaneous + GI)** Tx w/ steroids

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**Admission #2: GVHD**

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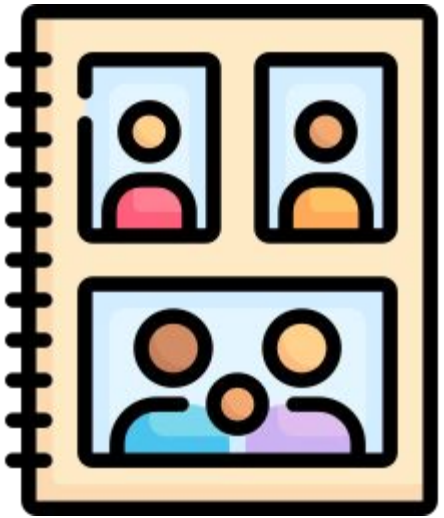
**Clinic**

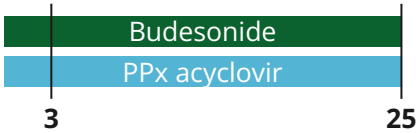
# Recap of pictures & treatments (thus far)



# Day 3

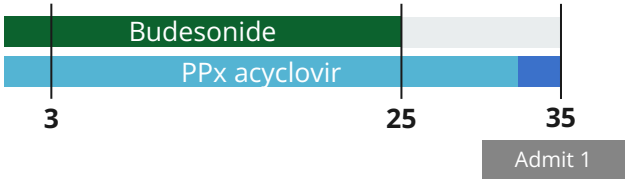
**Antivirals**
- PPx (val)acyclovir
- Therapeutic valacyclovir

# Day 25



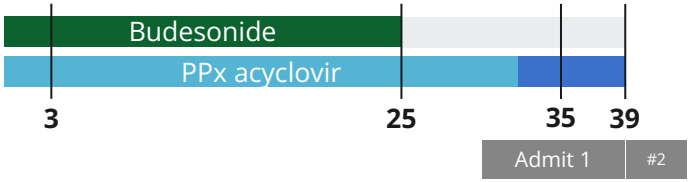

**Antivirals**
- PPx (val)acyclovir
- Therapeutic valacyclovir

# Day 35




**Antivirals**
- PPx (val)acyclovir
- Therapeutic valacyclovir

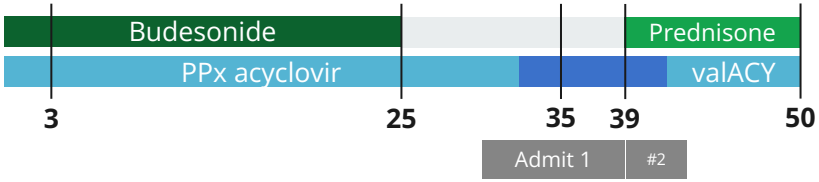
# Day 39




**Antivirals**

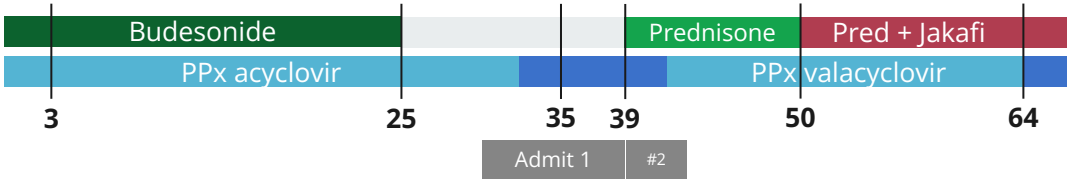
- PPx (val)acyclovir
- Therapeutic valacyclovir

# Day 50




**Antivirals**
- PPx (val)acyclovir
- Therapeutic valacyclovir

# Day 64




**Antivirals**
- PPx (val)acyclovir
- Therapeutic valacyclovir

# What would you do?

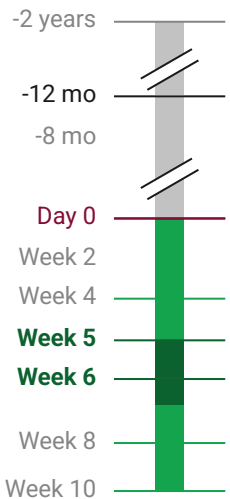
# Week 10 (day 64)

Heme/Onc clinic: Upper **lip lesion worsening** in past week. Now on pred 70 + Ruxolitinib

Derm: Feels this is consistent with HSV, but wants to get ID's input

- Sends **HSV & VZV** PCR
- Starts therapeutic valacyclovir (1g BID)

**PCR**: Positive for HSV-2
- Negative for VZV or HSV-1




**Clear cell renal carcinoma**

s/p nephrectomy (in remission)

**T-cell PLL s/p dUCBT HSCT**

**GVHD (cutaneous + GI)** Tx w/ steroids

**Symptom onset**

Bx of skin rash c/f drug eruption

**Lip biopsy (HSV-2), some meds held**

**Admission #1: Respiratory failure**

**Admission #2: GVHD**

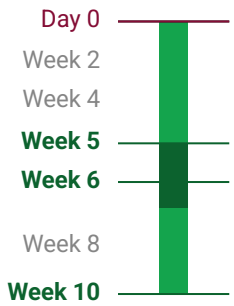
Started on high dose prednisone

Clinic: Started Jakafi

**Clinic**

# Week 10

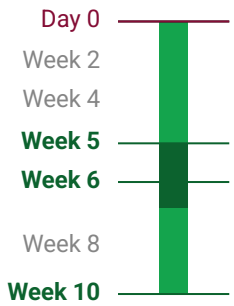
ID e-consulted: Should be admitted to get testing for **TK-deficient HSV** and consideration for IV therapy




**Symptom onset**
Bx of skin rash c/f drug eruption
Lip biopsy (HSV-2), some meds held
**Admission #1: Respiratory failure**
**Admission #2: GVHD**
Started on high dose prednisone
Started Jakafi
**Admission #3**

# Week 10 (day 66)

ID e-consulted: Should be admitted to get testing for **TK-deficient HSV** and consideration for IV therapy




**Symptom onset**
Bx of skin rash c/f drug eruption
Lip biopsy (HSV-2), some meds held
**Admission #1: Respiratory failure**
**Admission #2: GVHD**
Started on high dose prednisone
Started Jakafi
**Admission #3**

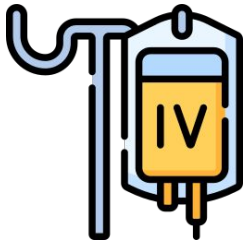
**Viral culture**
- Sent to ARUP
- Didn't grow :(

# Admission #3

ID e-consulted: Should be admitted to get testing for **TK-deficient HSV** and consideration for IV therapy

Started on **foscarnet** (day 67)

- Discharged on OPAT (renal fxn stable)
- Derm wanted topical cidofovir (insurance did not want this)




Day 0 — **Symptom onset**
Bx of skin rash c/f drug eruption

Week 2

Week 4 — Lip biopsy (HSV-2), some meds held

**Week 5** — **Admission #1: Respiratory failure**

**Week 6** — **Admission #2: GVHD**
Started on high dose prednisone

Week 8 — Started Jakafi

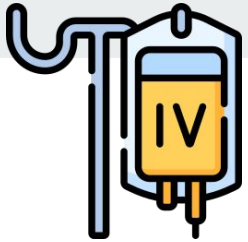
**Week 10** — **Admission #3** → foscarnet

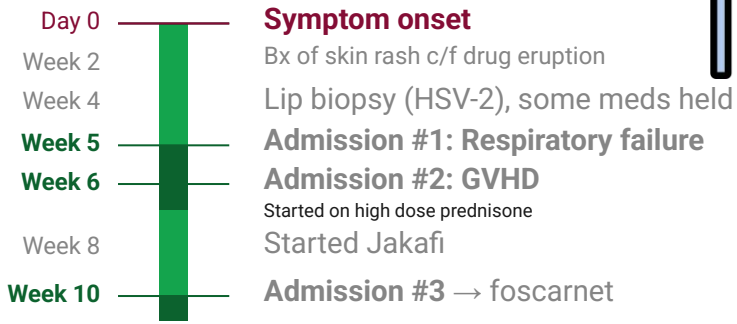
**Viral culture**
- Sent to ARUP
- Didn't grow :(

# OPAT

Discharged on 2 weeks of **foscarnet**

- Renal function was stable



# OPAT (day 75)

Discharged on 2 weeks of **foscarnet**

- Renal function was stable

Noticeable **improvement** **at** **one week** of Tx

| | |
|---|---|
| Day 0 | **Symptom onset** |
| | Bx of skin rash c/f drug eruption |
| Week 2 | |
| Week 4 | Lip biopsy (HSV-2), some meds held |
| **Week 5** | **Admission #1: Respiratory failure** |
| **Week 6** | **Admission #2: GVHD** |
| | Started on high dose prednisone |
| Week 8 | Started Jakafi |
| **Week 10** | **Admission #3** → foscarnet |

**Before foscarnet** (Day 64)

# Week 12 (day 78)

Transplant ID clinic:

- Renal function was stable
- Lip lesions looked better than they ever had (on **foscarnet** at that time; day 11 of 14)

# Week 12 (day 78)

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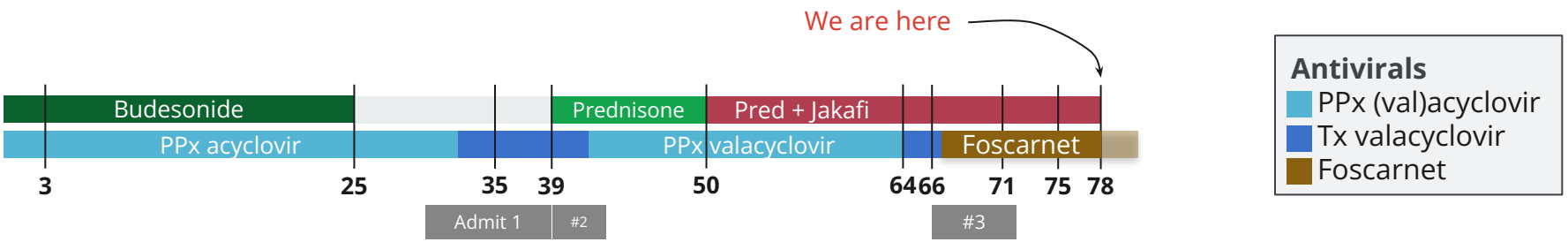
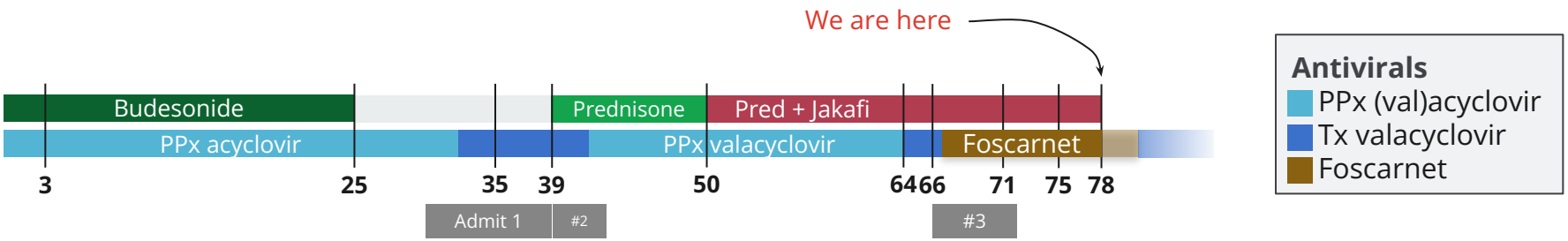


# Week 12 (day 78)

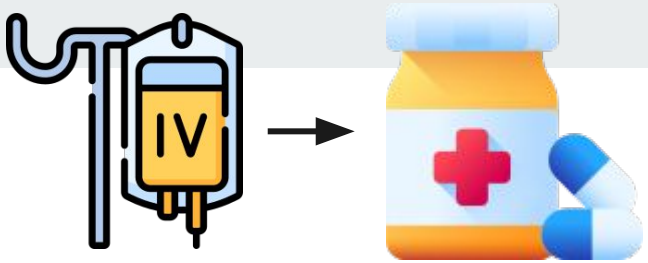
Transplant ID clinic:

- Renal function was stable
- Lip lesions looked better than they ever had (on **foscarnet** at that time; day 11 of 14)

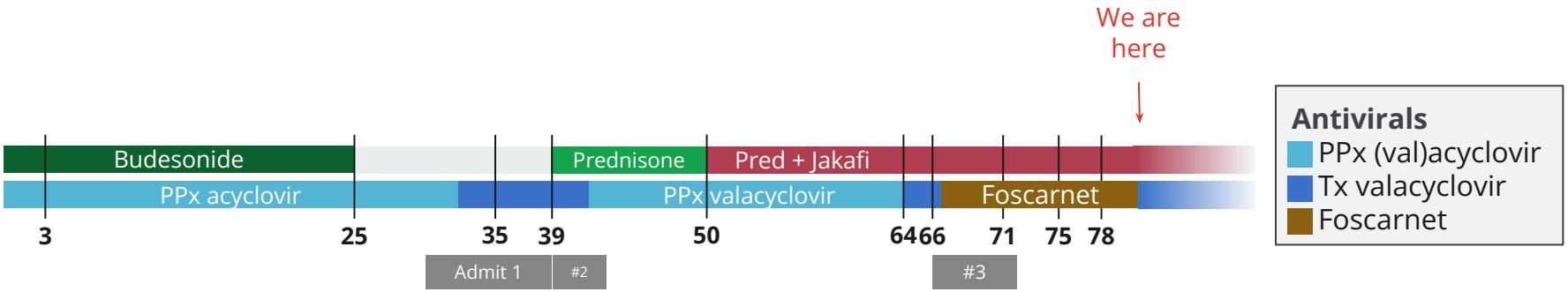
Planned for finishing 2 weeks of **foscarnet** followed by **valacyclovir** 1g BID



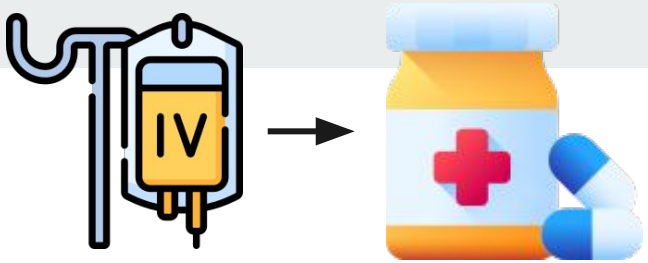
# Week 12 (day 81)




Finished two weeks of **foscarnet** → **valacyclovir** 1g BID



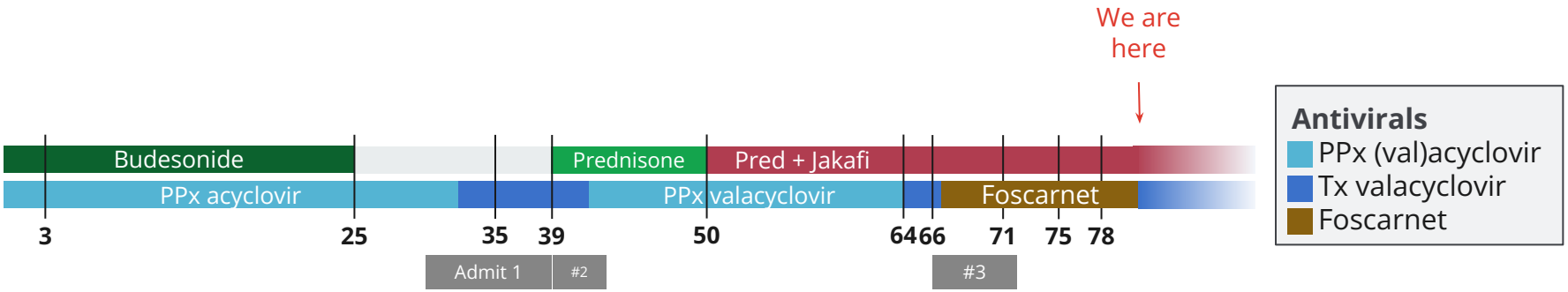
# Week 12 (day 81)




Finished two weeks of **foscarnet** → **valacyclovir** 1g BID

Around the same time, he noticed **oral thrush**

- No pictures in the EMR :(



# Week 12 (day 81)

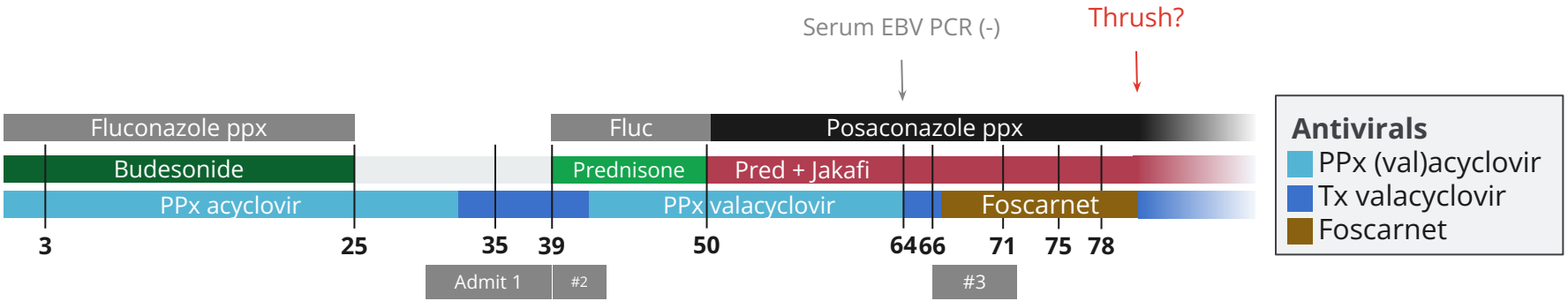
Finished two weeks of **foscarnet** → **valacyclovir** 1g BID

Around the same time, he noticed **oral thrush**

- No pictures in the EMR :(
- Notably had **been on posaconazole**
  - Serum **EBV PCR** was **negative** (day 64)

**Med list**

- Prednisone **40**
- Ruxolitinib (Jakafi)
- Atovaquone 1500 daily
- **Posaconazole** 300 daily
- Valacyclovir 1g BID
- ~~Letermovir 480 daily~~



# Week 12 (day 81)

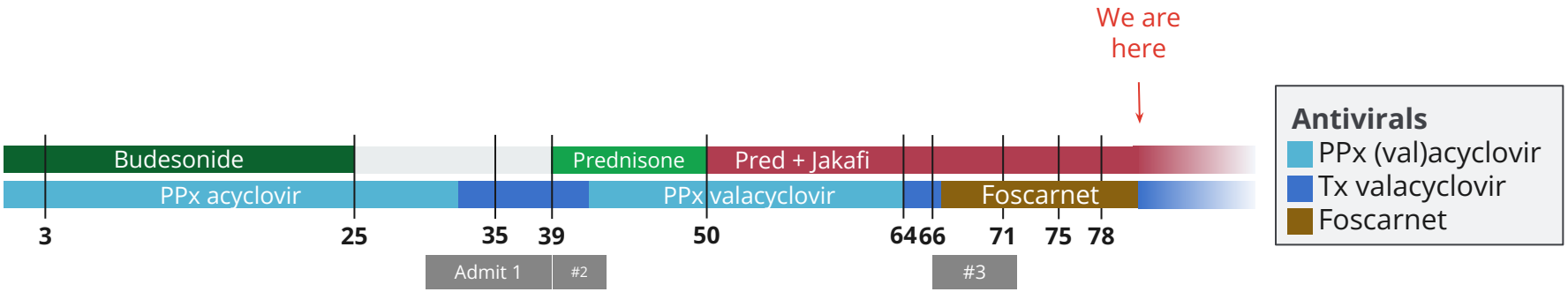
Finished two weeks of **foscarnet** → **valacyclovir** 1g BID

Around the same time, he noticed **oral thrush**

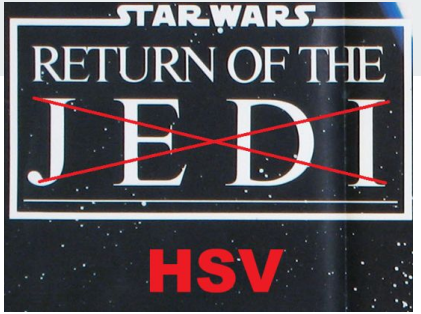
- No pictures in the EMR :(
- Notably had **been on posaconazole**
  - Serum **EBV PCR** was **negative** (day 64)
- Hematology Rx'ed **nystatin** **swish and swallow**

**Med list**

- Prednisone **40**
- Ruxolitinib (Jakafi)
- Atovaquone 1500 daily
- **Posaconazole** 300 daily
  - **Nystatin** S&S
- Valacyclovir 1g BID
- ~~Letermovir 480 daily~~

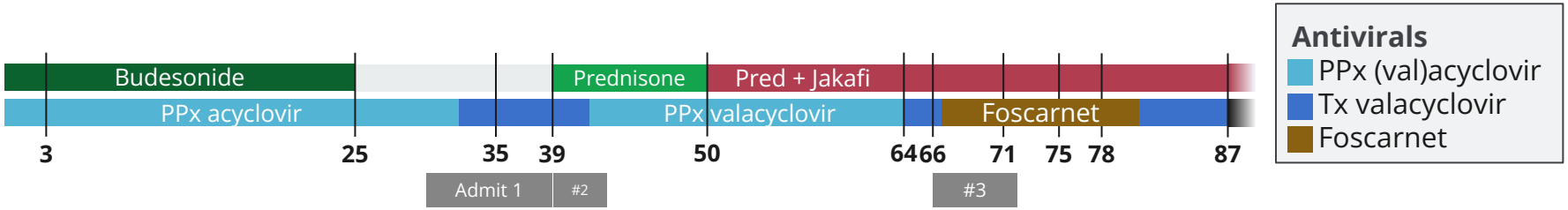


# Week 13 (day 87)

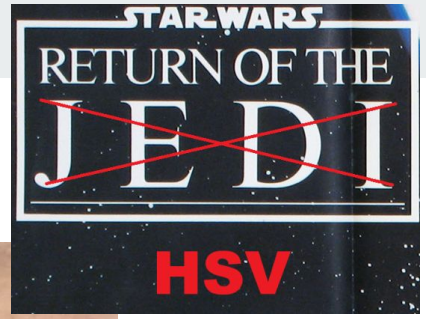



Transplant ID & derm clinic:

- **Good news**: Thrush is better with nystatin S&S (+posa)
- **Bad news**:

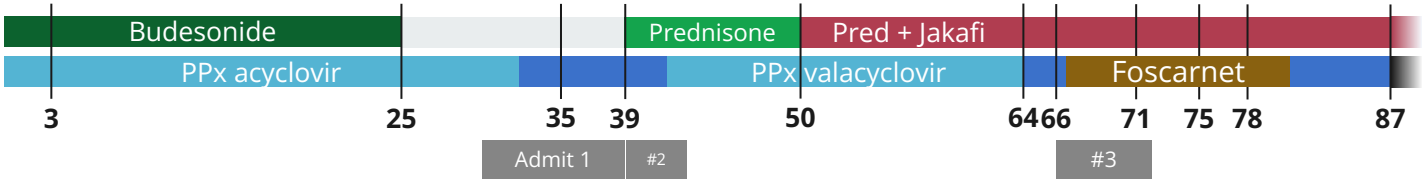


# Week 13 (day 87)



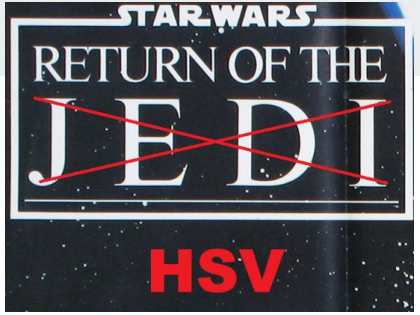

Transplant ID & derm clinic:

- Patient says **lip has gotten worse** since **stopping foscarnet**




**Antivirals**
- PPx (val)acyclovir
- Tx valacyclovir
- Foscarnet

# Week 13 (day 87)

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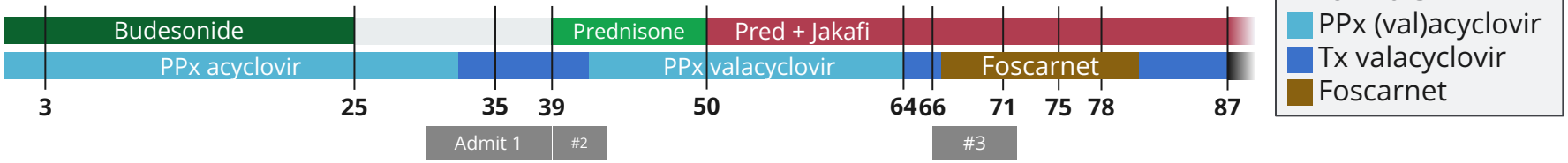
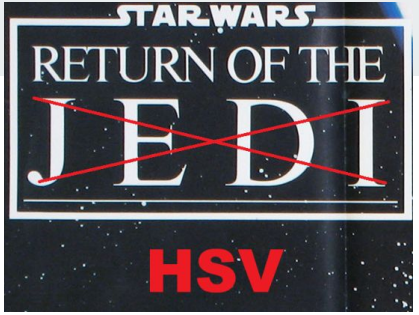


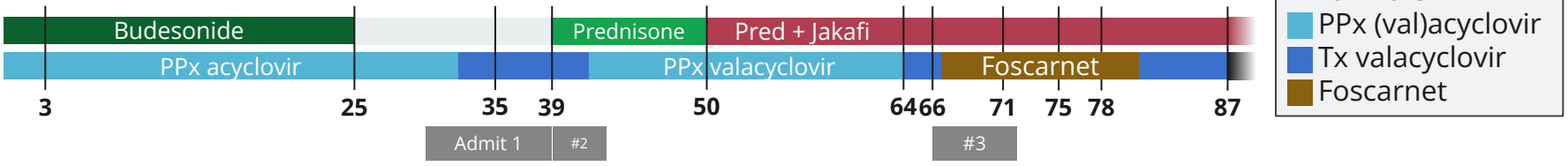
# Week 13 (day 87)

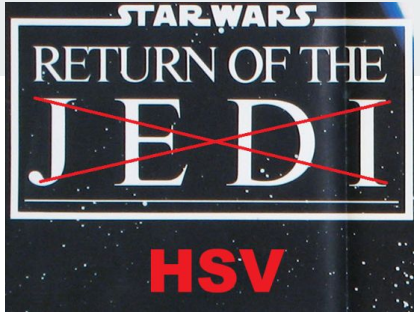



Transplant ID & derm clinic:

- Patient says **lip has gotten worse** since **stopping foscarnet**
- Still **fighting insurance** for **topical cidofovir**

United Healthcare



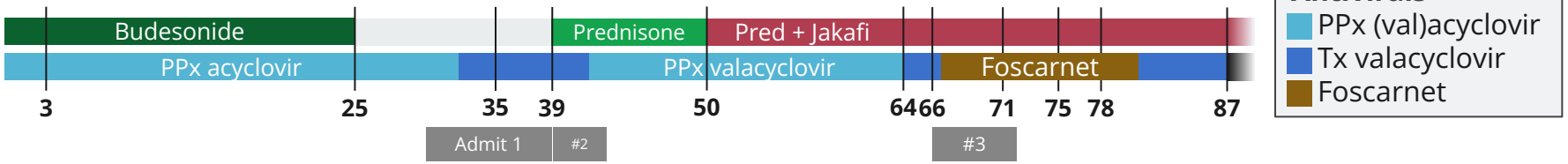



# Week 13 (day 87)

Transplant ID & derm clinic:

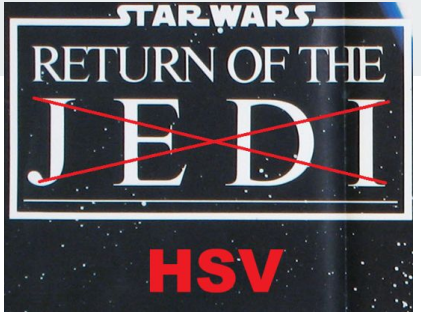
- Patient says **lip has gotten worse** since **stopping foscarnet**
- Still **fighting insurance** for **topical cidofovir**

**PCR**: Positive for HSV-2
- Negative for HSV-1



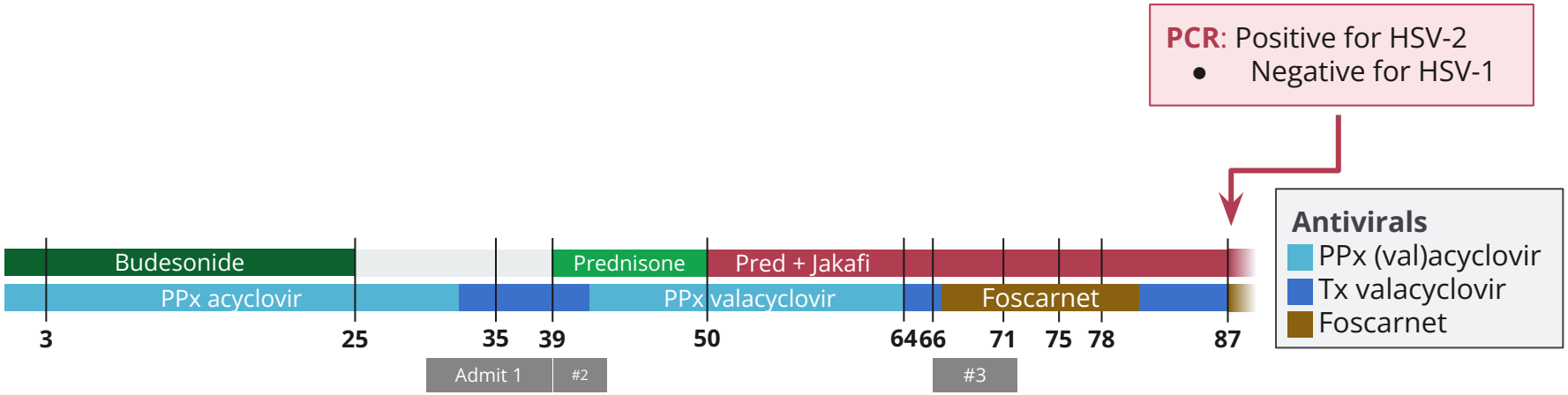
# What would you do?

# Week 13

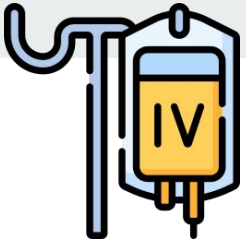



Transplant ID & derm clinic:

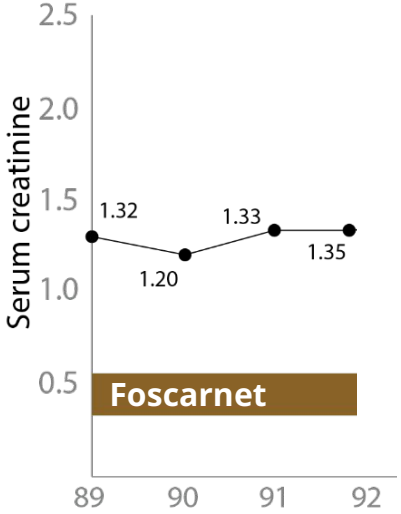
- Restart **foscarnet**
- Would take a few days to get PICC & OPAT set up



# OPAT: Week 14



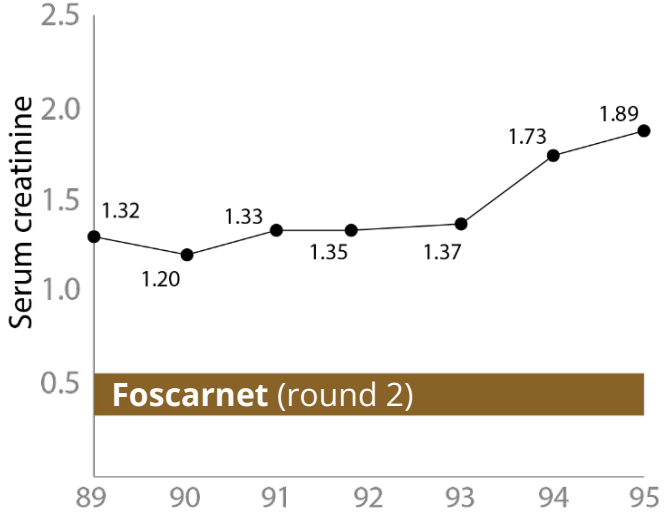

Started on **foscarnet** with stable renal function



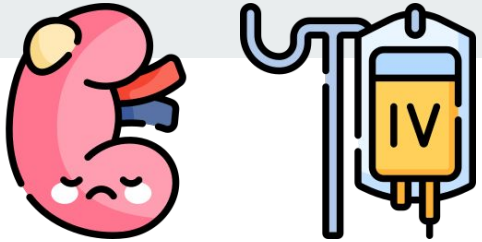
# OPAT: Week 14


Started on **foscarnet** with stable renal function **at first**

- On **day 5** of therapy, creatinine increases by 0.4 mg/dL above baseline

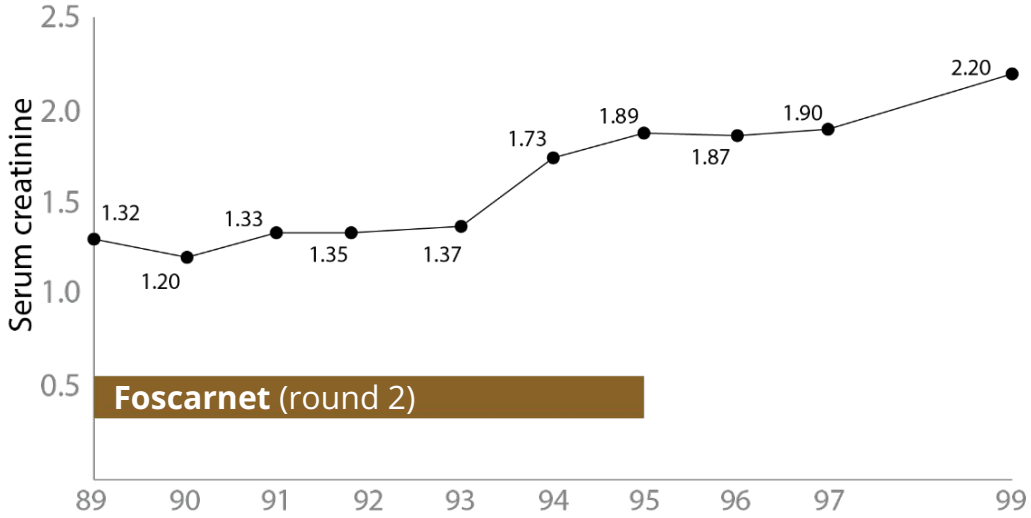


# OPAT: Week 14




Started on **foscarnet** with stable renal function **at first**

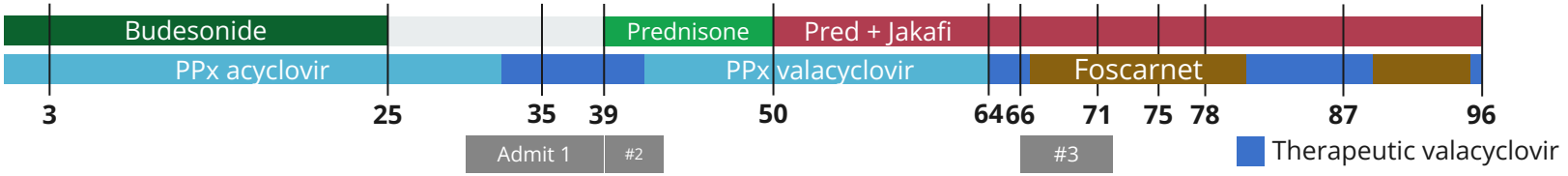
- On **day 5** of therapy, creatinine increases by 0.4 mg/dL above baseline
- **Foscarnet held**



# OPAT: Week 14 (day 96)

Started on **foscarnet** with stable renal function **at first**

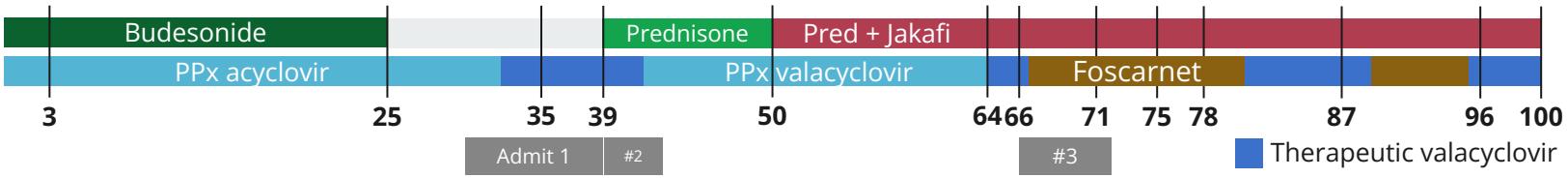
- On **day 5** of therapy, creatinine increases by 0.4 mg/dL above baseline
- **Foscarnet held**
- By time of AKI, patient **did not have any improvement with second round** of foscarnet



# Clinic: Week 15 (day 100)

Seen at next available clinic appointment

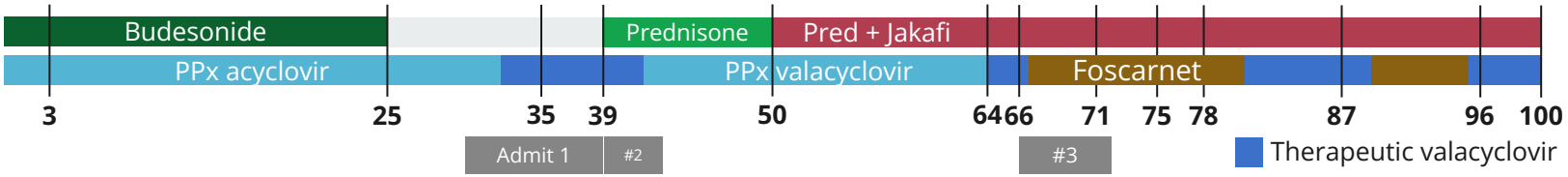
- Lesions worsening
- Not eating



# Clinic: Week 15 (day 100)

Seen at next available clinic appointment

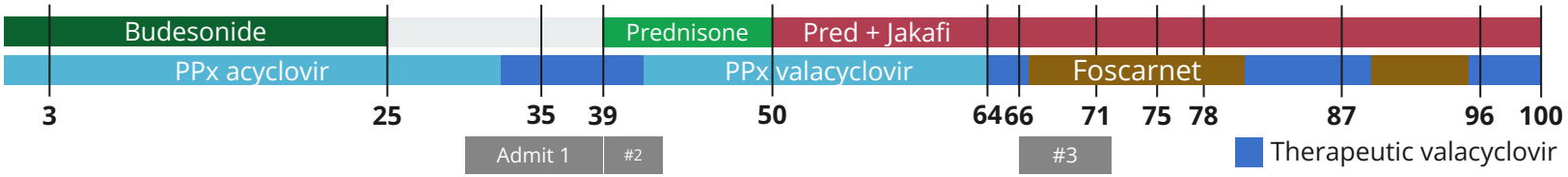
- Lesions worsening
- Not eating



# Clinic: Week 15 (day 100)

Seen at next available clinic appointment

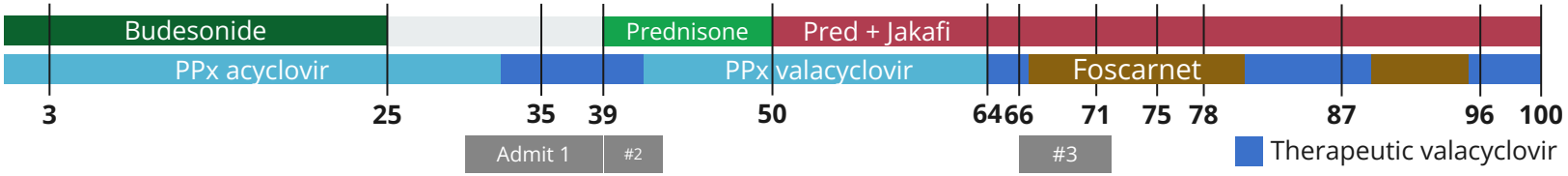
- Lesions worsening
- Not eating

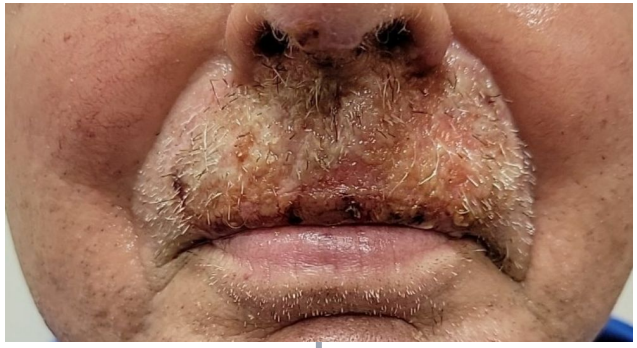


# Clinic: Week 15 (day 100)

Seen at next available clinic appointment

- Lesions worsening
- Not eating
- Still having thrush





GVHD

PCR (+)
HSV-2

Lip unimproved
--and-- AKI

Prednisone

Pred + Jakafi

PPx valacyclovir

Foscarnet

Tx valacyc

39

50

64

78

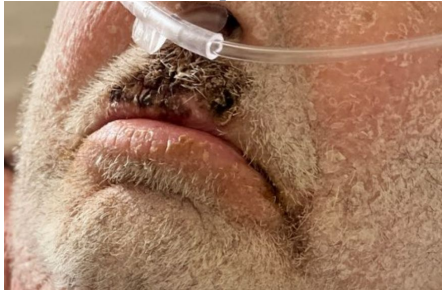
87

96

100

No growth
(viral media)

Thrush?



# What would you do?

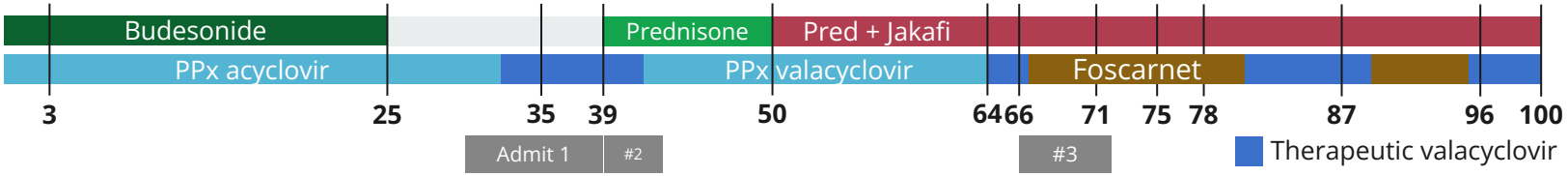
# Clinic: Week 15 (day 100)

Seen at next available clinic appointment

- Lesions worsening
- Not eating

**Recommendations**

- Admit for coordination of care with nephrology
  - Possible IV acyclovir
- Derm consult for Bx
  - Viral Cx
  - Fungal / AFB
  - Path to look for other causes

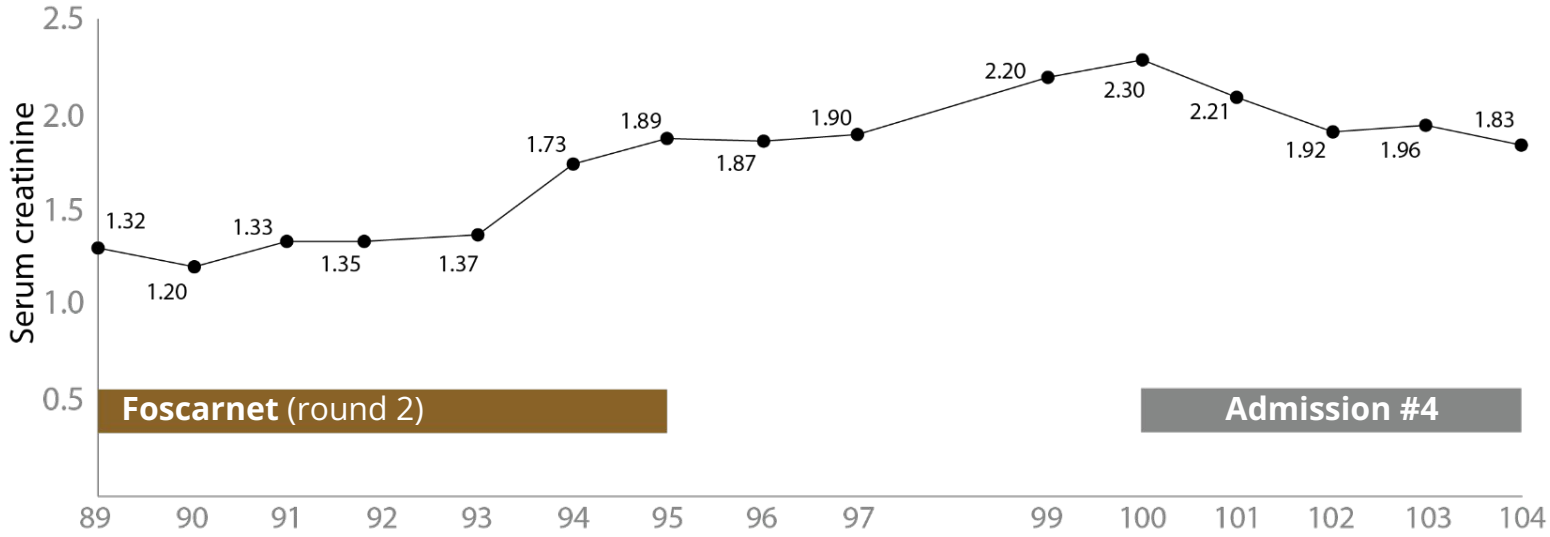


# Admission #4

Generous IV fluids →

# Admission #4

Generous IV fluids → **Still not much improvement** of renal fxn



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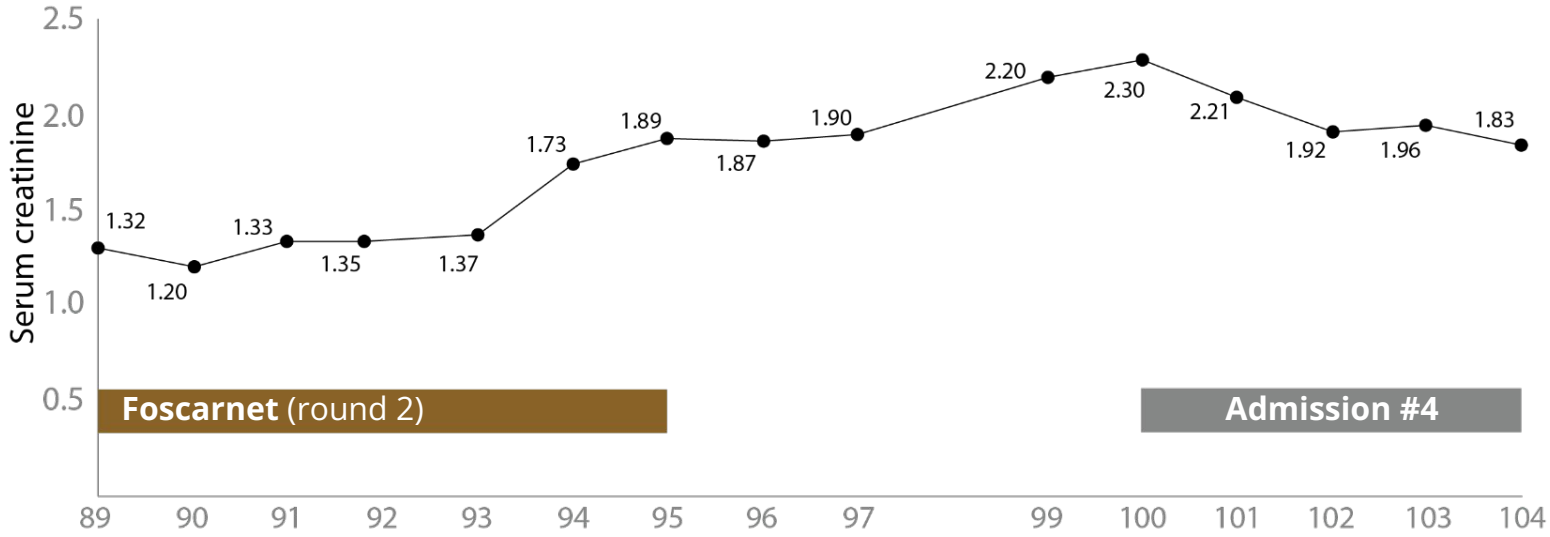

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Examination reveals a piece of skin with a **necrotic and ulcerated surface**. The underlying dermis reveals a dense **perifollicular mixed inflammatory infiltrate** with disruption and destruction of the follicles. **HSV1 and 2 immunohistochemical stain shows positive staining** within the follicular epithelium, supporting the above diagnosis. VZV and Gram stains are negative. Positive and negative controls stain as expected

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Virus was isolated…

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Generally not the most productive admission

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Generally not the most productive admission

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Generally not the most productive admission

- Didn't receive any IV antivirals
- Diagnostic testing was...frustrating

**Pathology report: Herpes folliculitis**

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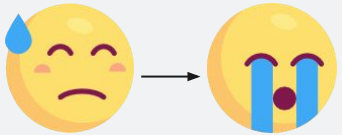
**Viral culture(s)**



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# Admission #4

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**Good news**: Dermatology did get topical cidofovir approved!

United Healthcare

**Pathology report: Herpes folliculitis**

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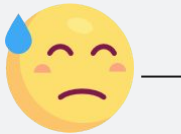

(Quest) (ARUP)

# Case 1: Discharge course

- Discharged from admission #4 on day 105
- Saw primary care on day 109

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  - Another lorazepam (Ativan) → apnea → bradycardia → PEA arrest
- ACLS (x2) → family called code off

# Discussion

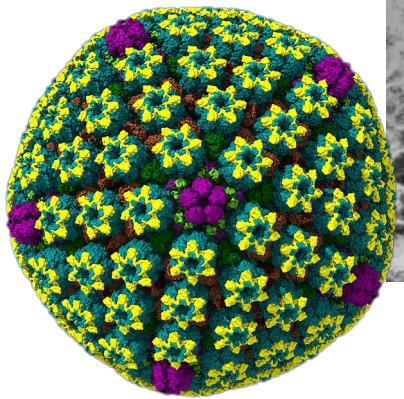
Links to articles discussed here

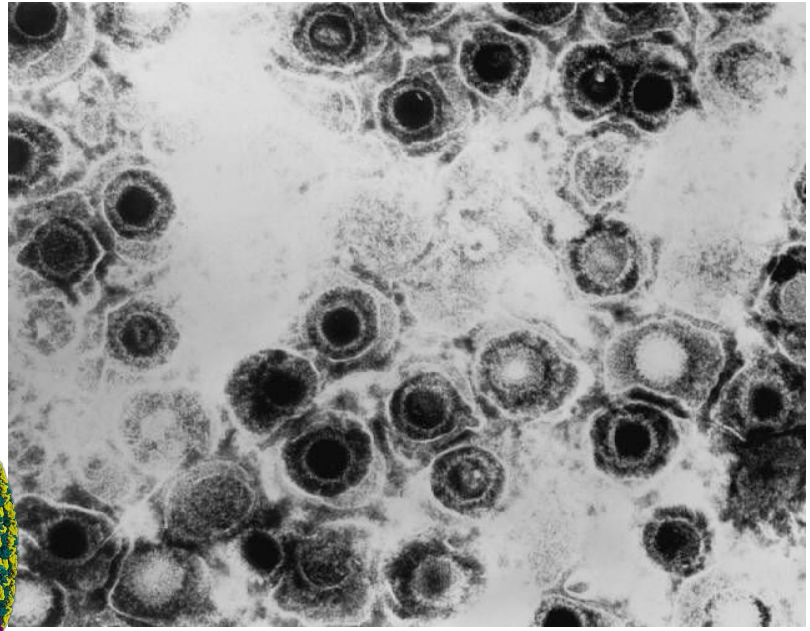
# Learning objectives

- Identify the **antivirals used in the treatment of HSV** and their potential **mechanisms of resistance**
  - Including **TK deficient HSV**
- Discuss **newer candidates** for the treatment of HSV
- A **trip to the kitchen**...

# Herpes simplex virus

- Enveloped dsDNA virus
- Viral genome of ~15,000 base pairs
  - One of the better studied viruses

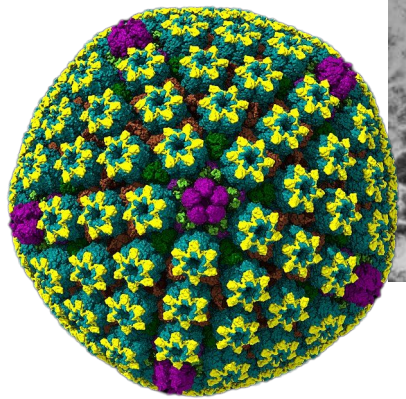


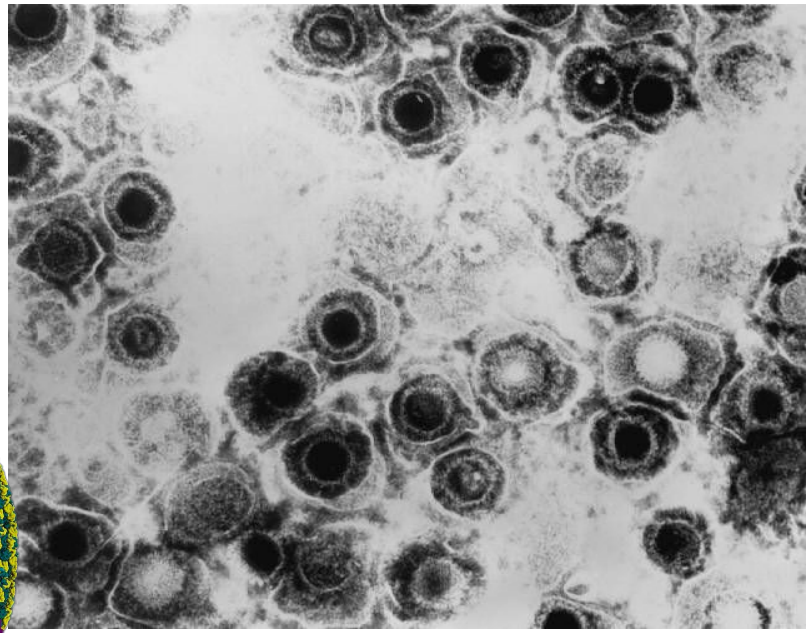


Wikipedia: Herpes simplex virus

# Herpes simplex virus

- Enveloped dsDNA virus
- Viral genome of ~15,000 base pairs
  - One of the better studied viruses
- Virus encodes key machinery used in viral life cycle (unique long regions; UL)
  - **UL30**: DNA polymerase
  - **UL23**: Thymidine kinase
  - **UL8**: DNA helicase



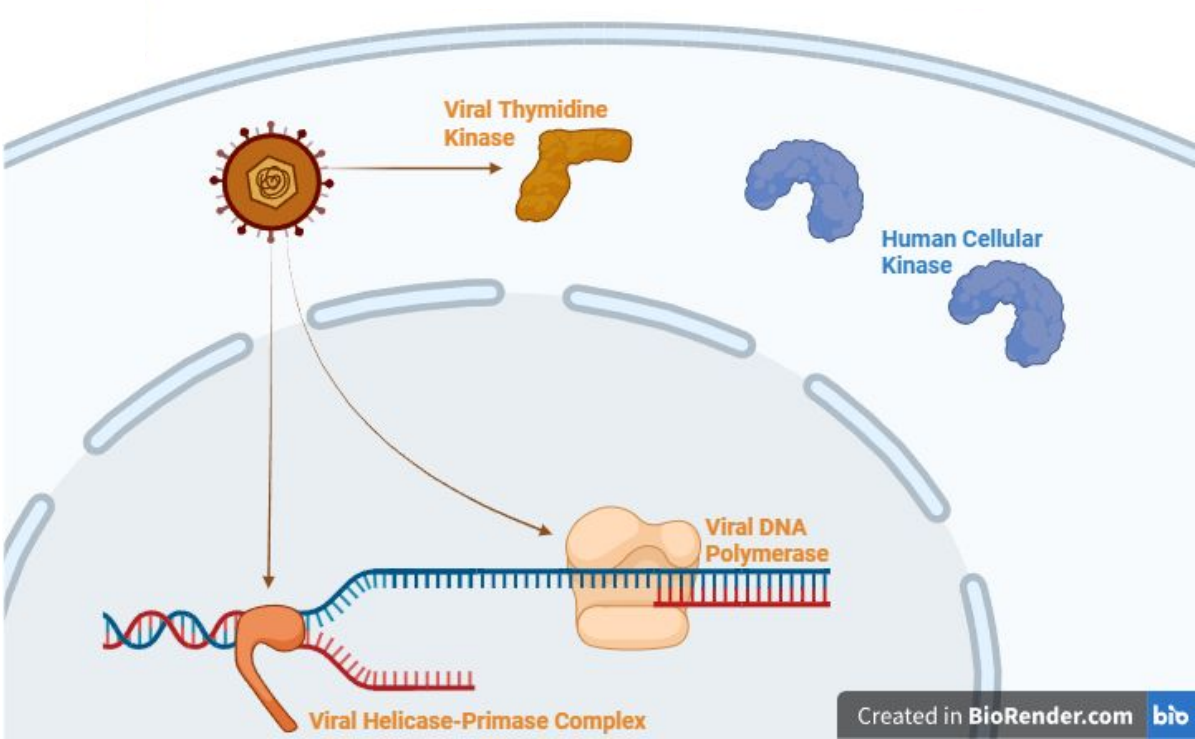


Wikipedia: Herpes simplex virus

# HSV lifecycle [1][2]

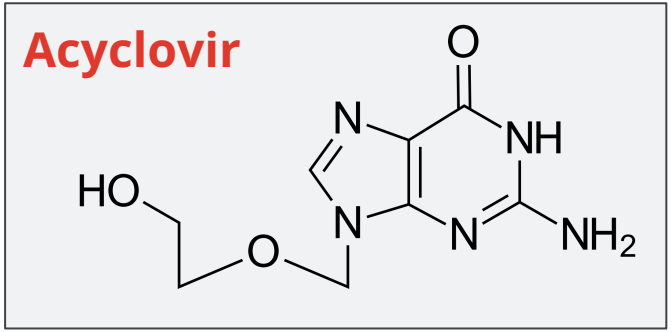
Key unique long (UL) regions

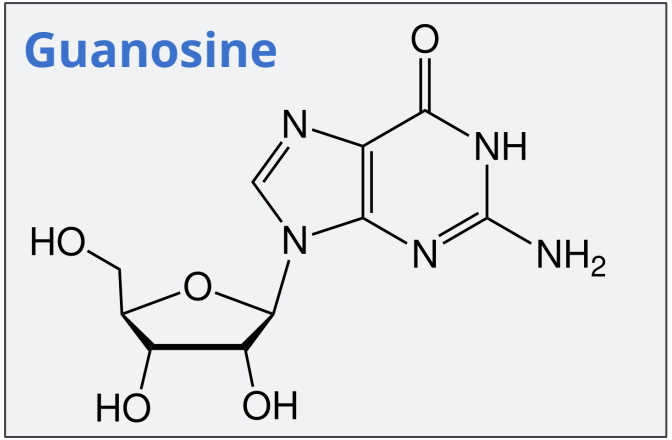
- **UL30**: DNA polymerase
- **UL23**: Thymidine kinase
- **UL8**: DNA helicase



# Mechanism of acyclovir

Acyclovir is the **prodrug** of a (guanosine) **nucleoside analogue**

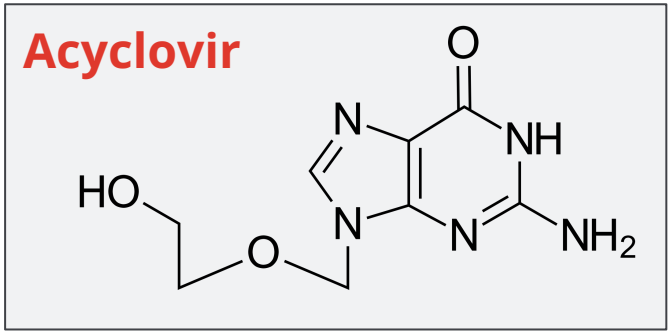


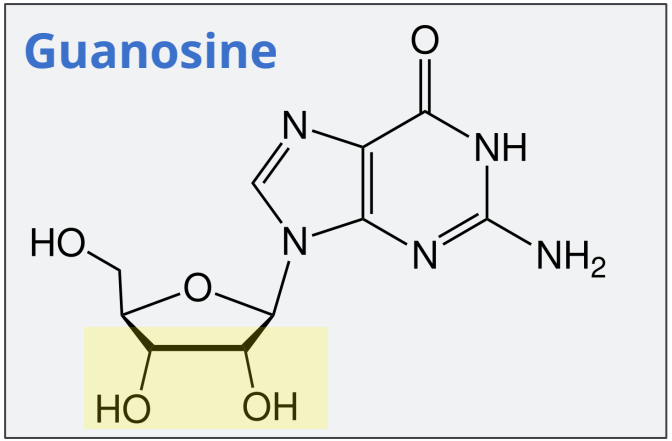



# Mechanism of acyclovir

Acyclovir is the **prodrug** of a (guanosine) **nucleoside analogue**

- **Active version** (acyclovir triphosphate, AKA acyclo-GTP) **lacks the 3'-OH group → halts DNA replication**

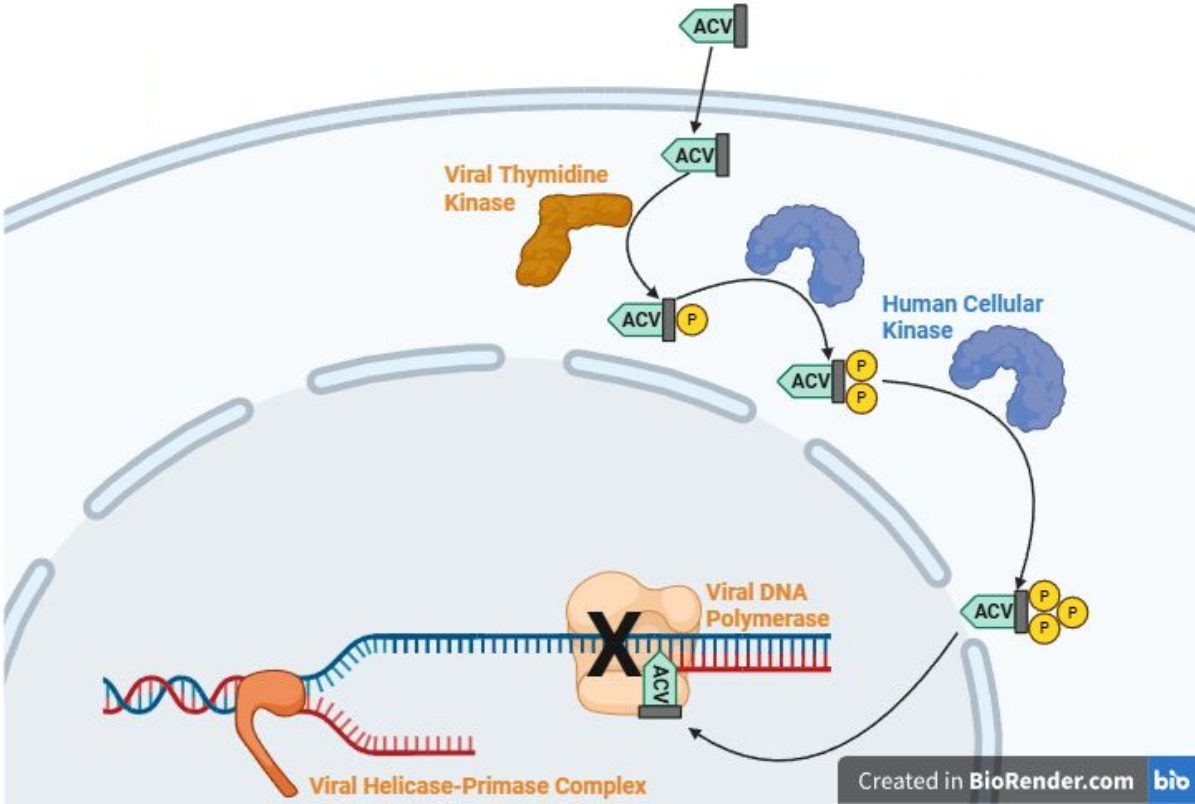


# Mechanism of acyclovir [2]

Acyclovir is the **prodrug** of a **nucleoside analogue**

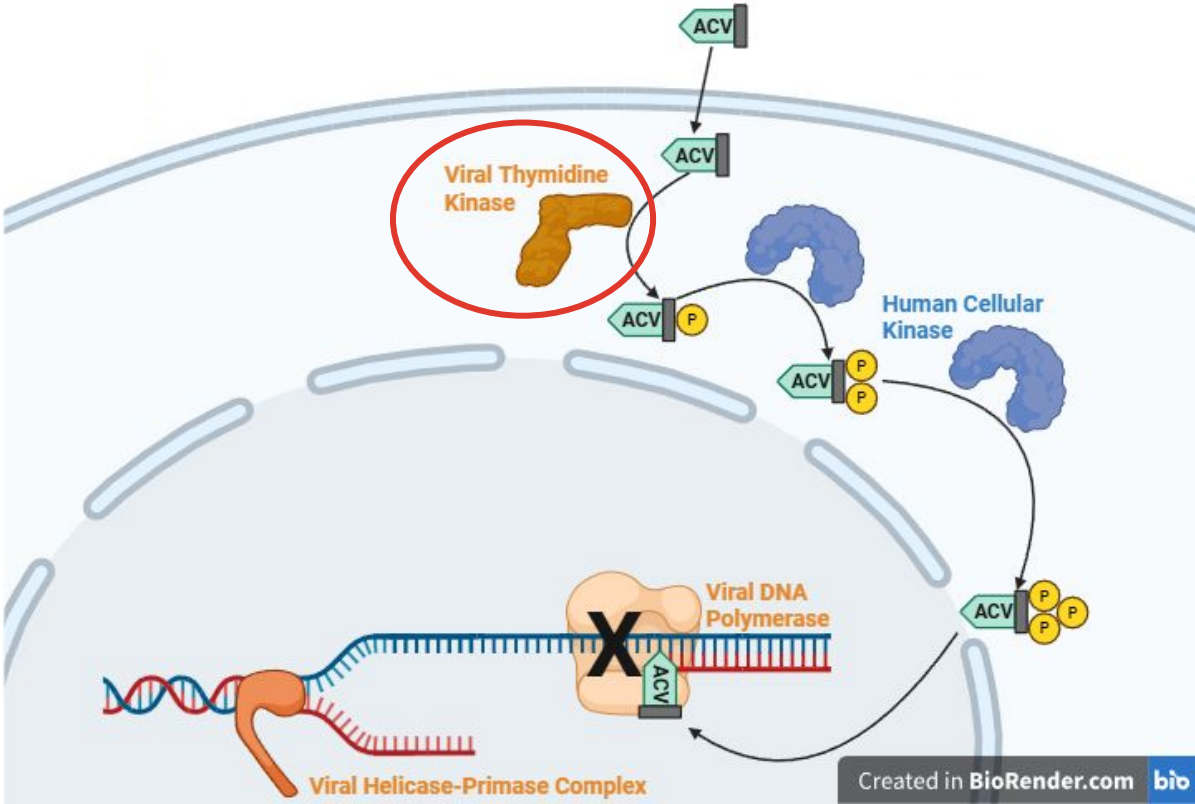
- To be converted into active version, **must be phosphorylated** (three times)



# Mechanism of acyclovir [2]

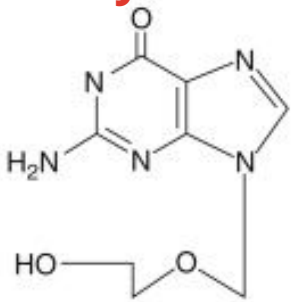
Acyclovir is the **prodrug** of a **nucleoside analogue**

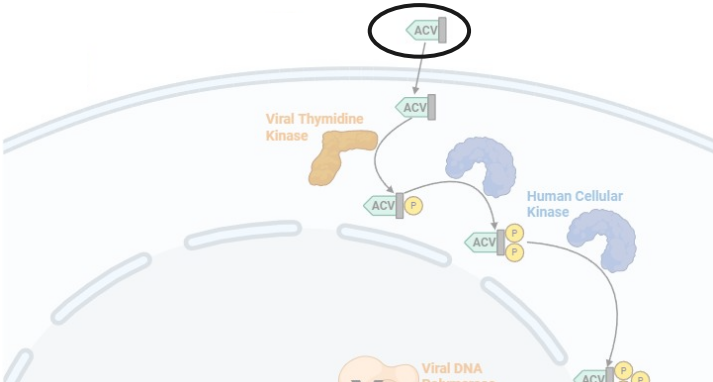
- To be converted into active version, **must be phosphorylated** (three times)
- First phosphorylation is done by the **viral thymidine kinase**



# Molecular mechanism of acyclovir

**Acyclovir**



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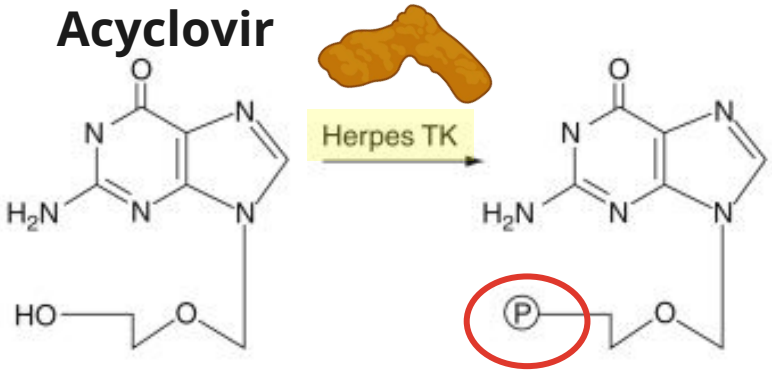


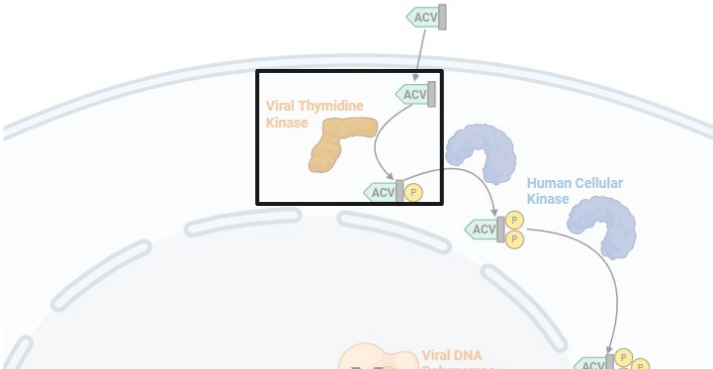

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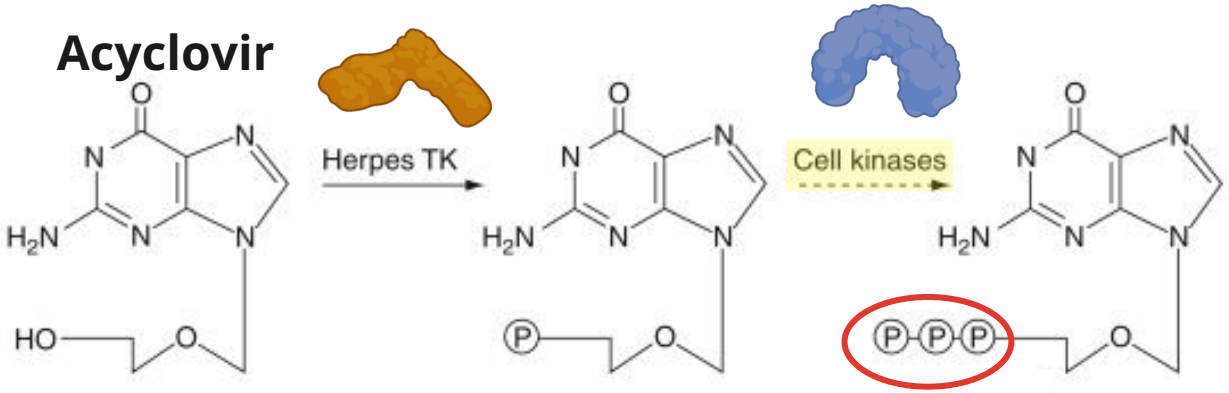
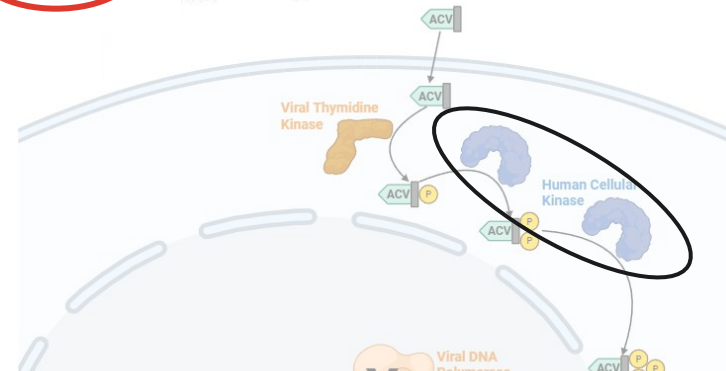
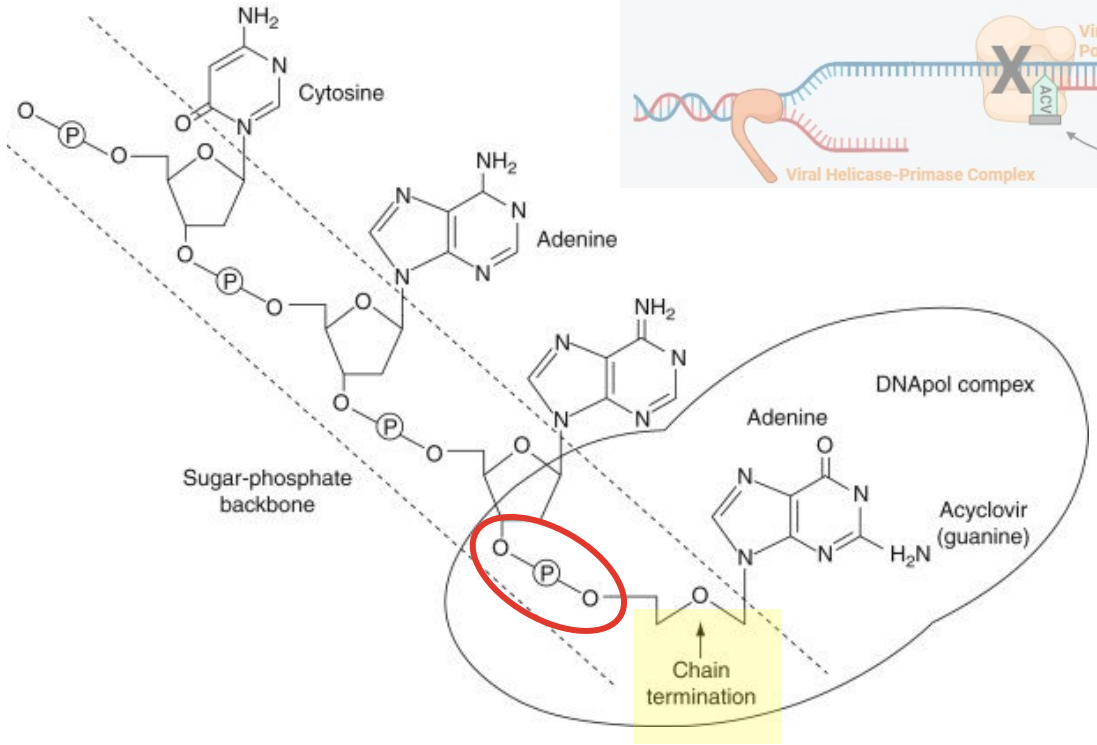
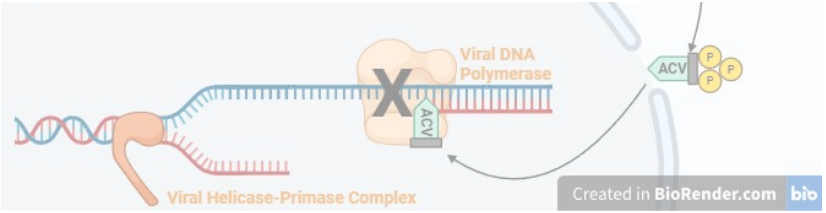


# Halting DNA replication (no 3'-OH group)



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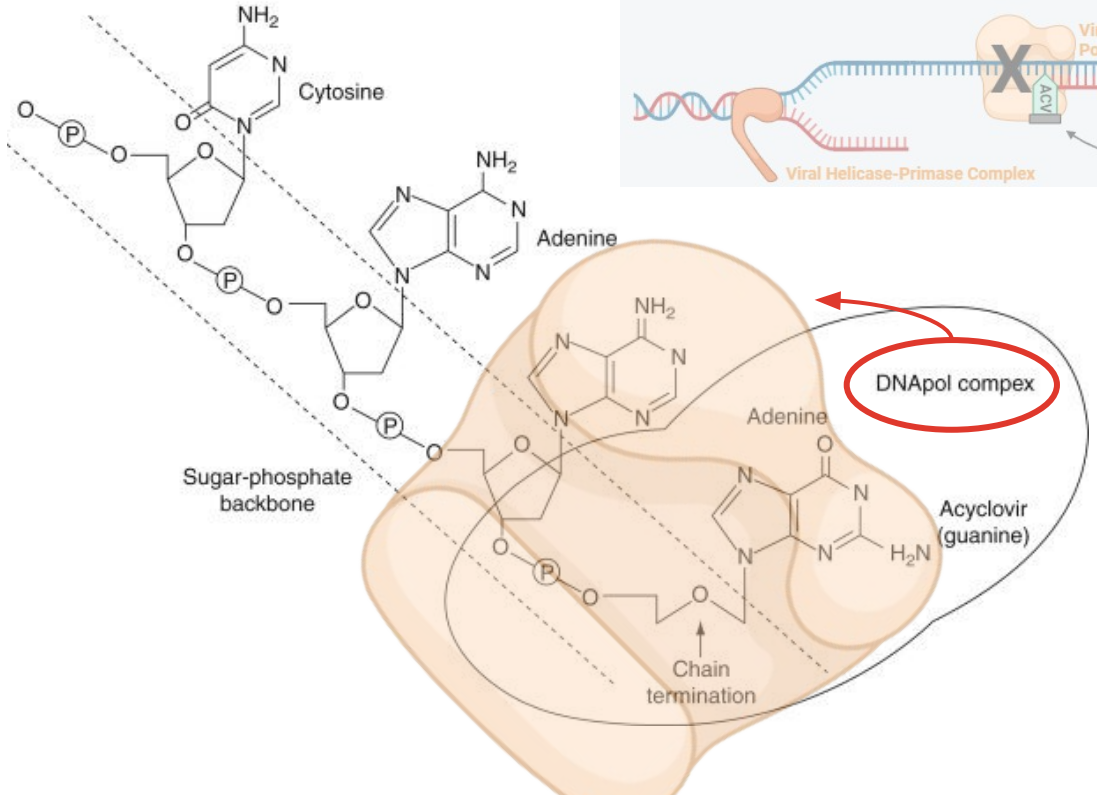
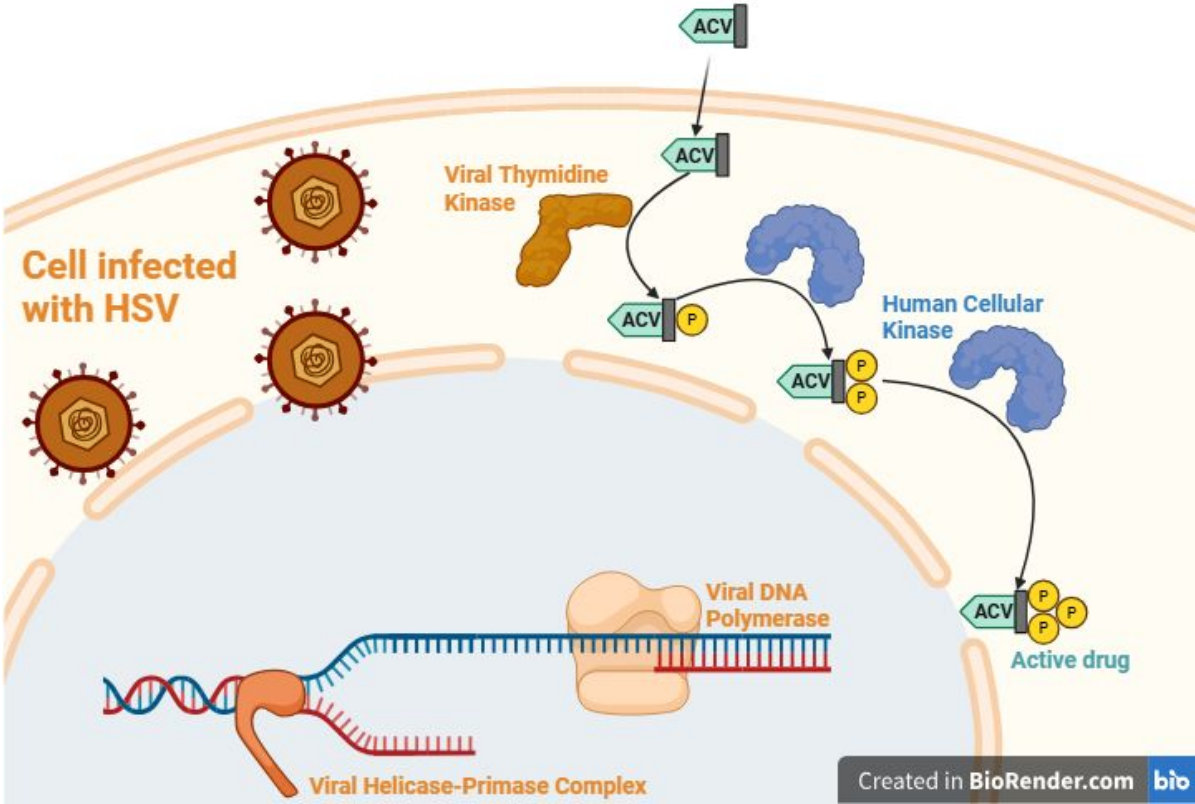


# Acyclovir's selectivity

Acyclovir has a much **higher affinity for viral TK** than for the **human analog** (dCK) [3]



# Acyclovir's selectivity [3]

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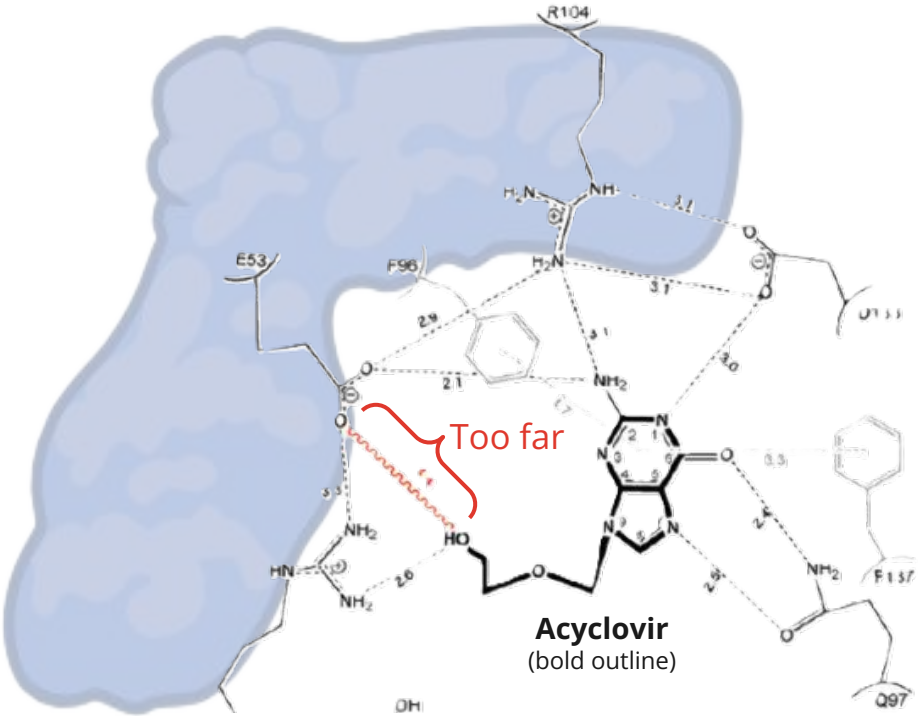
- Binds to both, but **acyclic sugar** prevents dCK from being able to phosphorylate

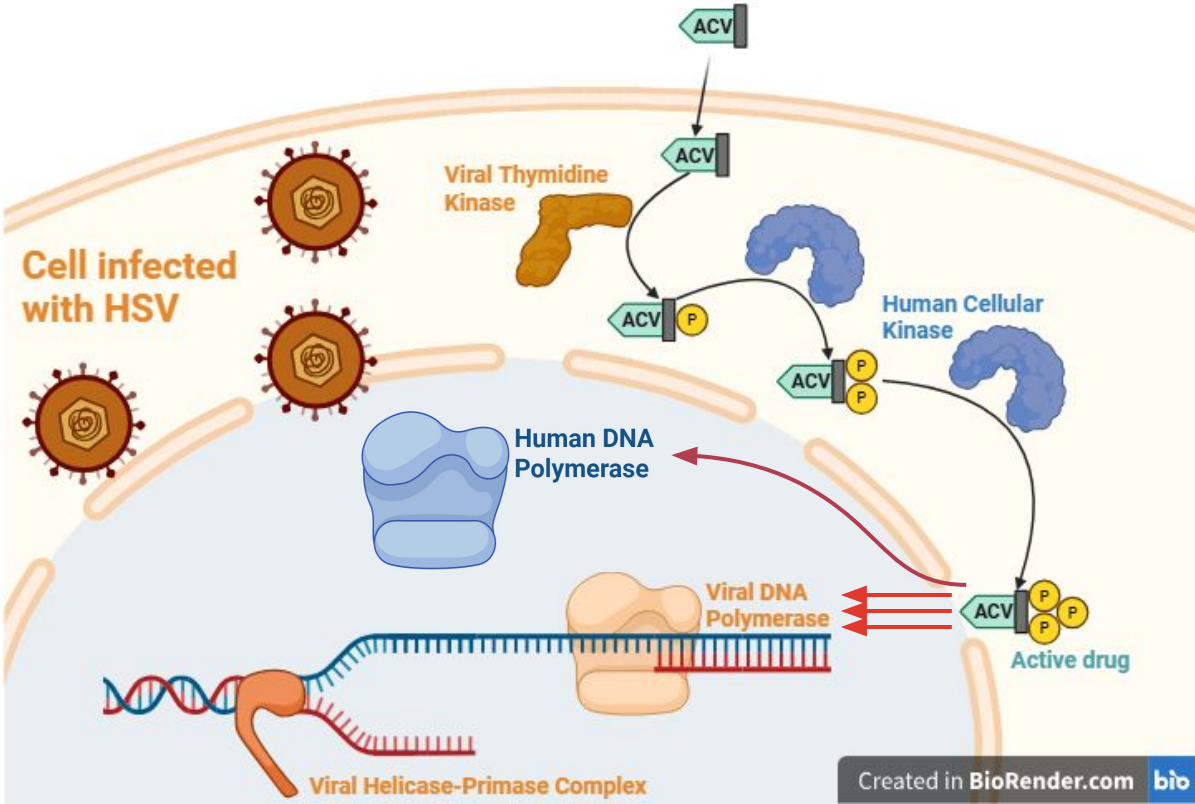


# Acyclovir's selectivity

Acyclovir has a much **higher affinity for viral TK** than for the **human analog** (dCK) [3]

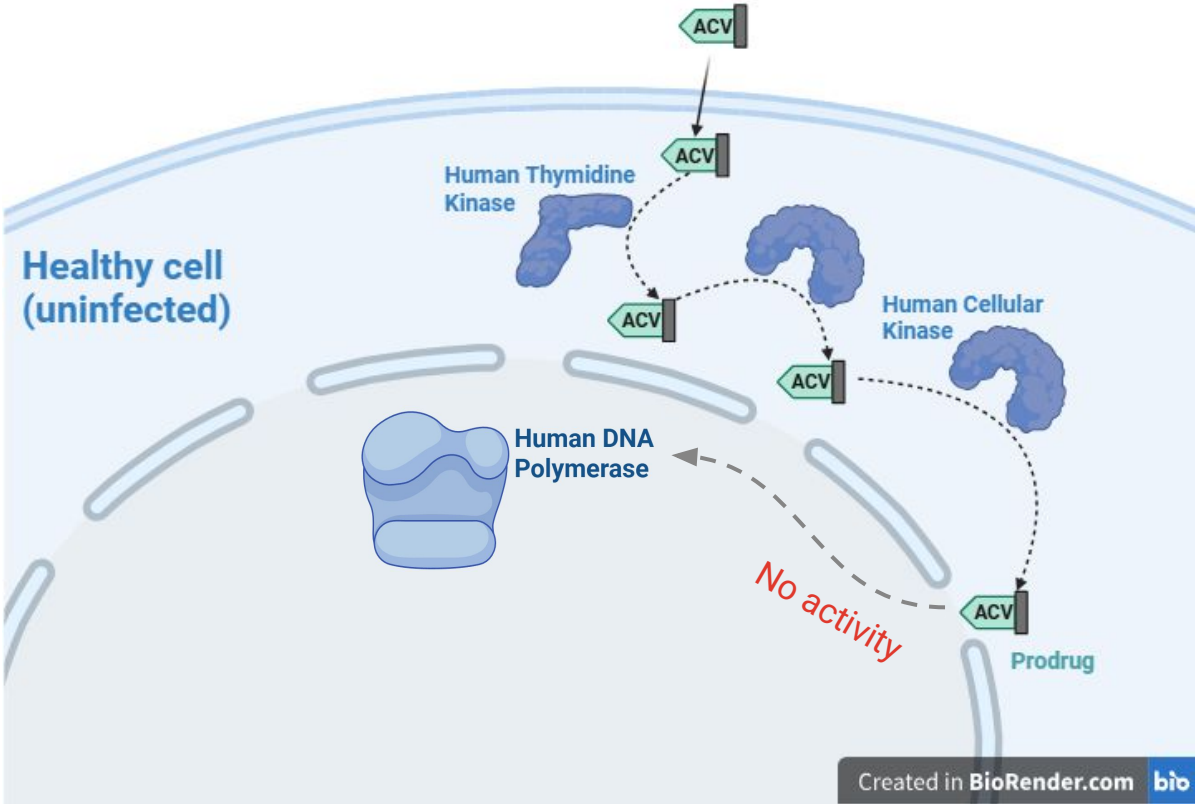
Acyclovir triphosphate (**active drug**) also *prefers* **viral DNA pol**, but is **not selective** (so still binds with human DNA pol) [4]

- Mainly mentioning this because this paper [4] was from my undergrad biochem professor



# Acyclovir's selectivity [3][4]

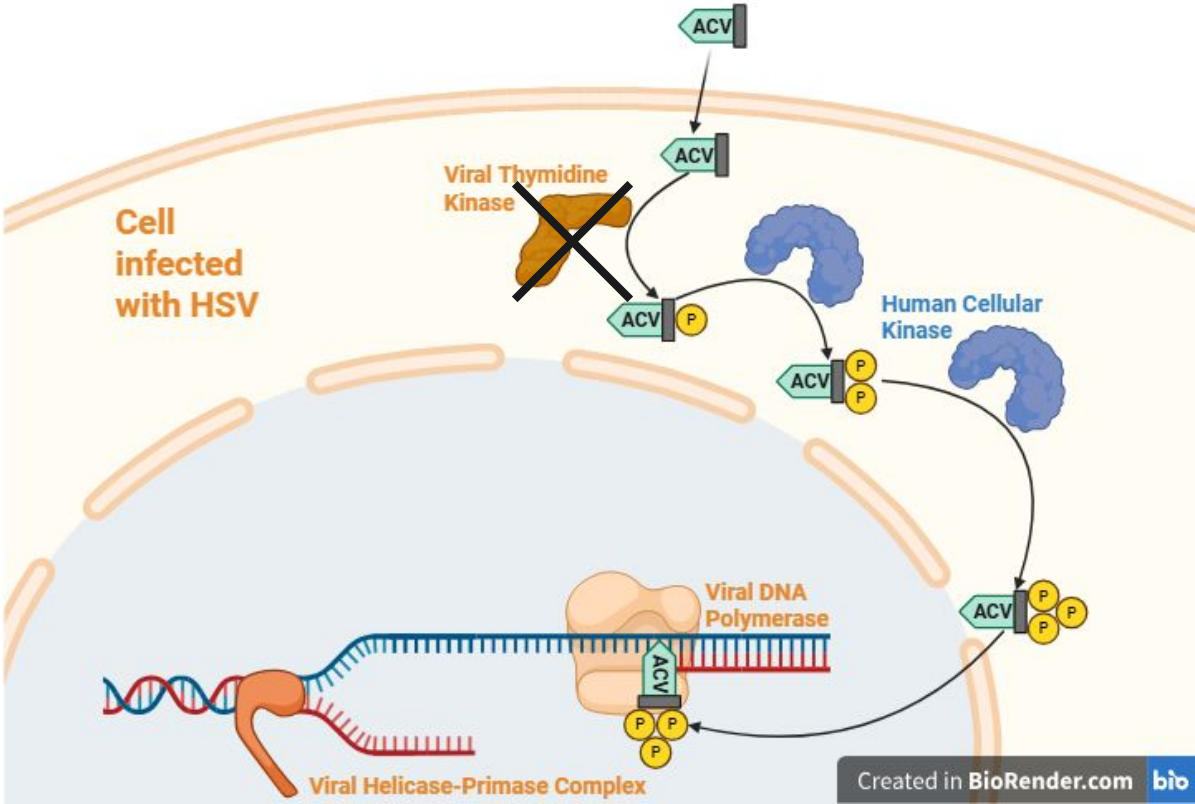
**Key point:** Acyclovir has a favorable **toxicity profile** because it only becomes active in **virally infected cells**, which express **viral TK**



# TK deficient HSV

**Key point:** Acyclovir has a favorable **toxicity profile** because it only becomes active in **virally infected cells**, which express ~~viral TK~~

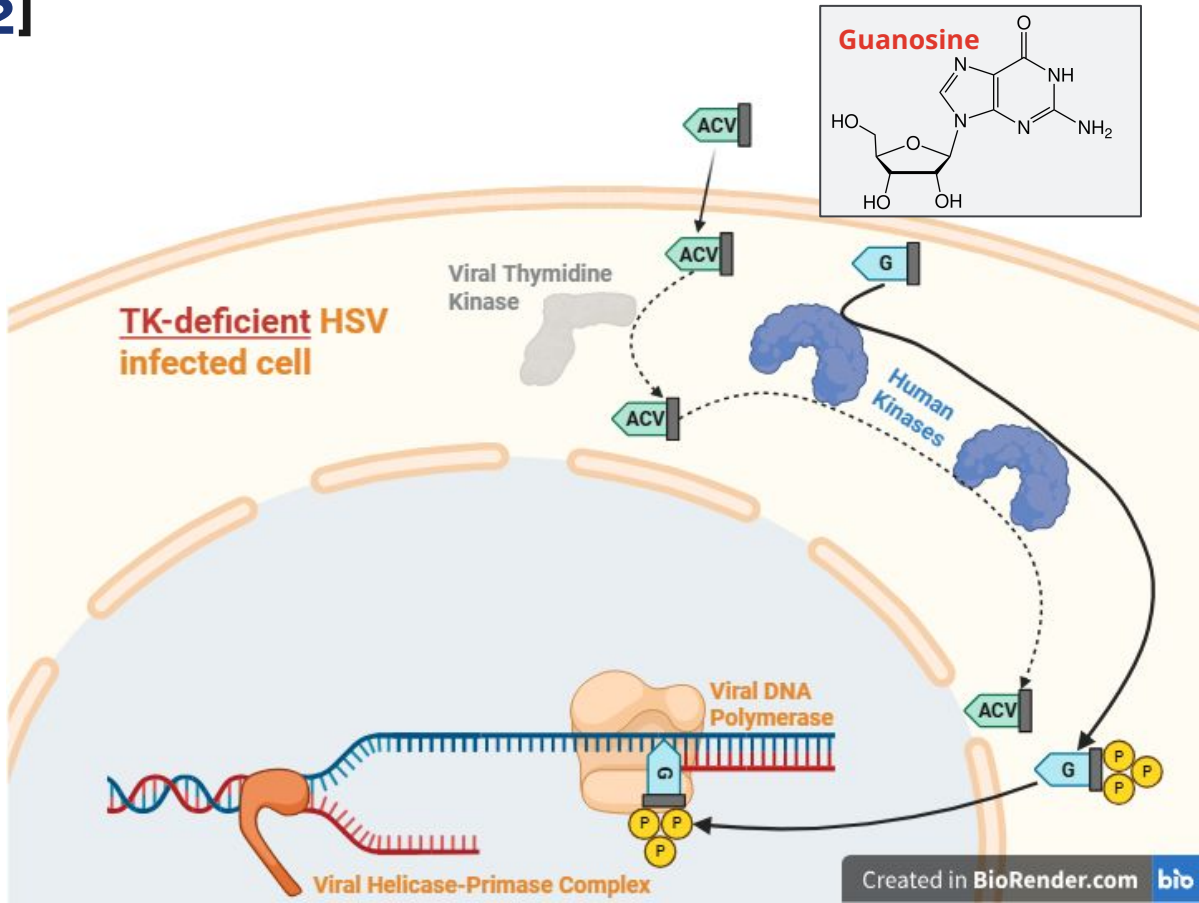
**What if the virus does not make viral TK?**



# TK deficient HSV [2]

For strains of the virus that do not produce HSV thymidine kinase:

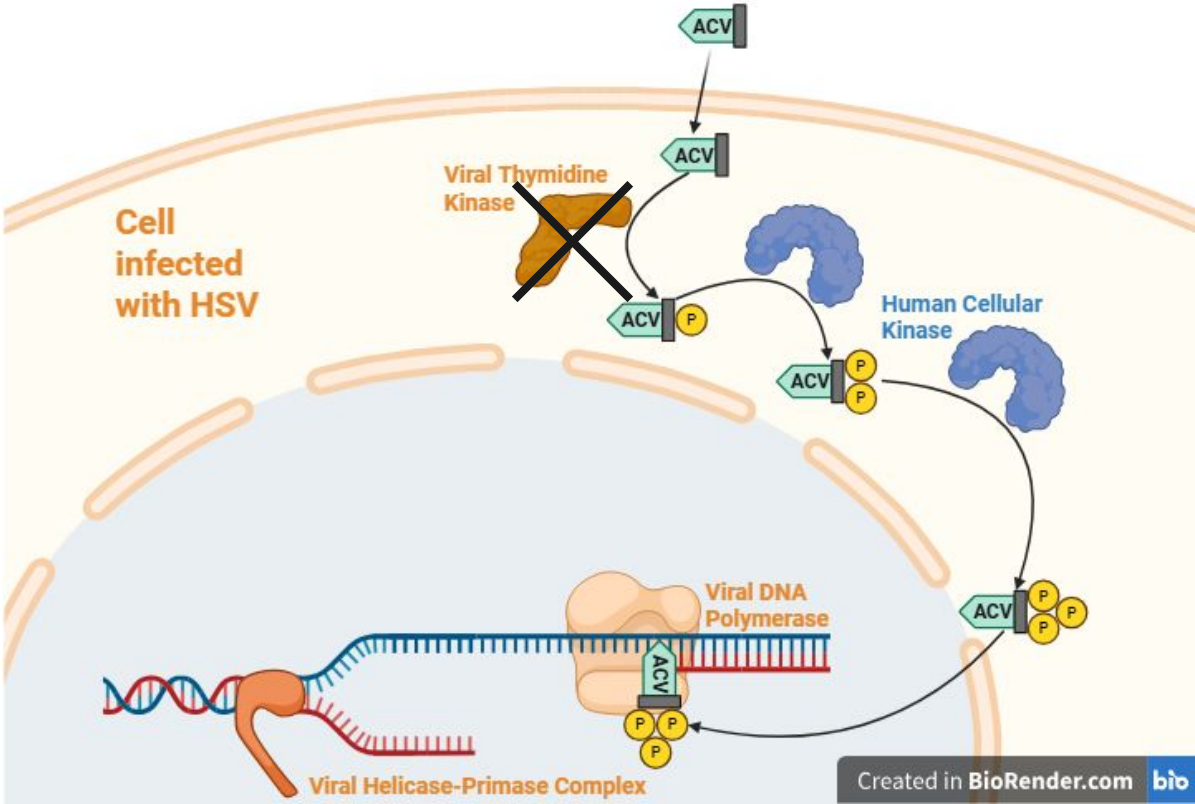
- Acyclovir **cannot be activated** (to acyclo-GTP)
- Thus no therapeutic effect



# TK deficient HSV[ 7]

Rates of acyclovir resistant HSV may be **10 times higher** in immunocompromised hosts

- Between **1 in 25** to **1 in 10**



# TK deficient HSV

Rates of acyclovir resistant HSV may be **10 times higher** in immunocompromised hosts

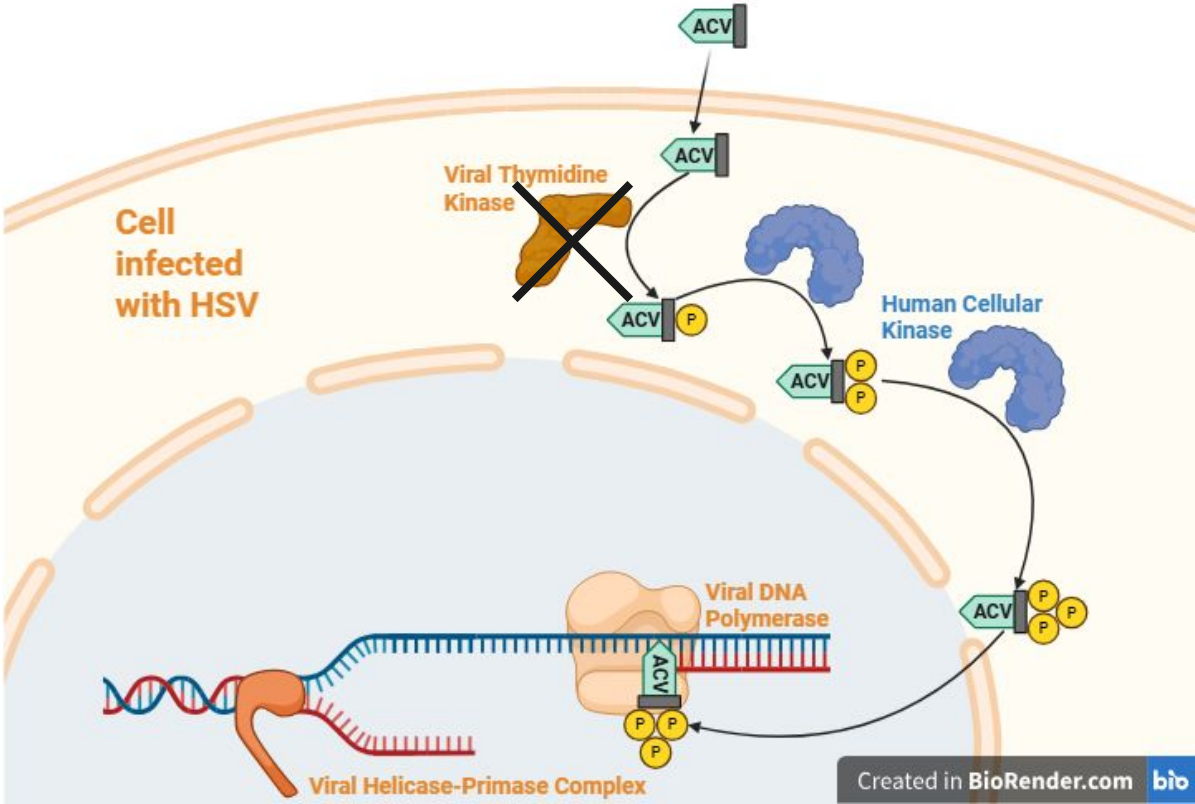
- Between **1 in 25** to **1 in 10**

Impaired host responses →

Less pathogenic viral strains able to survive →

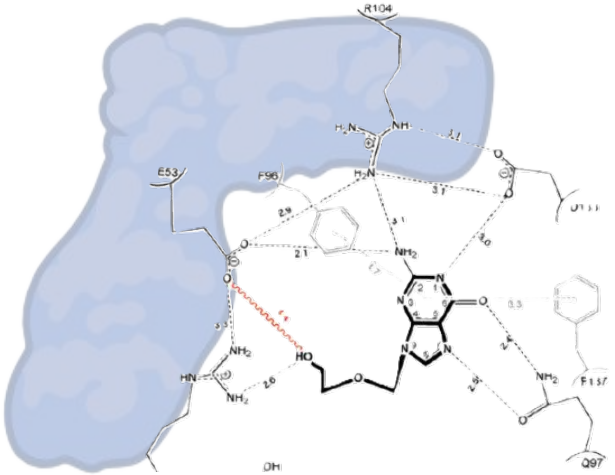
Selective pressure →

Emergence of resistant strains

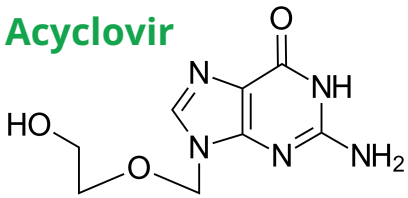


# What about ganciclovir? [2][3]

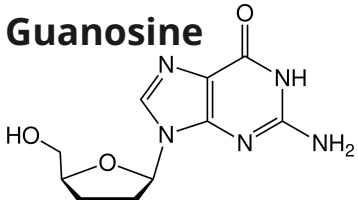
All of the nucleoside analogues rely on **viral kinases** to complete first phosphorylation




**Acyclovir**



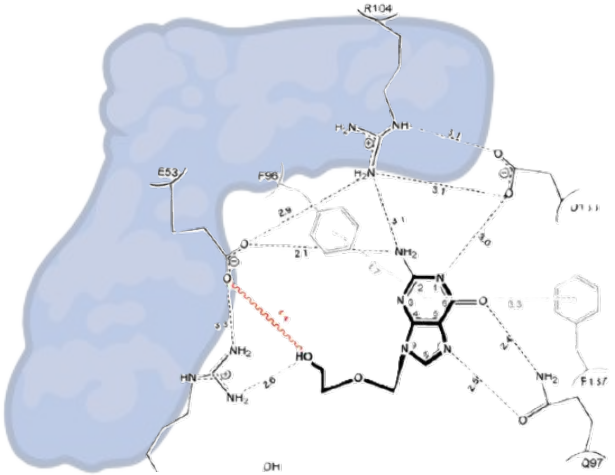

**Guanosine**



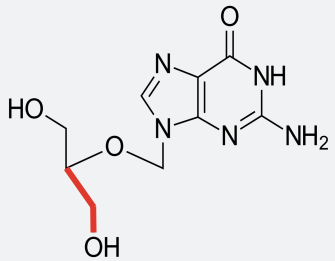
# What about ganciclovir? [2][3]

All of the nucleoside analogues rely on **viral kinases** to complete first phosphorylation

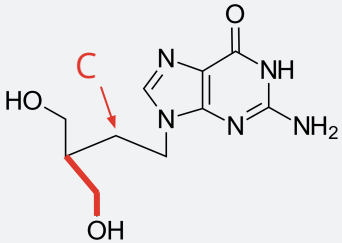
TK deficiency → **none of these will work**



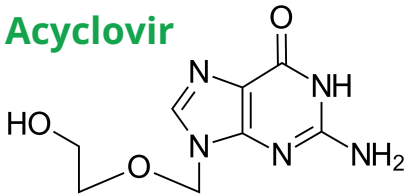

**Ganciclovir**




**Penciclovir**




**Acyclovir**

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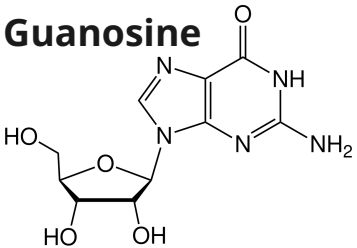
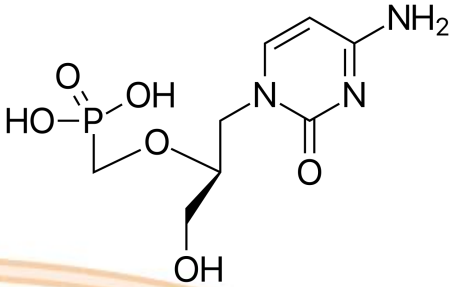
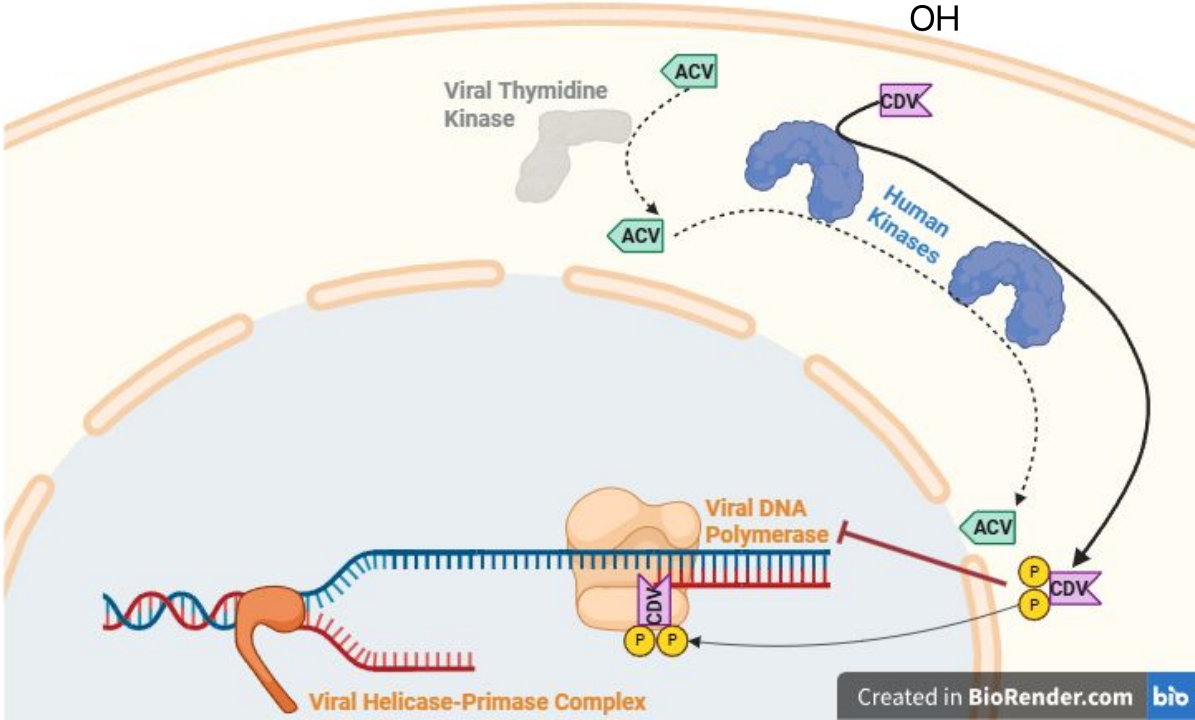


# Cidofovir

**Nucleo<u>tide</u> analog** (meaning it already has one phos on it)

- Does **<u>not</u> need** viral kinases to become active



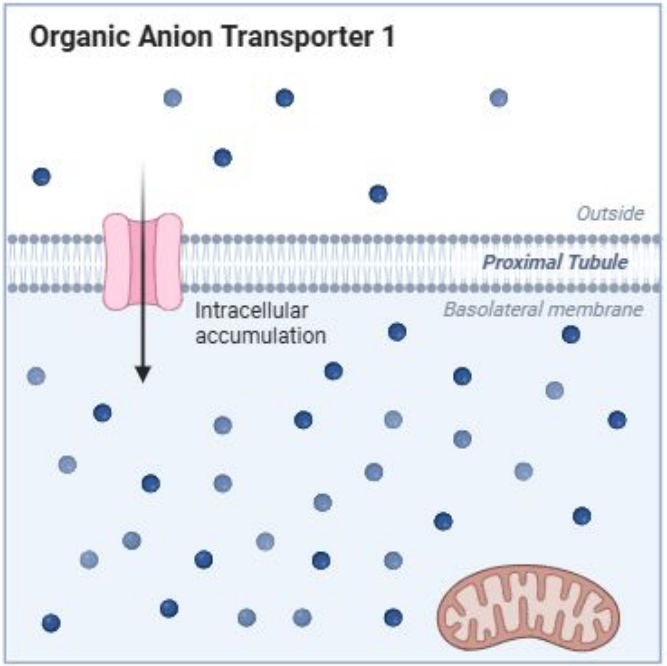
# Cidofovir [5]

**Nucleotide analog** (meaning it already has one phos on it)

- Does **not need** viral kinases to become active

But can be **toxic** to human cells, namely the **kidneys**

- Increased uptake via **OAT1** → mitochondrial toxicity



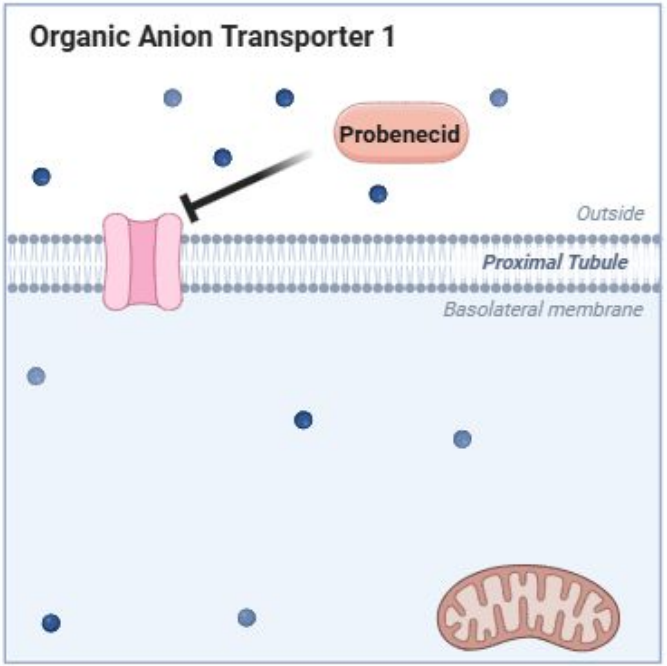
# Cidofovir [5]

**Nucleotide analog** (meaning it already has one phos on it)

- Does **not need** viral kinases to become active

But can be **toxic** to human cells, namely the **kidneys**

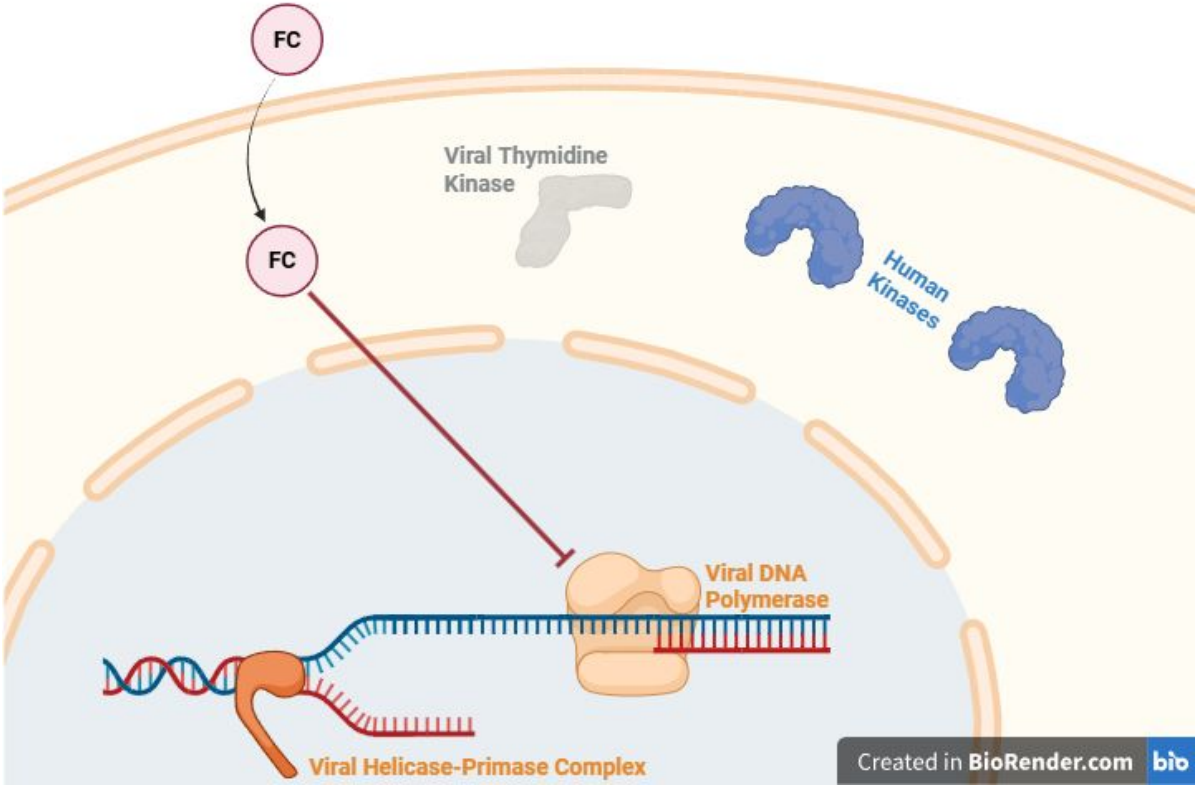
- Increased uptake via **OAT1** → mitochondrial toxicity
- Administer with **probenecid**



# Foscarnet

Pyrophosphate analog → **directly inhibits DNA polymerase**

- Prevents binding of deoxynucleotide triphosphates to DNA pol

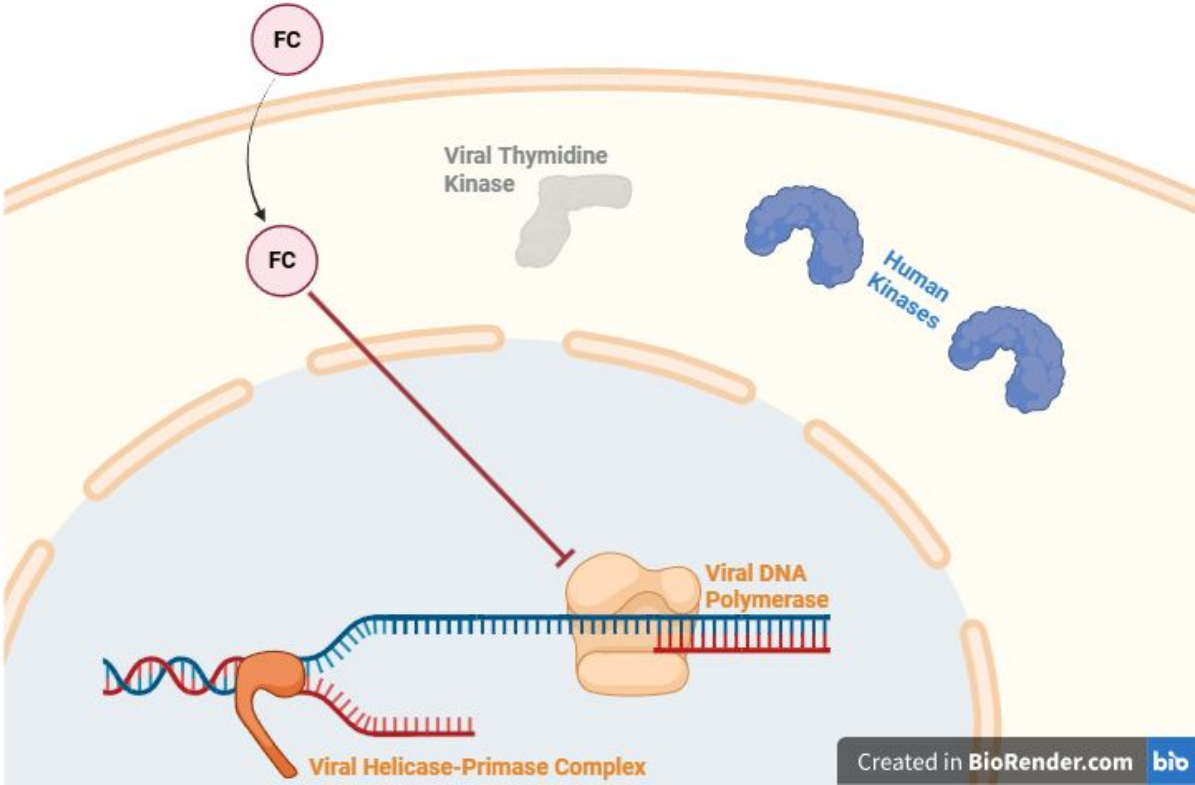


# Foscarnet [6]

Pyrophosphate analog → **directly inhibits DNA polymerase**

Perhaps a little less cytotoxic than cidofovir

- Binds to **viral DNA pol** with **x1000 greater affinity** than human DNA pol



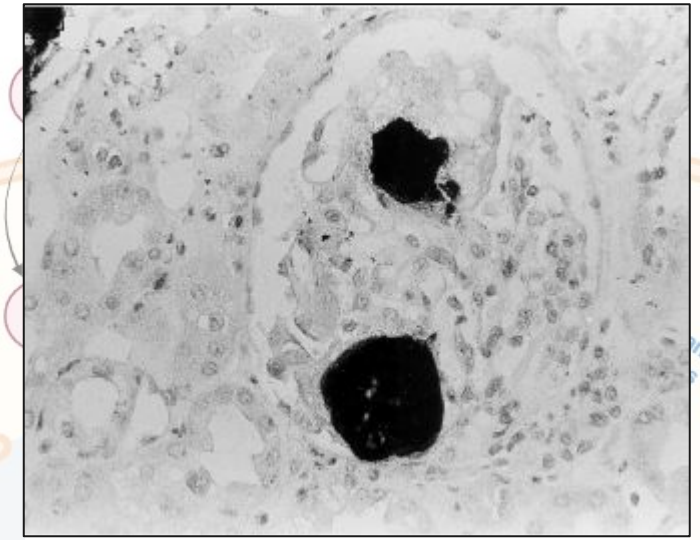
# Foscarnet [6]

Pyrophosphate analog → **directly inhibits DNA polymerase**

Perhaps a little less cytotoxic than cidofovir

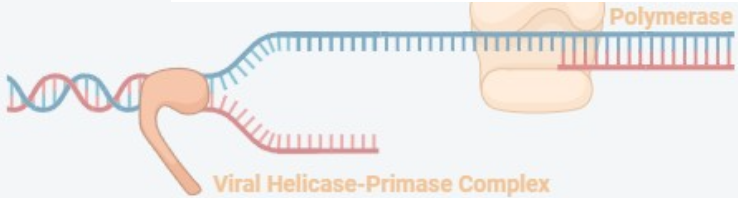
Still **quite nephrotoxic**

- Direct nephrotoxicity
- Crystal induced



Crystal nephropathy (black stain)

Zanetta et al (1999) PMID 10360595



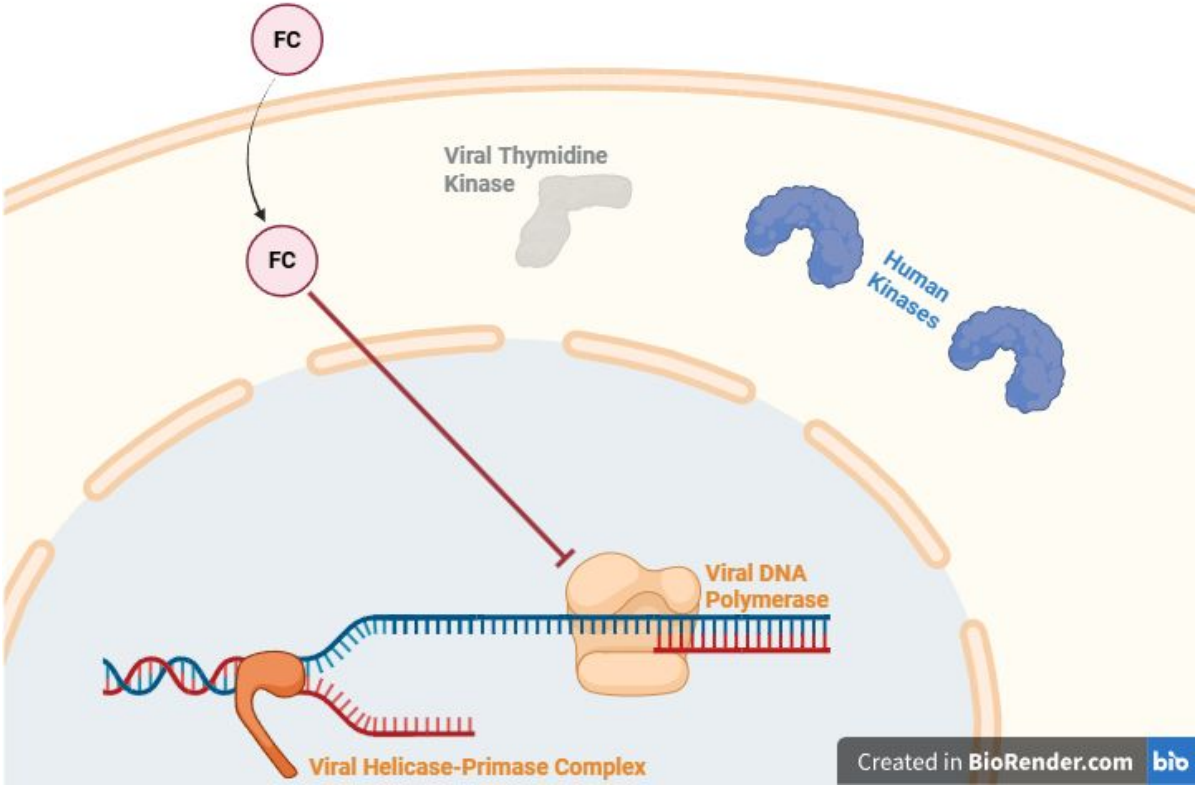
# Foscarnet

Pyrophosphate analog → **directly inhibits DNA polymerase**

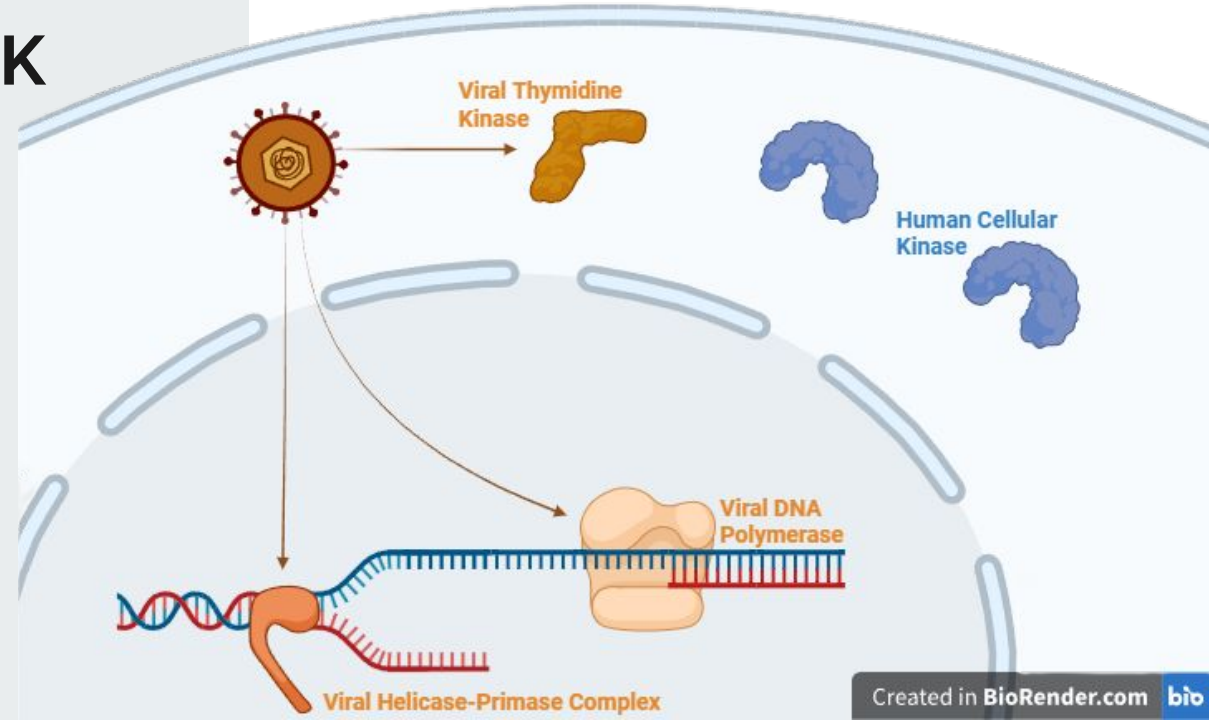
Perhaps a little less cytotoxic than cidofovir, but still **nephrotoxic**

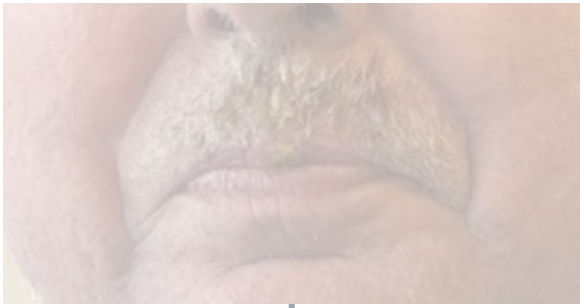
May also cause **genital ulcers**

- Likely a contact dermatitis due to high concentrations of foscarnet in urine

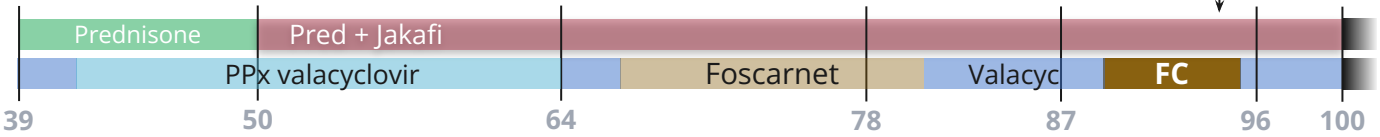


# *What if* the problem is **not** TK deficiency?





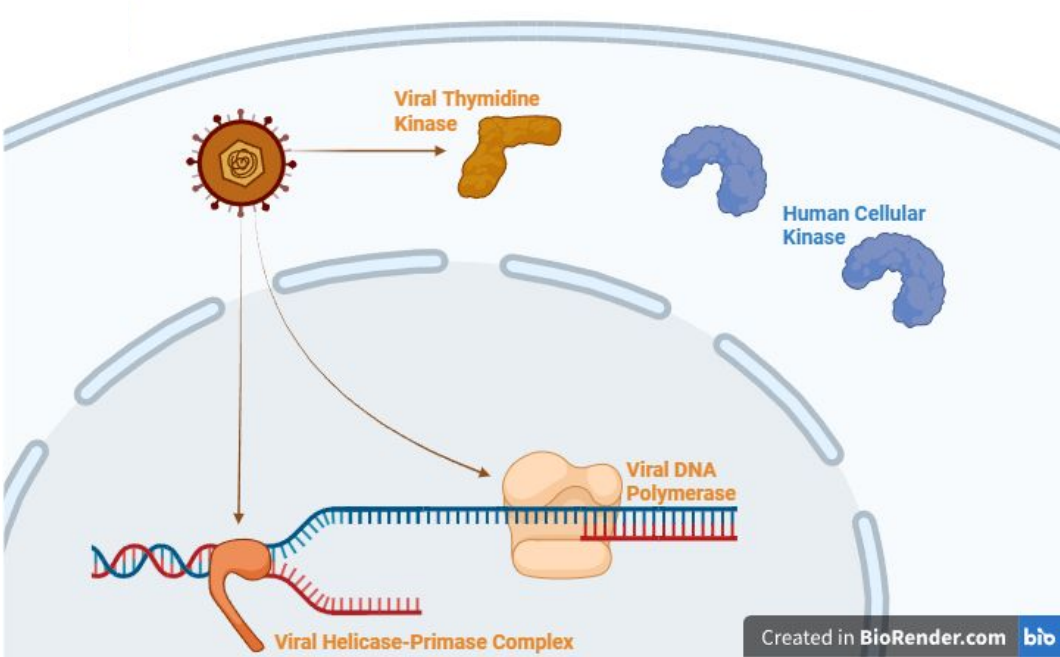
**Lip unimproved**
**at day 7** -and- AKI




# What if the problem is *not* TK deficiency?

TK deficiency is the most common reason for acyclovir resistance [2]

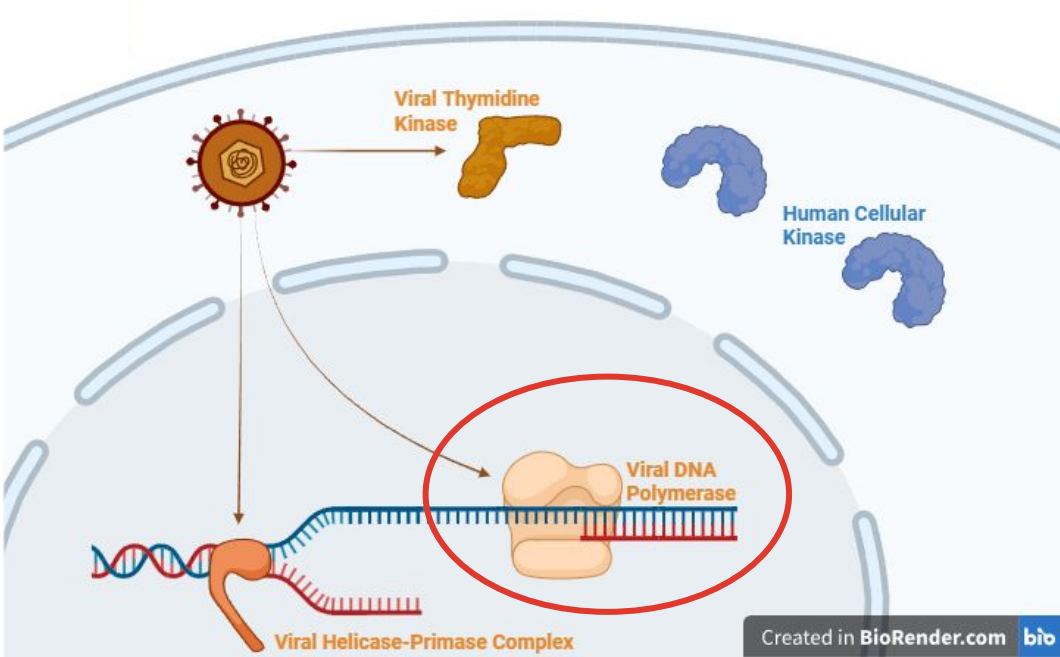
- But this is not the only reason



# What if the problem is *not* TK deficiency?

TK deficiency is the most common reason for acyclovir resistance [2]

- Some viral mutations (namely those **targeting DNA polymerase**) can confer resistance to **multiple agents**

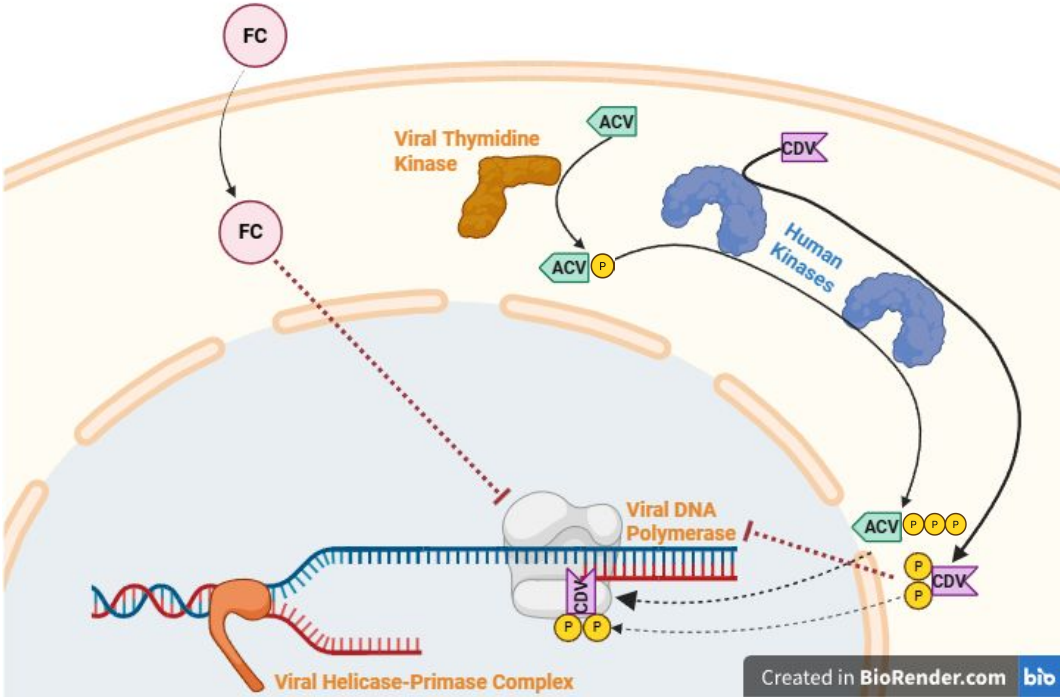


# What if the problem is *not* TK deficiency? [2]

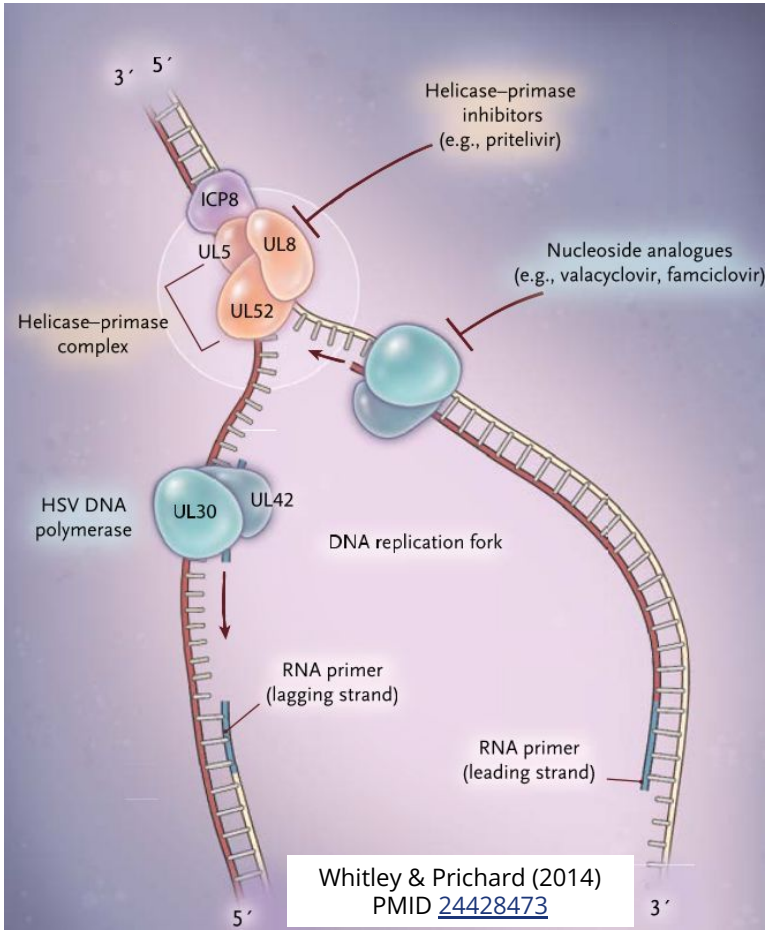
TK deficiency is the most common reason for acyclovir resistance

- Some viral mutations (namely those **targeting DNA polymerase**) can confer resistance to **multiple agents**

Examples (for HSV-1): Q727R, L778M, L802F, Y818C, W821M, G841C, R959H



# Helicase-Primase Inhibitors

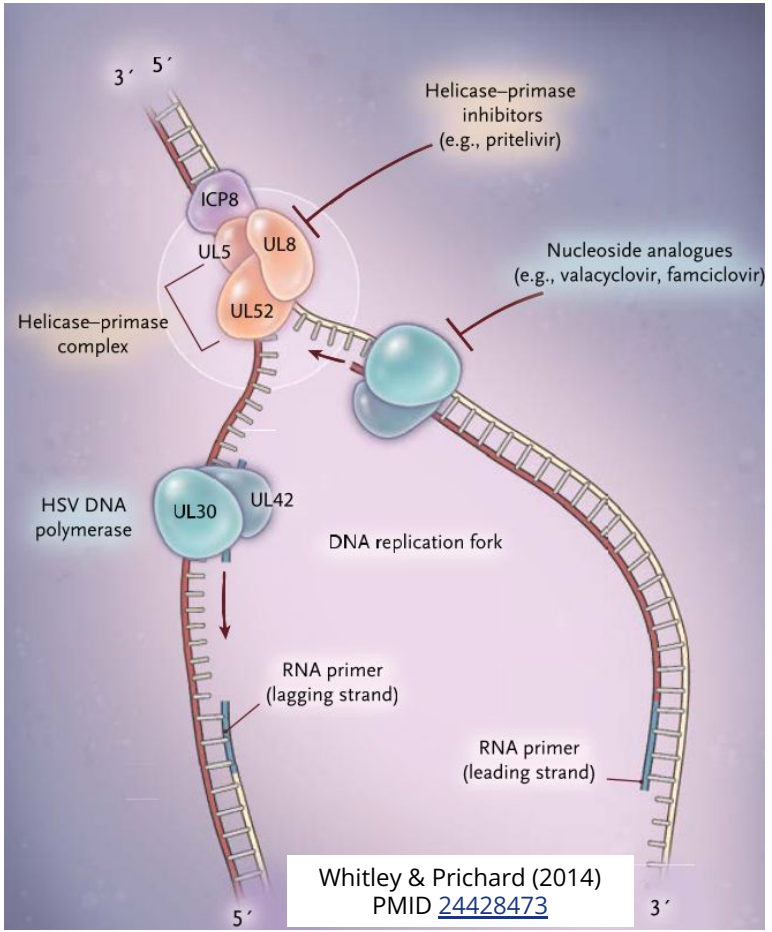



Whitley & Prichard (2014)
PMID 24428473

# Helicase-Primase Inhibitors [7]

**Helicase**: unwinds duplex DNA ahead of the fork & separates the double strand into two single strands

**Primase**: lays down RNA primers that the DNA polymerase extends




Whitley & Prichard (2014)
PMID 24428473

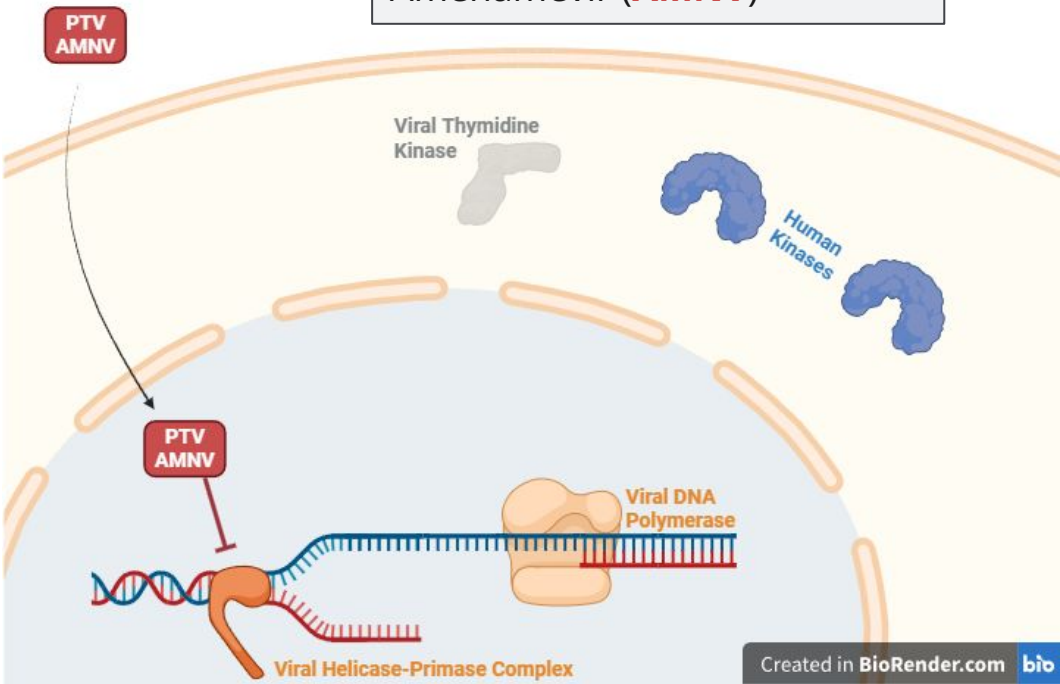
# Helicase-Primase Inhibitors

Bypasses both TK and viral DNA polymerase

Two drugs (in trials or approved elsewhere):

- Pritelivir
- Amenamevir

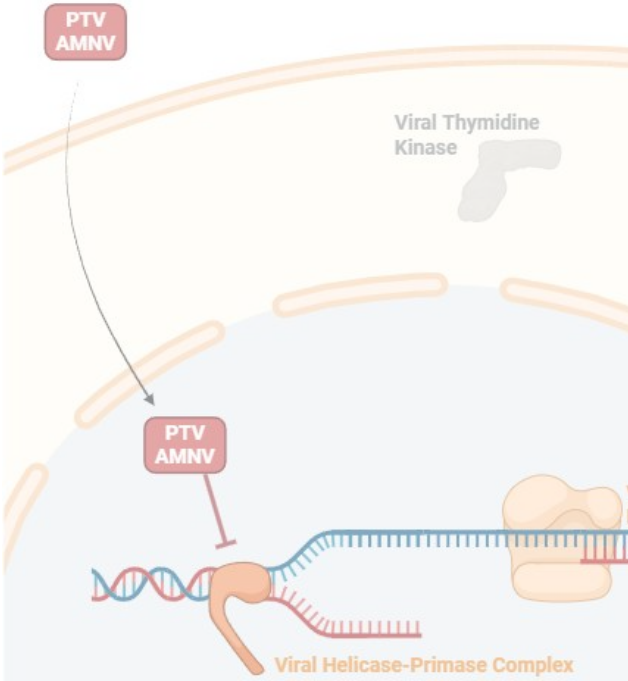
**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



# Pritelivir [8]

**Wald (2014) [8]** Phase II randomized trial
- Double blinded
- **Industry sponsored**

**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



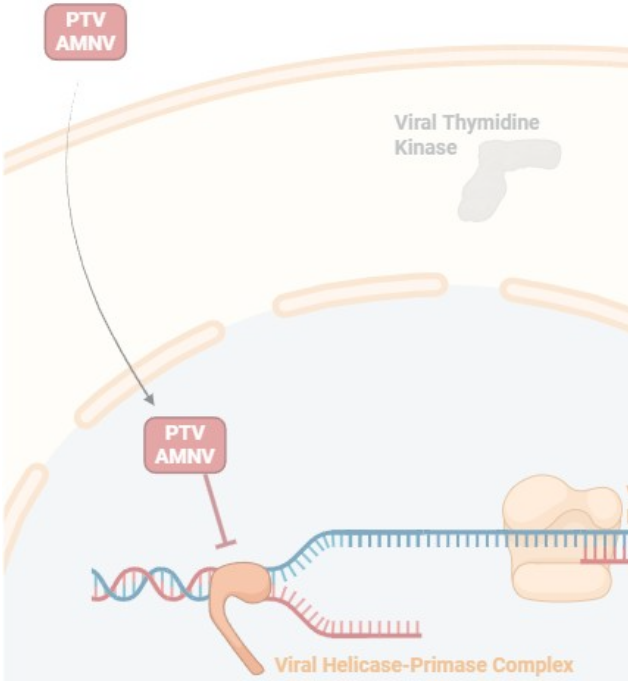
# Pritelivir [8]

**Wald (2014)** Phase II randomized trial (industry sponsor)

P: **Healthy adults** with HSV-2

- Seropositive for HSV-2
- **Recurrent** genital herpes (1-9 times per year)
- Immunocompetent
  - No HIV, HBV, HCV
- Not on other HSV meds
- **N = 150**

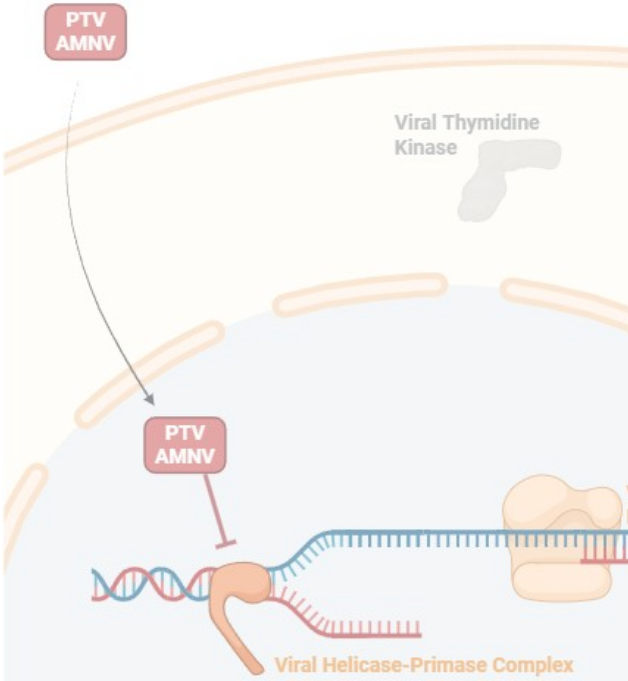
**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



# Pritelivir [8]

| **Wald (2014)** Phase II randomized trial (industry sponsor) |
| --- |
| **P**: Immunocompetent adults w/ recurrent HSV-2 (n=150) |
| **I**: **Pritelivir** (at one of four doses)<br>• 5 mg daily<br>• 25 mg daily<br>• 75 mg daily<br>• 400 mg <u>weekly</u> |

**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



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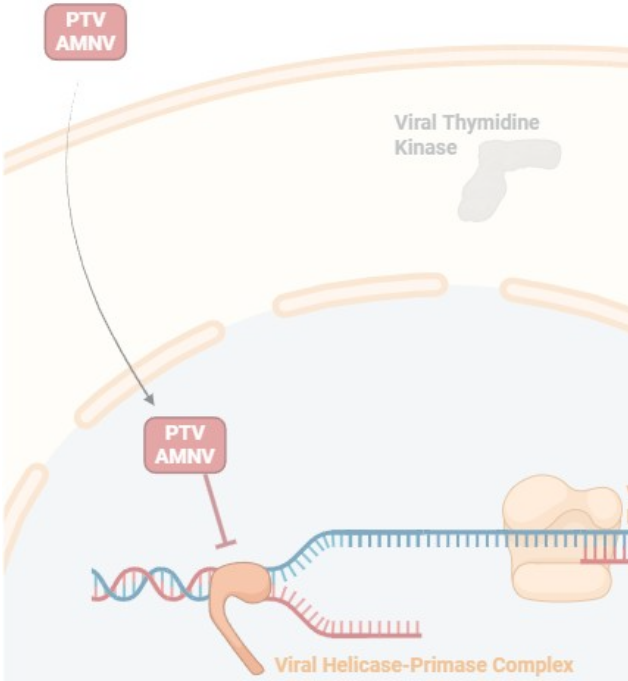
| **I**: **Pritelivir** (at one of four doses)<br>• 5 mg daily<br>• 25 mg daily<br>• 75 mg daily<br>• 400 mg weekly |
| **C**: **Placebo**<br>• Randomized in a 1:1:1:1:1 manner |

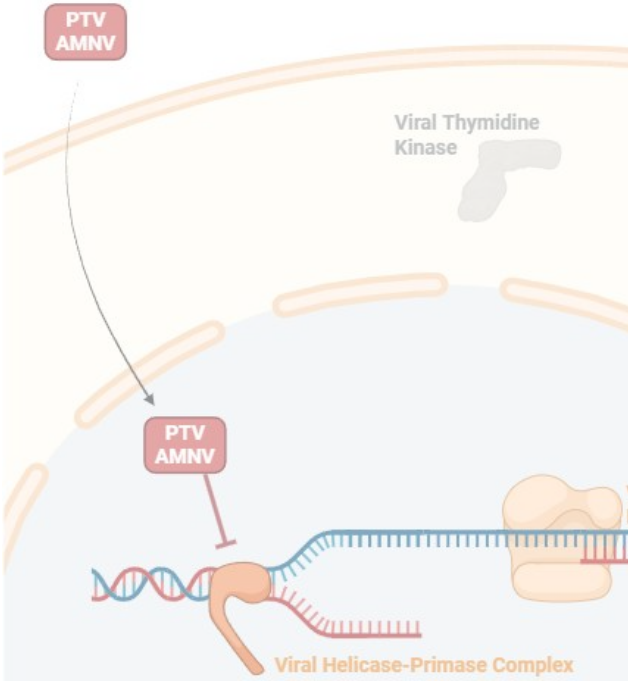
**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



# Pritelivir [8]

| |
|---|
| **Wald (2014)** Phase II randomized trial (industry sponsor) |
| **P**: Immunocompetent adults w/ recurrent HSV-2 (n=150) |
| **I**: Pritelivir (at one of four doses) |
| **C**: Placebo |
| **O**: Rate of genital **HSV shedding** (primary outcome)<br>• Participants did **daily swabs** (even if no lesions)<br>• If **developed lesion**, did extra swab of lesions and came to **clinic within 24 hours** |

**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



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| **O**: Rate of genital **HSV shedding** (primary outcome)<br><br>**Secondary outcomes**:<br>• Rates of lesions<br>• Reduction of HSV DNA copies<br>• Rates of subclinical shedding<br>• Safety / adverse events |

**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
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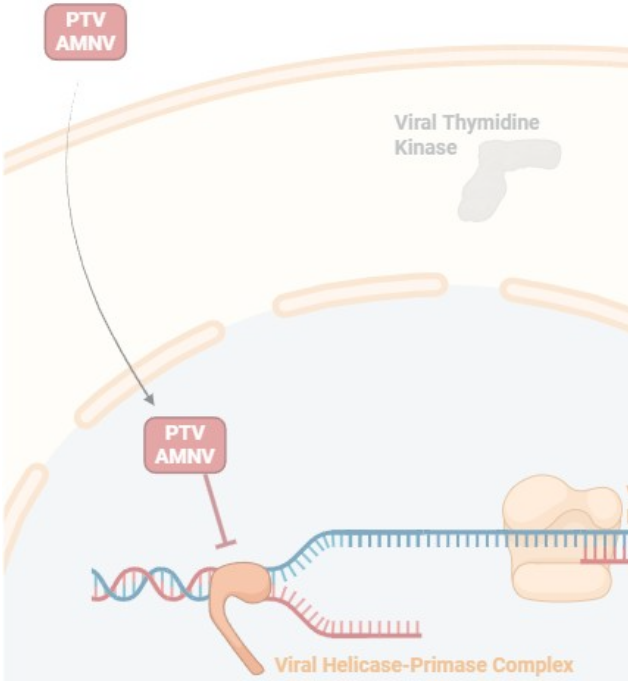


# Pritelivir [8]

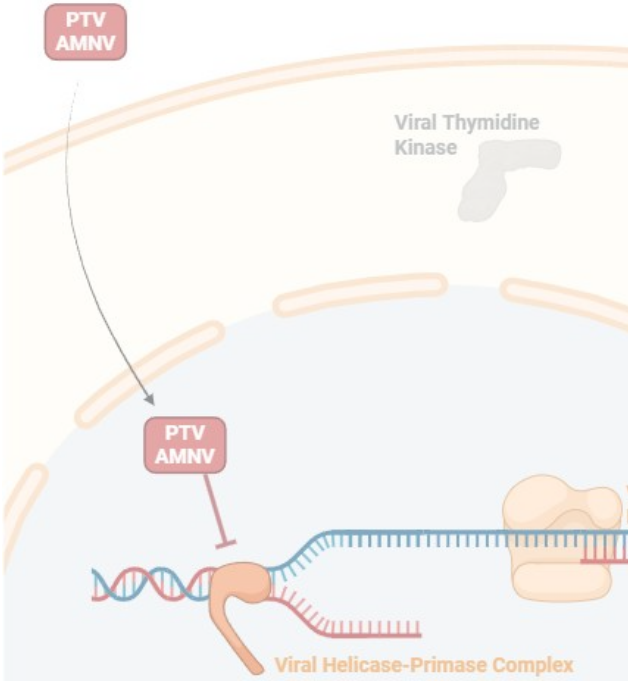
**Wald (2014)** Phase II randomized trial (industry sponsor)

**P**: Immunocompetent adults w/ recurrent HSV-2 (n=150)
**I**: Pritelivir (at one of four doses)
**C**: Placebo
**O**: Rate of genital HSV shedding

Before enrolling:

- Participants had median of 4 outbreaks per year
- 21% were on suppressive therapy

**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



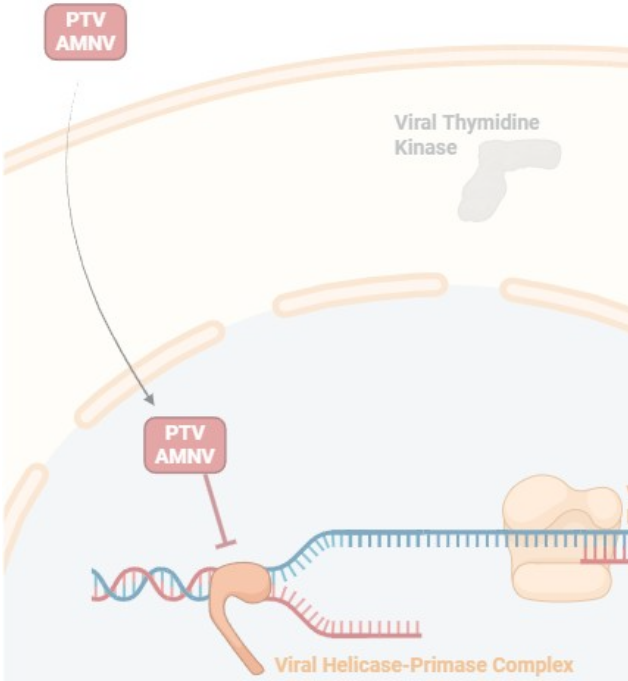
# Pritelivir [8]

**Wald (2014)** Phase II randomized trial (industry sponsor)

**P**: Immunocompetent adults w/ recurrent HSV-2 (n=150)
**I**: Pritelivir (at one of four doses)
**C**: Placebo
**O**: Rate of genital HSV shedding

| | **Placebo** | PTV **5 mg** daily | PTV **25 mg** daily | PTV **75 mg** daily | PTV 400 mg **weekly** |
|---|---|---|---|---|---|
| Days shedding | 16.6% of days | 18.2% | 9.3% | 2.1% | 5.3% |

**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



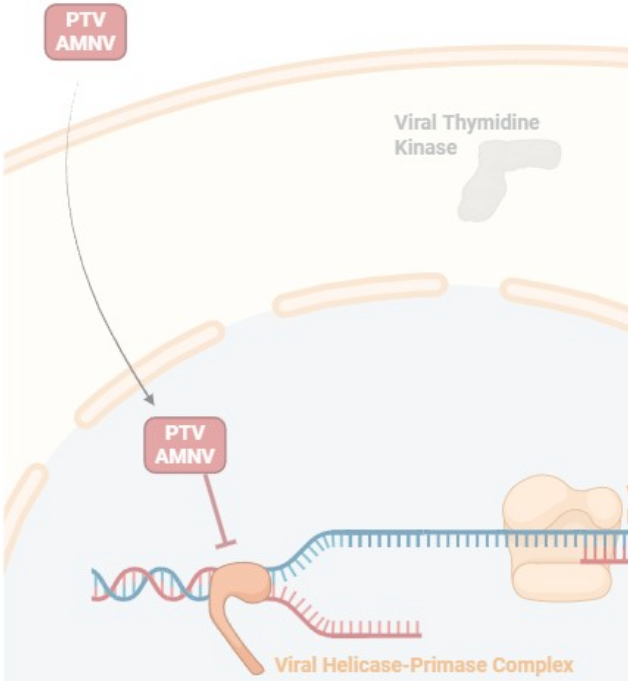
# Pritelivir [8]

**Wald (2014)** Phase II randomized trial (industry sponsor)

**P**: Immunocompetent adults w/ recurrent HSV-2 (n=150)
**I**: Pritelivir (at one of four doses)
**C**: Placebo
**O**: Rate of genital HSV shedding

| **Relative risk** (ref: placebo group) | PTV 75 mg daily | PTV 400 mg weekly |
|---|---|---|
| Days shedding | **0.13** (0.04 - 0.38) | **0.32** (0.17 - 0.59) |
| Days with lesions | **0.13** (0.02 - 0.70) | **0.13** (0.03 - 0.25) |

**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



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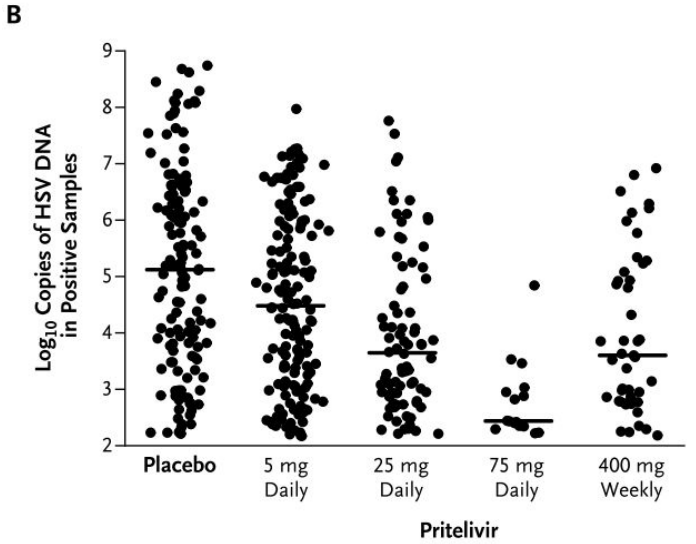
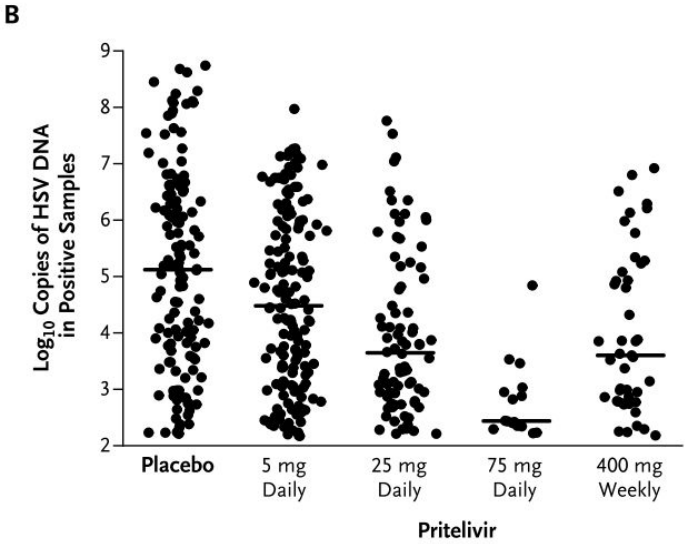


# Pritelivir [8]

**Wald (2014)** Phase II randomized trial (industry sponsor)

**P**: Immunocompetent adults w/ recurrent HSV-2 (n=150)
**I**: Pritelivir (at one of four doses)
**C**: Placebo
**O**: Rate of genital HSV shedding

- Similar rates of adverse events for
  - Drug compared to placebo
  - Across doses



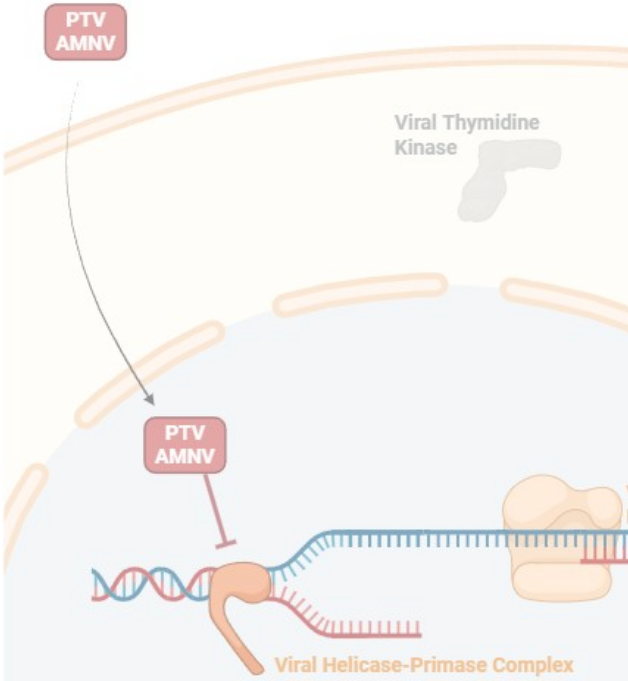
# Pritelivir [9]

**Wald (2016) [9]** Phase II randomized trial (industry sponsor)

**Cross over study** comparing Pritelivir to **valacyclovir**

- **Drug A** (x 28 days) →
- Washout (28 d) →
- **Drug B** (28 d)

**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



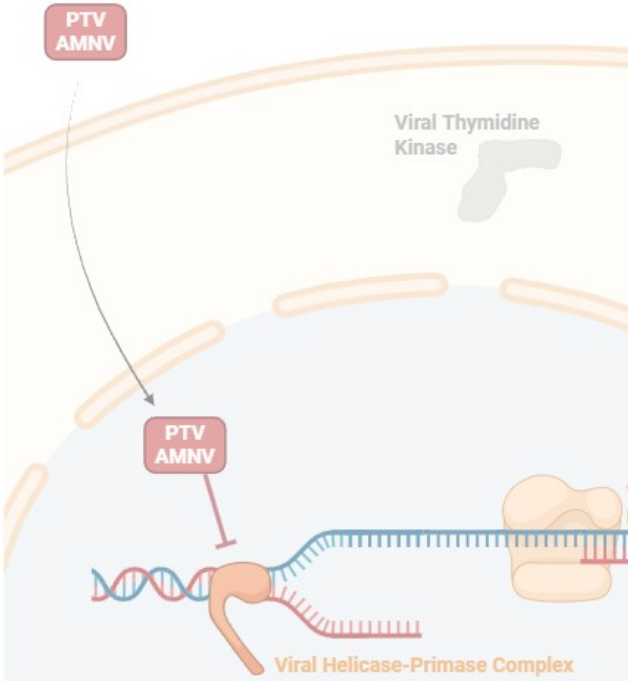
# Pritelivir [9]

**Wald (2016)** Phase II crossover RCT (industry sponsor)

P: **Healthy adults** with recurrent HSV-2 (**same as before**)

- **N = 91**

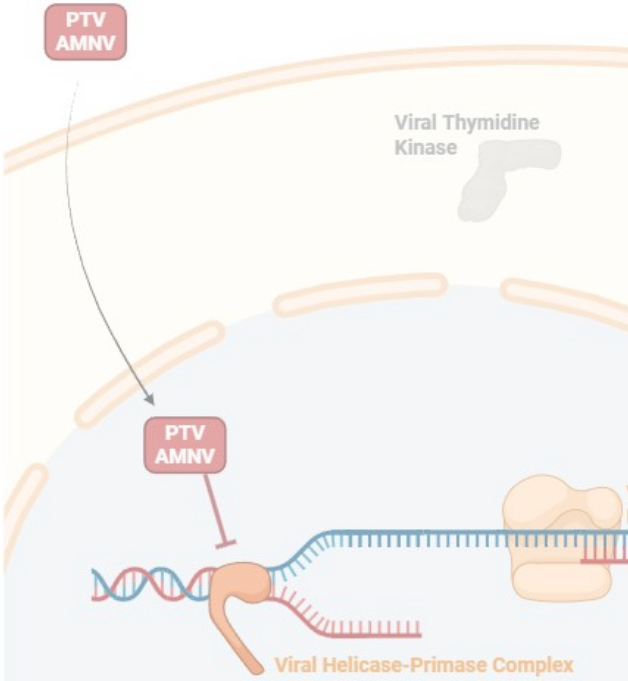
**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



# Pritelivir [9]

| **Wald (2016)** Phase II crossover RCT (industry sponsor) |
| --- |
| **P**: Immunocompetent adults w/ recurrent HSV-2 (n=91) |
| **I**: **Pritelivir** (100 daily) x 28 days |
| **C**: **Valacyclovir** (500 daily) x 28 days |

**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



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| **Wald (2016)** Phase II crossover RCT (industry sponsor) |
| --- |
| **P**: Immunocompetent adults w/ recurrent HSV-2 (n=91) |
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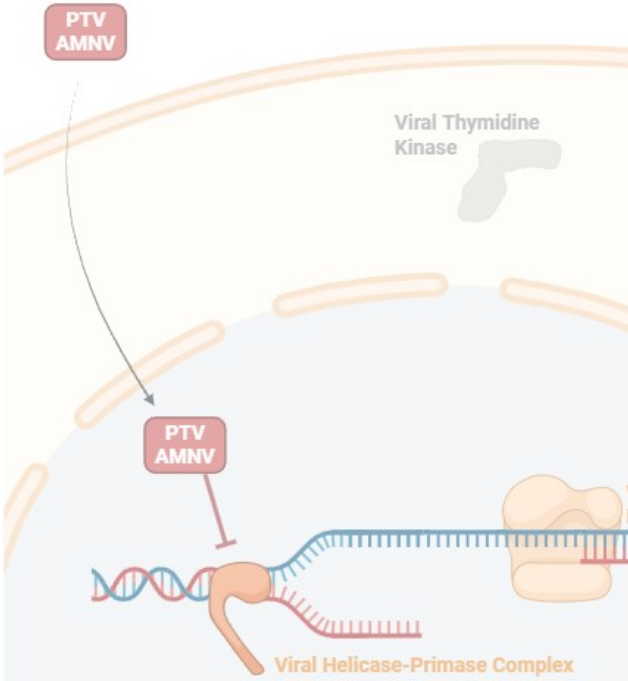
| **C**: Valacyclovir (500 daily)  x 28 days |
| **O**: Rate of genital **HSV shedding** (primary outcome)<br><br>**Secondary outcomes**:<br>• Rates of lesions<br>• Reduction of HSV DNA copies<br>• Rates of subclinical shedding<br>• Adverse events |

**Helicase-Primase Inhibitors**
Pritelivir (**PTV**)
Amenamevir (**AMNV**)



# Pritelivir [9]

**Wald (2016)** Phase II crossover RCT (industry sponsor)

P: Immunocompetent adults w/ recurrent HSV-2 (n=91)
I: Pritelivir 100 daily x 28 days
C: **Valacyclovir** 500 daily x 28 days
O: Rate of genital HSV shedding

**Terminated early**
During study **FDA imposed a clinical hold** (an order to the sponsor to suspend ongoing investigation), based on **hematologic** and **dermatologic findings** such as dry skin, crusty skin lesions, and alopecia in a chronic toxicity study **involving monkeys**

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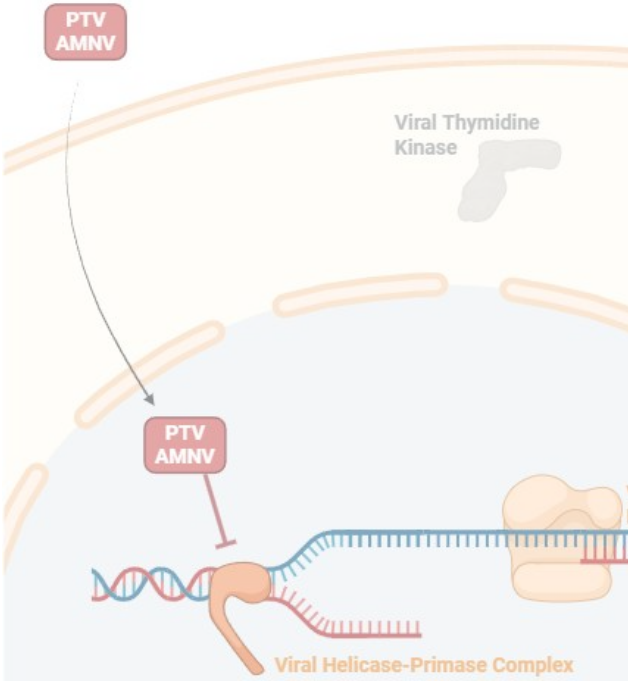

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**Terminated early**
During study **FDA imposed a clinical hold**, based on hematologic and dermatologic findings in a chronic toxicity study involving monkeys.

Because the duration of the clinical hold was uncertain, the **sponsor terminated the study**

**Helicase-Primase Inhibitors**
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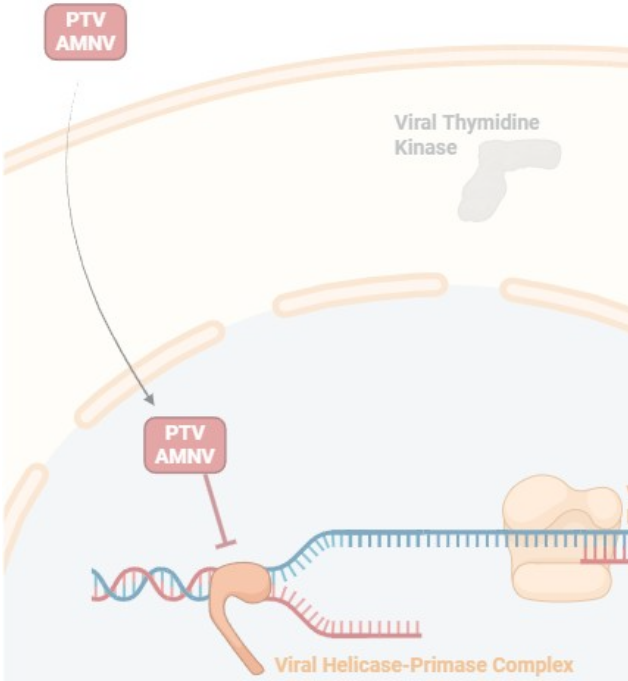

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| **Outcome** | Valacyclovir | Pritelivir | **Relative risk** |
|---|---|---|---|
| Days shedding | **5.3%** of daily swabs | **2.4%** of daily swabs | **0.42** (0.21 - 0.82) |
| Days with lesions | **3.9%** of days | **1.9%** of days | **0.40** (0.17 - 0.96) |

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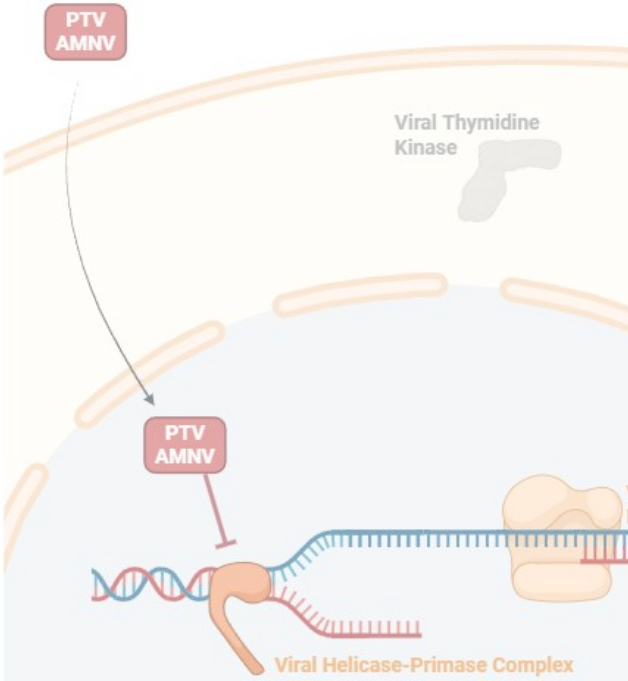

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- **Similar rates of adverse events**, but fairly high
- **Any AE**:
  - Valacyclovir: 69%
  - Pritelivir: 62%
- **Leading to discontinuation**:
  - 1.3% for both

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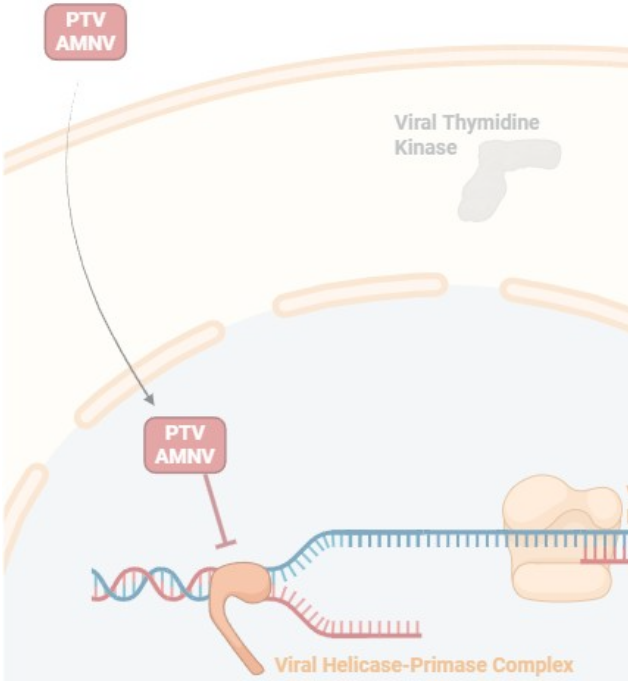

# Pritelivir

Has *breakthrough therapy designation* by FDA, with **ongoing phase III trial** (NCT03073967)

> Trial on Efficacy and Safety of Pritelivir for Treatment of Acyclovir-resistant **Mucocutaneous HSV Infections in Immunocompromised** Subjects

Part C: Pritelivir (vs foscarnet) in ACV-R HSV

Part D: Pritelivir in ACV-R and foscarnet-R / foscarnet intolerant HSV (enrollment closed)

Part E: Pritelivir in acyclovir susceptible HSV

Part F: Extension of Part D + those who had issues with foscarnet in Part C

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**Expanded Access Program** available from manufacturer for immunocompromised patients

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# Amenamevir [10]

- **Unlike pritelivir**, amenamevir has **VZV activity** as well
  - Approved for VZV (namely **shingles**) **in Japan** in 2017
  - Therefore, we have more data on amenamevir (vs pritelivir)

**Helicase-Primase Inhibitors**
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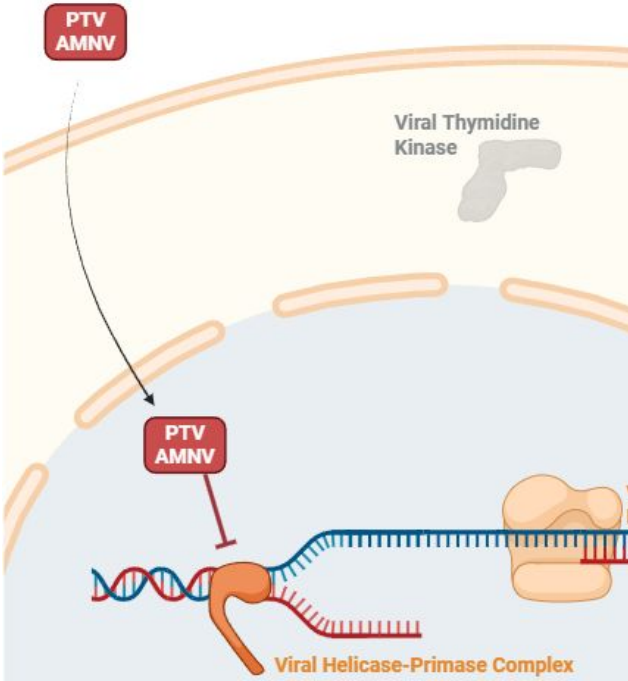

# Amenamevir [10]

- Unlike pritelivir, amenamevir has **VZV activity**
- **Unlike acyclovir**, the antiviral activity of amenamevir is **not influenced** by viral **replication cycle**
  - When **started later in the disease course** amenamevir was **more effective than valacyclovir** (mouse models)

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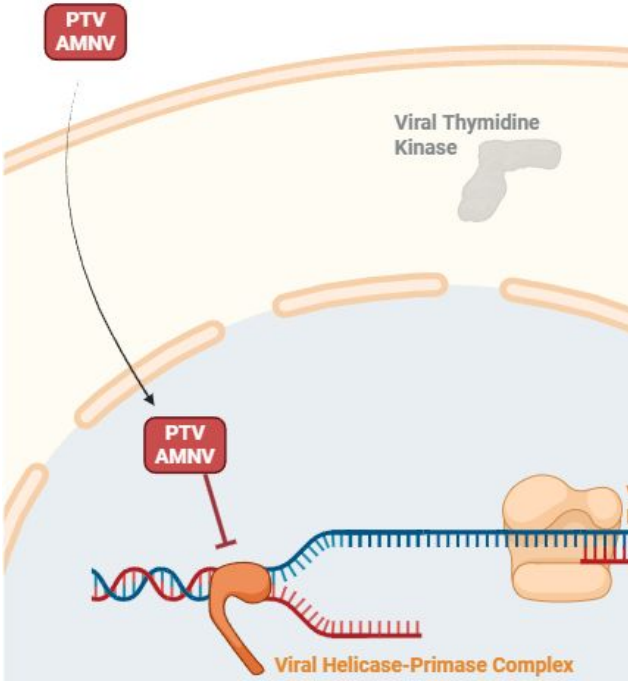

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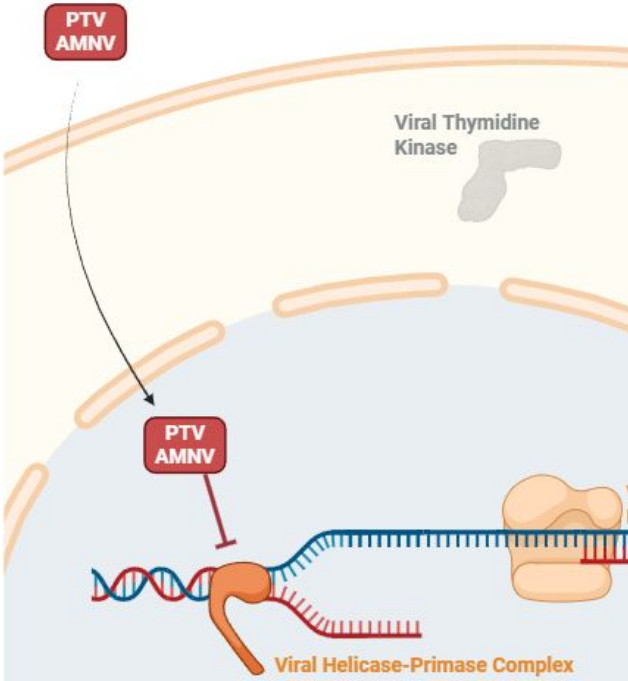

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- May have a **synergistic effect** with acyclovir
- Unlike TK deficiency, **HP deficiency** more drastically **affects viral fitness**
  - Amenamevir resistant strains have **attenuated growth** and are **less pathogenic** compared to wild type
  - Without HP, virus cannot replicate
  - **No cross-resistance** described between TK & HP

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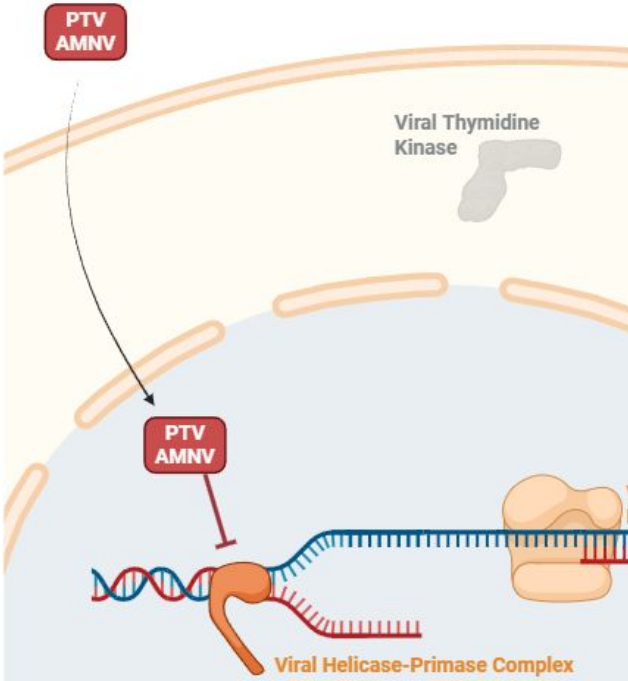

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- May have a **synergistic effect** with acyclovir
- Unlike TK deficiency, **HP deficiency** more drastically **affects viral fitness**
- **Post-marketing surveillance** implies it's **pretty safe**
  - Incidence of adverse drug reactions is **0.82%** (11 cases)
- Reported events (none were serious)
  - 4 cases of **GI upset**
  - 2 cases of **thrombocytopenia**
  - 1 case of **palpitations**

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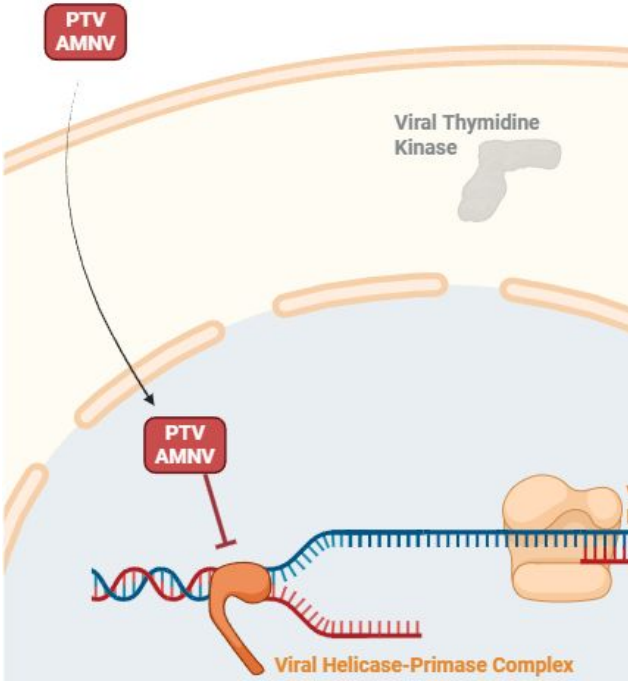

# Amenamevir in clinical trials

**Tyring 2012** [11] (phase 2, n=437)
**P**: Recurrent genital HSV (≥4 per year)
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**C**: **Placebo** or **Valtrex** x 3 days
**O**: **Time to lesion healing**

- Better than placebo
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*Similar adverse events*

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**P**: Immunocompetent **VZV** (w/in 72h of Zoster onset)
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- Amenamevir 400 non-inferior
- Superior for those under 65

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**P**: Recurrent genital HSV
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**C**: **Placebo alone**
**O**: **Time to lesion healing** (median, days)
- Amenamevir: 4.0 days (p = 0.002)
- Placebo: 5.1 days

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*Similar adverse events*

**Kawashima 2023** [14] (phase 3, n=605)
P: Recurrent **herpes labialis**
I: Amenamevir 1.2g once (@time of prodrome)
C: **Placebo alone**
O: **Time to lesion healing** (median, days)
- Amenamevir: 5.1 days (p = 0.008)
- Placebo: 5.5 days

Shorter time to crusting (by **8 hours**...)

*Similar adverse events*

# What would RFK do?

RCT of “natural” treatments

- **β-Glucan** from ***Pleurotus ostreatus***
  - Versus placebo
- **Topical olive leaf extract**
  - Versus topical acyclovir

The introductions say **both of these agents** are also **active against HIV** *in vitro*

Move over, Biktarvy!

# Urbancikova et al [15] (Evid Based Complement Alternat Med, 2020)

Randomized, multi-center, double blind, placebo controlled study looking at **pleuran** (insoluble β-1,3/1,6-D-glucan isolated from *Pleurotus ostreatus*)

- Adults & kiddos (> 6 y/o) with orolabial HSV
  - Excluded those who got systemic antivirals
  - Still **could receive** standard of care (**including topical antivirals**)

*Pleurotus ostreatus* AKA "**oyster mushrooms**" (Earth.com)

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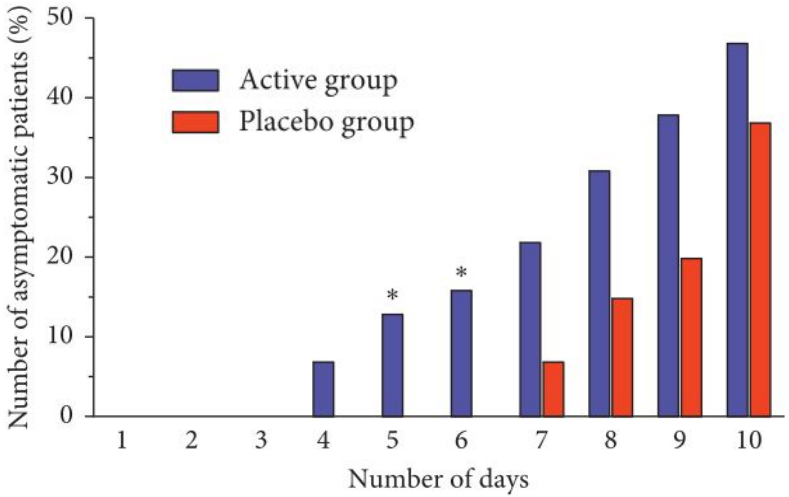
  - Excluded those who got systemic antivirals
  - Still **could receive** standard of care (**including topical antivirals**)
- 10 days of **treatment phase**
  - Daily vitamin C + Zinc + **300 mg pleuran** (n=49)
  - Daily vitamin C + Zinc (n=41)
- 120 days of **preventive phase**
  - Daily vitamin C + **100 mg pleuran**
  - Daily vitamin C

*Pleurotus ostreatus* AKA "**oyster mushrooms**" (Earth.com)

# Urbancikova et al [15] (Evid Based Complement Alternat Med, 2020)

**Active group** had **shorter duration of symptoms** (**11.0 days**) compared to **placebo** (**12.2 days**, p=0.046)

- This is a larger effect size than the amenamevir placebo trials...

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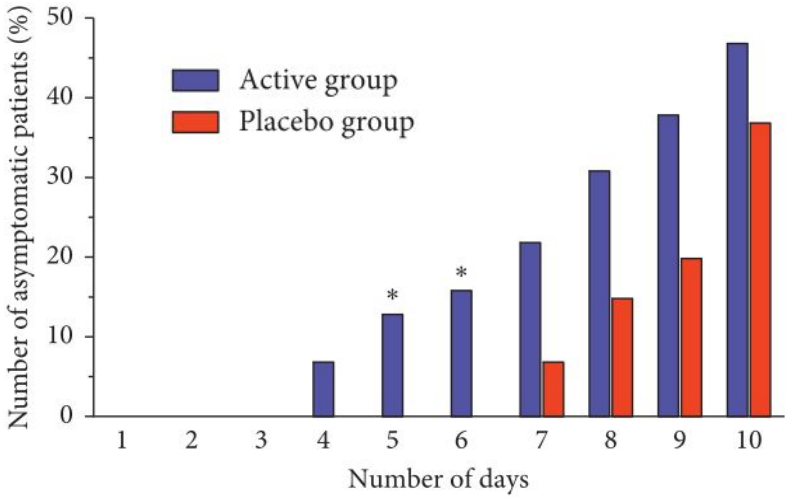


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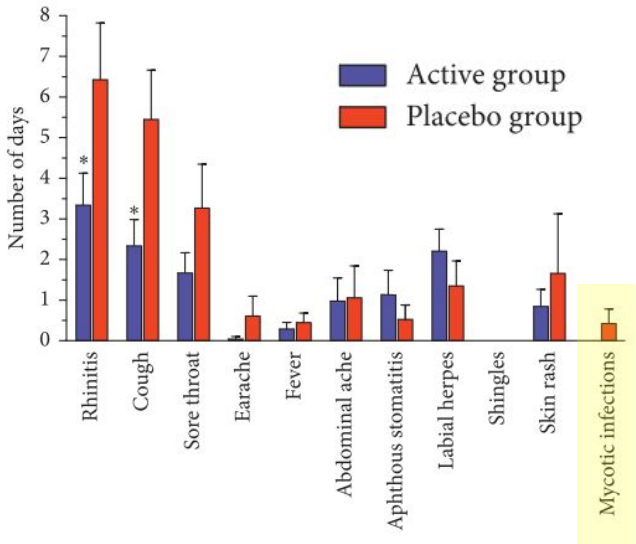
- More patient in the placebo group (**78%**) received **concomitant antiherpetic therapy** than the active group (**63%**)
- **No difference in recurrence** during preventive phase
- No mycotic infections in the active group (FYI)



# Toulabi et al [16] (Explore, 2022)

Randomized, single-center, double blind, placebo controlled study looking at **topical olive leaf extract (OLE)** vs **topical acyclovir (ACY)**

- Adults with orolabial HSV (diagnosed clinically)
  - Excluded those who got systemic antivirals
- Olive leaf extract (n=33)
- Topical acyclovir (n=33)

Olive leaf (Wikipedia.com)

# Toulabi et al [16] (Explore, 2022)

Randomized, single-center, double blind, placebo controlled study looking at **topical olive leaf extract (OLE)** vs **topical acyclovir (ACY)**

By **day 3 of treatment**, fewer subjects in the the **OLE group** had...

- Bleeding: **6.5%** --vs-- **25.8%** (p = 0.038)
- Pruritus: **12.9%** --vs-- **48.4%** (p = 0.002)
- Severe pain: **3.2%** --vs-- **35.5%** (p = 0.001)

Olive leaf (Wikipedia.com)

# Learning points & take aways

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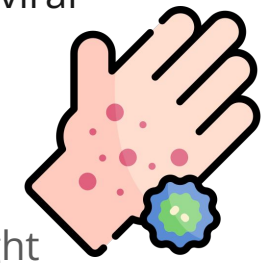
- The **acyclic nucleoside analogues**, such as **acyclovir**, are first line for treatment of HSV
- To become metabolically active, they must be first **be phosphorylated** by viral enzymes, namely **thymidine kinase** (TK)
  - Mutations in HSV's TK → acyclovir resistance
- For **TK-deficient HSV**, **foscarnet** and **cidofovir** are first line therapy
  - Somewhat limited by toxicity
  - Resistance to these agents (mutations in **viral DNA polymerase**) might **confer resistance to all** of the above drugs
- **Helicase-primase complex inhibitors** offer promising new treatment options
  - But then again, maybe rubbing olive oil on your face or eating mushrooms would work as well



Slides available on hunterratliff1.com/talk/; Citations available via QR code or via the "citations" button on the website