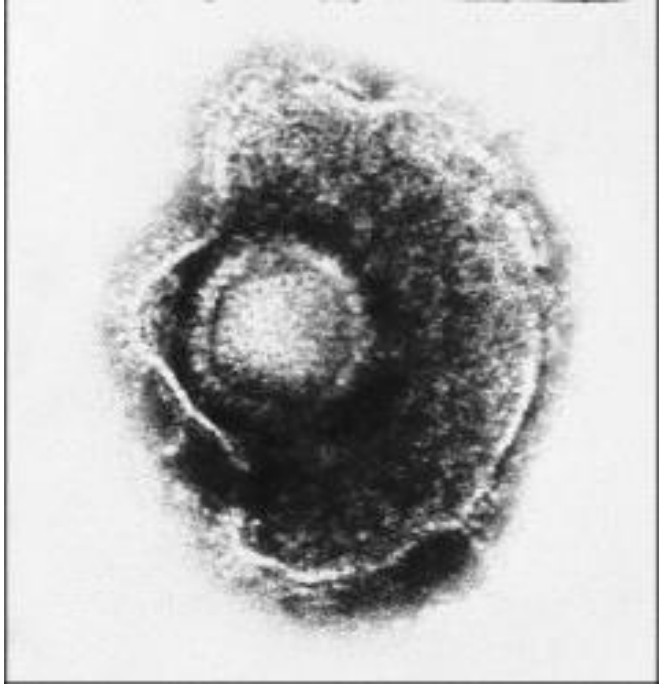
Herpesviruses: The Tired, the Rashy, and the Ubiquitous



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Disclosures

- Advisory board member for GSK (for belimumab pregnancy registry).
- Co-founder of Grid Therapeutics (formerly Cue Biologics).
- Chief Medical Officer, DHVI.

Educational Objectives

- Recognize the different presentations of human herpesvirus infections.
- Recommend testing for herpesvirus infections.
- Prescribe appropriate therapy for herpesviruses.

Definitions

herpes *n*

a disease characterized by patches of vesicles

derived from the Greek *ἑρπειν* (to creep)

originally applied to spreading vesicular lesions

Herpesviruses: basics

- enveloped DNA viruses
- icosahedral capsid (100 nm)
- virion spherical (120-200 nm)
- linear dsDNA 120-240 kbp
  (100+ proteins)

- large family, endemic in many animals

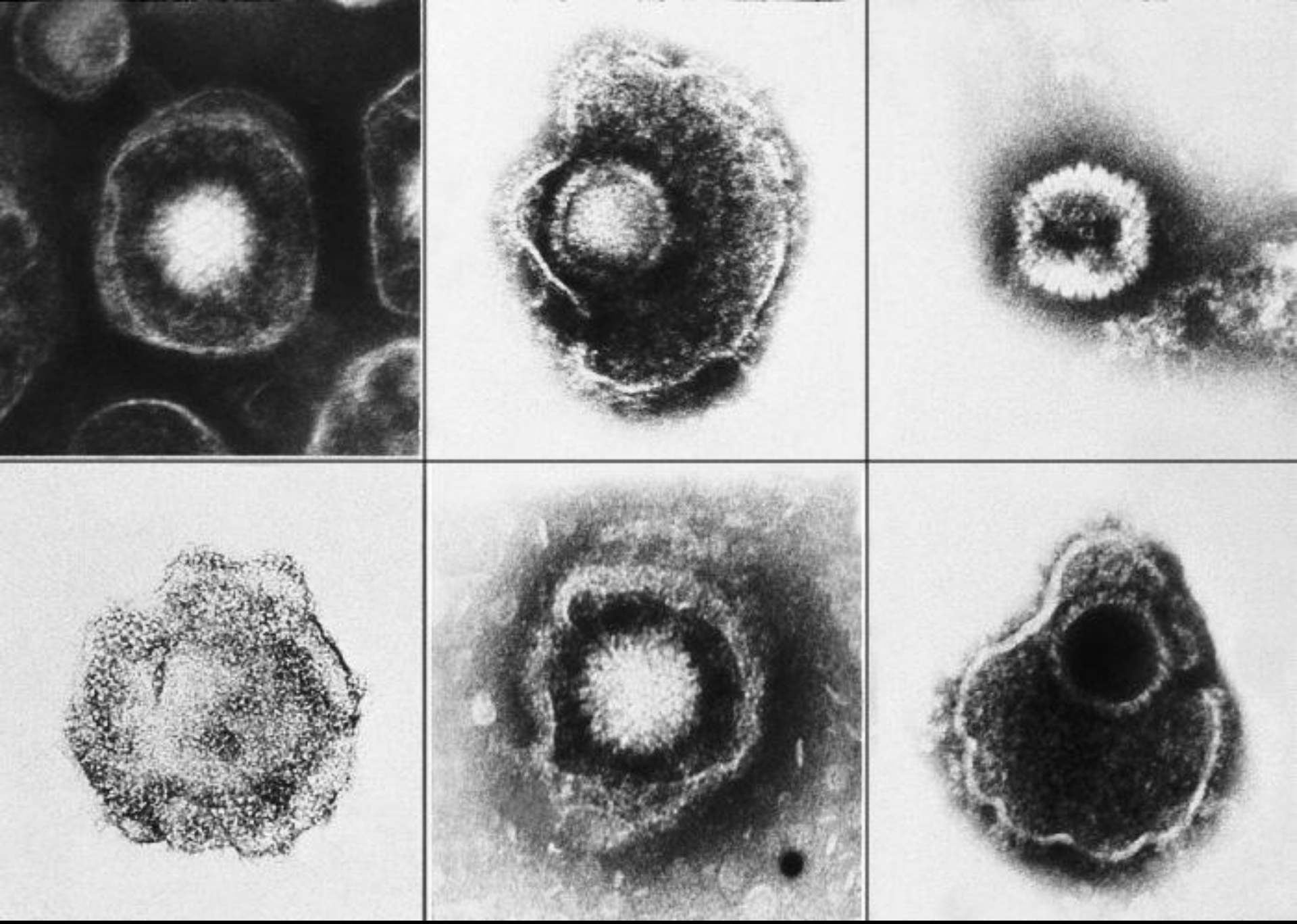


Image obtained from the Centers for Disease Control, Public Health Image Library.

Herpesviruses: life cycle (1)

- bind to receptors
  - heparan sulfates, other molecules
- fuses with cell membrane
- capsid transported to nuclear pore
- uncoating of dsDNA

Herpesviruses: life cycle (2)

- cascade of gene expression
  - immediate-early genes
  - early genes
  - late genes
  - latency-associated transcripts (LATs)
- DNA synthesis enzymes

Herpesviruses: life cycle (3)

- new viral DNA coated with icosahedral capsid
- buds through nuclear membrane
- most cells die by lysis (18-72 hrs)
- some cells express lytic genes, some express latency genes
- level of latency transcripts determine recurrence rates?

Herpesviruses: life cycle (4)

- primary infection of longer duration
- most primary infection asymptomatic
- reactivation / secondary infection
  shorter
- most human → human transmission
  asymptomatic shedding to naïve hosts

- animal → human transmission
  asymptomatic vs. severe disease

Human Herpes Viruses

- HHV-1/2 → Herpes Simplex Virus 1/2
- HHV-3 → Varicella-Zoster Virus
- HHV-4 → Epstein-Barr Virus
- HHV-5 → Cytomegalovirus
- HHV-6 → Roseolovirus
- HHV-7 → Roseolovirus
- HHV-8 → Kaposis Sarcoma-Associated Herpesvirus

Herpesviruses: classes (1)

- subfamily *Alphaherpesvirinae*
  - rapid growth cycle / cytolytic
  - genera
    Simplexvirus (HSV-1, HSV-2)
    Varicellovirus (VZV)
- target cells → mucoepithelial
- site of latency → neurons

Human Herpes Virus 1/2

Herpes Simplex Virus 1/2

- ~50% DNA homology
  - cross-protection?
- transmission by contact
  - infect mucosal / epithelial cells
- establish latency in sensory neurons
  - trigeminal ganglion
  - dorsal nerve roots
  - sacral ganglion

Human Herpes Virus 1/2

Herpes Simplex Virus 1/2

- incubation period 2-20 days

- ubiquitous human infections
- HSV-1 > HSV-2

Human Herpes Virus 1/2

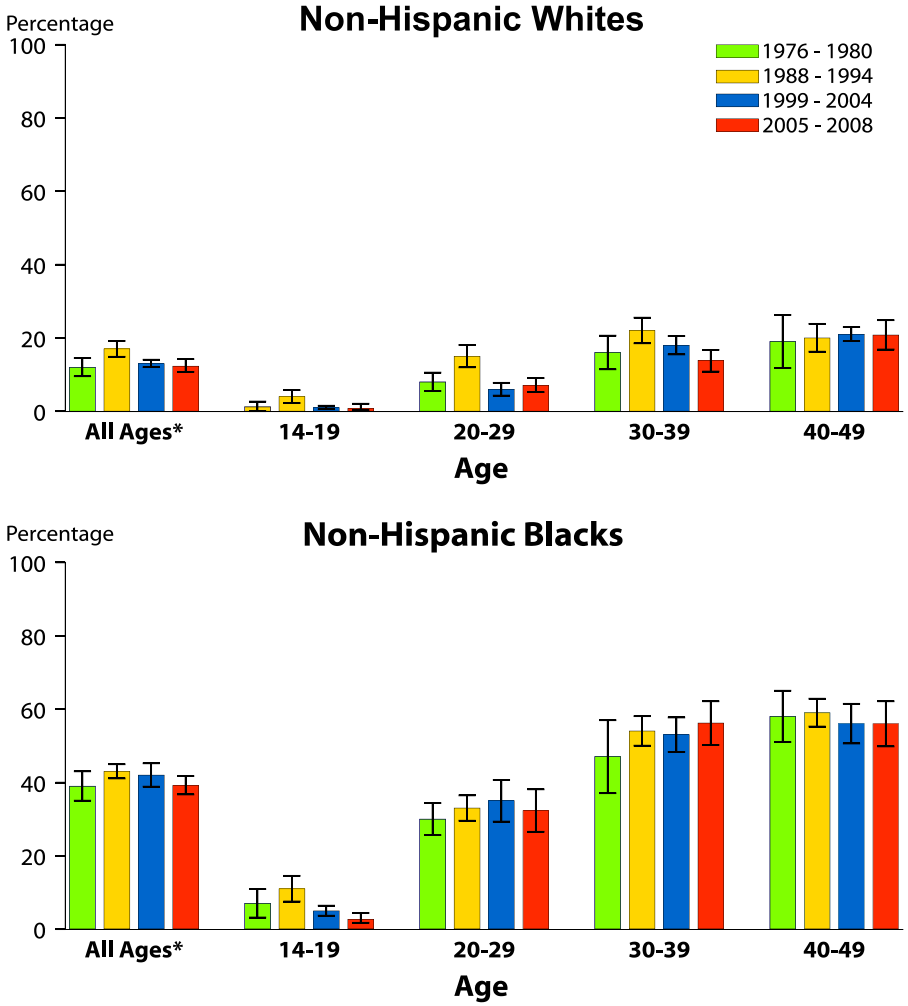
HSV-1

- acquired in childhood
- 40-60% by 5 yo
- 70-90% by late adulthood

HSV-2

- acquired throughout life
- some perinatal transmission
- increases in adolescence
- 10-60% in adults

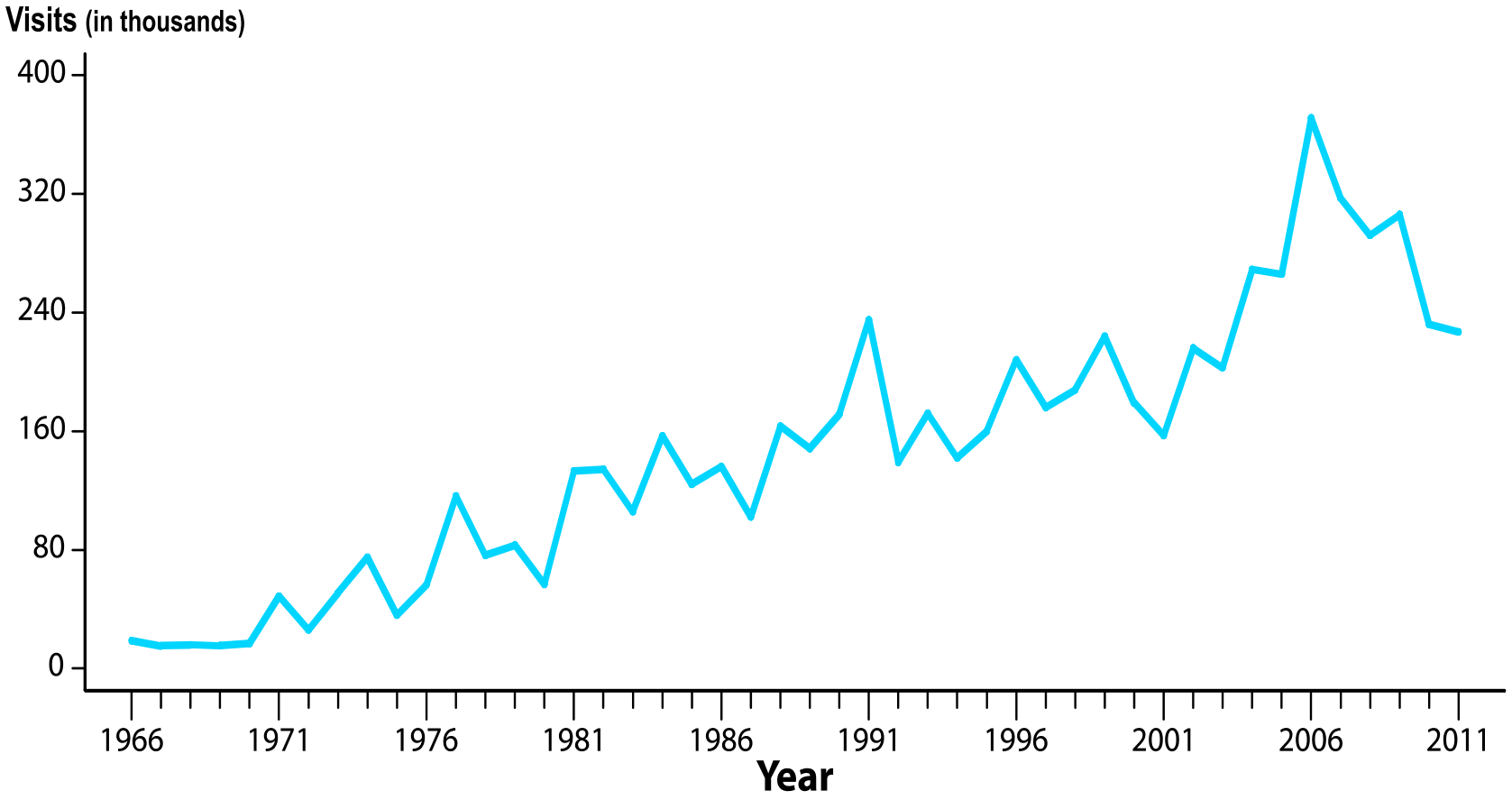
Herpes Simplex Virus Type 2—Seroprevalence in Non-Hispanic Whites and Non-Hispanic Blacks by Age Group, National Health and Nutrition Examination Survey, 1976–1980, 1988–1994, 1999–2004, 2005–2008



*Age-adjusted by using the 2000 U.S. Census civilian, non-institutionalized population aged 14-49 years as the standard.

NOTE: Error bars indicate 95% confidence intervals.

Genital Herpes—Initial Visits to Physicians' Offices, United States, 1966–2011



NOTE: The relative standard errors for genital herpes estimates of more than 100,000 range from 18% to 30%. **SOURCE:** IMS Health, Integrated Promotional Services ™. IMS Health Report, 1966–2011.

Human Herpes Virus 1/2

Primary Infection

- lesions vesicular (d1-7)
  → ulcerative (d7-14)
  → crusting / healing (d14-21)

Secondary Infection

- lesions vesicular (d1-2)
  → ulcerative (d3-4)
  → crusting / healing (d4-7)

Human Herpes Virus 1/2

Gingivostomatitis

- HSV-1 > HSV-2
- ulcerative oral disease
- gums / lips / tongue
- recurrence on lips (cold sores)
- posterior pharyngitis (teens / adults)
  - ¼ of pharyngitis in college
  - symptoms overlap EBV

Image obtained from the Centers for Disease Control, Public Health Image Library.

Human Herpes Virus 1/2

Vulvovaginitis / Genital HSV

- HSV-2 > HSV-1
- ulcerative genital lesions
- recurrence
- cervix often involved
  - source for perinatal transmission

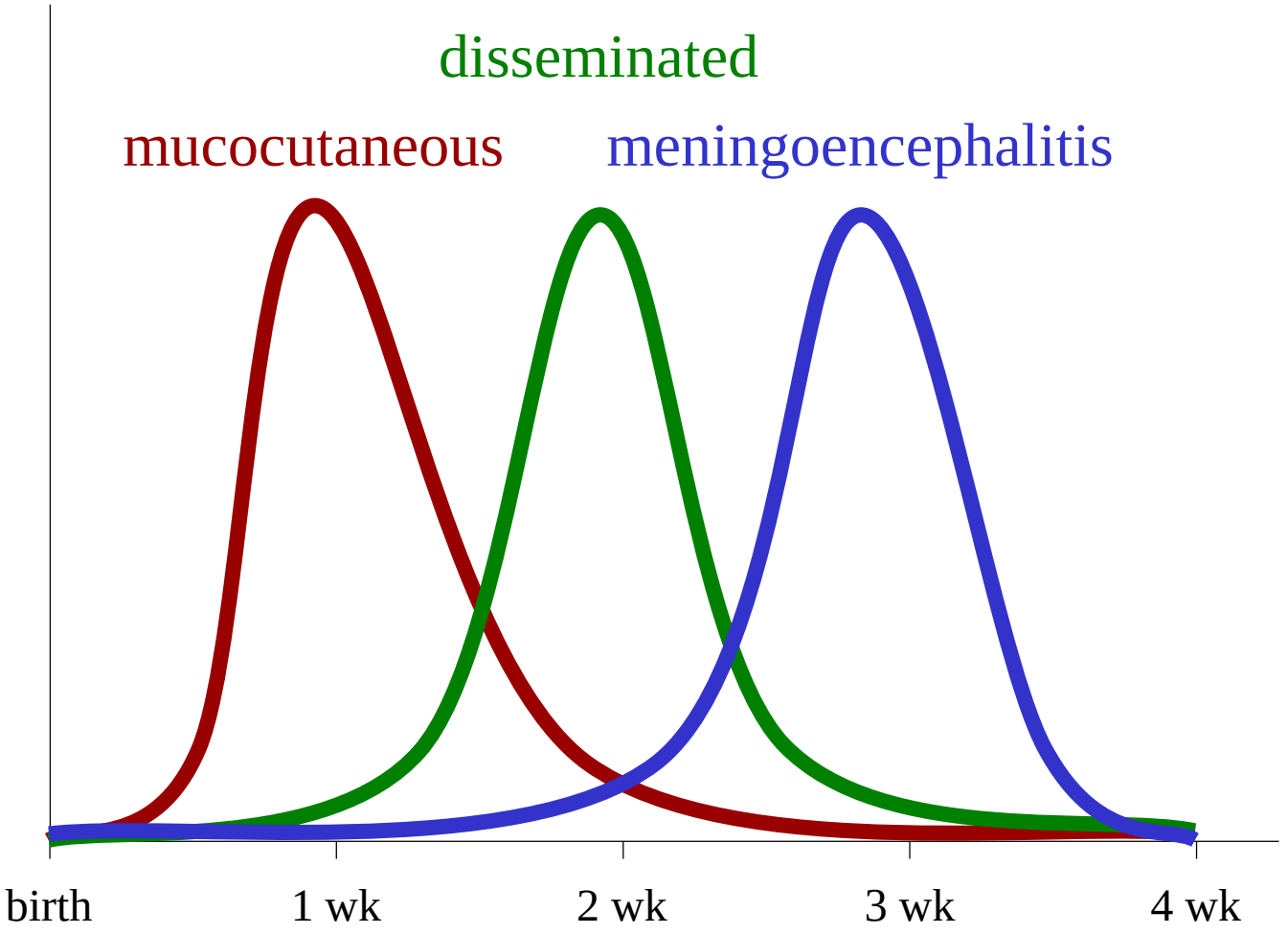
- primary genital herpes
  HSV-1 > HSV-2 ?

Human Herpes Virus 1/2

Perinatal

- HSV-2 > HSV-1
- lesions at presenting part
- mother's cervix often involved
- recurrence risk in future?

Image obtained from the Centers for Disease Control, Public Health Image Library.


disseminated
mucocutaneous
meningoencephalitis
birth
1 wk
2 wk
3 wk
4 wk

Human Herpes Virus 1/2

Encephalitis

- HSV-1 > HSV-2
  - reversed in neonates
- meningitis alone HSV-2 > HSV-1
  - associated with genital disease
- Mollaret meningitis
  - “benign” recurrent

Human Herpes Virus 1/2

Cutaneous
- herpes gladiatorum
- eczema herpeticum

Whitlow
- nail biting

Ocular
- keratitis

HSV: diagnosis

- Tzanck smear (obsolete)
- serology (unreliable / unhelpful)
- DFA (dependent on quality of specimen)

- culture of lesion or CSF

- **PCR of lesion / CSF**
  gold standard

Image obtained from the Centers for Disease Control, Public Health Image Library.

Human Herpes Virus 3

Varicella-Zoster Virus

- varicella (diminutive of variola)
- zoster (Greek word: girdle)

- transmission by respiratory route
  - highly contagious (80-90% attack)
- establishes latency in neurons
  - most recurrences in dermatomes with most primary lesions?

Human Herpes Virus 3

Varciella-Zoster Virus

- incubation period 10-23 (14) days

- ubiquitous human infection
- was 8-9%/yr from 1-9yo
  (5% subclinical)
- higher rates in temperate zones
  vs tropical zones

Varicella Cases by Month: Antelope Valley, CA, 1995–2004

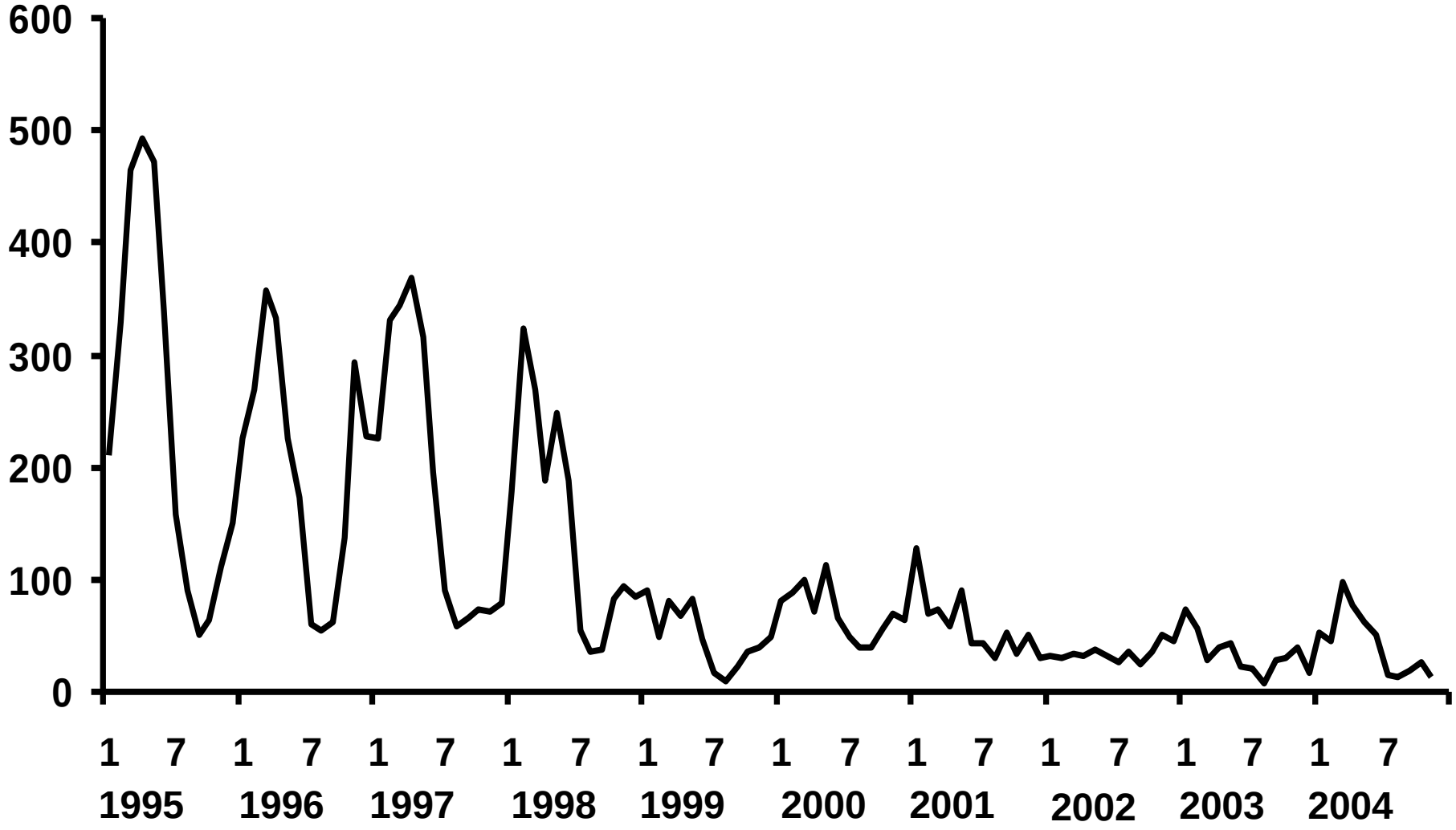


Image obtained from the Centers for Disease Control.

Human Herpes Virus 3

Primary: **Varicella (chickenpox)**

- prodrome (adults > children)
  → fever with crops of vesicular lesions (d1-2)
  → fever with evolution (d3-5)
  → crusting / healing (d5+)

- disease in adults often severe

Image obtained from the Centers for Disease Control, Public Health Image Library.

Human Herpes Virus 3

Secondary: **Zoster**

- lesions localized (1-3 dermatomes)
  vesicular / confluent (d1-3)
  → crusting (d3-5)
  → slow healing (d5-28)

- post-herpetic neuralgia 25-50%
  in those >50 yo

VZV: diagnosis

- usually a clinical diagnosis

- serology (unhelpful)
- DFA (dependent on quality of specimen)
- culture of lesion or CSF

- **PCR of lesion / CSF**
  gold standard

Herpesviruses: classes (2)

- subfamily *Betaherpesvirinae*
  - slow growth cycle / cytomegalic
  - genera
    Cytomegalovirus (CMV)
    Roseolovirus (HHV-6A/B, HHV-7)
- target cells → T cells (monocytes?)
- site of latency → T cells (monocytes?)

Human Herpes Virus 5

Cytomegalovirus

- originally called salivary gland virus
- largest of herpesviruses

- transmission via body fluids
  - saliva / urine / breast milk
  - evidence for sexual transmission
    - semen / CVL
  - blood products (nosocomial)
- establishes latency in leukocytes

Human Herpes Virus 5

Cytomegalovirus

- incubation period unclear

- ubiquitous human infection
- ~1% congenital
- ~50% attack rate in breast milk
- 50-80% +ve in daycares
- adults with high SES 40-60% vs low SES >80%

Human Herpes Virus 5

Diseases: **Protean**

- most asymptomatic
- mononucleosis syndrome
  - heterophile antibody
- hepatitis / marrow suppression
- severe disease in AIDS

Human Herpes Virus 5

Diseases: **Congenital**

- most asymptomatic
- intracranial calcifications
- retinitis
- thrombocytopenia
- hearing loss
- mental retardation
    - role for therapy unclear / evolving

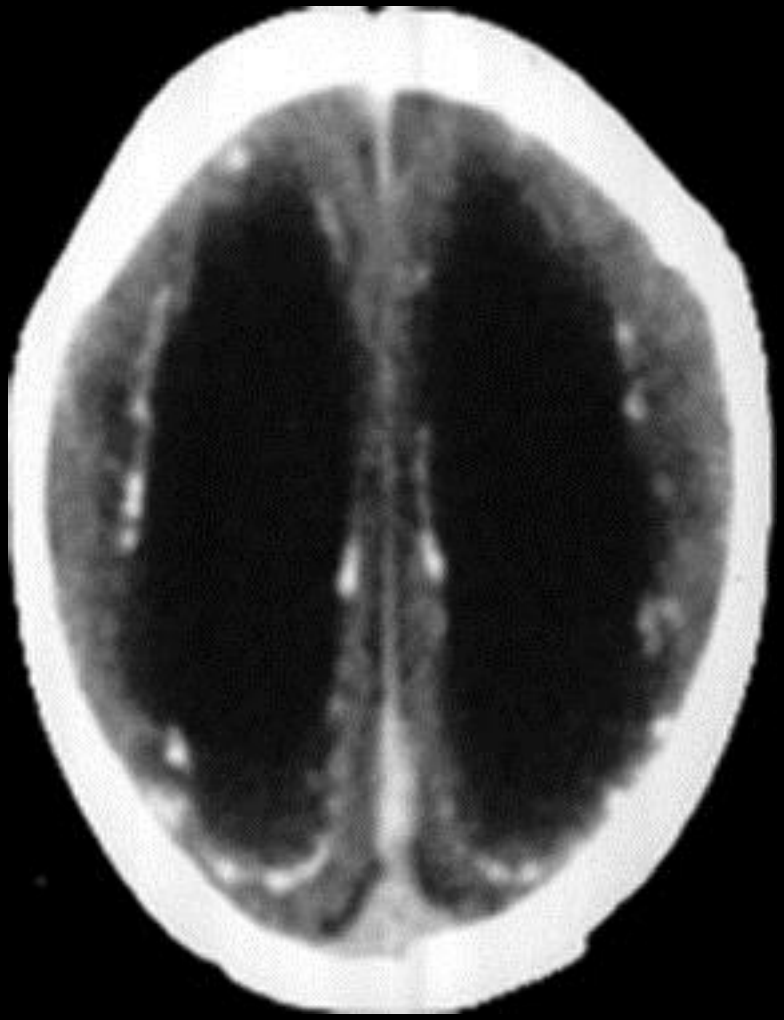


Image obtained from the University of California at San Francisco Neuroradiology website.

Image obtained from the
National Cancer Institute.

CMV: diagnosis

- serology (immune screen)
- culture of urine (shell vial)
- PCR of blood (viral levels)

Human Herpes Virus 6A/B, 7

HHV-6A / HHV-6B / HHV-7

- genetically distinct

- transmission probably via body fluids
  - saliva
  - congenital
  - nosocomial
- establish latency in T cells / monocytes / bone marrow stem cells (integration?)

Human Herpes Virus 6A/B, 7

HHV-6A / HHV-6B / HHV-7

- incubation period unclear
- ubiquitous human infections
- ~100% HHV-6 infected by 2 yo
- ~65% HHV-7 infected by 3 yo,
  but ~100% by 6 yo

Prevalence of HHV-6/7 Infections in British Children by Age

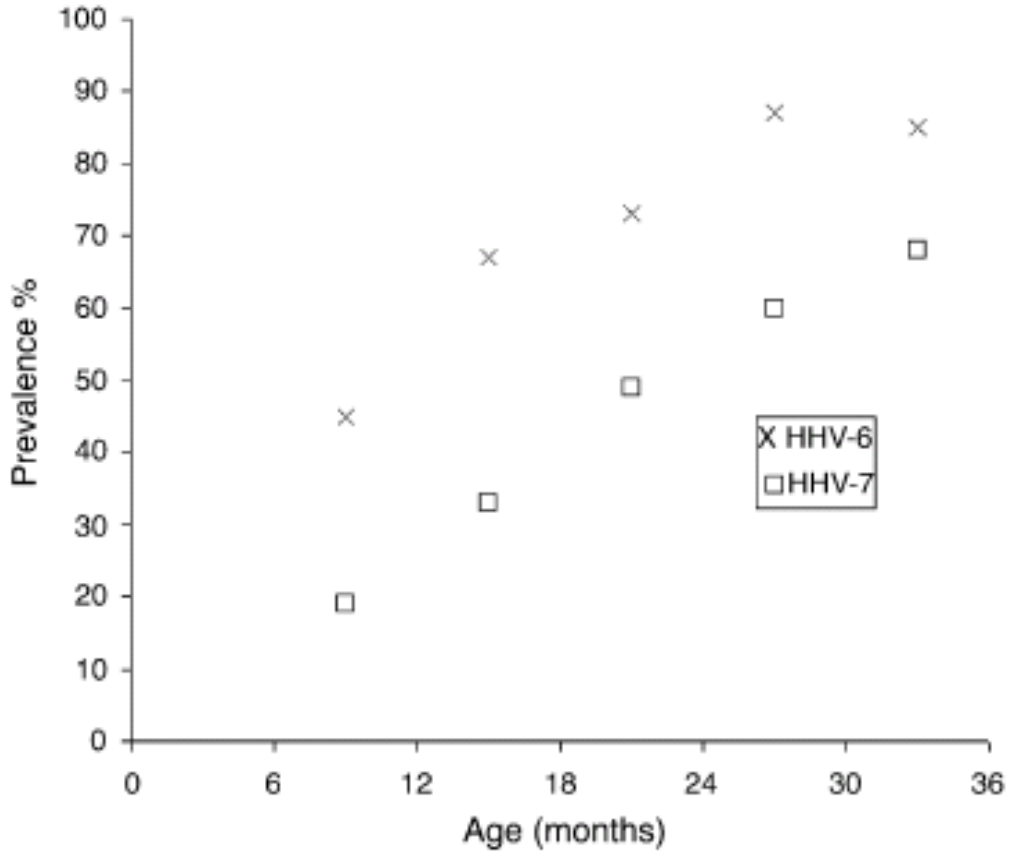


Figure from Ward KN, *J Clin Virol* **32:** 183-193 (2005).

Human Herpes Virus 6A/B, 7

Primary disease: **Exanthem subitum**

- aka: roseola infantum, 6th disease
- fever (~3d), fine rash after fever breaks
- can be rash-less
- association with febrile seizures
  - definitive association with HHV-6B
  - strong evidence for HHV-7
  - not clear disease caused by HHV-6A

Human Herpes Virus 6A/B, 7

Recurrent disease: **Unclear**

- asymptomatic shedding common
- pityriasis rosea (HHV-7)?
- CNS reactivation in immunocompromised

HHV-6A/B, 7: diagnosis

- clinical diagnosis
- serology (not helpful in acute disease)
- culture (hard to get)
- PCR of blood / other fluids
  (only helpful in immunocompromised)

Herpesviruses: classes (3)

- subfamily *Gammaherpesvirinae*
  - variable growth cycle
  - malignant transformation potential
  - genera
    Lymphocryptovirus (EBV)
    Rhadinovirus (KSHV)
- target cells → B cells, epithelial cells
- site of latency → B cells

Human Herpes Virus 4

Epstein-Barr Virus

- recognized as a cause of infectious mononucleosis
  - transmission via body fluids
    - saliva
    - blood products (nosocomial)
- establishes latency in B cells

Human Herpes Virus 4

Epstein-Barr Virus

- incubation period unclear

- ubiquitous human infection
- congenital rare / no clear disease
- childhood acquisition common
- 80-95% +ve in adults

Human Herpes Virus 4

Diseases: **Protean**

- most asymptomatic
  (increased symptoms with older age?)
- chronic active disease rare
- hepatitis / marrow suppression
- malignant disease
  - Burkitt lymphoma
  - Hodgkin disease
  - PTLD

Human Herpes Virus 4/5

Diseases: **Infectious Mononucleosis**

- highest incidence 15-19 yo
- heterophile antibody (after age 4-5)
- pharyngitis / lymphadenopathy
- fever
- hepatosplenomegaly (1-3 months)
- fatigue (1-3+ months)

EBV: diagnosis

- serology (specific antibodies)
- monospot (heterophile antibody)
- PCR of blood (viral levels)

EBV: serologic diagnosis

disease stage	Antibody against EBV antigen			
	VCA IgM	VCA IgG	EA	EBNA
acute infectious mononucleosis	positive	positive	positive	negative
late stage / recovery	falling	high	falling	rising
previous infection	low / negative	positive	low / negative	positive
reactivation	positive	high	high	positive

Human Herpes Virus 8

Kaposi Sarcoma-Associated Herpesvirus

- cause of Kaposi sarcoma

- transmission via body fluids
  - saliva / semen? / CVL?

- establishes latency in B cells

Human Herpes Virus 8

KSHV

- incubation period unclear
  - appears to have long delay from acquisition to sarcoma

- variable rates of infection
- 0-20% in Asia, NA, Europe
- >50% in Africa / Amazon

Human Herpes Virus 8

Disease: **Kaposi Sarcoma**

- disease of older adults
- disease of AIDS
- no clear disease states in childhood
- multicentric Castleman disease

Diagnosis: symptomatic

THERAPY

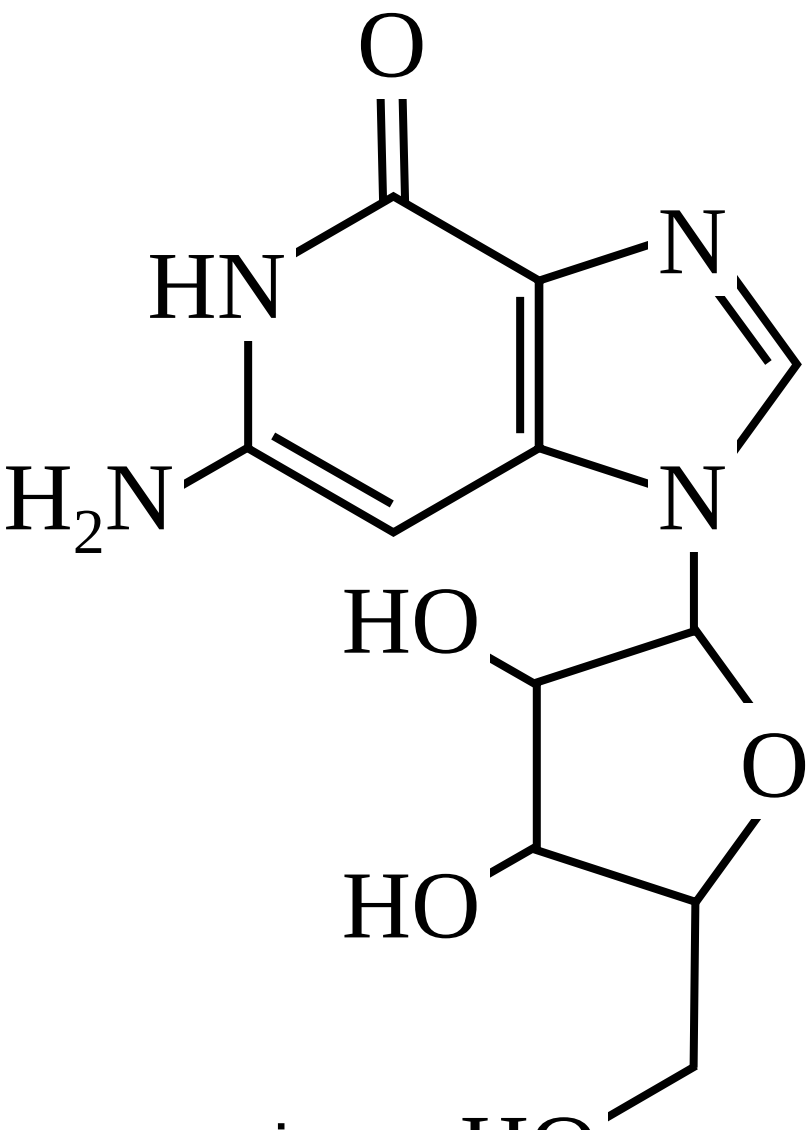
HHV: therapy

- drugs interfere with nucleic acid sythesis

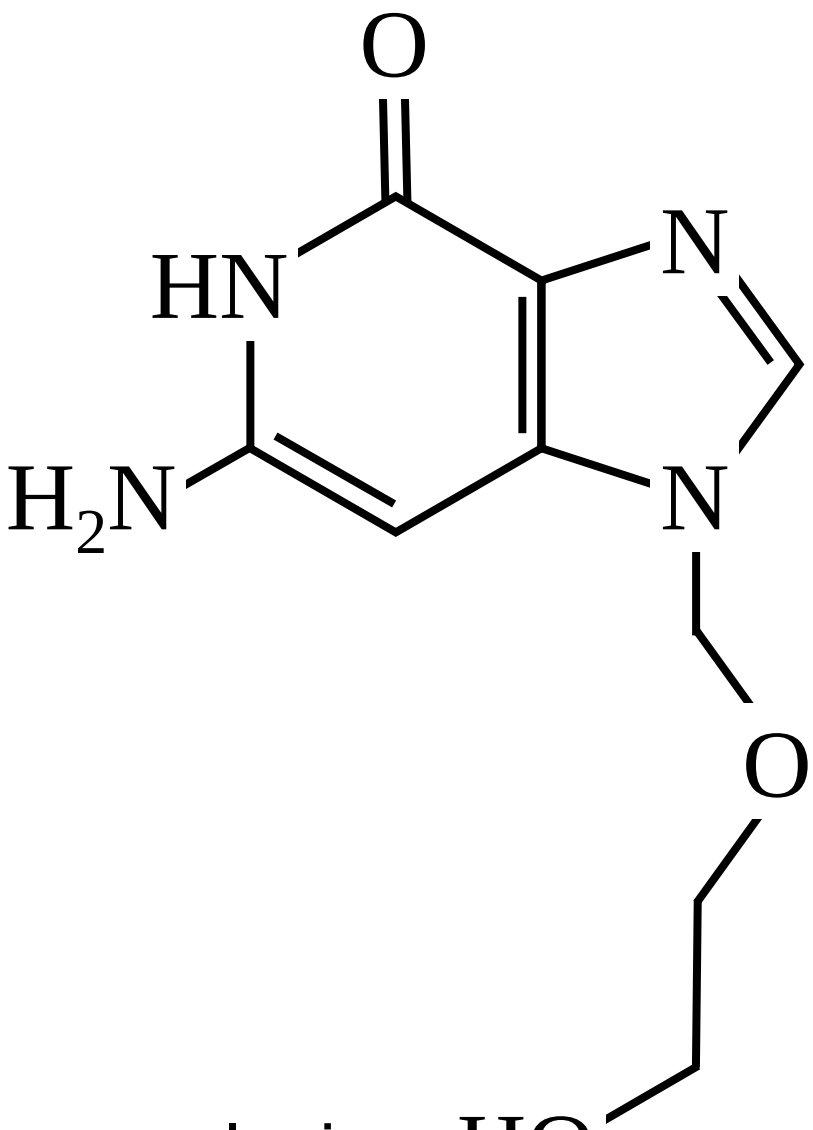
- goals of therapy
  - reduce severity and duration of primary and recurrent outbreaks
  - prophylaxis of outbreaks

HHV: therapy

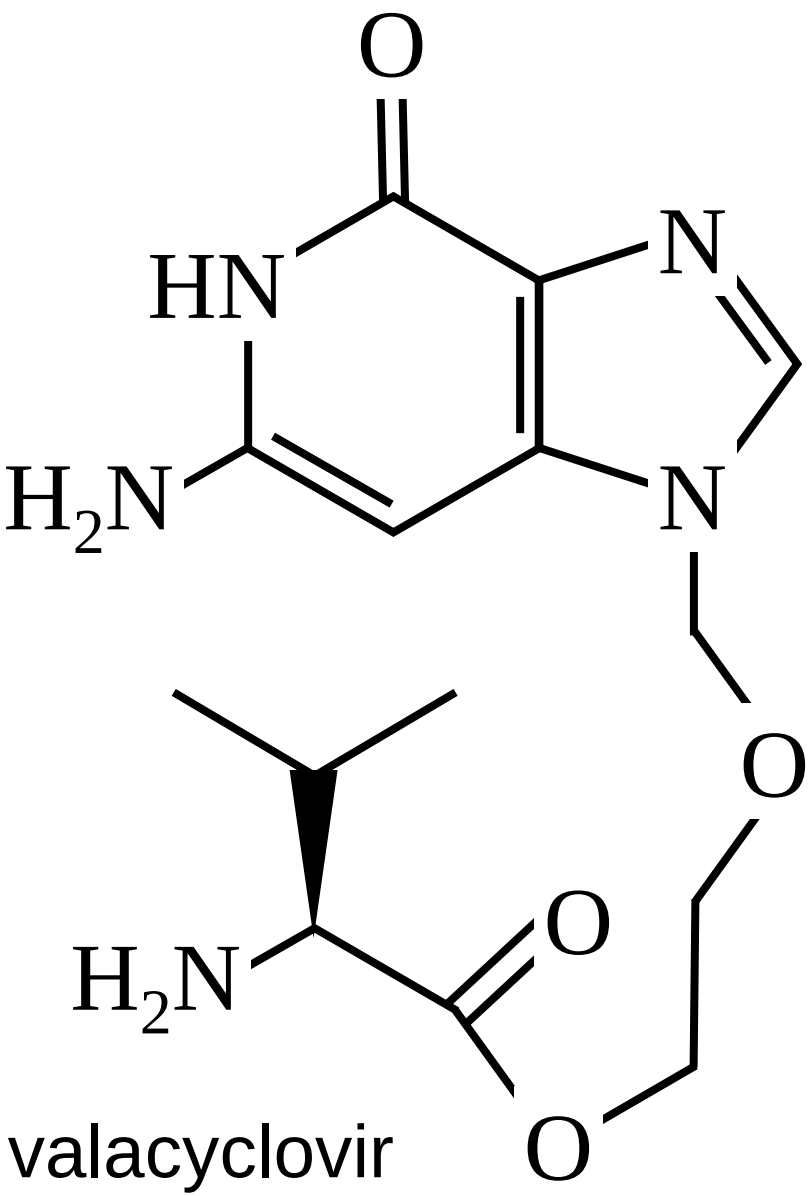
- guanosine analogs
  - acyclovir and valacyclovir
  - ganciclovir and valganciclovir
  - penciclovir and famciclovir
- phosphate analogs
  - foscarnet
- cytosine analogs
  - cidofovir



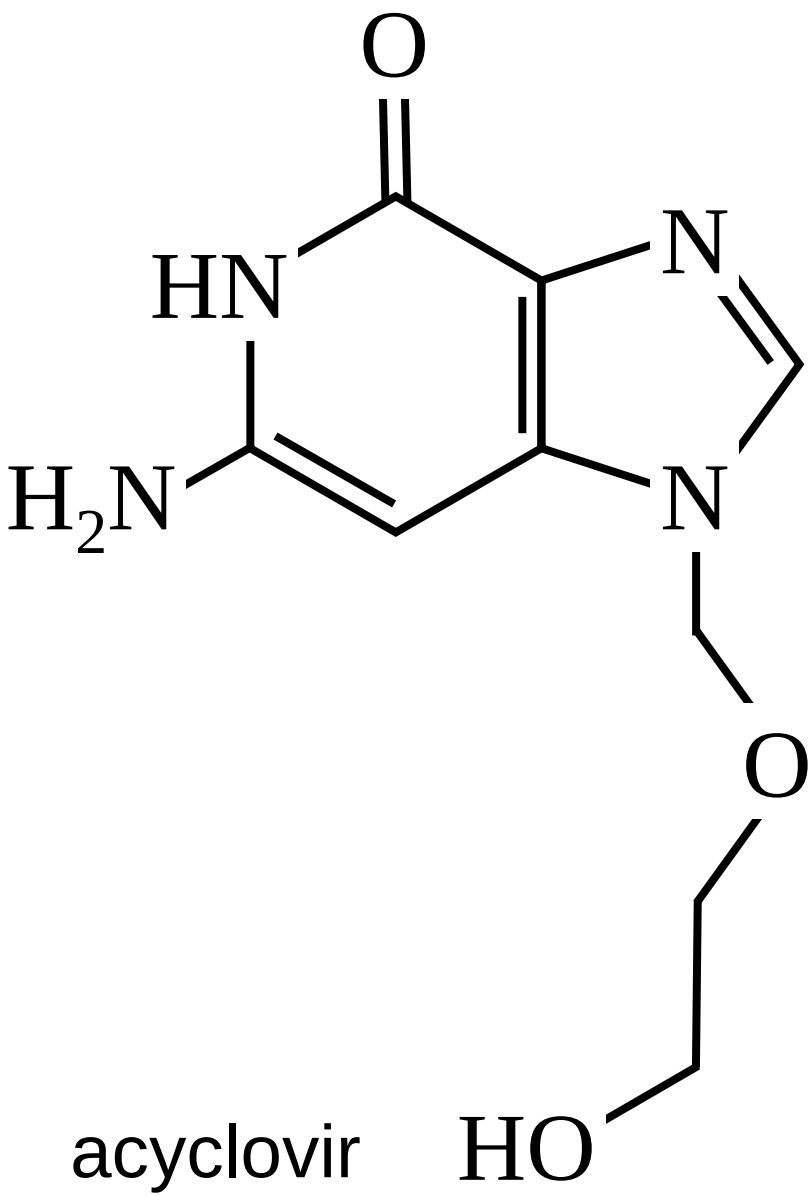
guanosine



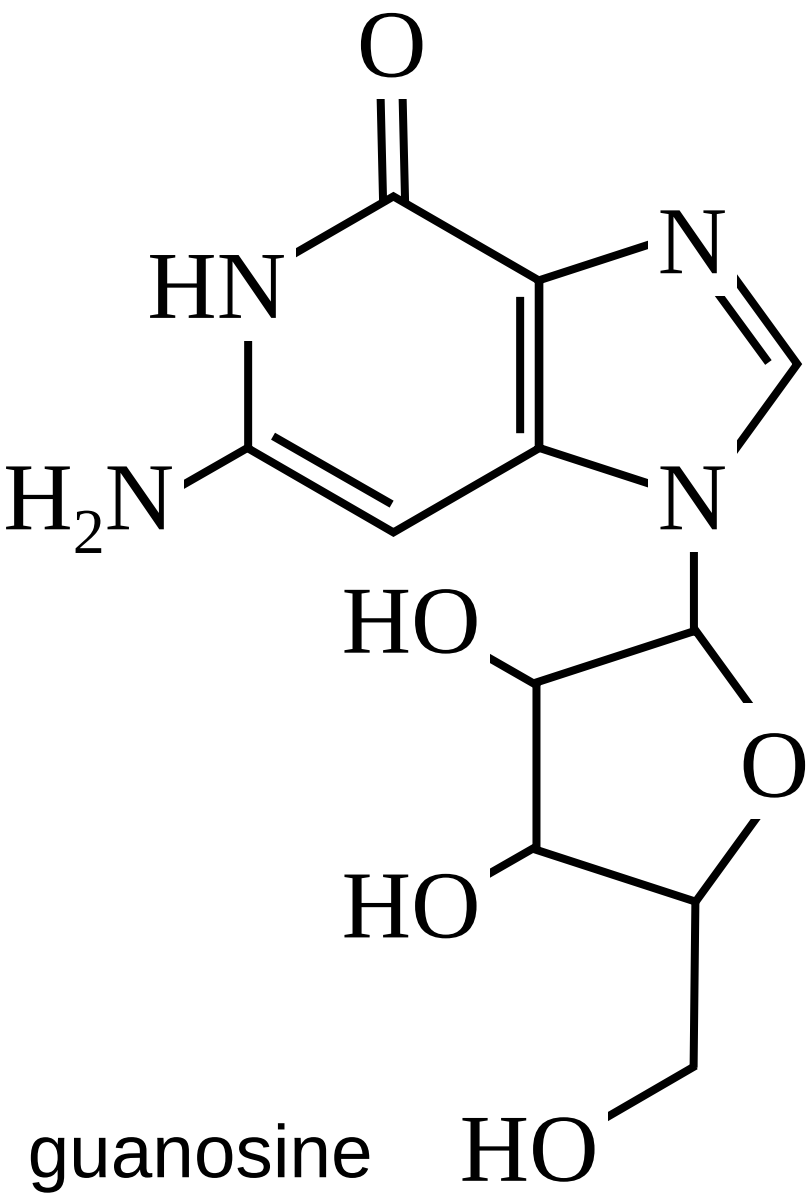
acyclovir



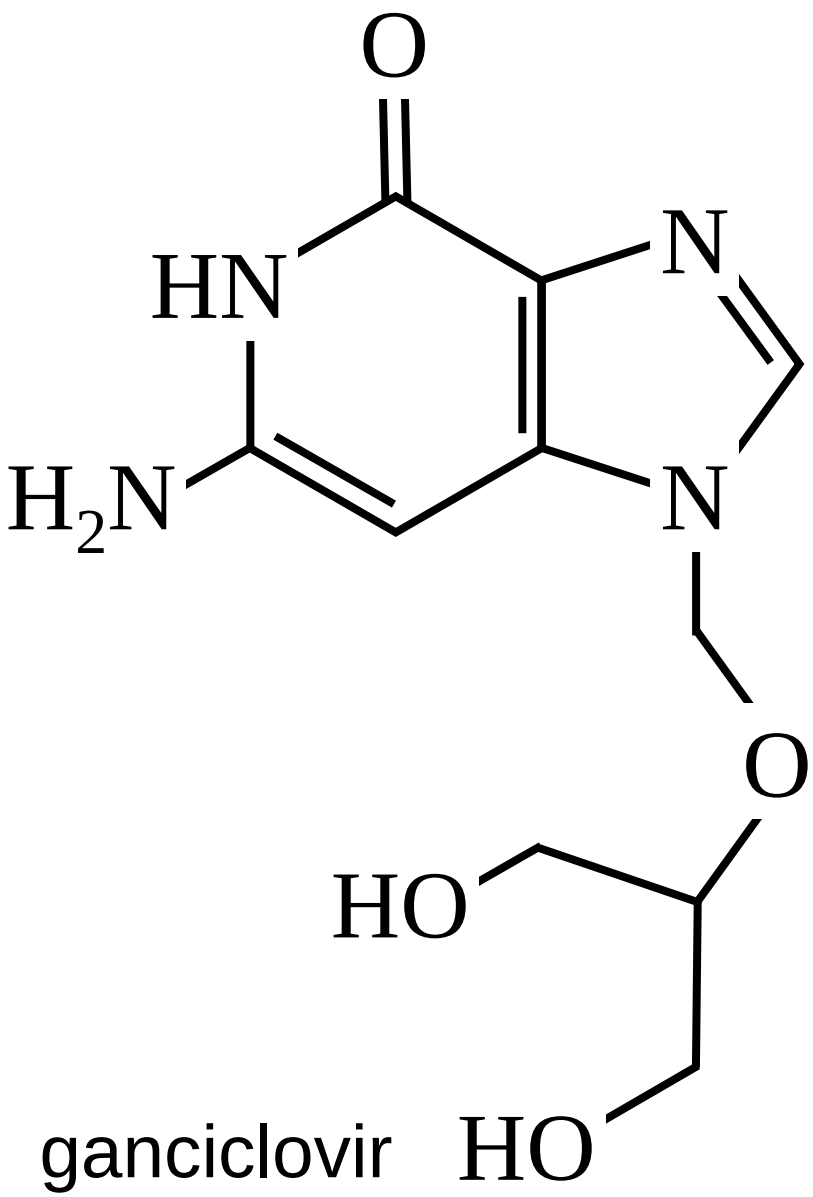
valacyclovir



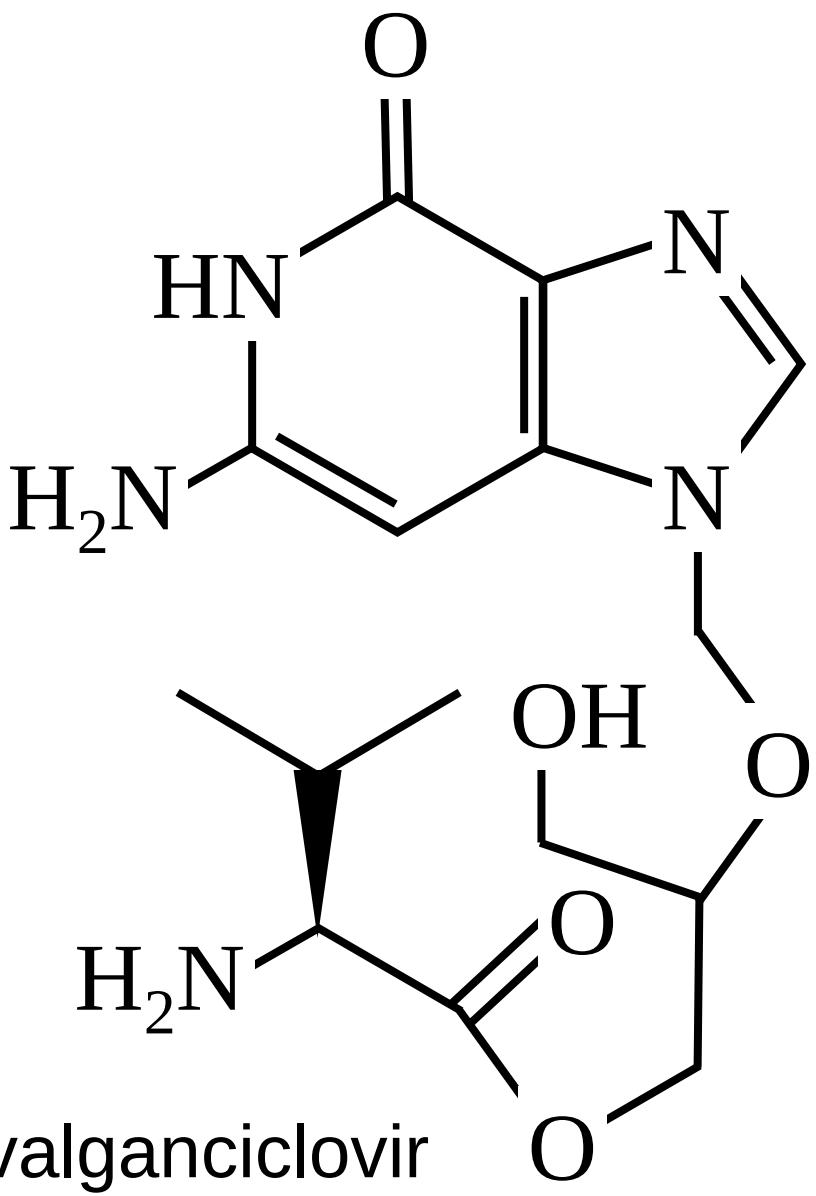
acyclovir



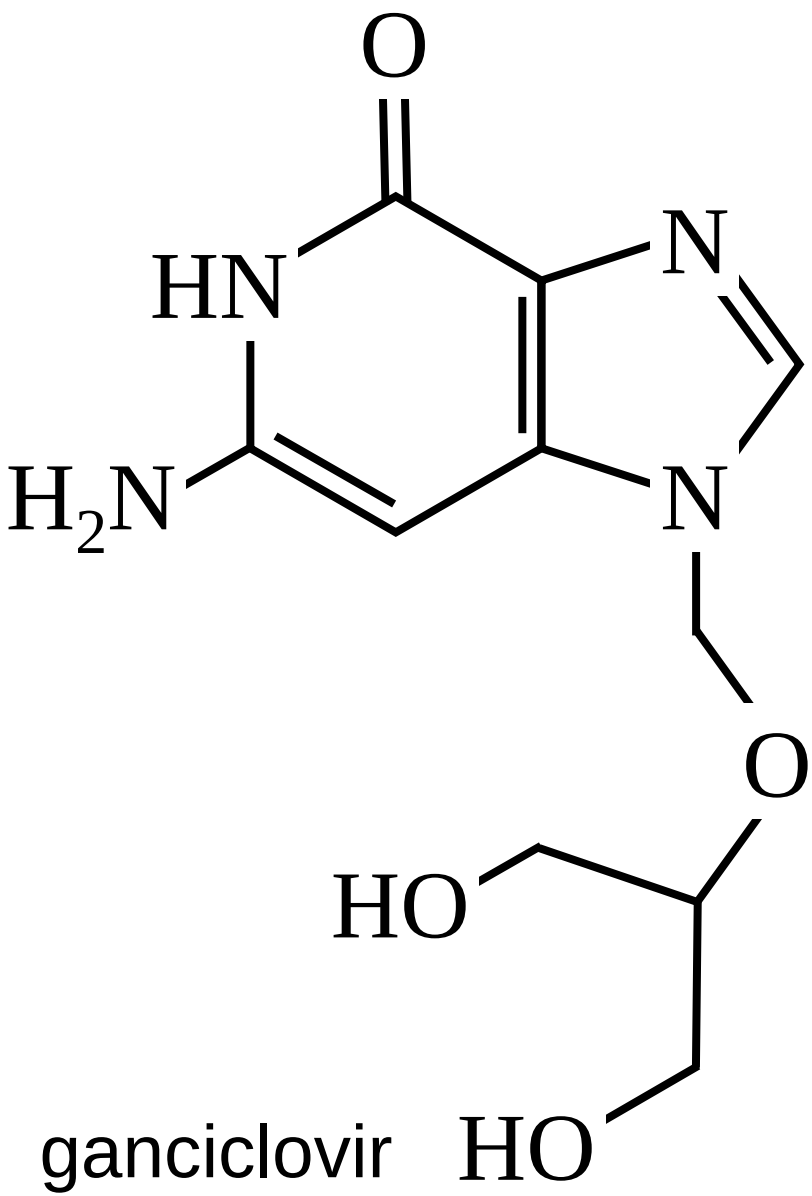
guanosine



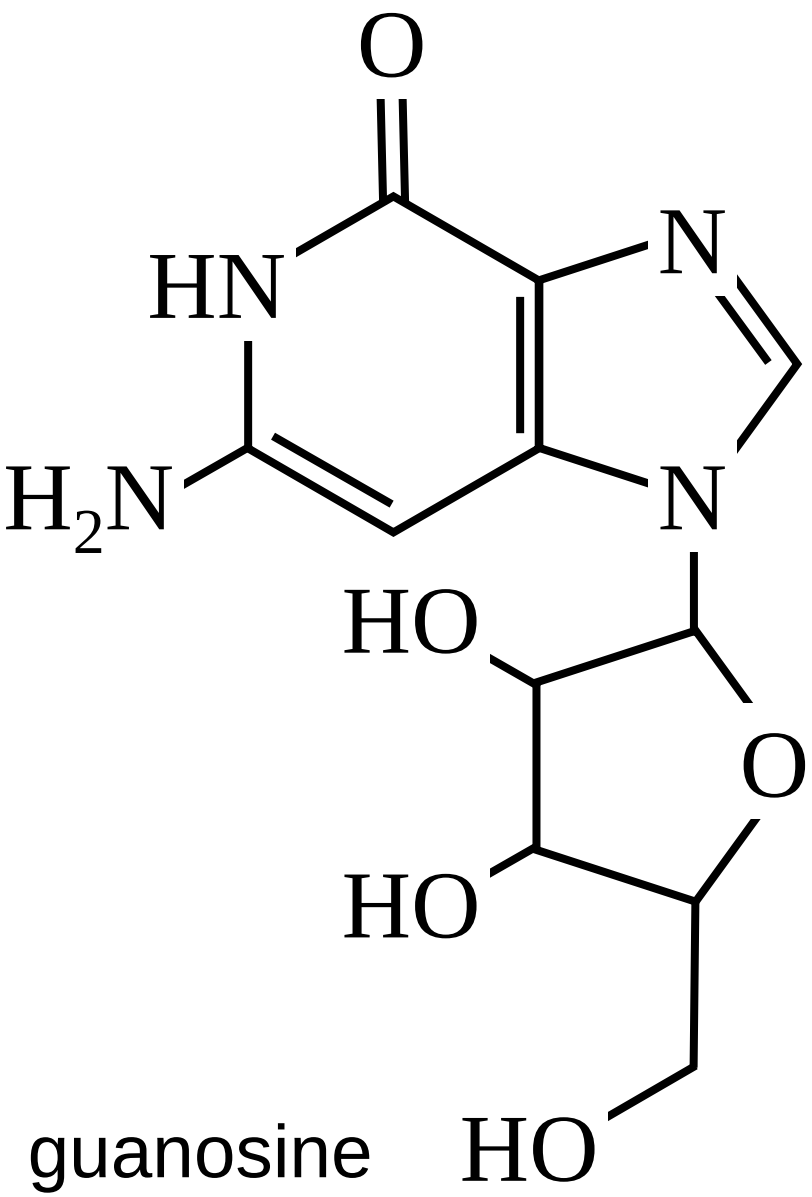
ganciclovir



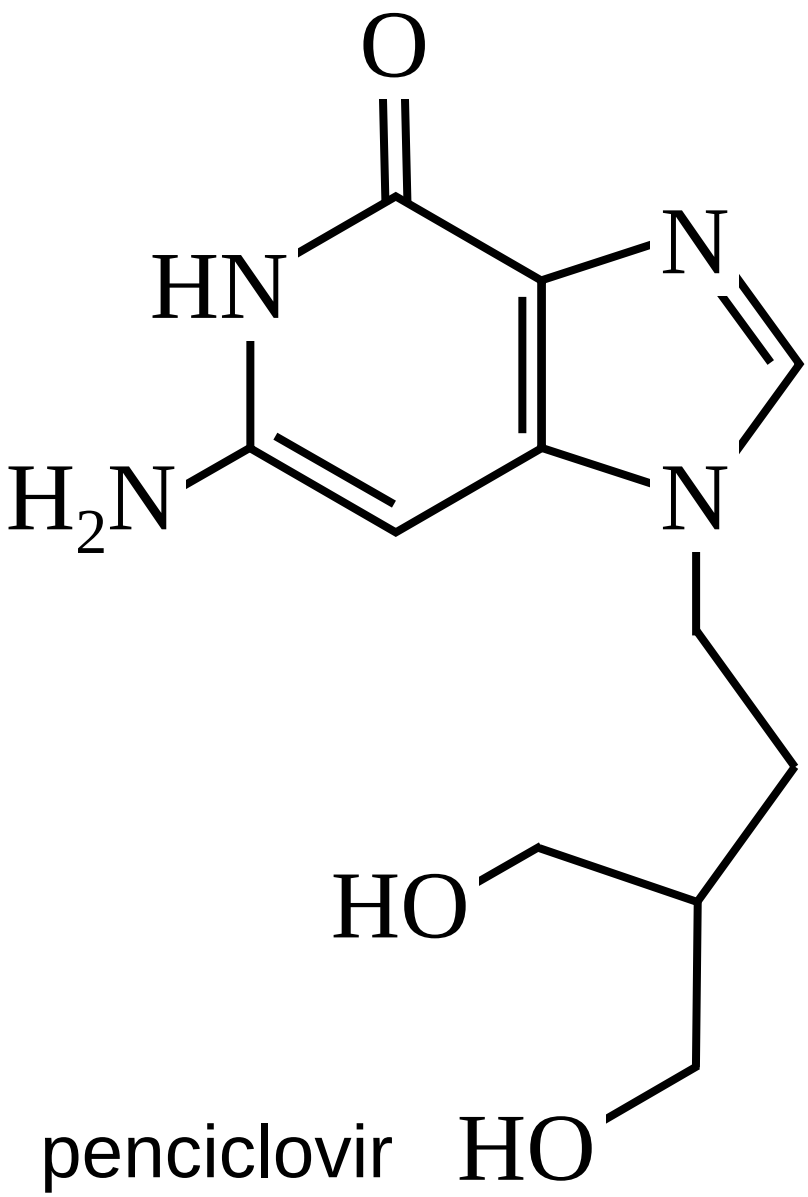
valganciclovir



ganciclovir

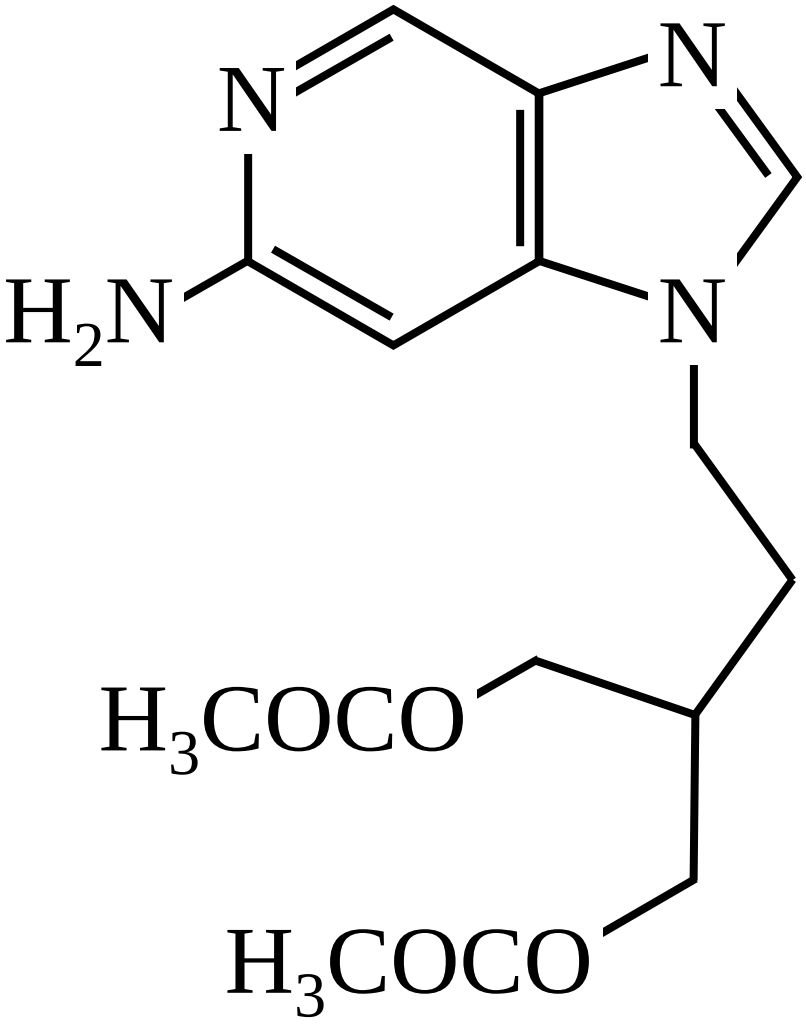


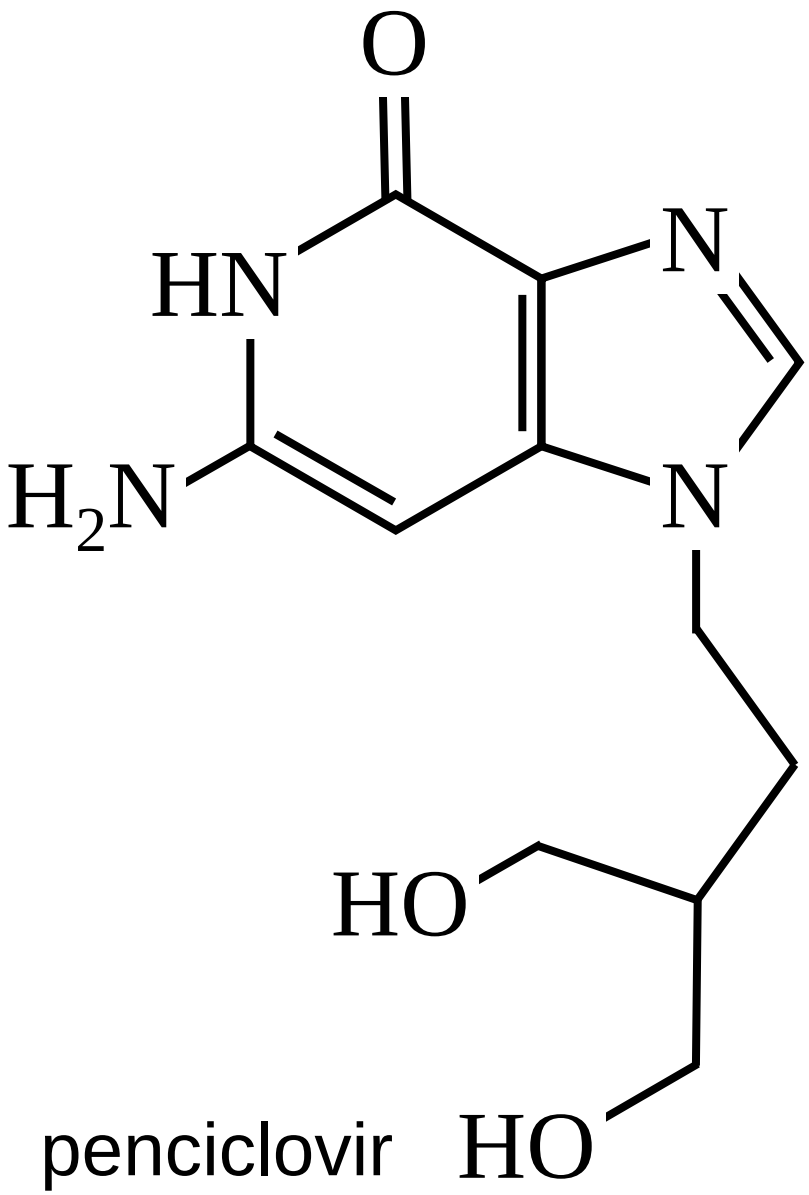
guanosine



penciclovir

famciclovir





penciclovir

HHV: therapy

- guanosine analogs
  - acyclovir and valacyclovir
  - ganciclovir and valganciclovir
  - penciclovir and famciclovir

- activated by viral thymidine kinase
  - variable activation by cellular enzymes

HHV: therapy: acyclovir

- studied in all age groups
- very effective given IV
- poor GI absorption (10-20%)
- saturable absorption
  (↓ bioavailability with ↑ dose)
- oral liquid formulation almost pure sugar
  - well tolerated
  - dental caries

HHV: therapy: valacyclovir

- prodrug (valine ester of acyclovir)
  - rapidly converted to acyclovir in bloodstream
- approved by FDA 1995
- under study in children
- 3-5x greater bioavailability

- do not use for CNS disease

HHV: therapy: famciclovir

- prodrug (analog of penciclovir)
  - converted to penciclovir by aldehyde oxidase
- approved by FDA 1994
- being studied in children
- ~75% bioavailability
- longer half-life intracellularly

HHV: therapy: ganciclovir

- similar to acyclovir but with activity against CMV
- much greater bone marrow toxicity
- valganciclovir $$$$$
- utility in resistant HSV, CMV
- utility in congenital CMV unclear

HHV: drug activity

Drug	HSV-1/2	VZV	EBV	CMV	HHV-6	HHV-7 KSHV
acyclovir / valacyclovir	+	+	–	+	+/–	?
penciclovir / famciclovir	+	+	–	?	?	?
ganciclovir / valganciclovir	+	+	–	+	+/–	?
foscarnet	+	?	–	+	+	?
cidofovir	+	?	–	+	?	?