Herpes Viruses: HSV and VZV in Immunocompetent and Immunosuppressed Patients

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8/5/2025

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Steering Committee: NIAID COVID-19 Recover Study, NIAID Recover VITAL Study
- Scientific Advisory Board: Treovir, LLC
- Scientific Advisory Board: Altesa Biosciences
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- Member, Board of Directors at Virios Therapeutics
- Past Chairperson: Merck Letermovir DMC, GSK IDMC for Zoster and NIAID COVID-19 Vaccine DSMB

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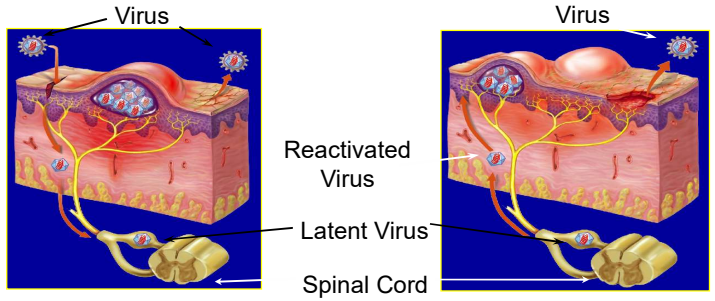
Herpes Viruses: The Family

- Herpes simplex virus, type 1 (HSV-1)
- Herpes simplex virus, type 2 (HSV-2)
- Varicella zoster virus (VZV)
- Cytomegalovirus (CMV)
- Epstein Barr virus (EBV)
- Human herpesvirus 6 (HHV 6 A and B)
- Human herpesvirus 7 (HHV 7)
- Human herpesvirus 8 (HHV 8)

3

Viral Latency and Reactivation



Netter FH. ©2001 by Icon Learning Systems.

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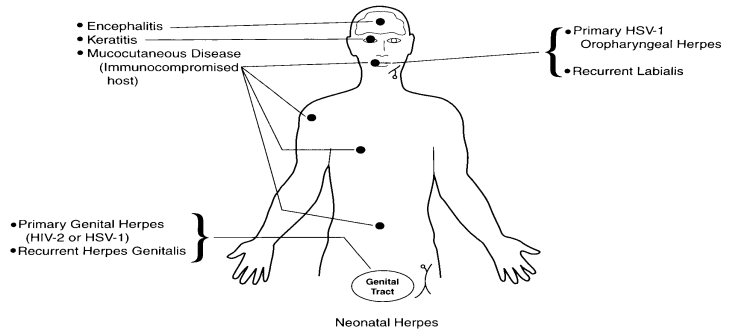
45 Herpes Simplex
Speaker: Richard Whitley, MD

Clinical Manifestations of Herpes Simplex Virus Infections



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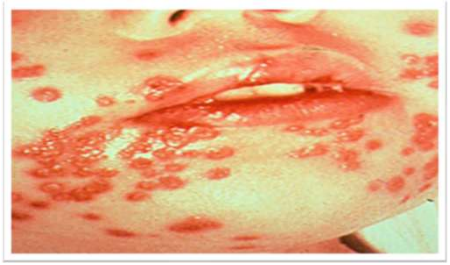
Primary Herpes Simplex Virus Infection: Cutaneous Lesions



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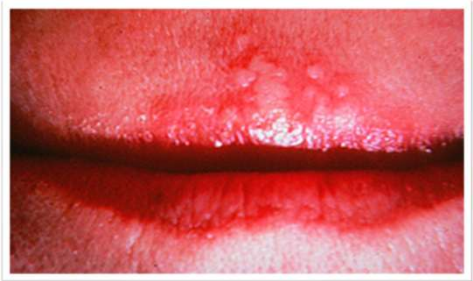
Herpes Simplex Labialis



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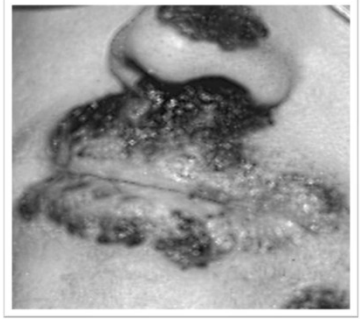
Immunocompromised Host



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Most Widely Used Systemic Anti-HSV and VZV Drugs

- Acyclovir (ACV, Zovirax)
- Famciclovir (FCV, Famvir)
- Valacyclovir (VACV, Valtrex)
- Foscarnet (PFA, Foscavir)
- Ganciclovir (GCV, Cytovene)
- Val-Ganciclovir (Valcyte)
- Others:
  - Cidofovir

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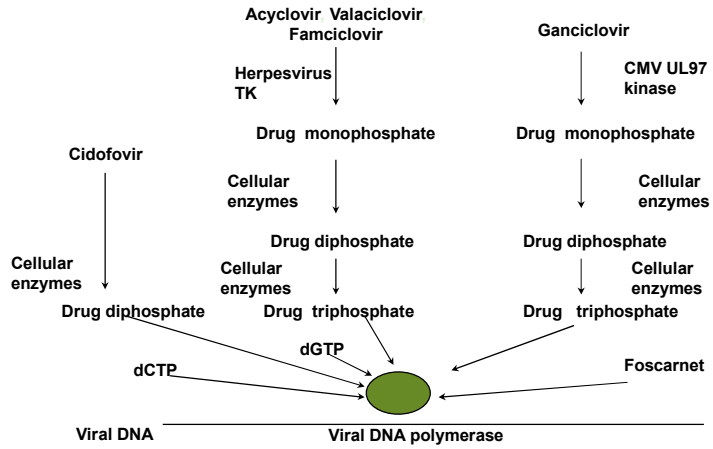

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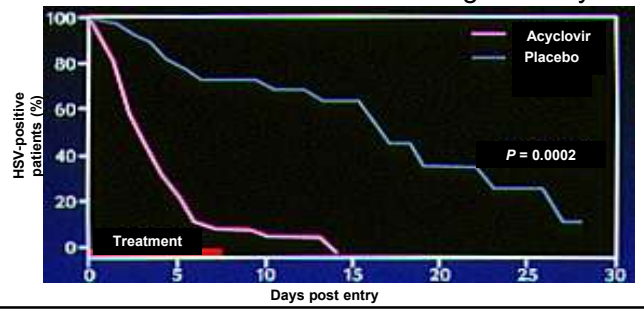
Intravenous Acyclovir for Herpes Simplex Virus Infections in Immunocompromised Hosts

Time to cessation of viral shedding with acyclovir



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Acyclovir Prophylaxis for HSV Infection in BMT Patients

Acyclovir (250 mg iv/m2 /tid) or placebo for 18 days beginning 3 days before transplant

Group	Number of Patients	Number of HSV Infections	P
Acyclovir	10	0	~0.003
Placebo	10	7	

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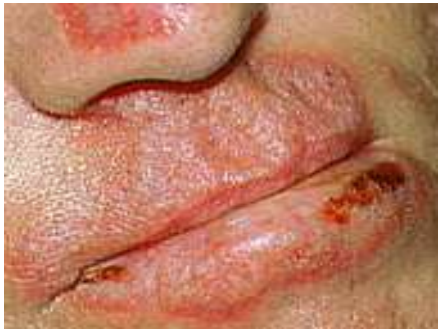

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Question #1

PREVIEW QUESTION

INFECTIOUS DISEASE BOARD REVIEW 2025

A 30-year-old heart transplant has received acyclovir for the past 60 days for cutaneous HSV infection. The lesions are now progressive despite high-dose intravenous therapy.

Instead of healing, as shown a previous slide, the lesions progress despite antiviral therapy.

A deficiency or alteration of which of the following is the most likely cause for disease progression?

A. Ribonucleotide reductase
B. Reverse transcriptase
C. Protease
D. Thymidine kinase
E. DNA polymerase

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Question #2

Which is the best treatment choice for this patient?

A. Give high-dose of intravenous acyclovir
B. Give intravenous ganciclovir
C. Give oral famciclovir
D. Give oral ganciclovir
E. Give intravenous foscarnet

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Global Prevalence of HSV-2 Infection

Total estimated number of people (in millions) infected with HSV-2 in 2012 by WHO region, gender and age range.
Source: WHO, as published in PLOS ONE (21 Jan 2015)

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Acyclovir Therapy of Genital Herpes

Summary of clinical benefit for treatment of:

- Primary
- Recurrent
- Suppressive

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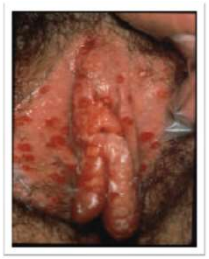
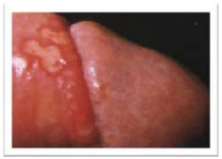
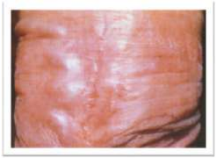
Spectrum of HSV Clinical Presentation



First infection



Classical recurrence



Atypical recurrence

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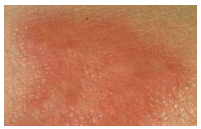
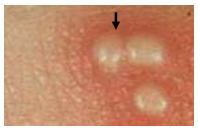
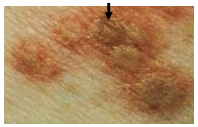
Progression of Lesions



Early Redness/Swelling



Thin-Walled Fluid-Filled Vesicles and Pustules



Early Healing of Vesicles, Erosions, or Ulcers

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Clinical Spectrum of HSV-2

HSV-2 Seroprevalence

Mertz GJ. *Infect Dis Clin North Am.* 1993;7:825-839.

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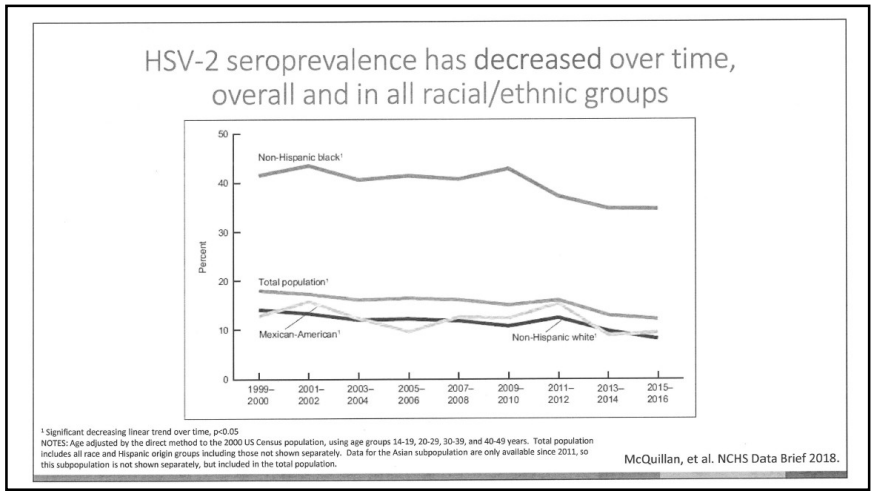

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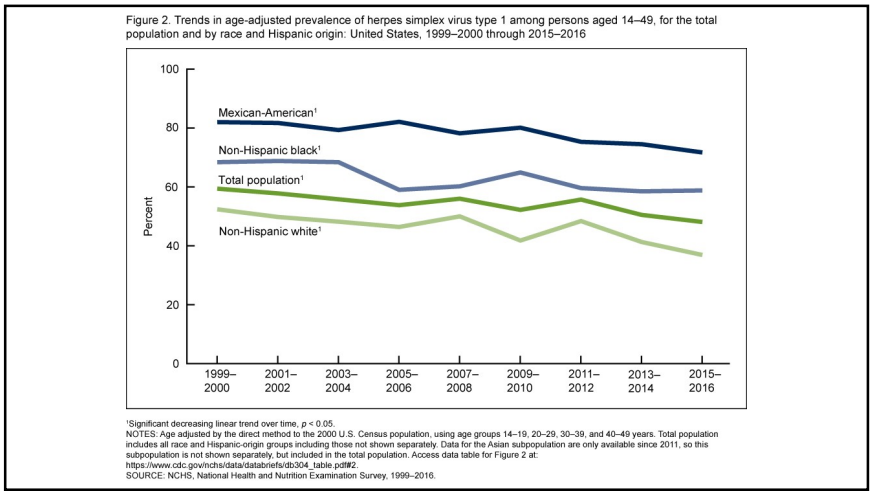

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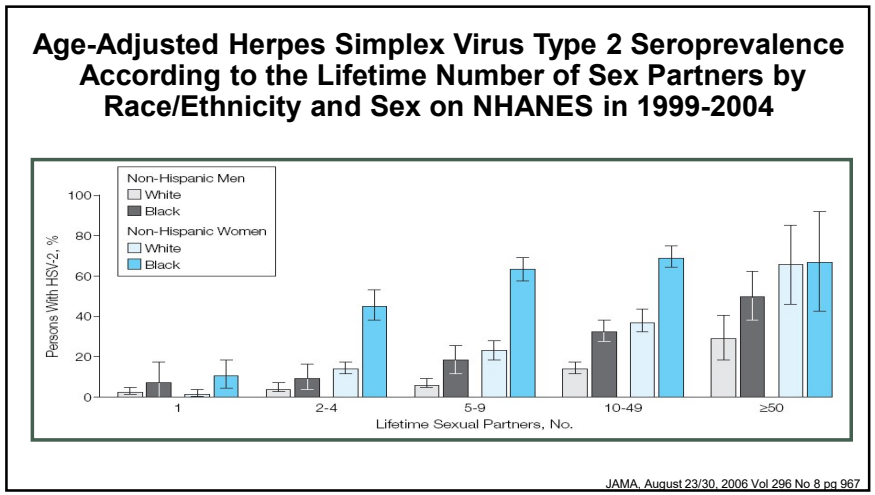

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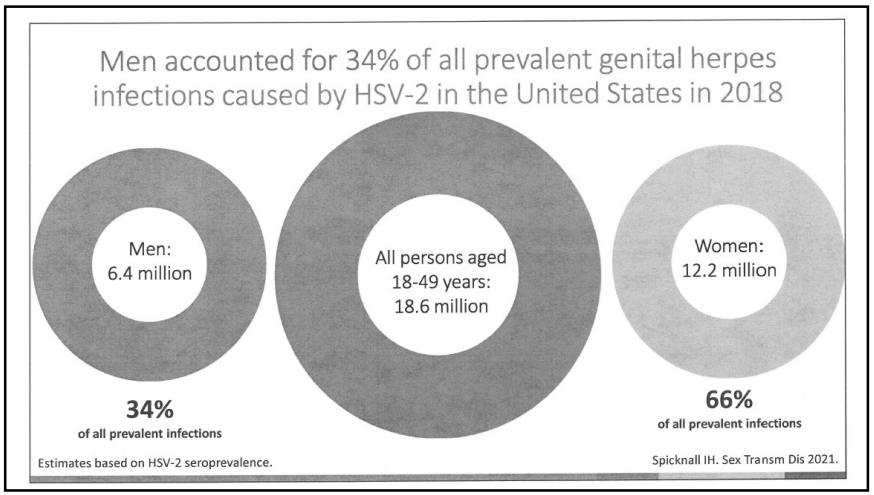

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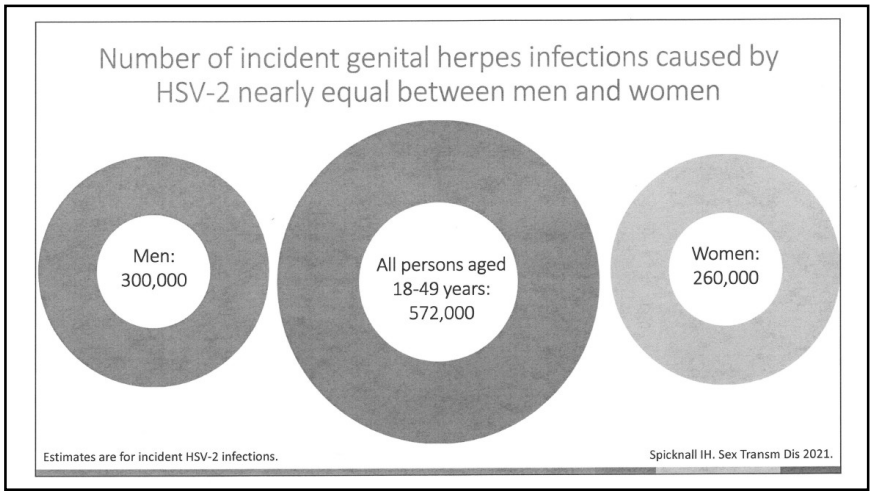
45 Herpes Simplex

Speaker: Richard Whitley, MD



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Genital Herpes: Transmission

Men — Asymptomatic Recurrence ⇄ Women

Transmission → Symptomatic Recurrence: 30%

70%

Corey L. *Sex Transm Dis*. 1994;21(S38-S44.
Mertz GJ, et al. *Ann Intern Med*. 1992;116:197-202

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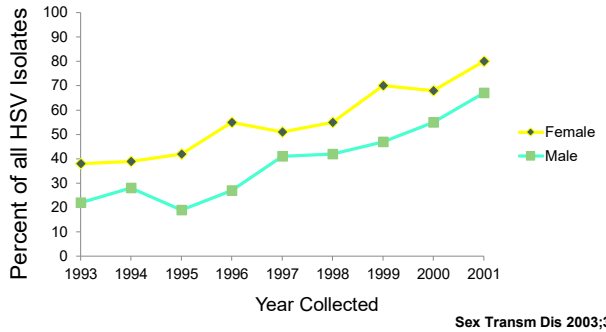
HSV-1 Genital Isolates Among U.S. College Students



Sex Transm Dis 2003;30:797-800

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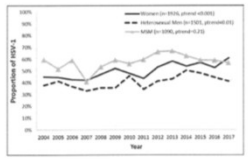
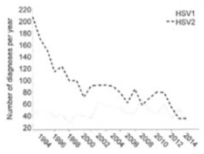
Changing epidemiology of first episode genital herpes

Melbourne Sexual Health Center



In 2017, 54% of first episode genital herpes was due to HSV-1

Public Health-Seattle & King County



Each decade, 52% increase in proportion of first episode genital HSV-1

Durukan STI 2019
Dabestani, STD 2019

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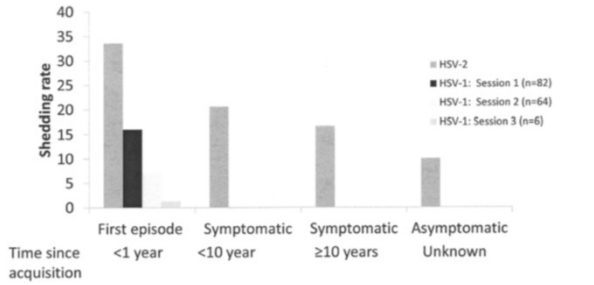
Genital Shedding Rate: HSV-2 vs. HSV-1



Johnston et al, ISSTDR 2019
Phipps et al, JID 2011
Tronstein et al, JAMA 2011

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Genital Herpes: Viral Shedding

- Duration is longer in primary than in recurrent episodes
- Higher rates in:
  - People with frequent outbreaks
  - First year after acquisition
  - Primary: 12 days
  - Recurrent: 2-3 days
- Oral antiviral suppressive therapy shortens the duration of, but does not eliminate, viral shedding

Genital Herpes – A Clinician´s Guide to Diagnosis and Treatment. American Medical Association. 2001:1-20.
Whitley RJ, et al. *Clin Infect Dis.* 1998;26:541-555.

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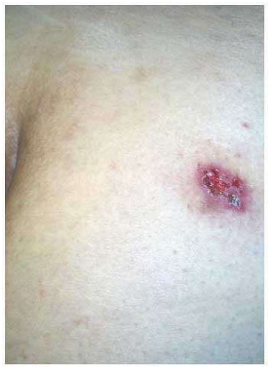
Herpes Presenting as Ulceration



- **The patient had been to her doctor 3 times over the past 8 months with this pruritic and mildly painful rash on her right buttock. She had been told that it was an irritation from riding a bicycle.**
- **What is the key to the diagnosis?**
  - **A. The fact that lesions recurred**
  - **B. Site of involvement is not unusual**
  - **C. Trauma can induce reactivation**

Photo courtesy of Jeffrey Gilbert, MD

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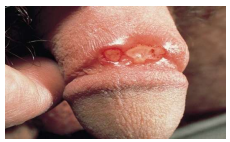
Question #3

An 18-year-old man presents with a history of malaise, low-grade fevers, and new-onset painful genital lesions seen in the picture below. He had unprotected sexual intercourse with a female partner 2 weeks earlier. Neither he nor his partner has traveled outside the United States.



Which of the following diagnostic tests is most likely to yield the specific diagnosis?

A. Serum RPR
B. Serum FTA-Abs
C. Darkfield microscopy
D. Glycoprotein-G 1 serum antibodies
E. PCR on lesion swab

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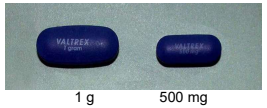
Oral Antiviral Therapies

- **Famciclovir [Famvir®]**

500 mg 250 mg 125 mg

- **Valaciclovir [Valtrex®]**



1 g 500 mg

- **Acyclovir [Zovirax®]**

800 mg 600 mg 200 mg

Valtrex® and Zovirax® are registered trademarks of GlaxoSmithKline.

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Impact of Acyclovir Therapy on Primary Genital HSV Infection

	Treatment Group (Days)			
	Acyclovir	**Placebo**	**RR**	**P**
Virus Shedding	**2.8**	**16.8**	**6.82**	**0.0002**
Pain	**8.9**	**13.1**	**2.00**	**0.01**
Scabbing	**9.3**	**13.5**	**2.21**	**0.004**
Healing	**13.7**	**20.1**	**1.83**	**0.04**

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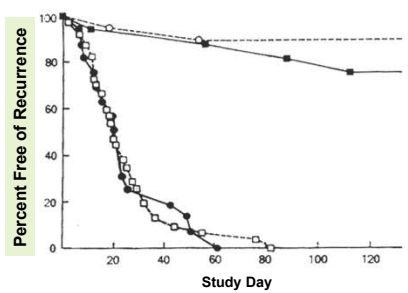
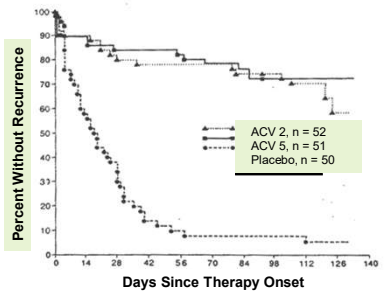
Effect of Acyclovir Prophylaxis on Recurrent Genital Herpes



Straus, et al. *NEJM*, 1984



Douglas, et al, *NEJM*, 1984

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Second Generation Anti-Herpetic Medications

- Valacyclovir (prodrug of acyclovir)
- Famciclovir (prodrug of penciclovir)

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45 Herpes Simplex
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Acyclovir/Valacyclovir Kinetics

DRUG	DOSE	PHARMACOKINETICS	
		C_{max} (µg/mL)	Daily AUC (µg/mL•h)
VALTREX	1 g 3x/d	5.0	47
Oral ZOVIRAX	800 mg 5x/d	1.6	24
IV ZOVIRAX	5 mg/kg 3x/d	9.8	54
	10 mg/kg 3x/d	20.7	107

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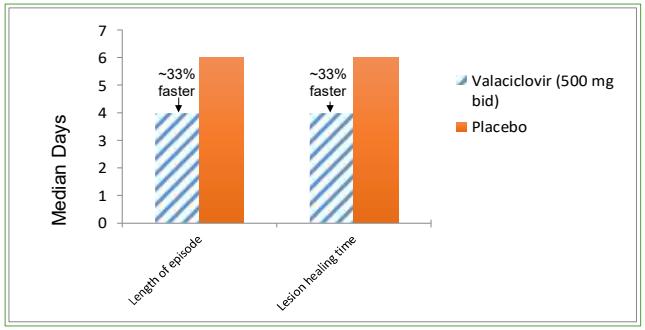
Therapy of Recurrent Genital Herpes: Duration of Disease



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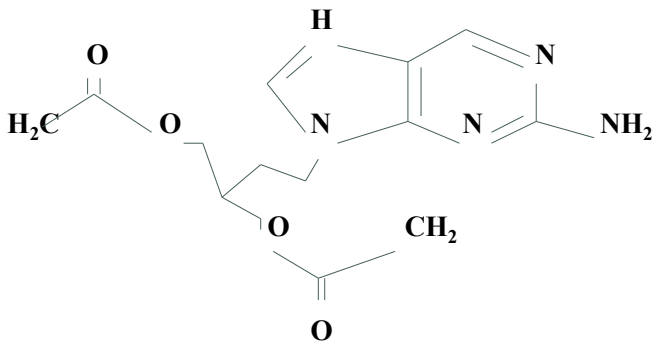
Famciclovir



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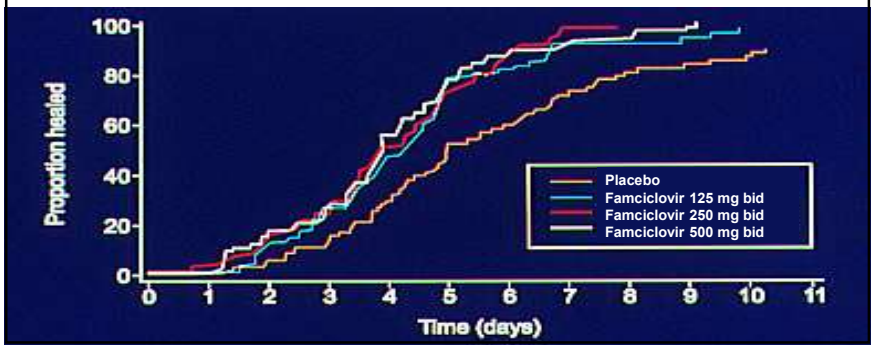
Famciclovir Therapy of Recurrent Genital Herpes



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45 Herpes Simplex

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Shorter and Shorter Therapy

- Genital Herpes
  - Valacyclovir: three days
  - Famciclovir: one day
- Labial Herpes
  - Valacyclovir: two days
  - Famciclovir: one day

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Prevention of Person-to-Person Transmission

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Valacyclovir Prevention of HSV Transmission to Susceptible Partners

Susceptible Partner	Val-ACV N = 743	Placebo N = 741	Total
No. acquired HSV-2	14	28	42
No. acquired HSV-1	0	4	4
No. developed clinical HSV-2	4	17	21

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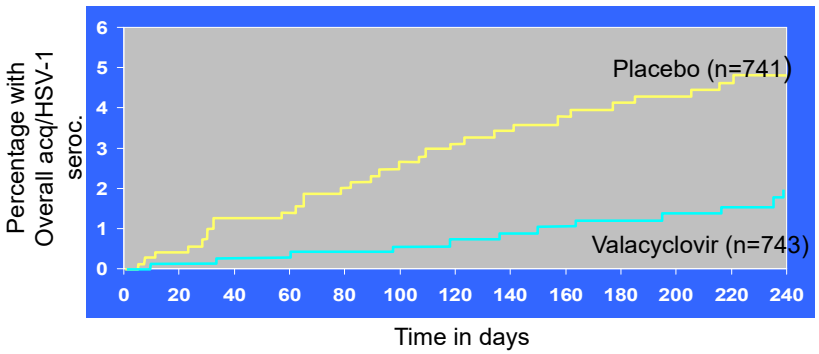
Time to Acquisition of HSV-1 or HSV-2 in Susceptible Partners



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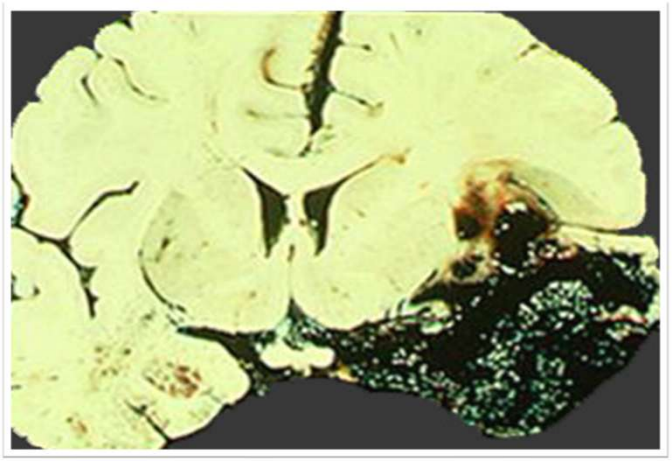

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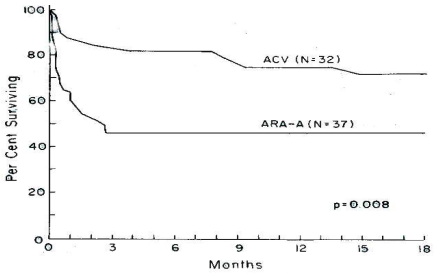
Herpes Simplex Encephalitis Survival



Vidarabine (ARA-A)
vs
Acyclovir (ACV);
P=0.008

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HSE Morbidity

Percent Patients
Patient Normal / Mild Impairment

Age	Glasgow Coma Scale	
	<6	>6
<30	0	60
>30	0	36

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Sensitivity and Specificity of PCR

	Biopsy Positive	Biopsy Negative
PCR Positive	53	3
PCR Negative	1	44

Sensitivity 98%
Specificity 94%
Positive Predictive Value 95%
Negative Predictive Value 98%

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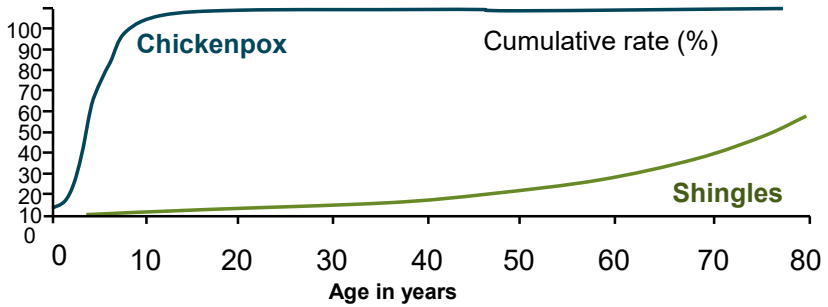
Varicella Zoster Virus Infection



Adapted from Weller TH. *N Engl J Med.* 1983;309:1362-1368

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CHICKEN POX: Is Therapy of Value?

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Treatment of Chicken Pox: Adults (>18 Years) < 24 Hour Duration

	Acyclovir (n=38)	Placebo (n= 38)	*P*
Time to maximum number of skin lesions (days)	1.5	2.1	0.002
Days of new lesion information	2.7	3.3	0.03
Time to onset of cutaneous healing (days)	2.6	3.3	<0.001
Time to 100% crusting (days)	5.6	7.4	0.001
Maximum number of lesions	268	500	0.04

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Thoracic Herpes Zoster

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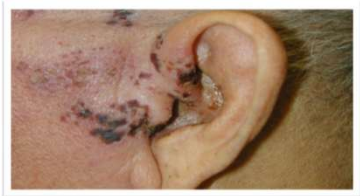
Questions

1. What is the most likely diagnosis?
2. How would you prove the etiology?



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Answer

- Clinically this is herpes zoster
- The lesion shown is Tzank prep positive on skin scraping. The sensitivity of this test is only ~60% and, therefore, is not recommended
- Immunofluorescence is positive for VZV, having a sensitivity of ~80%
- Preferably, PCR can be performed even when lesions are scabbed and has the highest sensitivity

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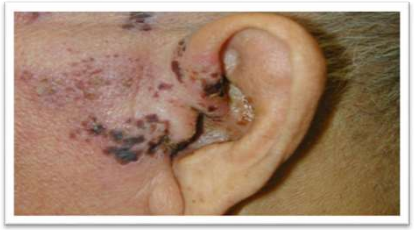
Question #4

What complication would you be most concerned about?

A. Facial paralysis
B. Keratitis
C. Encephalitis
D. Optic neuritis
E. Oculomotor palsies



http://www.itfnoroloji.org/kranyalnoropatiler/Kranyalnoropatiler.html

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Question #4

- This patient has Ramsay Hunt syndrome (Herpes zoster oticus), caused by VZV reactivation in the geniculate ganglion, i.e. zoster of CN VII, presenting with severe ear pain and reduced hearing or deafness. When vesicle are seen in the auditory canal, abnormalities in cranial nerves VII, and sometimes VIII, IX or X, can occur. Thus A, facial paralysis is the best answer. Acyclovir is usually recommended although its not clear if it's effective. The facial paralysis is more severe and less likely to resolve than the usual HSV related Bells Palsy.
- Keratitis would be more typical of a lesion on the tip of the nose, or zoster ophthalmicus involving the CN V ophthalmic branch.
- Encephalitis can be caused rarely by VZV and would not be the best answer. Stroke syndromes due to carotid intimal involvement are associated with zoster, and often with cranial nerve V (trigeminal involvement), but are not offered as an answer
- Optic neuritis and oculomotor paralysis would be uncommon.

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Question #5

The patient has only the observed finding on his nose.

- What is your most likely diagnosis?
- What is the name of this sign?

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Question #5

What complication is most likely to be associated with this illness?

A. Deafness
B. Vertigo
C. Optic neuritis
D. Keratitis
E. Stroke

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Question #5

This patient has Hutchison's sign, which indicates involvement of the cranial nerve V, i.e., ophthalmic branch of the trigeminal nerve, which innervates the tip of the nose and the globe. After a prodrome of fever and headache for 1-4 days, patients develop a cutaneous rash. Days or up to 3 weeks later, the sclera and cornea can be involved. Thus, keratitis is the correct answer.

Deafness or vertigo would be more characteristic of geniculate ganglion (CN VII) involvement, i.e., Ramsay Hunt, which is a polyneuropathy involving the cranial nerve VII, and then often involves VIII, IX, X. Thus, A and B are not the best answers.

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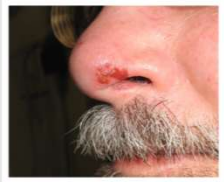
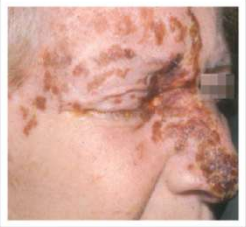
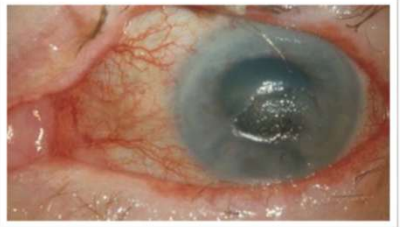
Hutchison's Sign

Zoster Involving nasociliary branch, Cranial Nerve VII which innervates the tip of the nose and the cornea







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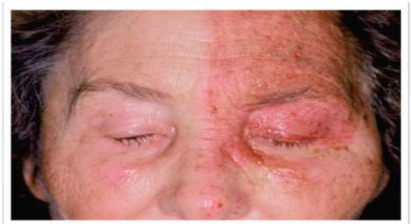
Zoster Ophthalmicus



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Natural History of Zoster in the Normal Host

- Acute neuritis may precede rash by 48 - 72 hours
- Maculopapular eruption, followed by clusters of vesicles
- Unilateral dermatomal distribution

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Natural History of Zoster in the Normal Host

- Events of healing:
  - Cessation of new vesicle formation: 3 - 5 days
  - Total pustulation: 4 - 6 days
  - Total scabbing: 7 - 10 days
  - Complete healing 2 - 4 weeks
- Cutaneous dissemination can occur
  dissemination is extremely rare
- Postherpetic neuralgia in 10% - 40% of cases

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Complications of Zoster

Common	Uncommon
• Postherpetic neuralgia	• Cutaneous dissemination
• Ocular complications	• Herpes gangrenosum
• Ophthalmic zoster	• Hepatitis
• (Uveitis, keratitis, scleritis, optic neuritis)	• Encephalitis
• Pneumonitis	• Motor neuropathies
• Scarring	• Myelitis
• Bacterial superinfection	• Hemiparesis (granulomatous CNS vasculitis)

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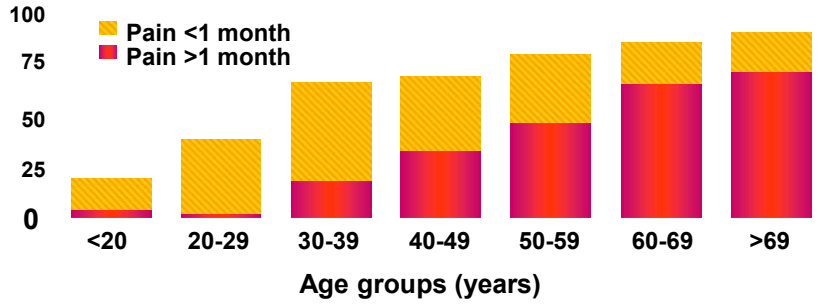
Prevalence and Duration of Pain



de Moragas et al. *Arch Derm.* 1957;75:193-196.

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Goals of Therapy

- Accelerate cutaneous healing
- Accelerate loss of pain acute / chronic
- Prevent complications

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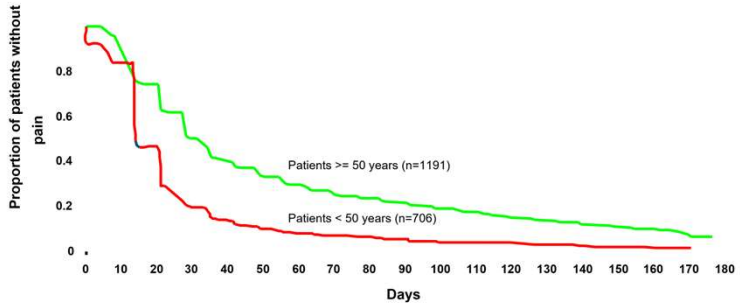
Time to Cessation of Zoster-Associated Pain



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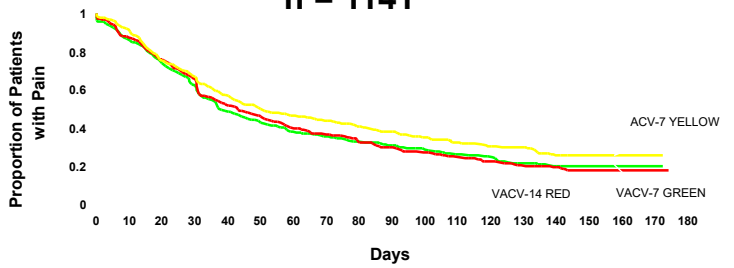
Time to Cessation of Zoster-Associated Pain

n = 1141



* Beutner, et al. Acyclovir versus Valacyclovir in the treatment of herpes zoster in patients > 50 years old.

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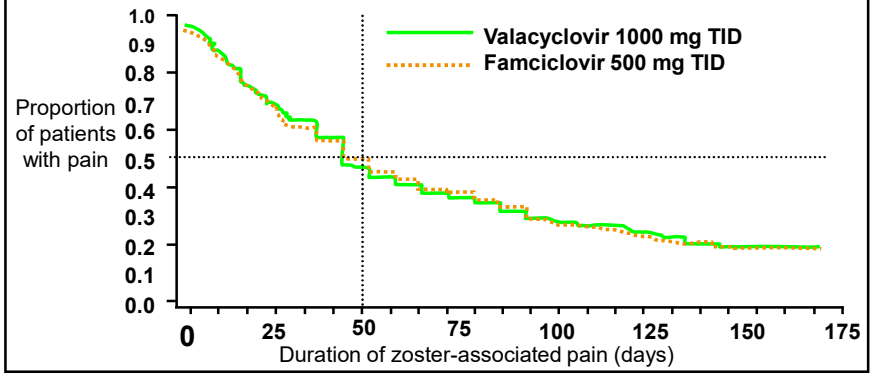
Resolution of Pain in Herpes Zoster With Valacyclovir and Famciclovir



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Summary of Efficacy of Concomitant Steroid Therapy with Acyclovir

- Accelerates resolution of acute neuritis
- Accelerates:
  - Return to usual activity P<0.001
  - Unaroused sleep P<0.0001
  - Cessation of analgesic use P<0.001
- Effect on chronic pain P=0.06

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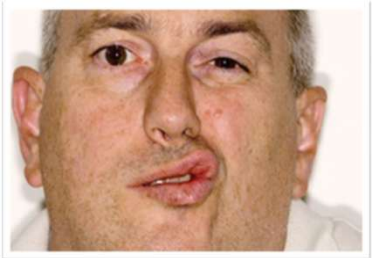
Question #6

What is the most likely etiologic agent?

A. HSV
B. VZV
C. CMV
D. EBV
E. HHV6



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Question #6

- This patient has facial palsy, also known as Bells palsy. The most likely cause of this lesion is HSV. HIV and Lyme disease are less common causes. Answers d and e are not the best answer. Of note, Lyme is rarely the cause of Bells palsy unless there are other manifestations of Lyme disease.
- For typical facial palsy, prednisone is the preferred therapy, optimally given within 3 days of onset, for one week (prednisone 60-80mg qd). Acyclovir alone is not better than placebo, although there might be some rational (unproven) to add acyclovir to prednisone.
- Ganciclovir would be a therapy for CMV, a rare cause of facial paralysis and thus not the best answer.

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Methods of Preventing / Modifying Varicella

Pre-exposure: Oka varicella vaccine

Post-exposure: VZIG (now available in US)

Oka varicella vaccine
(<3 days after exposure)
Acyclovir
(7-14 days after exposure)

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Second Generation Vaccine: Shingrix

- **Recombinant adjuvanted vaccine**
  - **Two shots**
  - **> 50 years of age**
- **Efficacy**
  - **Both PHN and incidence of shingles**
  - **>90% for >4 years**
- **Adverse events**
  - **Local reactogenicity: redness and pain ~ 50-70%**
  - **Systemic malaise/fever: ~30%**

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Thank You

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