

Herpes Simplex Virus

HERPES SIMPLEX VIRUS

Pathogenesis • Morphology • Clinicopathologic correlations

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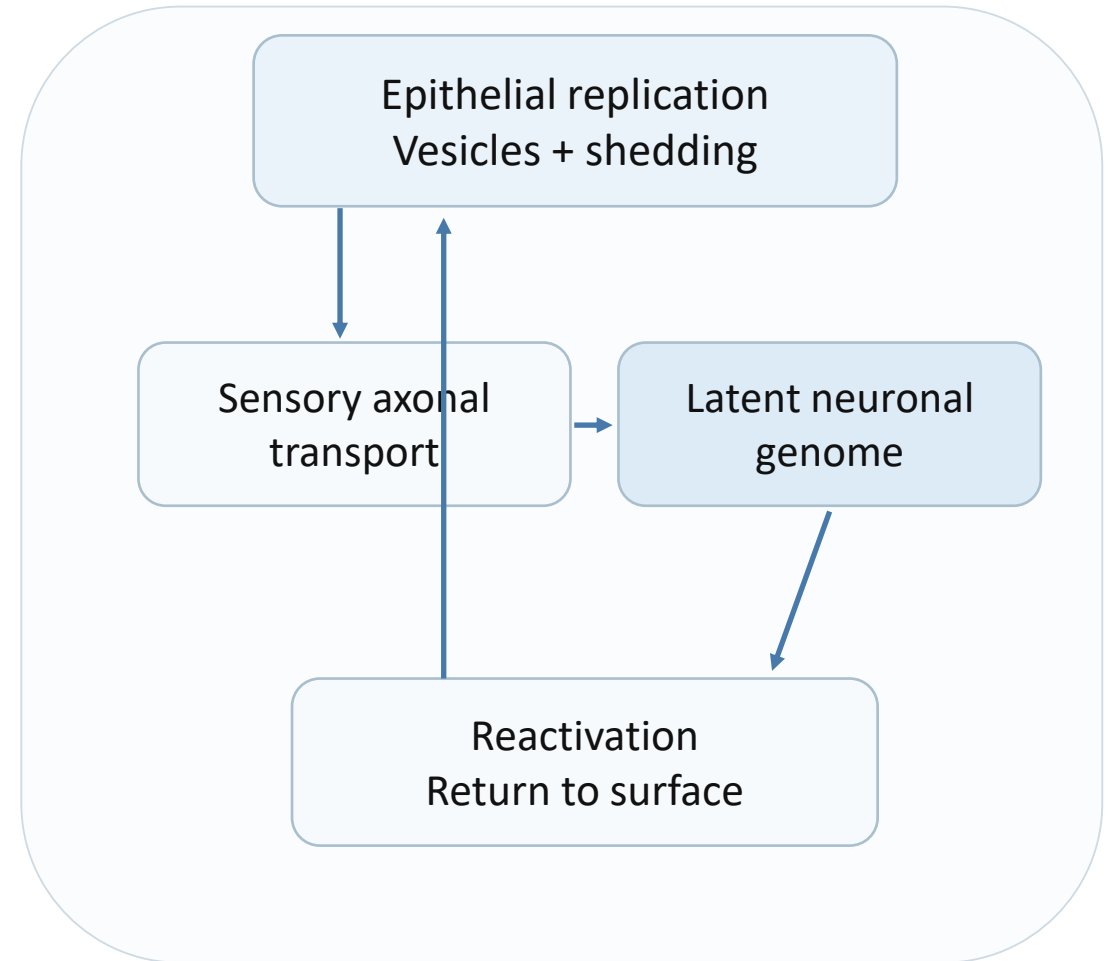
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Learning objectives

- Distinguish productive epithelial infection from neuronal latency
- Explain reactivation and HSV immune evasion
- Recognize the characteristic cytopathic morphology
- Relate the lesions to oral, genital, corneal, neurologic and disseminated disease

HSV: Acute disease and lifelong persistence

- HSV-1 and HSV-2 cause primary and recurrent infections
- Productive replication occurs in skin and mucosal epithelium
- The viral genome persists latently in sensory neurons
- Clinical recurrence can follow reactivation from latency



HSV belongs to the α -herpesvirus group

- The group includes HSV-1, HSV-2 and varicella-zoster virus
- α -Herpesviruses infect epithelium and establish neuronal latency
- Epithelial damage and neuronal persistence are biologically distinct phases

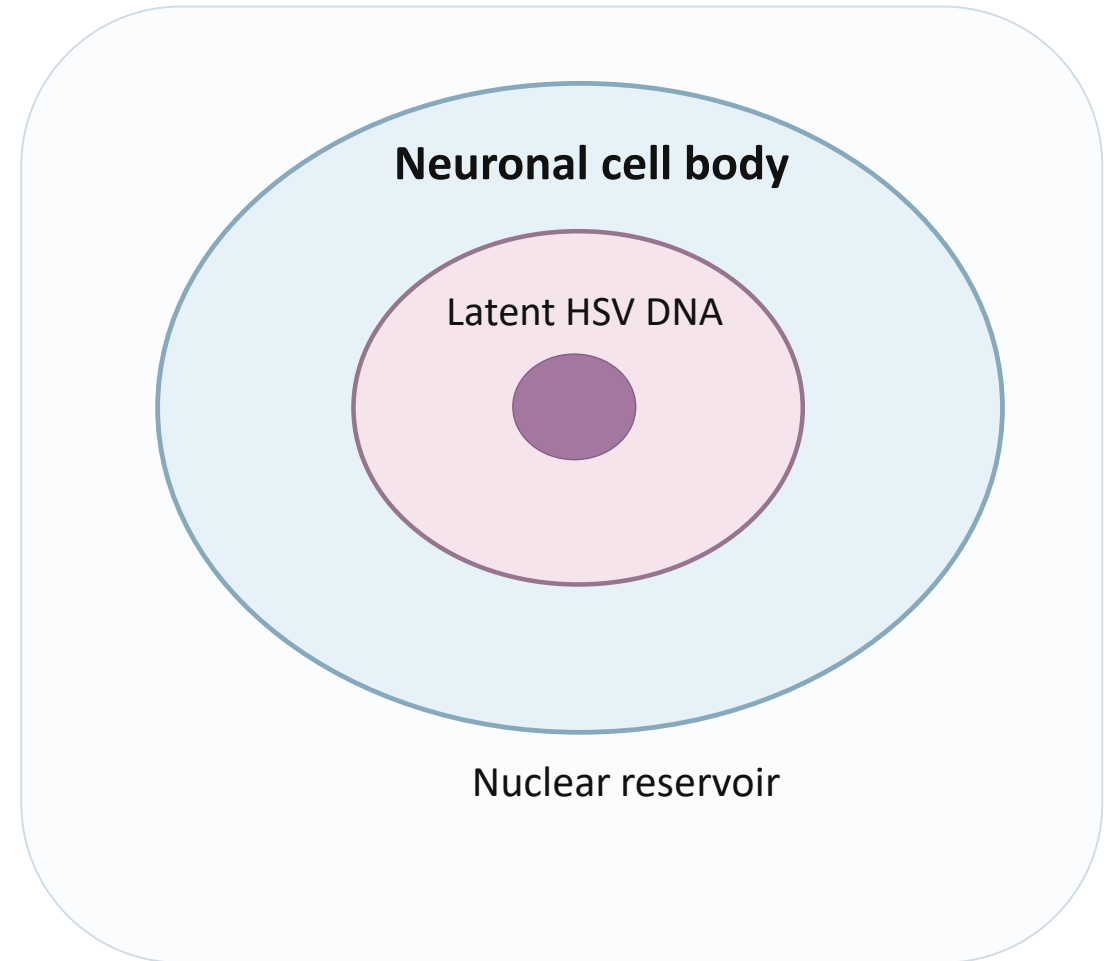
HSV-1

HSV-2

VZV

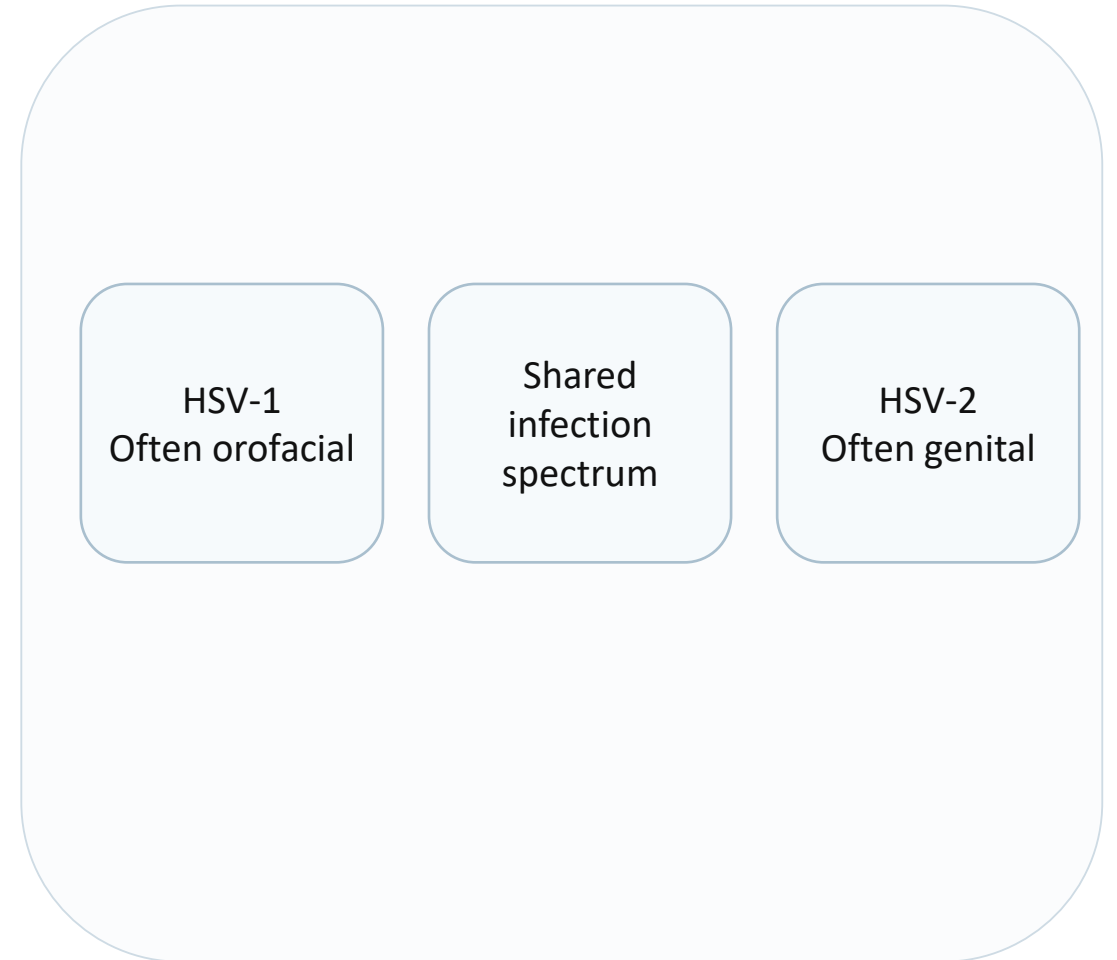
Herpesviruses: A latency-defining family

- Large, enveloped double-stranded DNA viruses
- Latency means genomic persistence without infectious virus production
- Reactivation causes productive infection and infectious shedding



HSV-1 and HSV-2: Closely related viruses

- The two viruses are genetically closely related
- Both cause overlapping primary and recurrent syndromes
- Virus type does not define an exclusive anatomic site



Type-specific distinction: Glycoprotein G

- Antibodies to variant forms of viral glycoprotein G distinguish the types serologically
- Type-specific antibody response is distinct from identifying the site of active disease
- Either viral type may infect oral or genital mucosa

HSV-1
Glycoprotein G

Type-specific
Antibody

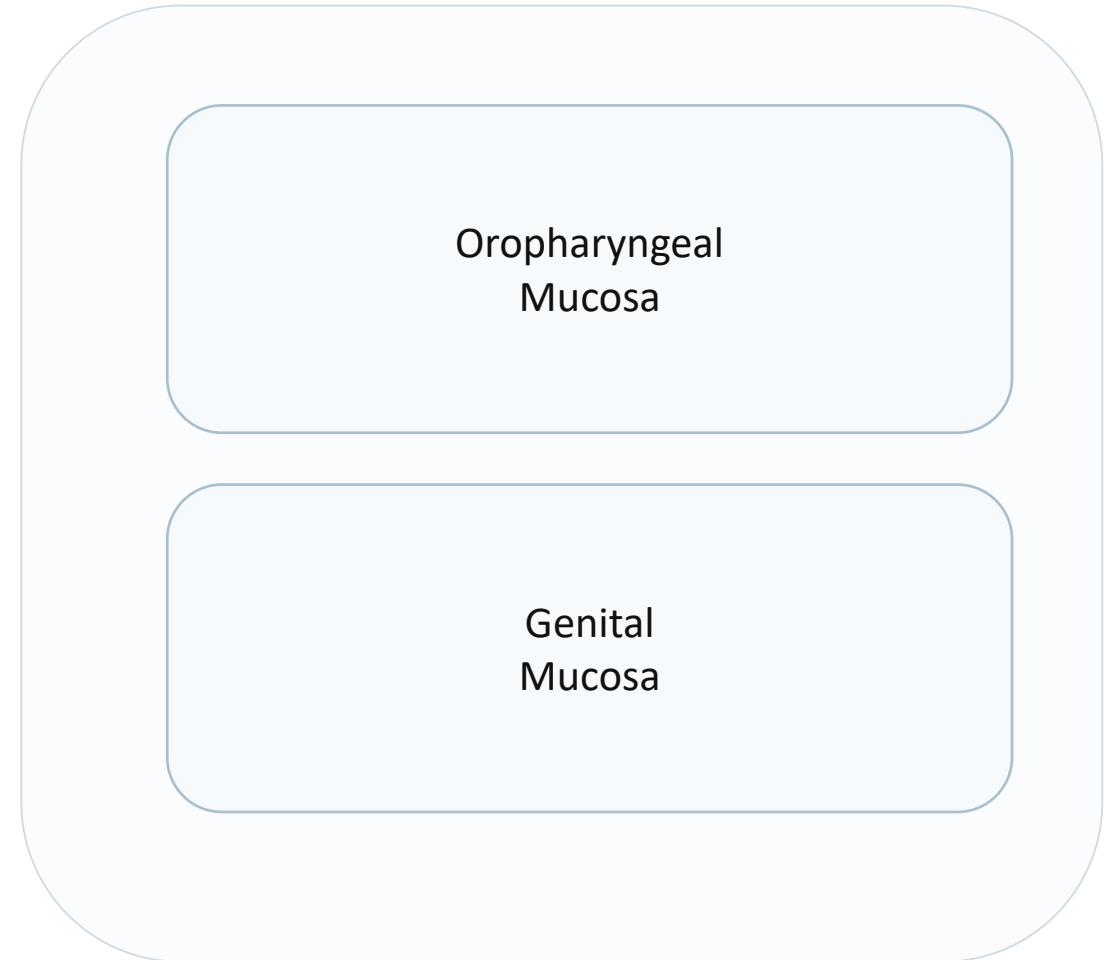
HSV-2
Glycoprotein G

Worldwide burden

- The 11th-edition chapter estimates approximately 4 billion HSV infections globally
- The figure conveys the enormous scale of persistent infection
- Do not interpret this textbook estimate as a real-time 2026 surveillance count

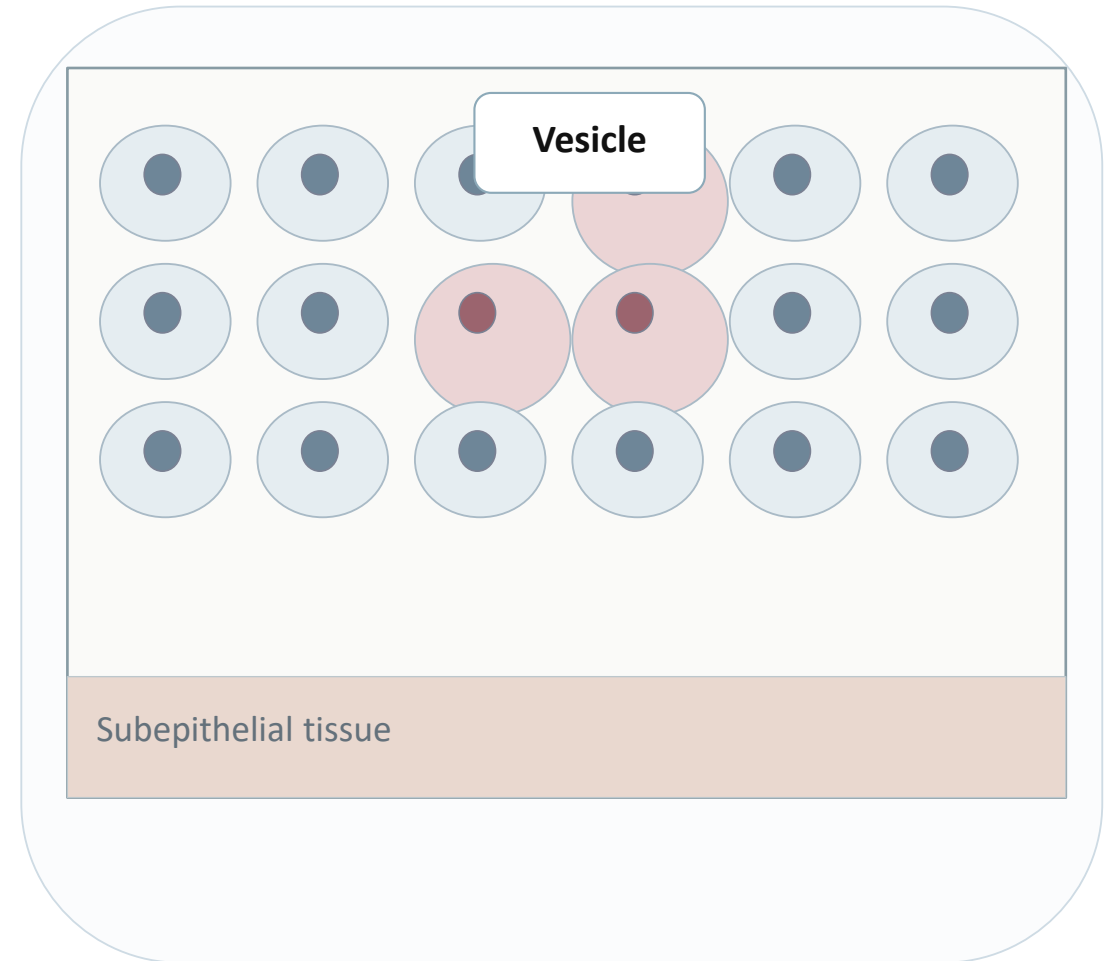
Sites of entry and early viral replication

- Typical entry sites are the oropharynx and genital tract
- Replication at entry produces infectious virions
- Vesicles arise from injured epithelial cells
- The local lesion also provides access to sensory nerve endings



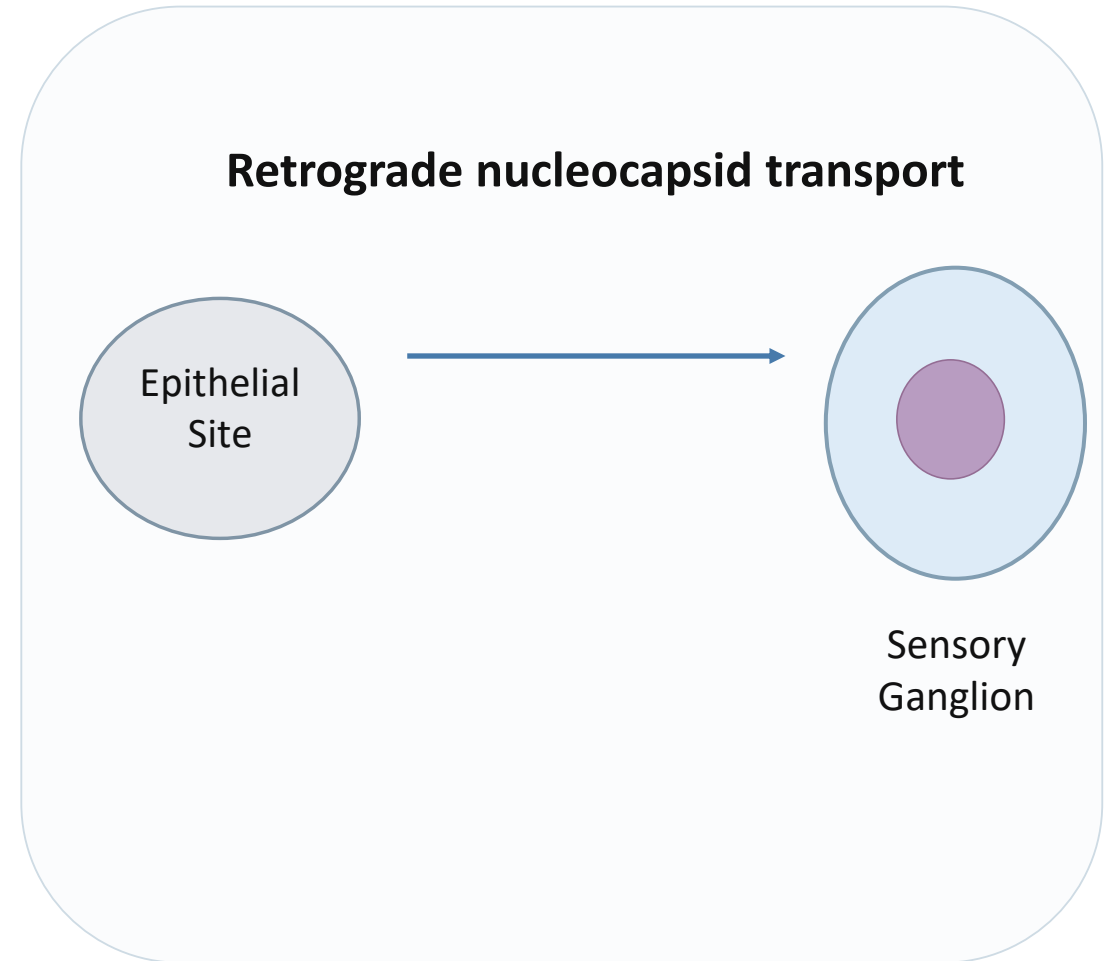
Productive epithelial infection

- The epithelial phase generates newly infectious virus
- Virus-induced cytolysis damages infected epithelial cells
- Tissue destruction accounts for vesicles and superficial ulcers



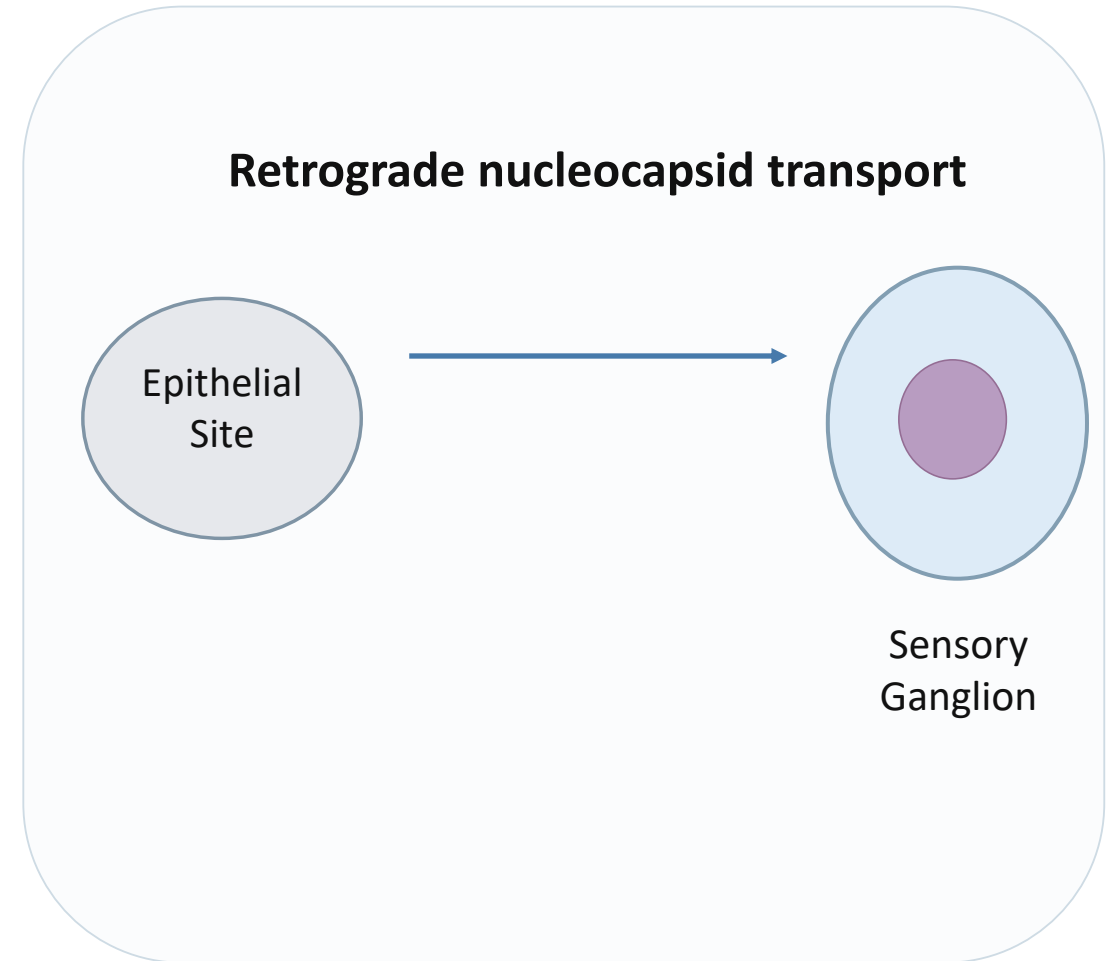
Neuronal entry: The transition to persistence

- HSV reaches sensory neurons innervating the infected surface
- Viral nucleocapsids travel along axons toward neuronal cell bodies
- Replication at the surface and latency in the neuron have different outcomes



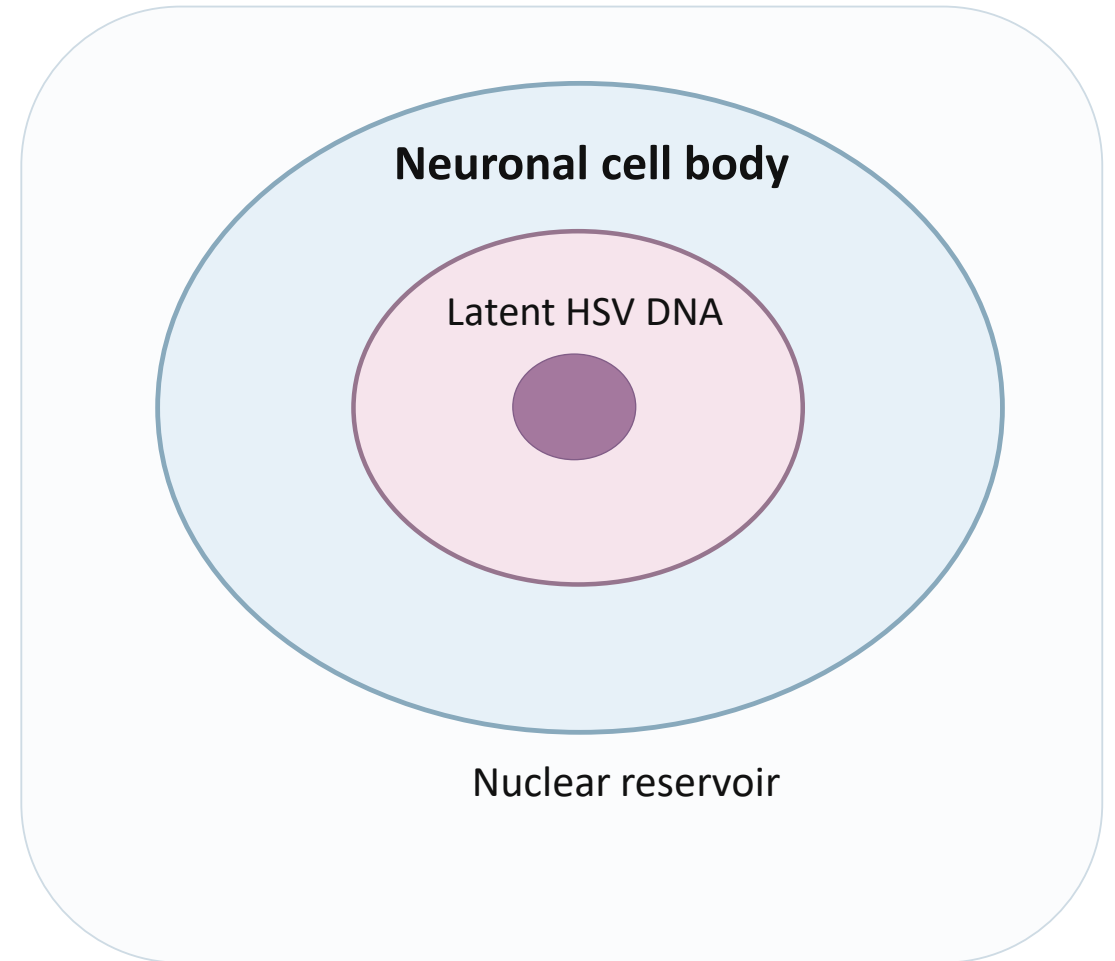
Retrograde transport toward sensory ganglia

- Transport is directed from peripheral axons to cell bodies
- Sensory neurons connect the primary epithelial site with the latent reservoir
- This neural route explains the relationship between initial and recurrent locations



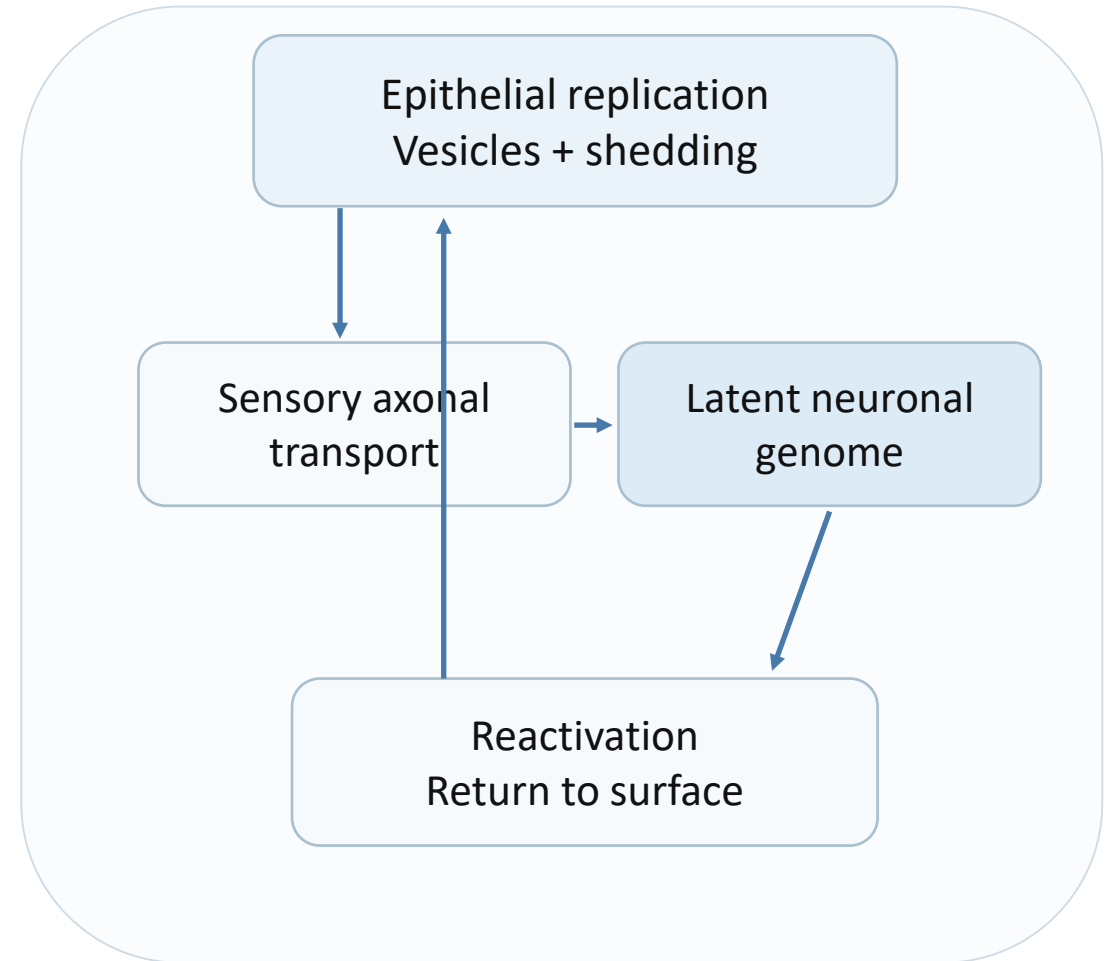
HSV latency: A precise definition

- Latent viral DNA persists inside the neuronal nucleus
- Latency is not the same as continuing production of virions
- Viral persistence remains possible after epithelial lesions heal



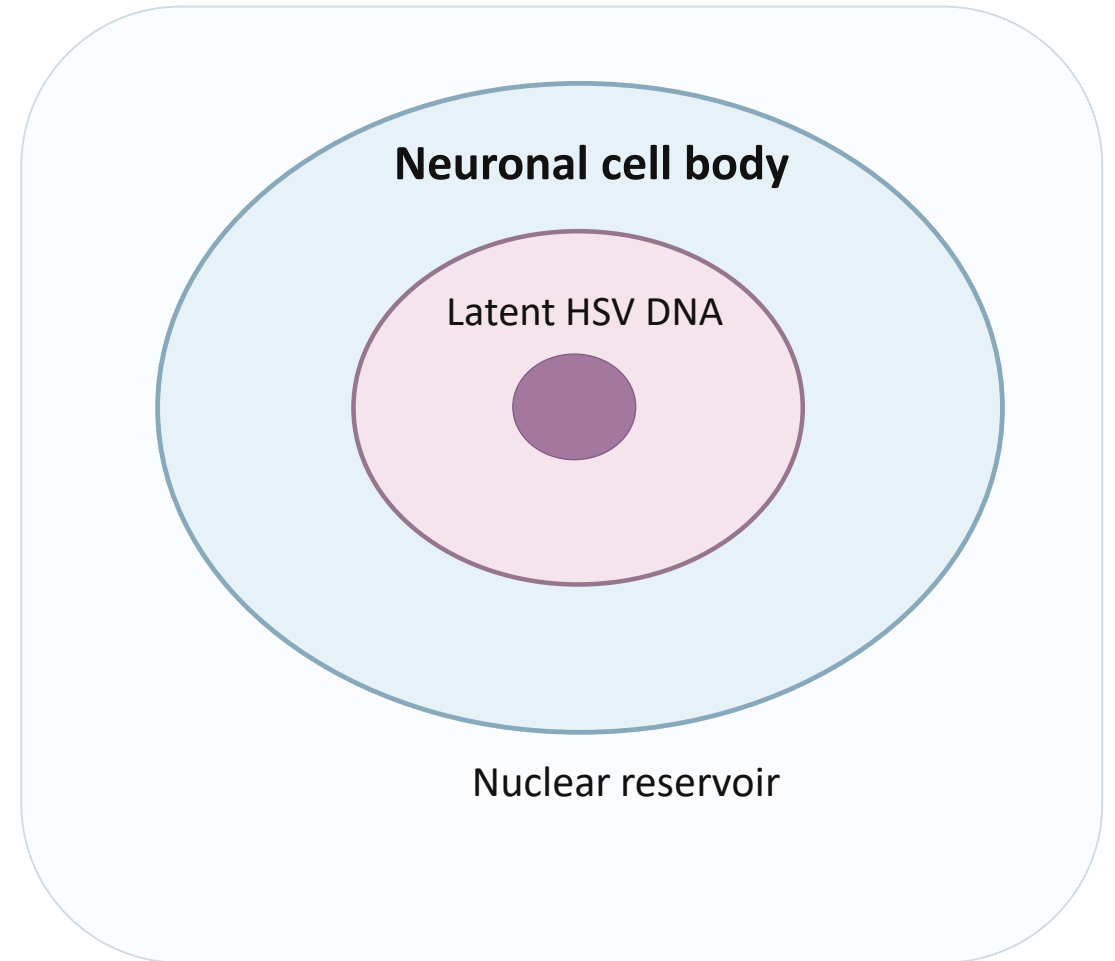
Why clinical healing is not eradication

- Primary infection typically resolves within weeks in immunocompetent hosts
- Resolution of visible vesicles does not remove latent neuronal DNA
- Consequently, prior infection can be followed by further reactivation



Latency-associated transcripts (LATs)

- During neuronal latency, latency-associated RNAs are transcribed
- The text describes no apparent viral protein production during latency
- LATs are associated with maintenance of the nonproductive state



LATs: A proposed anti-apoptotic role

- LATs may protect infected neurons from apoptosis
- Survival of the host neuron helps preserve the latent genome
- This is a proposed contribution to latency, not a demonstrated sole mechanism

Proposed anti-apoptotic
Role

Proposed chromatin-mediated
Lytic silencing

Proposed miRNA-mediated
Lytic gene repression

LATs: Transcriptional silencing

- LATs may promote heterochromatin-associated repression of lytic genes
- Silencing of lytic gene expression favors the latent state
- This mechanism with appropriate uncertainty

Proposed anti-apoptotic
Role

Proposed chromatin-mediated
Lytic silencing

Proposed miRNA-mediated
Lytic gene repression

LAT-derived microRNAs

- LAT transcripts may serve as precursors for microRNAs
- These microRNAs can downregulate critical HSV lytic genes
- Reduced lytic gene expression can reinforce viral latency

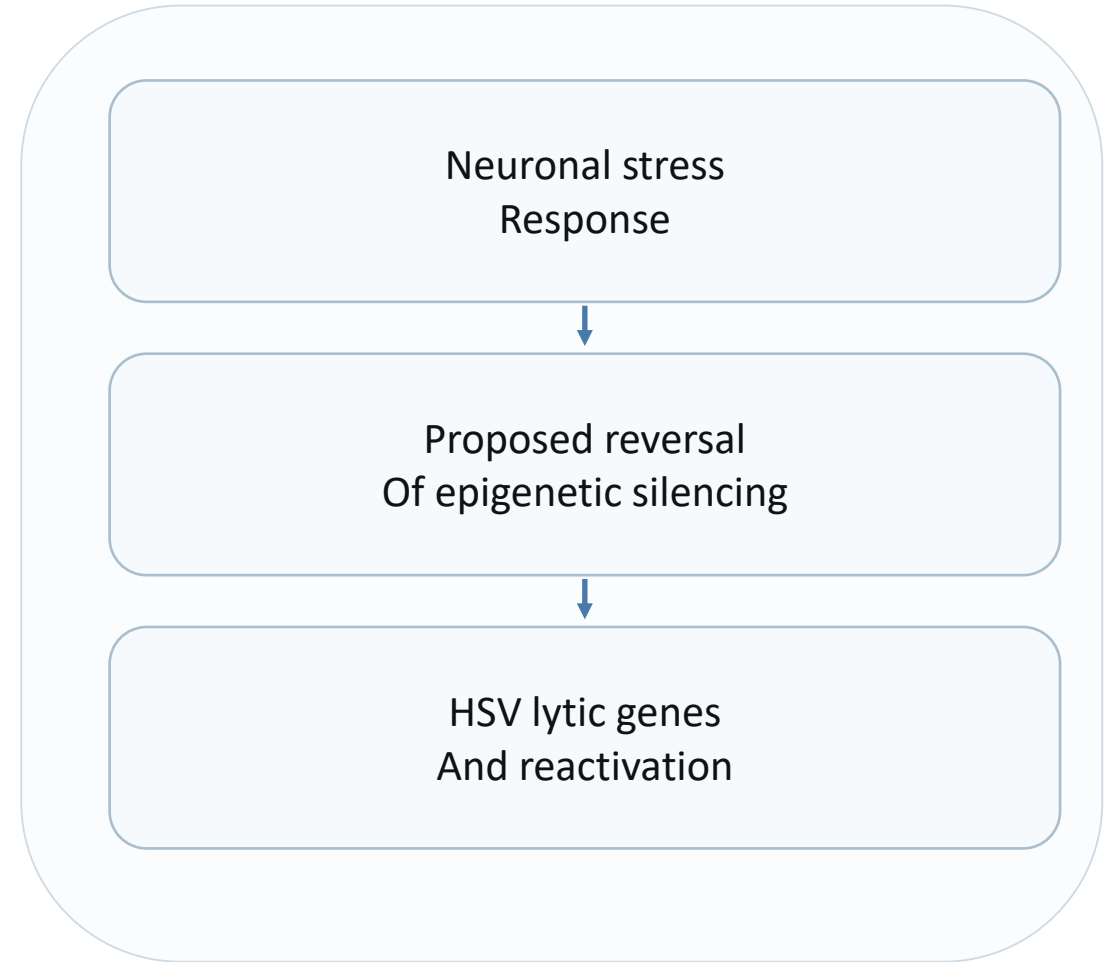
Proposed anti-apoptotic
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Proposed chromatin-mediated
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Lytic gene repression

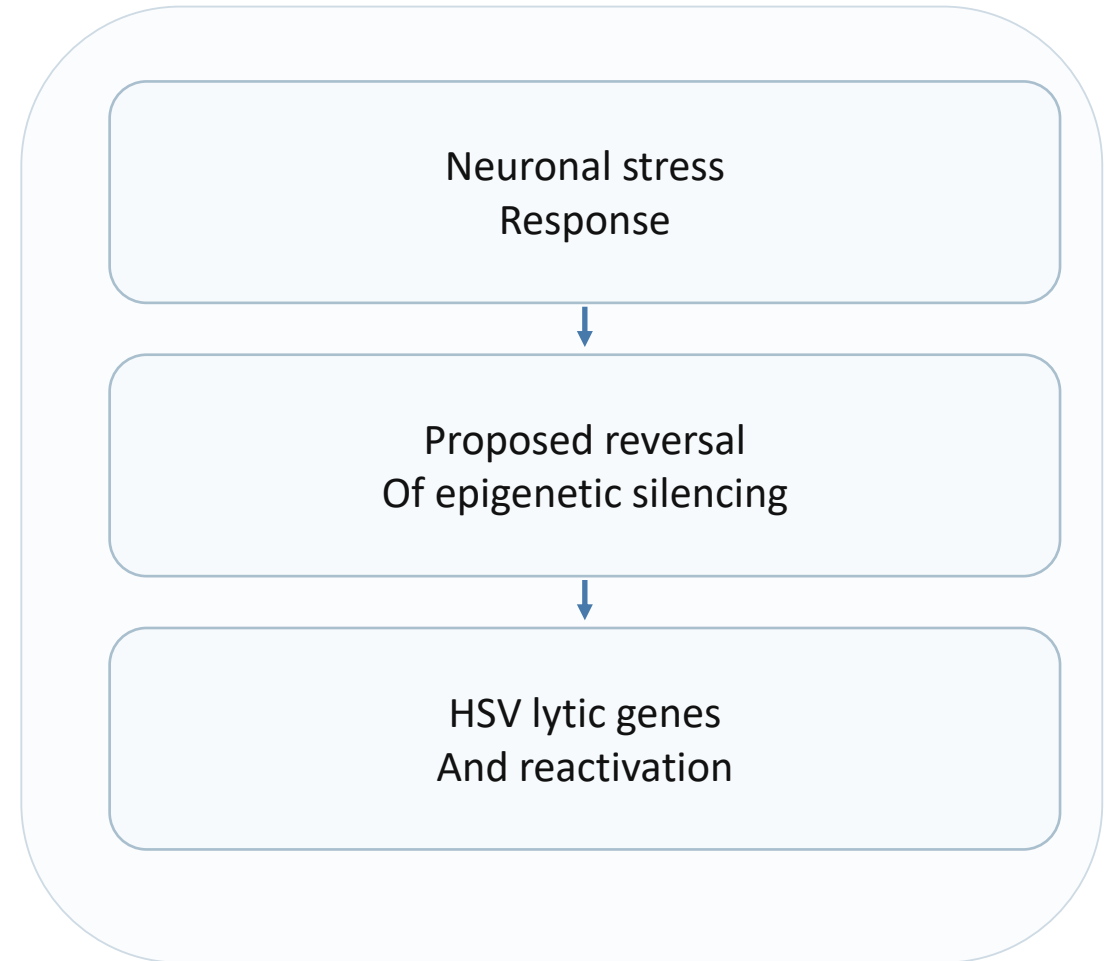
From latent genome to reactivation

- Reactivation may occur repeatedly during the infected person's life
- Neuronal stress-response pathways have been implicated
- The chapter proposes release from epigenetic silencing during reactivation



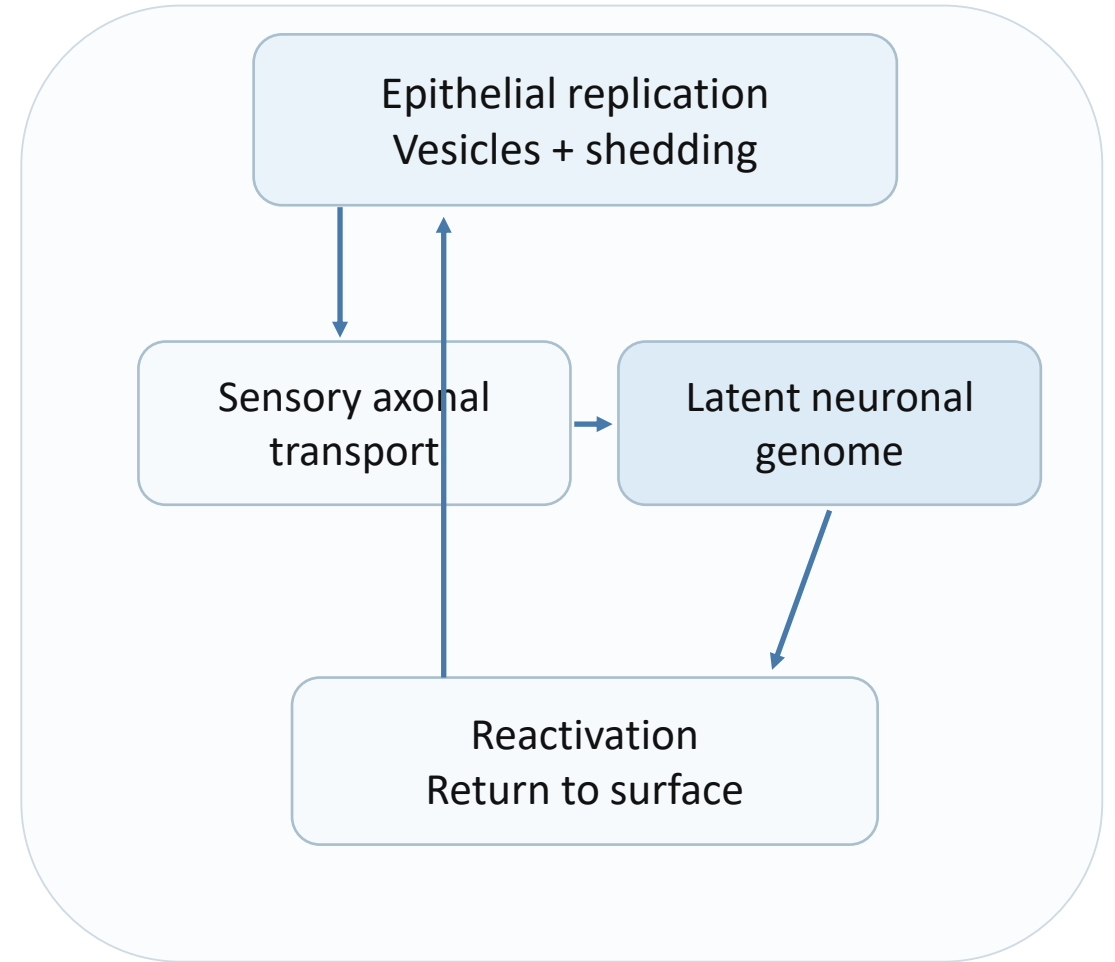
Epigenetic model of reactivation

- A proposed methylation/phosphorylation process releases lytic genes from repression
- The process is linked to cellular stress responses in neurons
- Exact mechanistic links should be understood as proposed, not settled



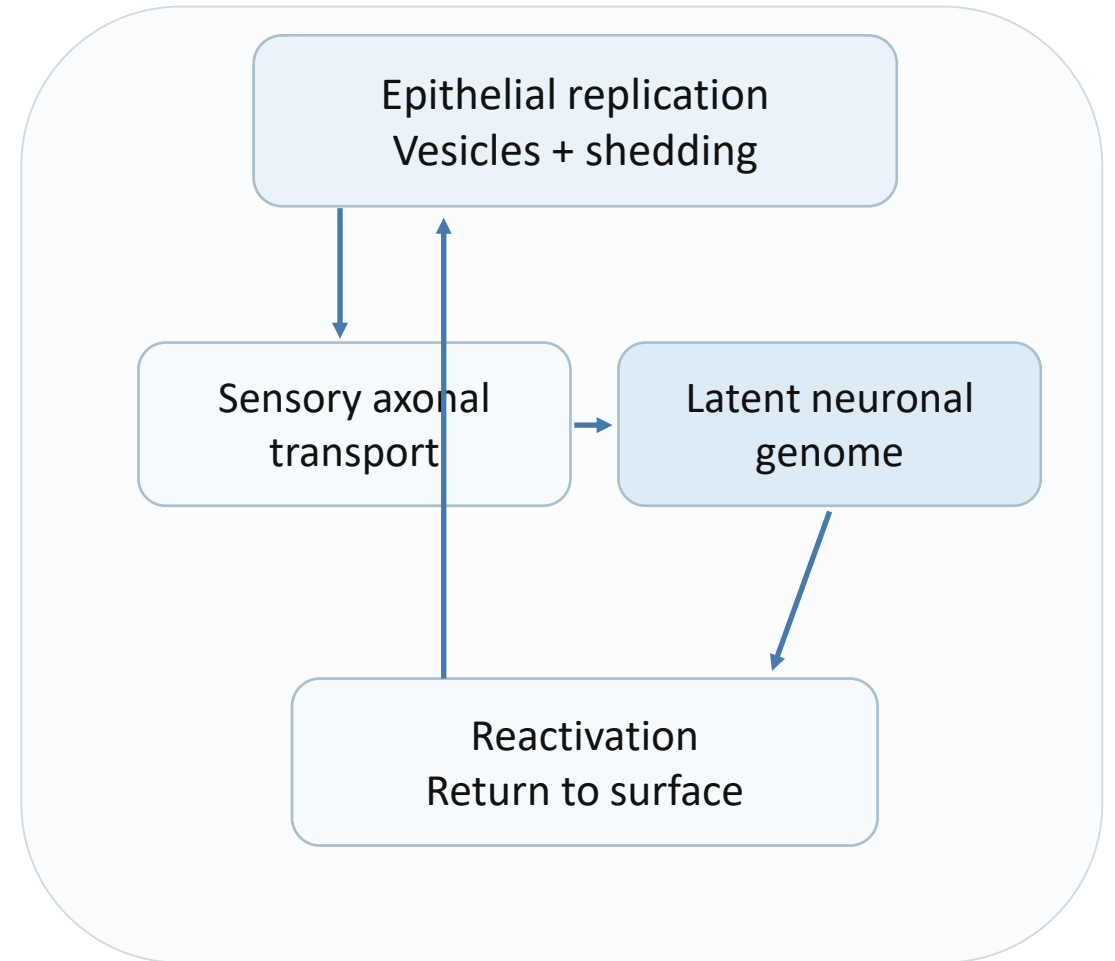
Recurrence need not be clinically obvious

- Reactivation may produce typical recurrent lesions
- Reactivation also occurs without symptoms
- Asymptomatic episodes matter because active shedding can transmit infection



Return of virus from neuron to epithelium

- Reactivated infection leads to spread from neurons toward skin or mucosa
- Infectious viral release again occurs at a peripheral epithelial site
- The surface–neuron–surface cycle produces recurring disease



Immunity restrains HSV but does not clear latency

- Immune control usually limits primary epithelial disease
- HSV has mechanisms that impair both cellular and humoral responses
- These mechanisms help explain recurrence despite pre-existing host immunity

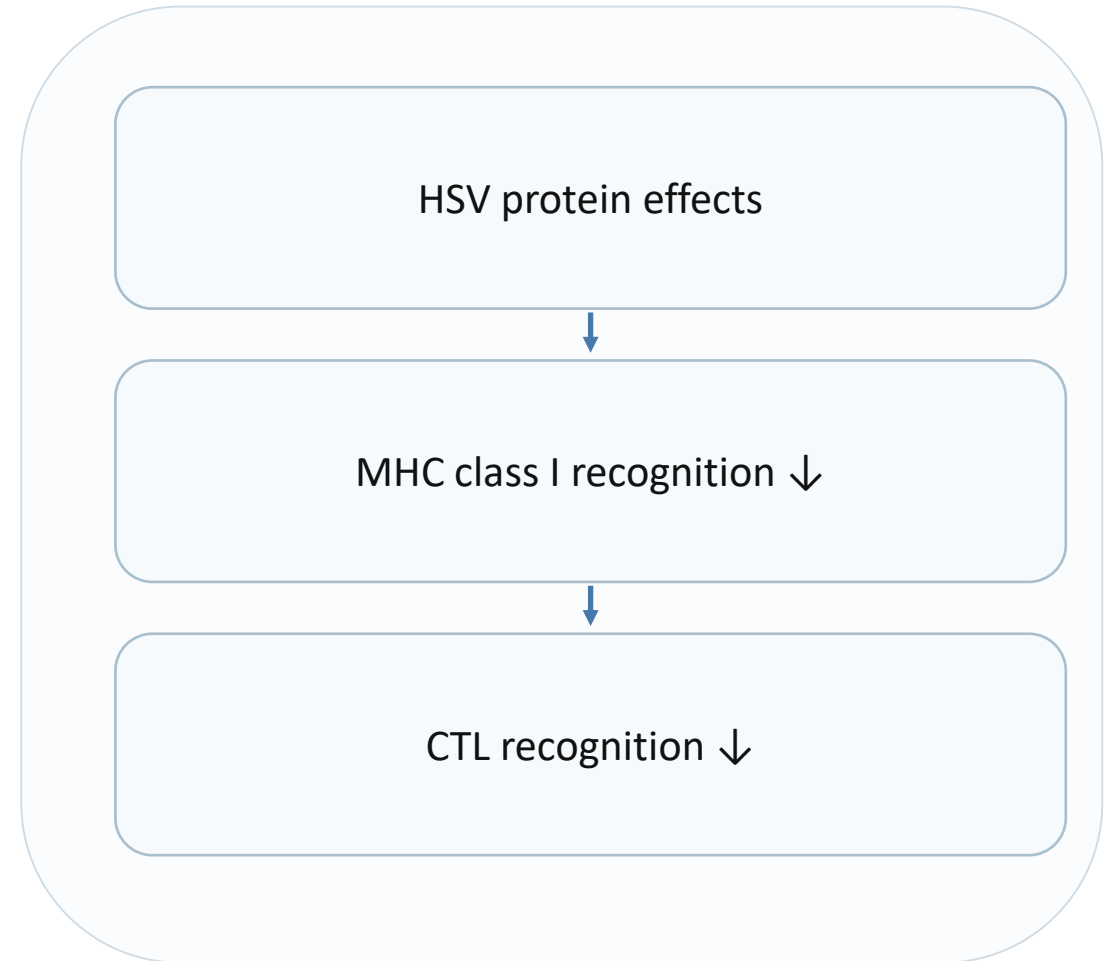
MHC I pathway

GE → IgG Fc

GC → C3

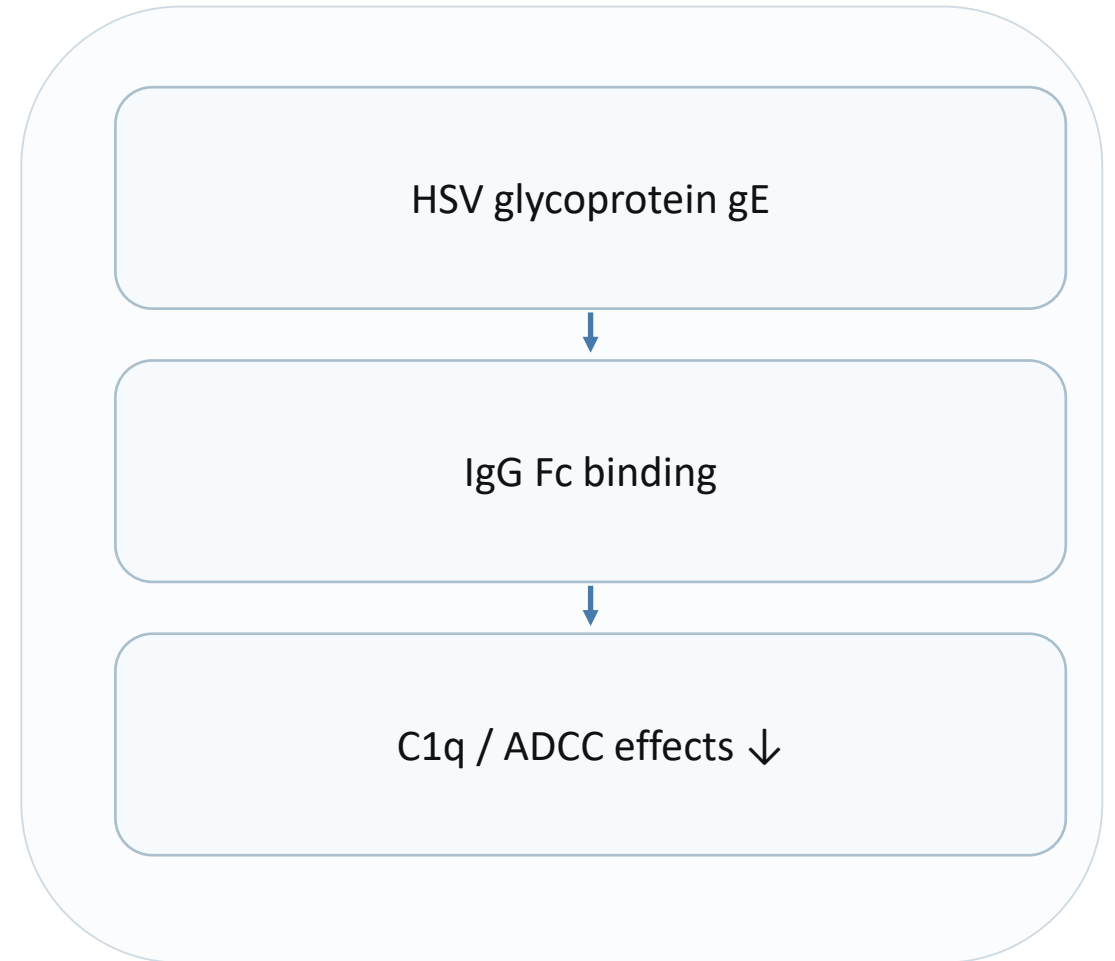
HSV interference with CD8 T-cell recognition

- HSV inhibits the MHC class I antigen-recognition pathway
- Reduced recognition impairs antiviral cytotoxic T lymphocytes
- The target is an important mechanism of cellular immune surveillance



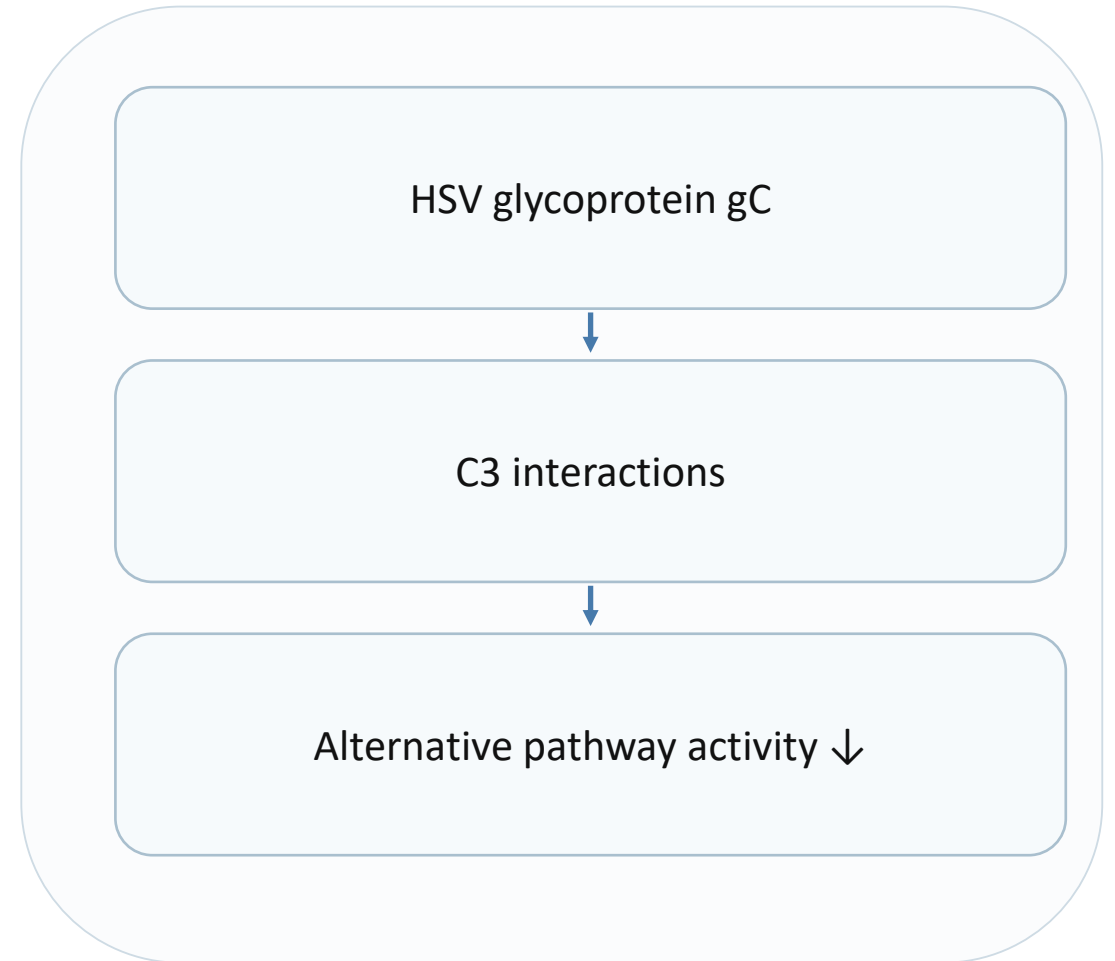
Glycoprotein gE binds the Fc region of IgG

- Viral gE binds the Fc domain of IgG
- The interaction interferes with C1q binding and antibody-dependent cellular cytotoxicity
- Antibodies can therefore be less effective at antiviral clearance



Glycoprotein gC counteracts complement

- HSV gC binds complement component C3 and its activation products
- It accelerates decay within the alternative complement pathway
- Complement interference is a separate route of immune evasion



HSV immune evasion is multi-layered

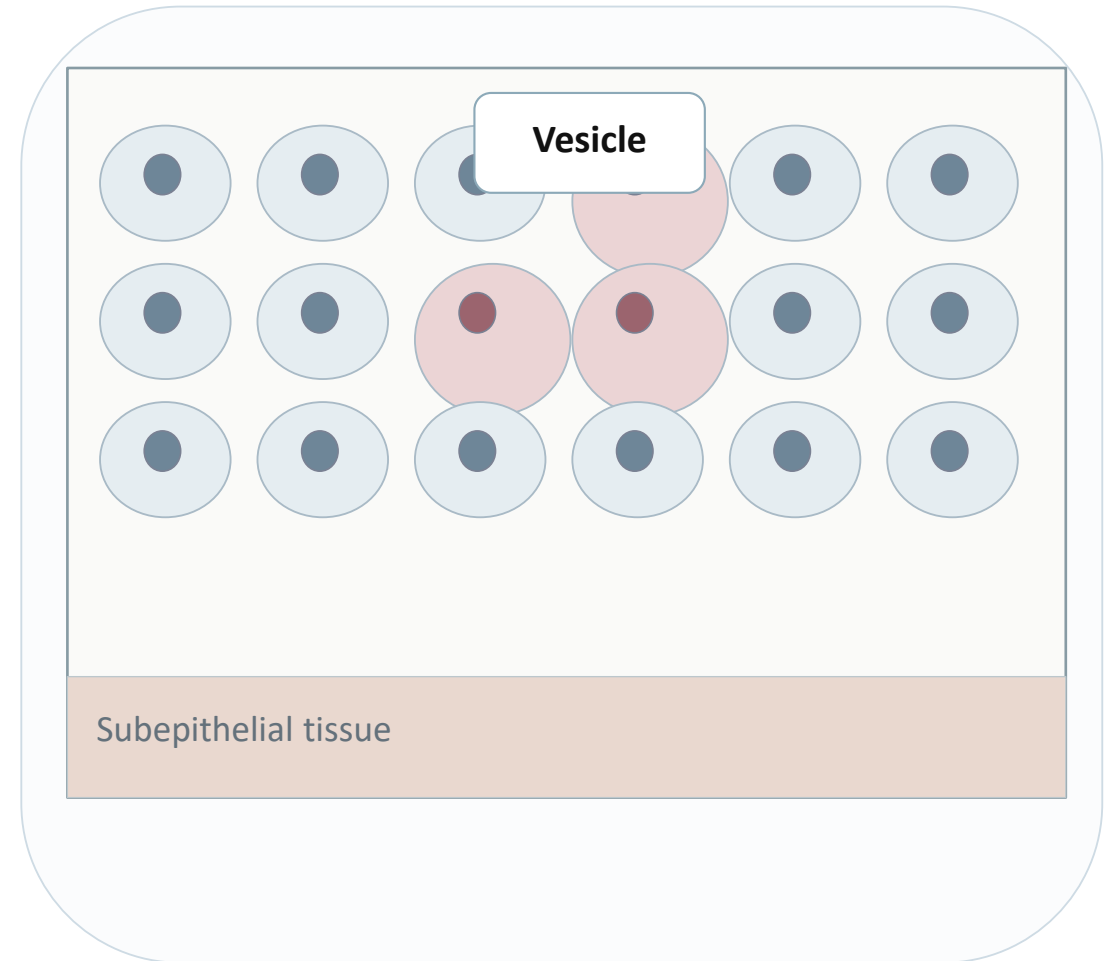
Evasion mechanism	Host defense disrupted
MHC class I inhibition	CTL antigen recognition
gE: IgG Fc binding	C1q binding; antibody-dependent cytotoxicity
gC: C3 interactions	Alternative complement pathway

Dendritic cells and antiviral defense

- HSV can infect multiple cellular lineages
- Dendritic cells are among the susceptible cell types
- Infection of antigen-presenting cells has relevance to antiviral immune responses

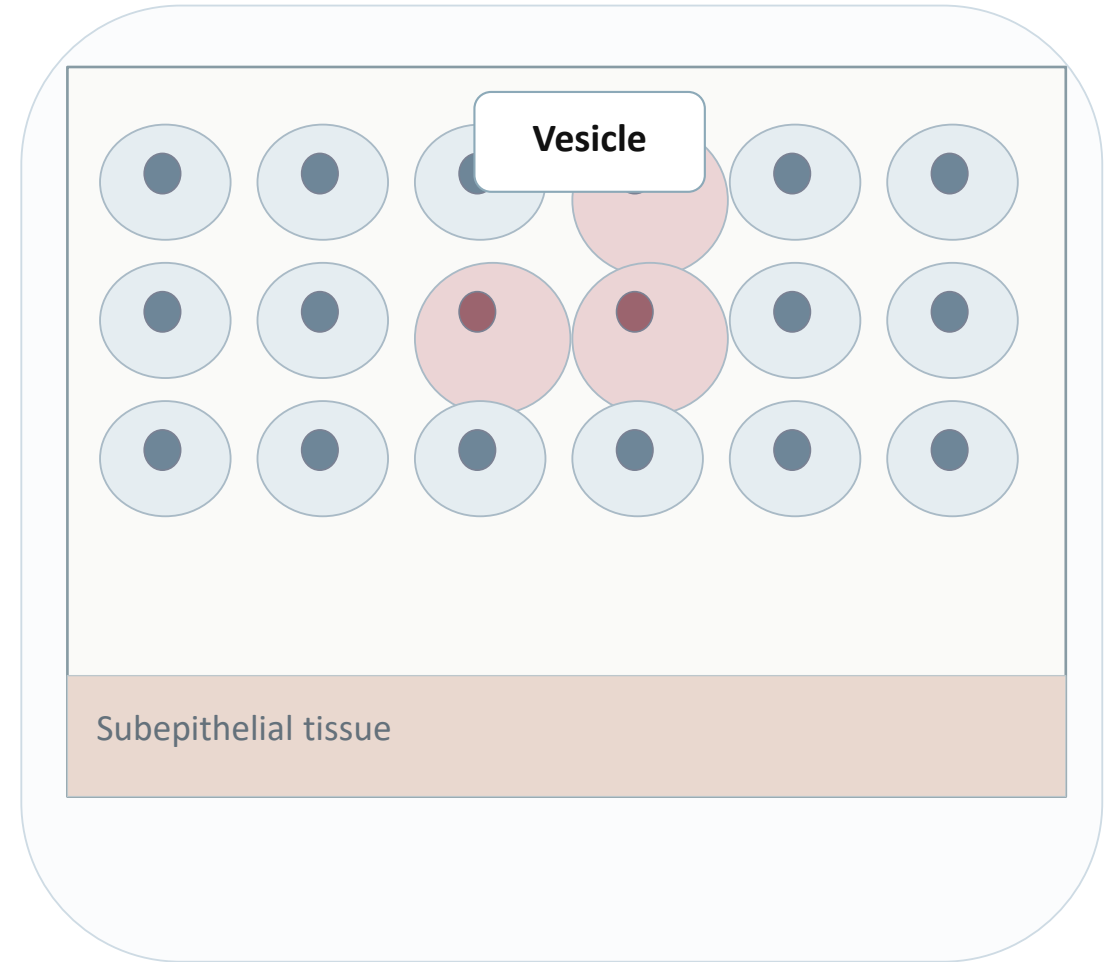
The principal HSV epithelial lesion

- Intraepithelial vesicles are the defining blister morphology
- Cell injury combines ballooning degeneration and intracellular edema
- Vesicular fluid contains virus during productive infection



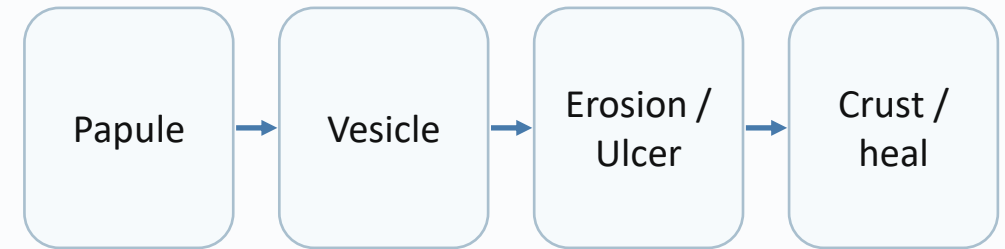
Ballooning degeneration of epithelial cells

- Infected epithelial cells enlarge as they accumulate intracellular fluid
- Swelling disrupts normal epithelial cohesion
- Grouped swollen cells contribute to intraepithelial blister formation



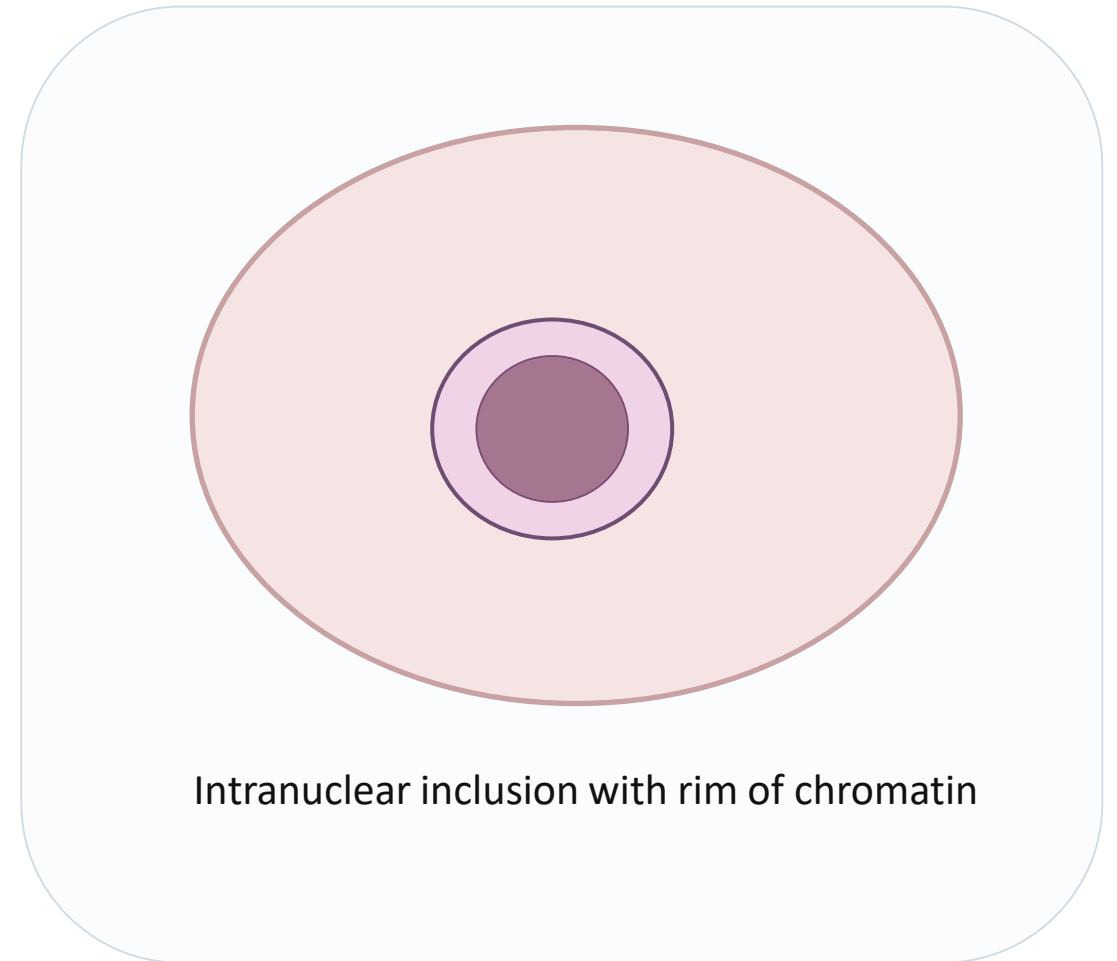
Intraepithelial blister to superficial ulcer

- HSV vesicles are fragile and frequently rupture
- The denuded surface may form a superficial erosion or ulcer
- Healing lesions often crust over in exposed skin



Cowdry type A: The nuclear inclusion

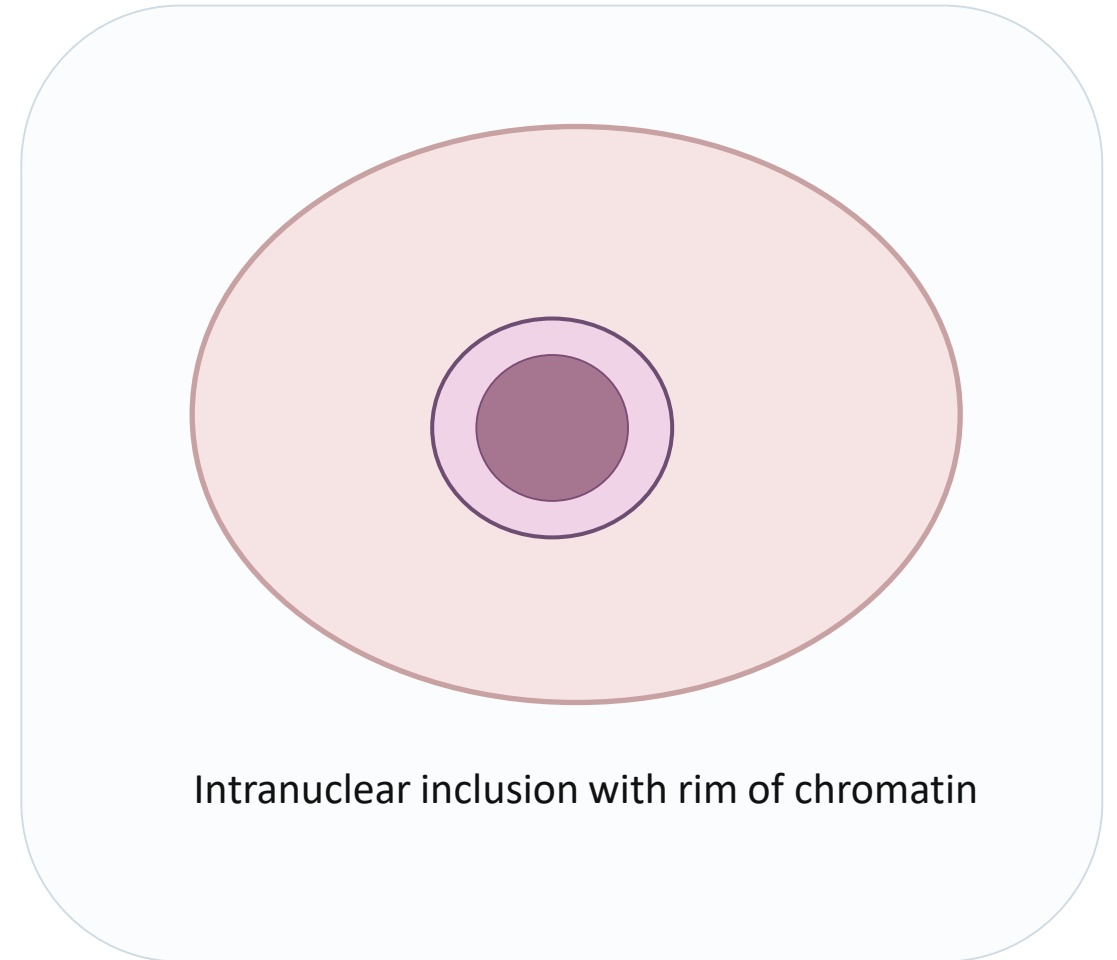
- Infected nuclei contain large pink-to-purple intranuclear inclusions
- The inclusion consists of viral replication proteins and assembling virions
- The finding points to a productive viral cytopathic effect



Schematic — not a clinical or histologic specimen

Margination of nuclear chromatin

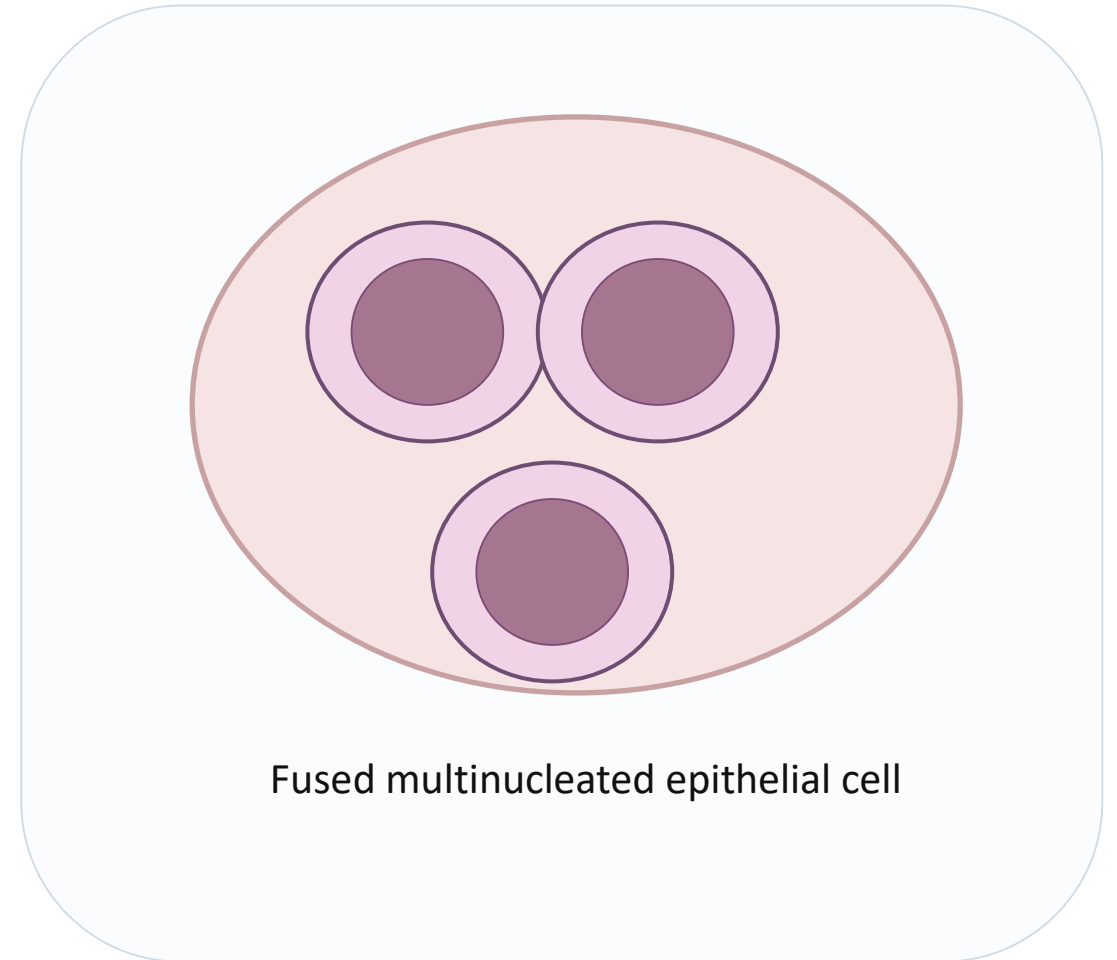
- Intranuclear viral material pushes host chromatin toward the nuclear periphery
- Peripheral chromatin accentuates the abnormal inclusion-bearing nucleus
- The appearance may be described as a ground-glass nuclear change



Schematic — not a clinical or histologic specimen

Multinucleated syncytia from cell fusion

- HSV induces fusion of infected epithelial cells
- The fused cells contain multiple nuclei
- Several nuclei may show herpetic intranuclear changes simultaneously



Fused multinucleated epithelial cell

Schematic — not a clinical or histologic specimen

Recognition pattern of HSV cytopathology

Morphologic element	Interpretive significance
Ballooning + vesicle	Lytic epithelial injury
Cowdry type A inclusion	Intranuclear viral replication material
Multinucleation	Cell fusion / syncytial cytopathic effect

Orofacial cold sores: Preferred location

- Cold sores occur around mucosal orifices
- Lips and the skin around the nose are common locations
- Perioral lesions are not necessarily restricted to one side

Lips

Nostrils

Oral mucosa

Distribution: HSV is not a typical dermatomal rash

Feature	HSV	VZV reactivation
Latency	Sensory neurons	Sensory neurons
Typical lesion pattern	Recurrent orofacial/genital	Painful dermatomal zoster
Recurrence	May recur repeatedly	Usually later in life

Primary gingivostomatitis in children

- Primary oral disease is usually associated with HSV-1
- Vesicles and ulcers may extend from tongue toward the retropharynx
- Cervical lymphadenopathy accompanies the oral inflammatory process

Tongue / gingiva

Lips / hard palate

Pharynx

The oral spectrum changes with age

Context	Typical manifestation
Children	Acute gingivostomatitis
Adults	Acute herpes pharyngitis
Immunosuppression	Persistent mucocutaneous disease

Recurrent oral herpes: Sites and timing

- Grouped small vesicles may involve lip, nostrils, buccal mucosa, gingiva or hard palate
- Recurrences arise in the area of primary inoculation or territory of the same ganglion
- The oral chapter describes usual resolution within 7–10 days

Lips

Nostrils

Oral mucosa

Herpetic whitlow: Painful digital infection

- HSV can cause swollen, erythematous lesions of fingers or palm
- Herpetic whitlow occurs in infants and sometimes through occupational exposure
- Painful vesicular lesions should prompt consideration of HSV

Genital HSV: Both virus types are possible

- Genital infection is more often caused by HSV-2 than HSV-1
- The vulva, vagina, cervix and external genital skin can be involved
- Oral–genital site overlap prevents reliable typing by anatomy alone

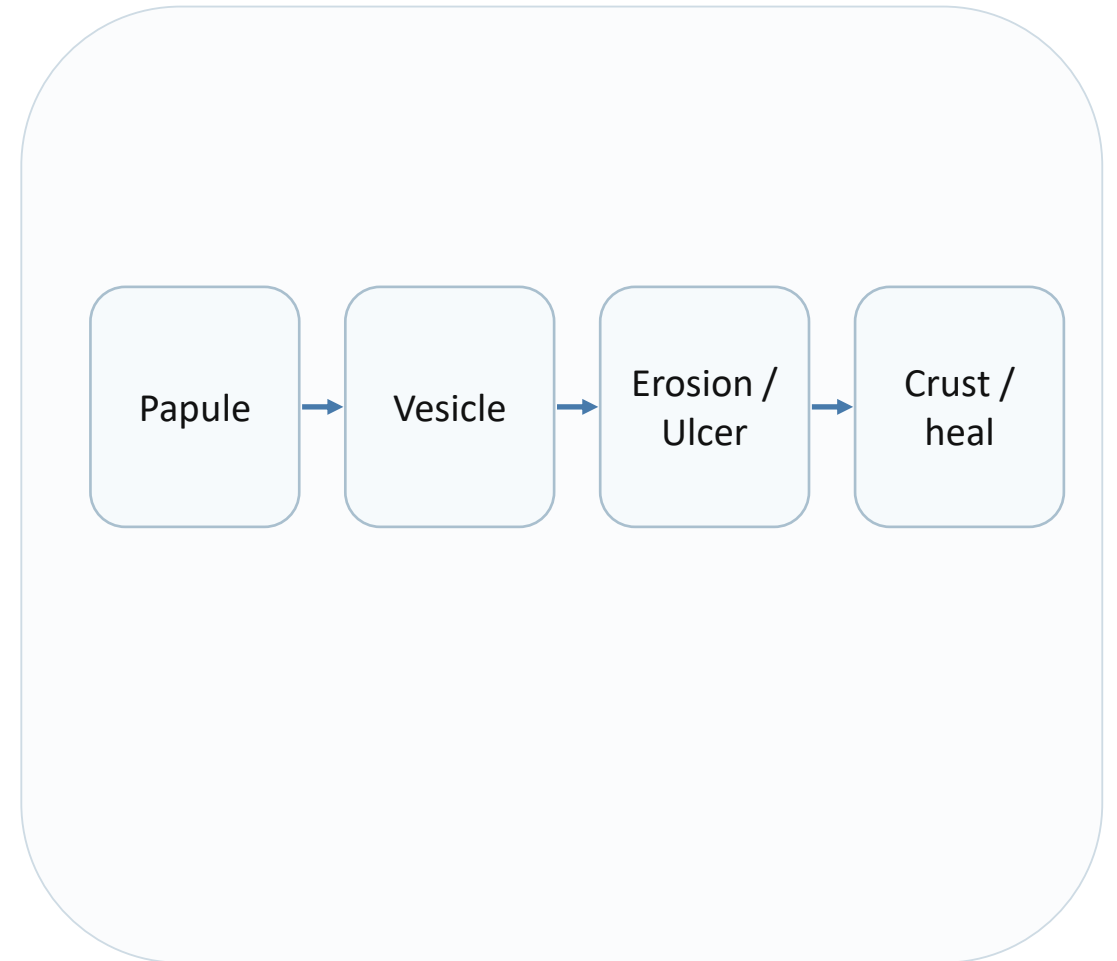
HSV-1
Often orofacial

Shared
infection
spectrum

HSV-2
Often genital

Genital lesions progress from papules to ulcers

- The genital-tract chapter describes early erythematous papules
- Papules become vesicles and then painful confluent superficial ulcers
- Inflammatory response contributes to the rim and ulcer-bed exudate

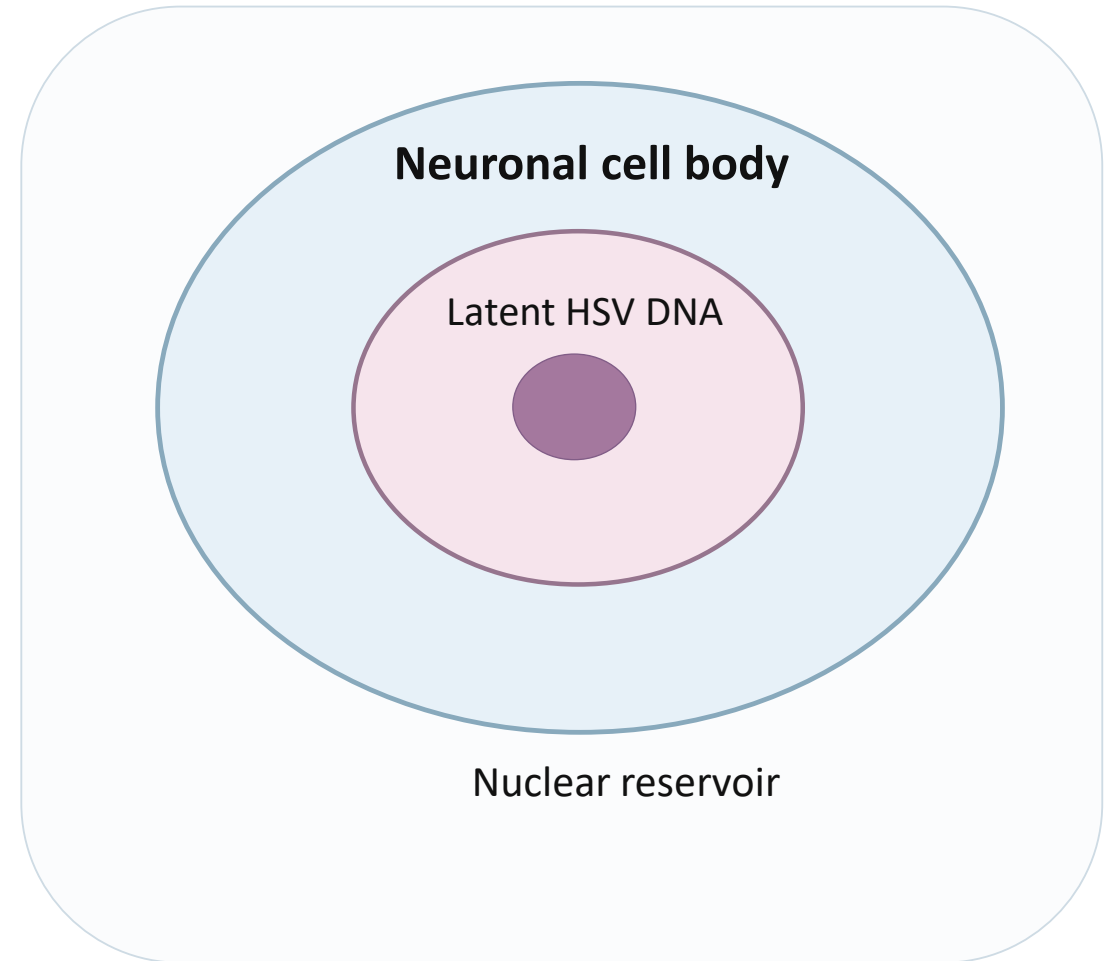


Symptoms may reflect lesion location

- Acute genital disease may cause fever, malaise and tender inguinal nodes
- Vaginal or cervical disease may present with discharge and pelvic pain
- Periurethral ulcers may cause dysuria or urinary retention

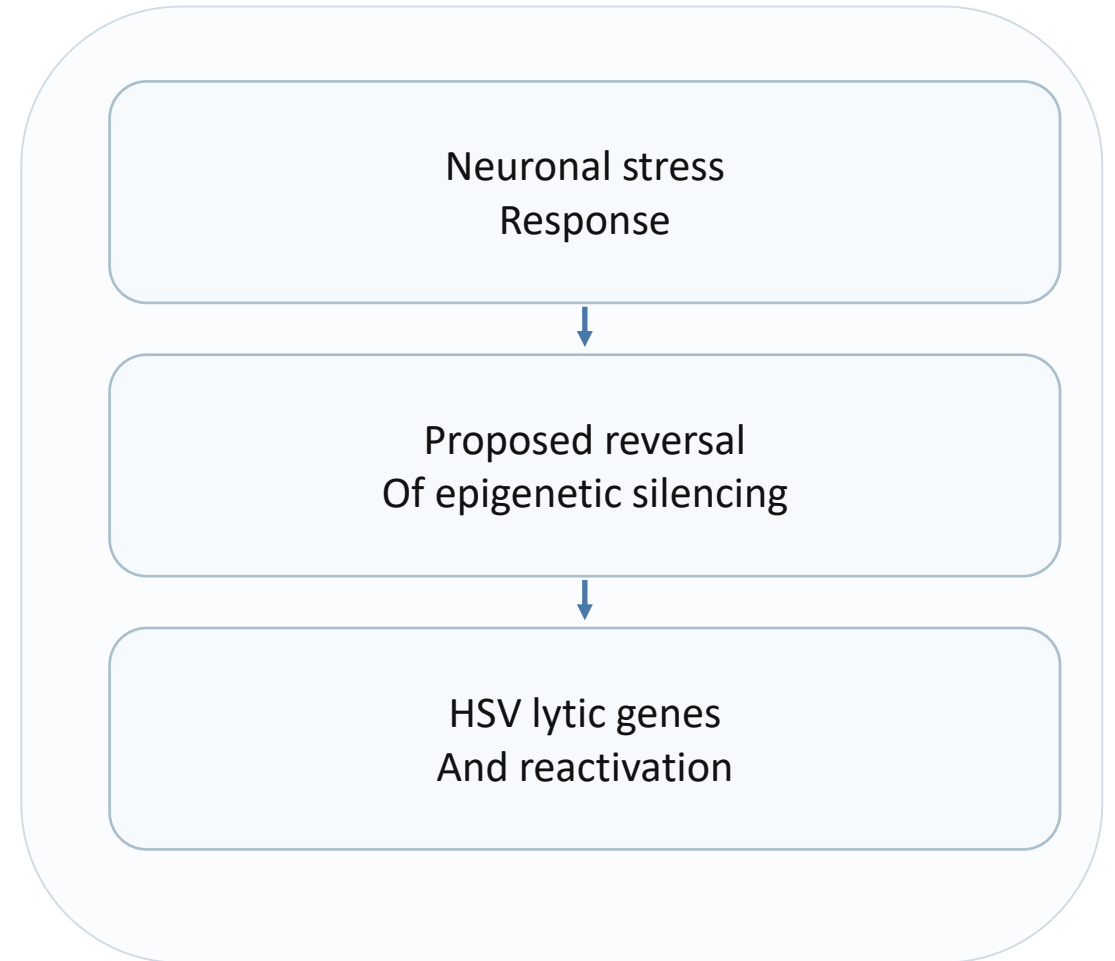
Genital HSV and lumbosacral latency

- During genital infection HSV travels to regional lumbosacral ganglia
- The virus then persists in a neuronal reservoir
- Reactivation can produce mucosal or cutaneous lesions at related sites



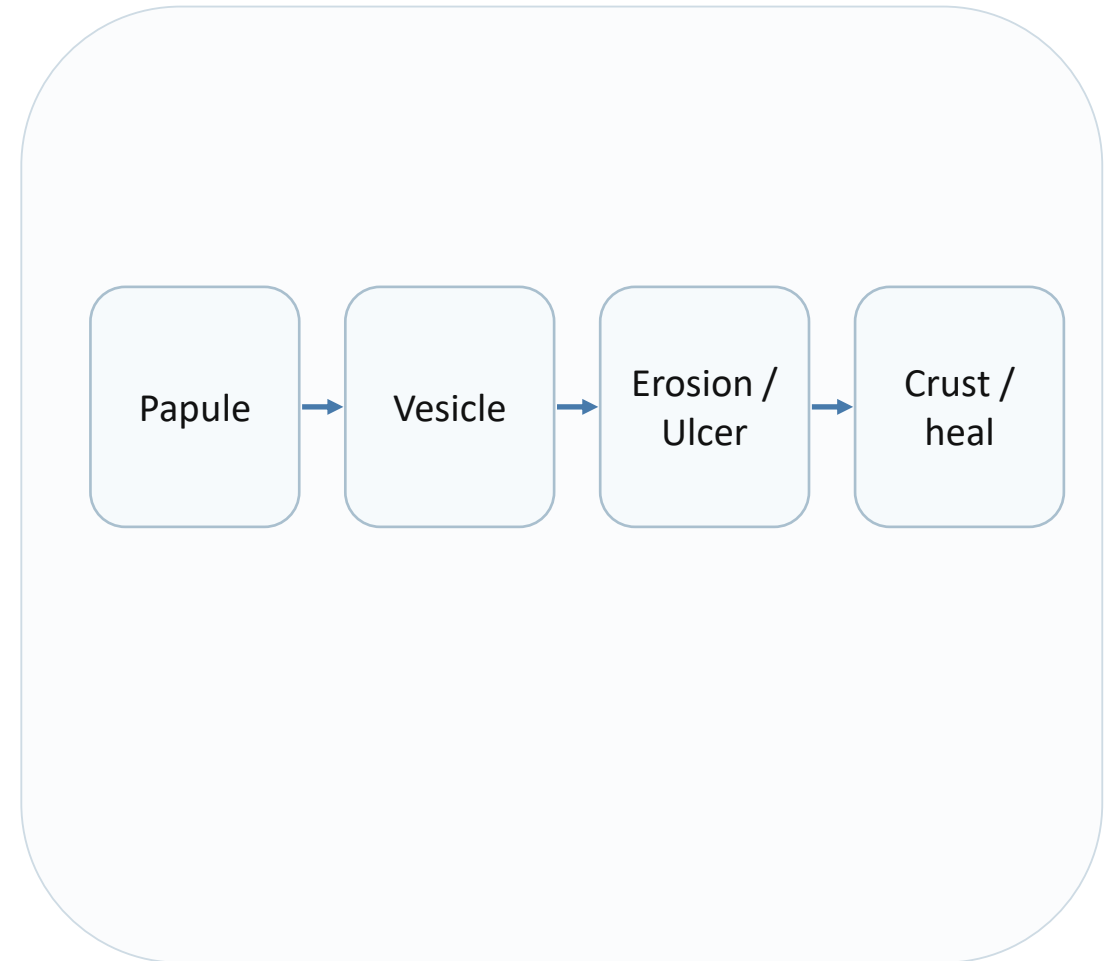
What can precipitate recurrence?

- The genital chapter associates recurrence with altered immune function
- Stress, trauma, concurrent viral infection and hormonal changes are listed
- Recurrent episodes are more frequent in immunosuppressed individuals



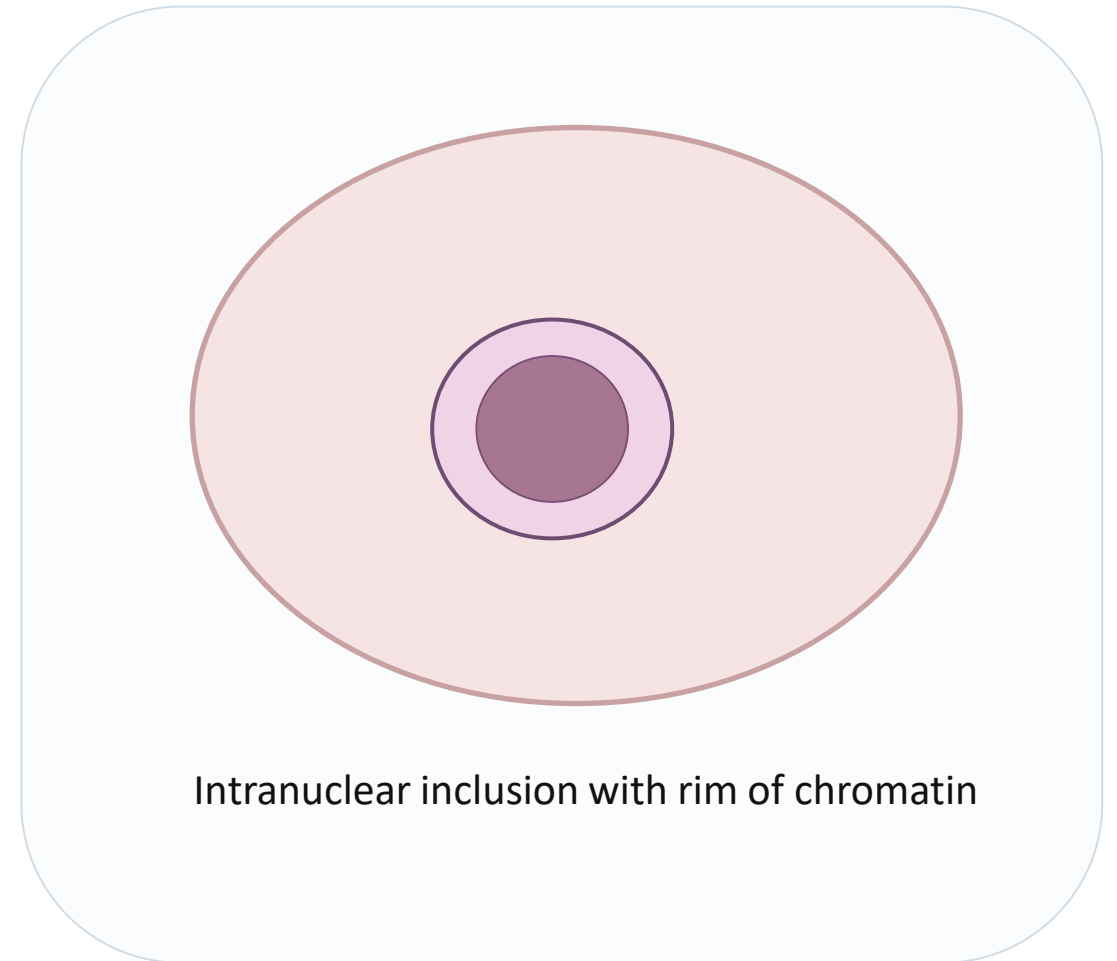
Genital biopsy: Stage affects the findings

- Lesions are often already ulcerated when biopsied
- The epithelial surface may have been lost by desquamation
- The ulcer bed may show marked acute inflammation



Genital cytology: Characteristic changes

- Exudate may contain multinucleated squamous epithelial cells
- Nuclei may contain eosinophilic-to-basophilic inclusions
- Ground-glass nuclear change supports HSV cytopathic injury



Intranuclear inclusion with rim of chromatin

Schematic — not a clinical or histologic specimen

HSV versus VZV: Compare the patterns

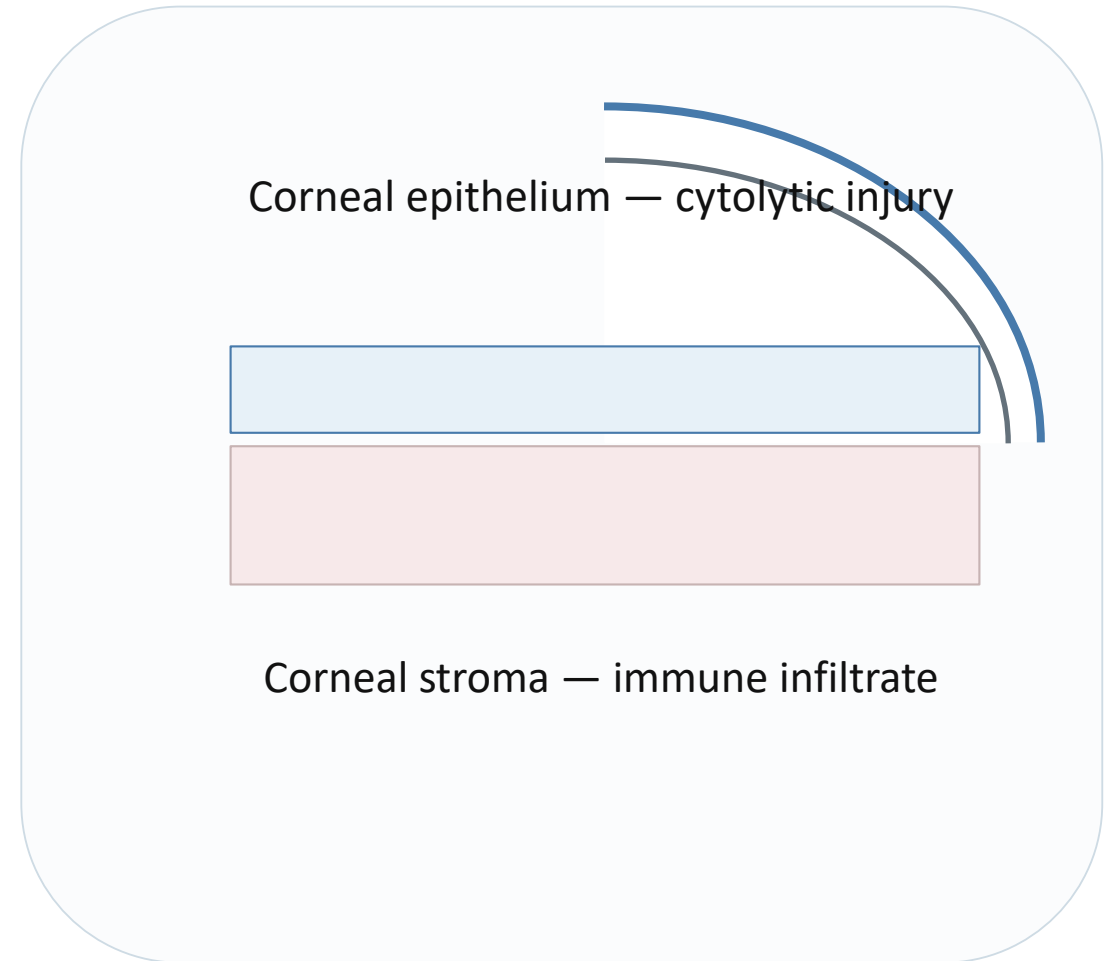
Feature	HSV	VZV reactivation
Latency	Sensory neurons	Sensory neurons
Typical lesion pattern	Recurrent orofacial/genital	Painful dermatomal zoster
Recurrence	May recur repeatedly	Usually later in life

HSV versus CMV: Different nuclear morphology

Feature	HSV	CMV
Prominent cell change	Syncytia / ballooning	Cytomegaly
Nuclear inclusion	Cowdry type A	Haloed owl-eye type
Common context	Skin and mucosal disease	Immunosuppressed visceral disease

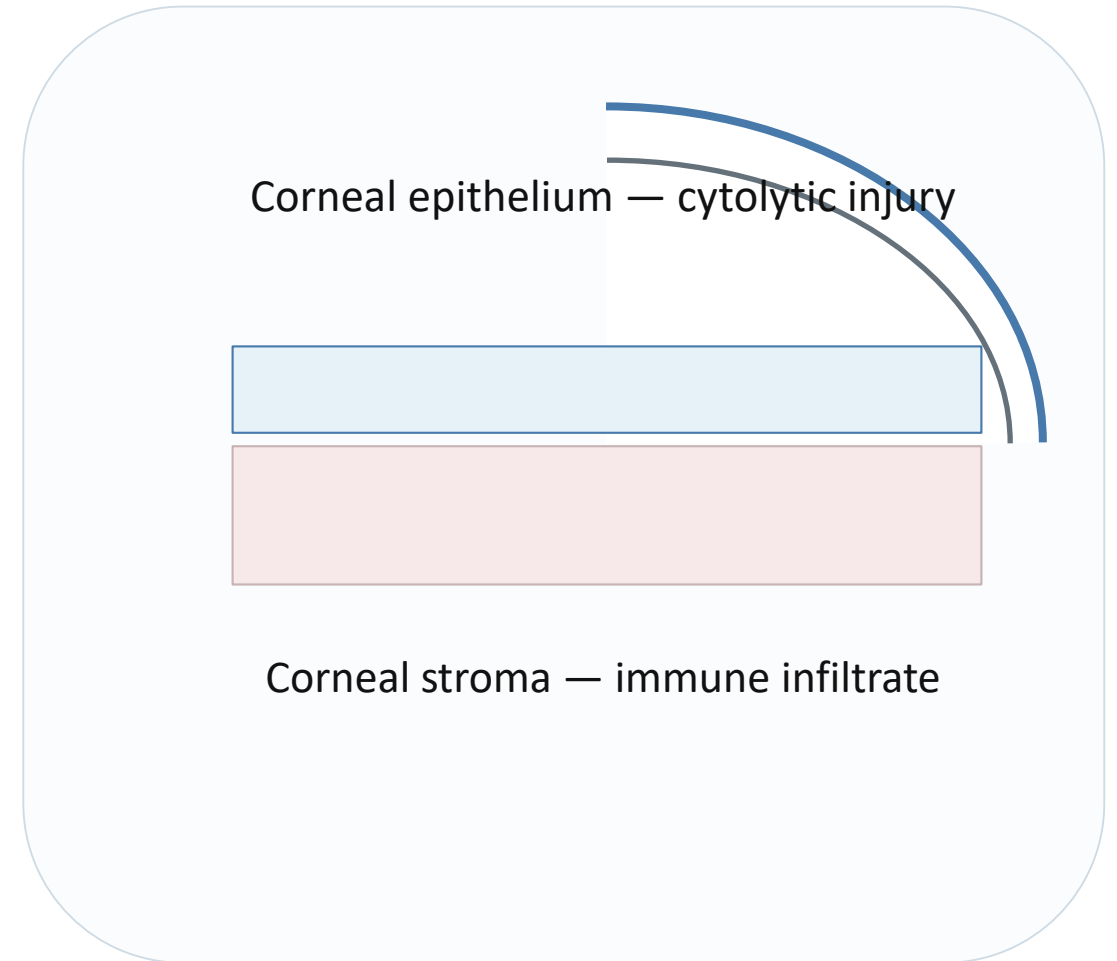
HSV epithelial keratitis: Direct damage

- Corneal epithelial disease is associated with viral cytolysis
- Infected superficial epithelial cells are injured directly by HSV
- Mechanism differs from the stromal form of herpetic keratitis



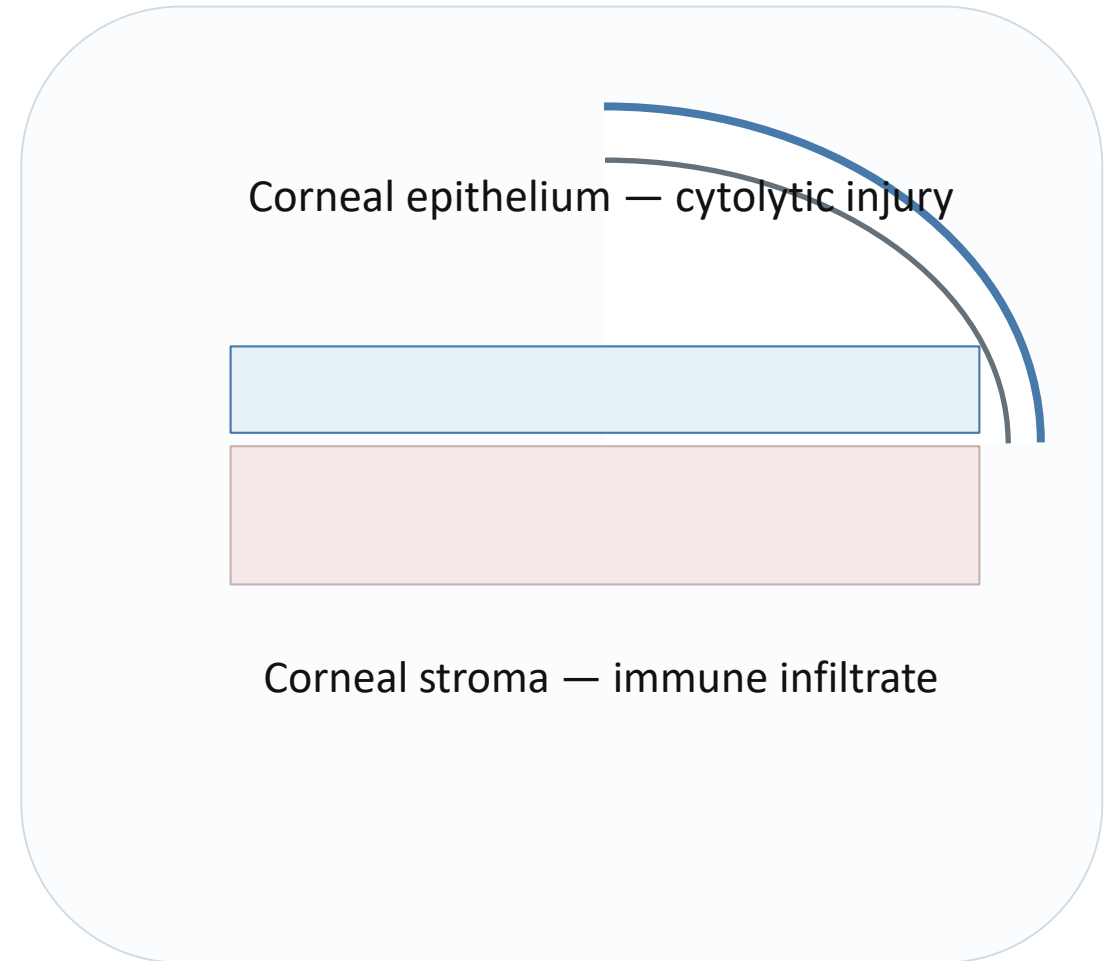
Stromal keratitis: Predominantly immune injury

- The stromal form shows mononuclear inflammatory infiltration
- Cells accumulate around stromal cells and endothelial structures
- The text attributes stromal injury mainly to the immune response



Why herpetic stromal disease threatens vision

- Inflammation promotes corneal neovascularization and scarring
- Stromal opacification compromises corneal transparency
- Repeated or severe injury may culminate in blindness



HSV-1 encephalitis: Characteristic topography

- HSV-1 is an important cause of sporadic fatal encephalitis
- The temporal lobes and orbital gyri of frontal lobes are characteristically involved
- Recognizing the topography supports the clinicopathologic differential

Temporal lobes

Orbital frontal gyri

Characteristic involvement in HSV-1
encephalitis

CNS tissue injury in HSV-1 encephalitis

- The CNS chapter describes necrotizing infection
- Hemorrhage may accompany severe tissue destruction
- The anatomic pattern and injury type are more useful than an isolated symptom

Temporal lobes

Orbital frontal gyri

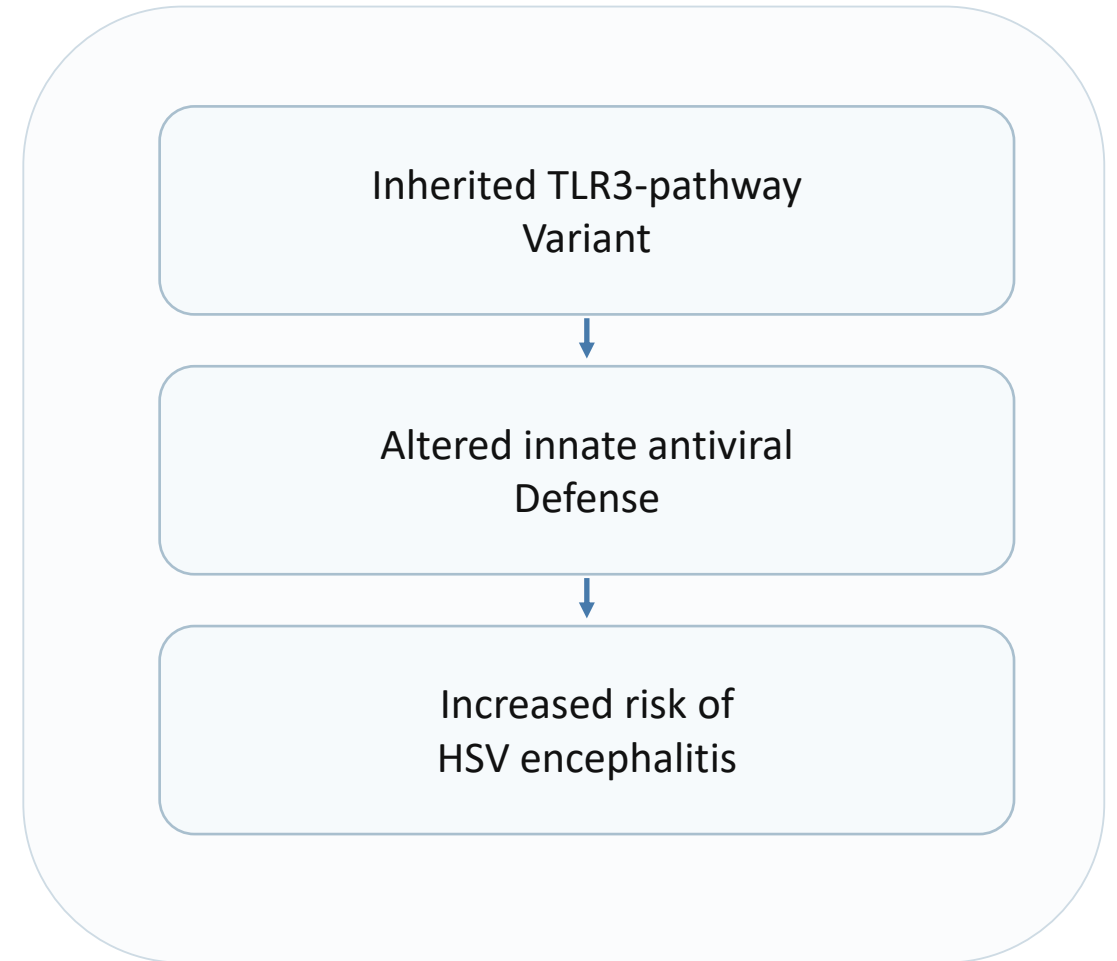
Characteristic involvement in HSV-1
encephalitis

Clinical clues to HSV-1 encephalitis

- Changes in behavior, memory or mood may predominate
- Seizures, weakness, lethargy or ataxia may occur
- The neurologic presentation relates to the affected temporal and frontal regions

TLR3 signaling and susceptibility

- Inherited changes in TLR3 or components of its signaling pathway raise HSV encephalitis risk
- The association implicates innate antiviral defense in the CNS
- Genetic susceptibility does not imply that most infections cause encephalitis

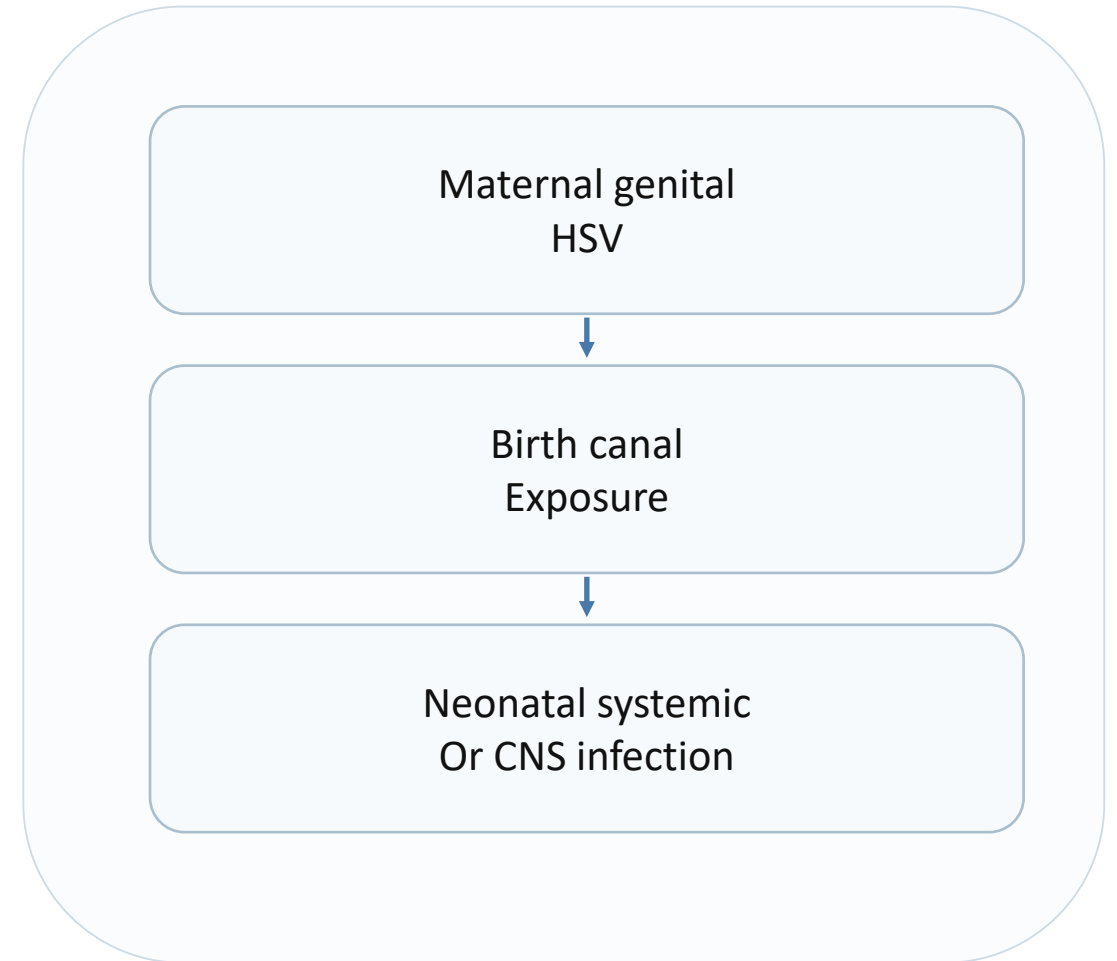


HSV-2 can also involve the CNS

- HSV-2 may cause meningitis in adults
- Neonatal CNS infection can be severe
- In patients with active HIV, HSV-2 may cause necrotizing hemorrhagic encephalitis

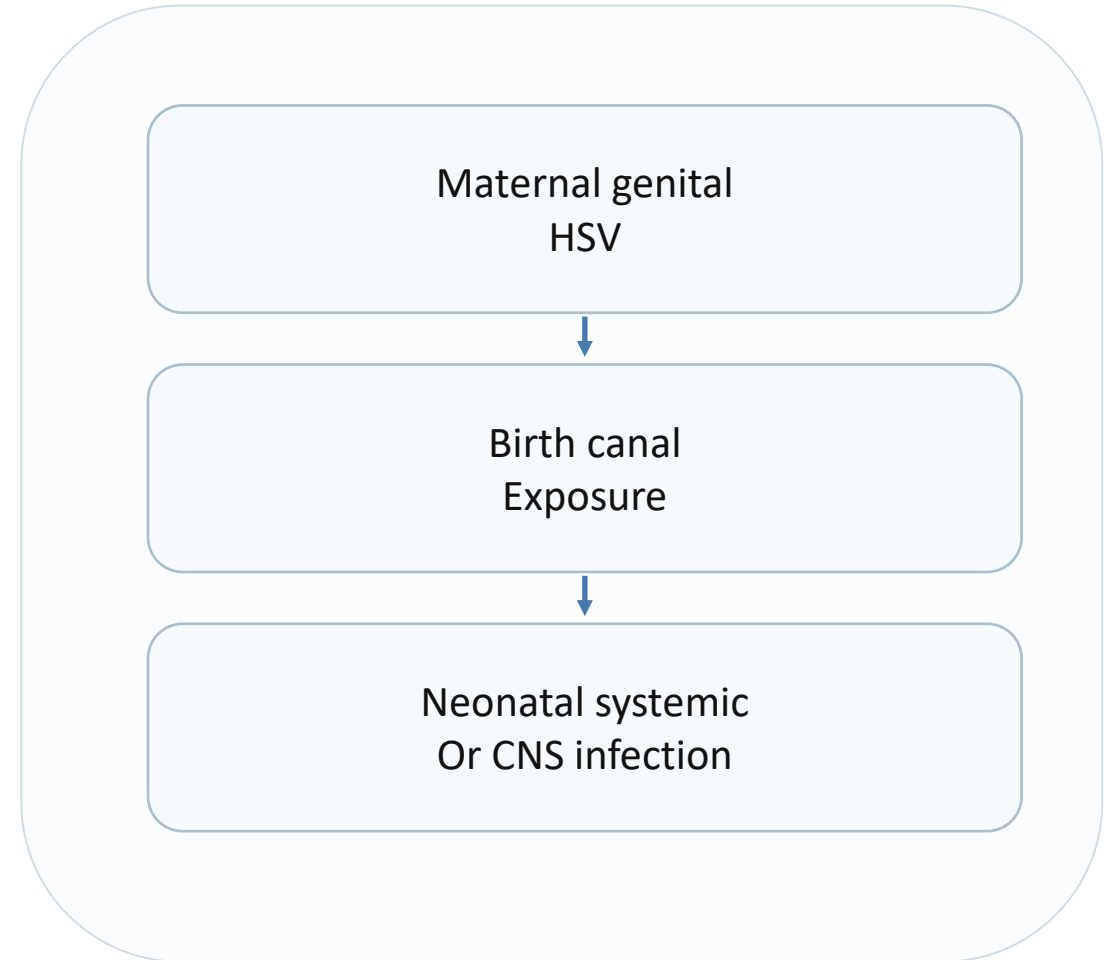
Neonatal HSV: Acquisition during birth

- Transmission may occur while passing through an infected birth canal
- The chapter most often associates neonatal transmission with HSV-2
- Active maternal primary genital disease presents particularly serious transmission risk



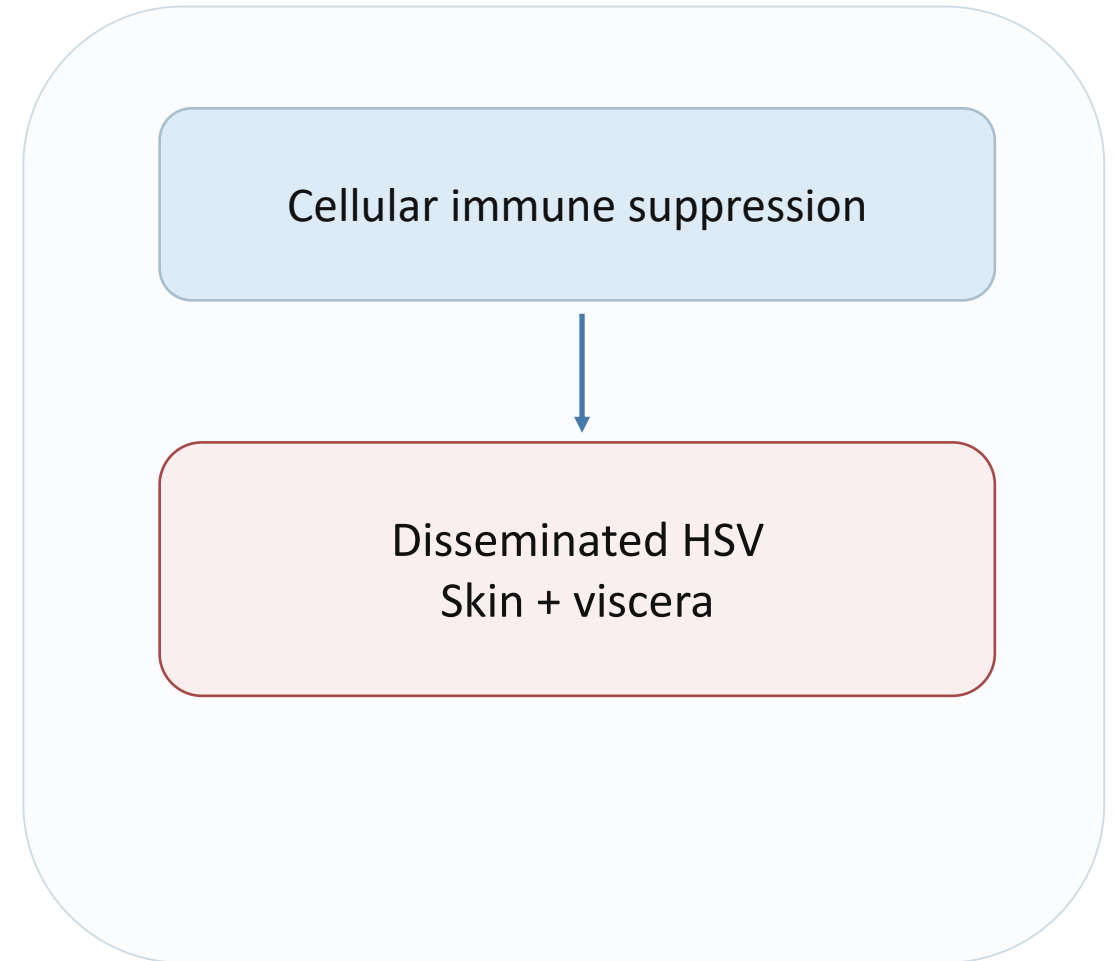
Disseminated neonatal disease

- Neonatal infection may be fulminant rather than restricted to mucosa
- Generalized lymphadenopathy and splenomegaly can occur
- Necrotic foci may involve lung, liver, adrenal glands and CNS



Impaired cellular immunity permits dissemination

- Patients receiving chemotherapy or living with HIV may develop extensive HSV
- Immunosuppression weakens containment of epithelial infection
- Hospitalized individuals with malignancy or immunosuppression are at risk for visceral disease



HSV esophagitis and superinfection

- HSV can cause esophageal disease in susceptible hosts
- Damaged mucosa may become secondarily infected by bacteria or fungi
- The combination complicates interpretation of an ulcerated lesion

Esophagus

Lung

Liver

HSV bronchopneumonia may be necrotizing

- HSV bronchopneumonia is often a severe necrotizing infection
- Some cases follow airway instrumentation when active oral HSV is present
- Anatomic setting and host immune status are clinically important

Esophagus

Lung

Liver

HSV hepatitis and systemic consequences

- Disseminated HSV may involve the liver
- Severe hepatic tissue damage may produce liver failure
- The outcome illustrates how HSV disease differs between host contexts

Esophagus

Lung

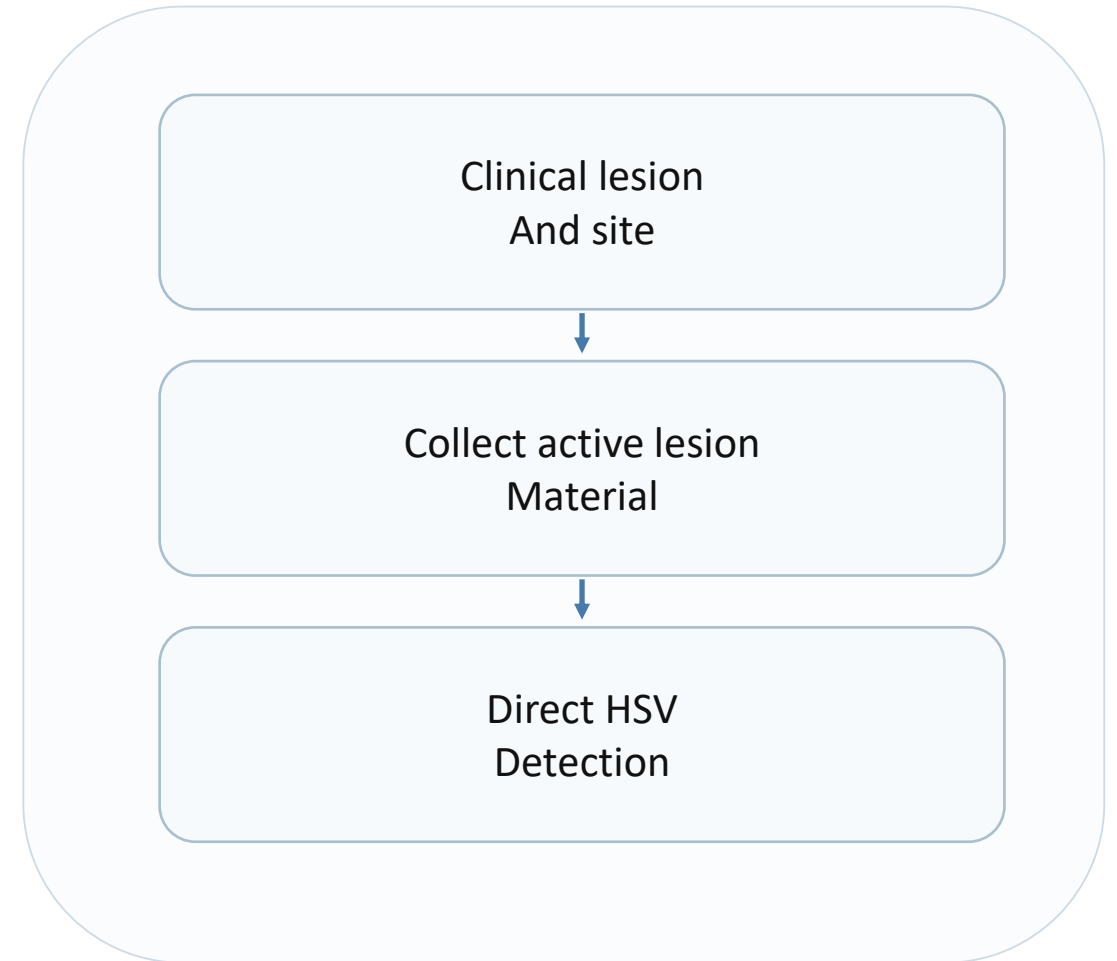
Liver

HSV-2 genital ulceration and HIV risk

- The textbook associates HSV-2 with increased HIV transmission
- Ulcerated genital epithelium disrupts mucosal barriers
- The chapter additionally cites modulation of antiviral host immunity

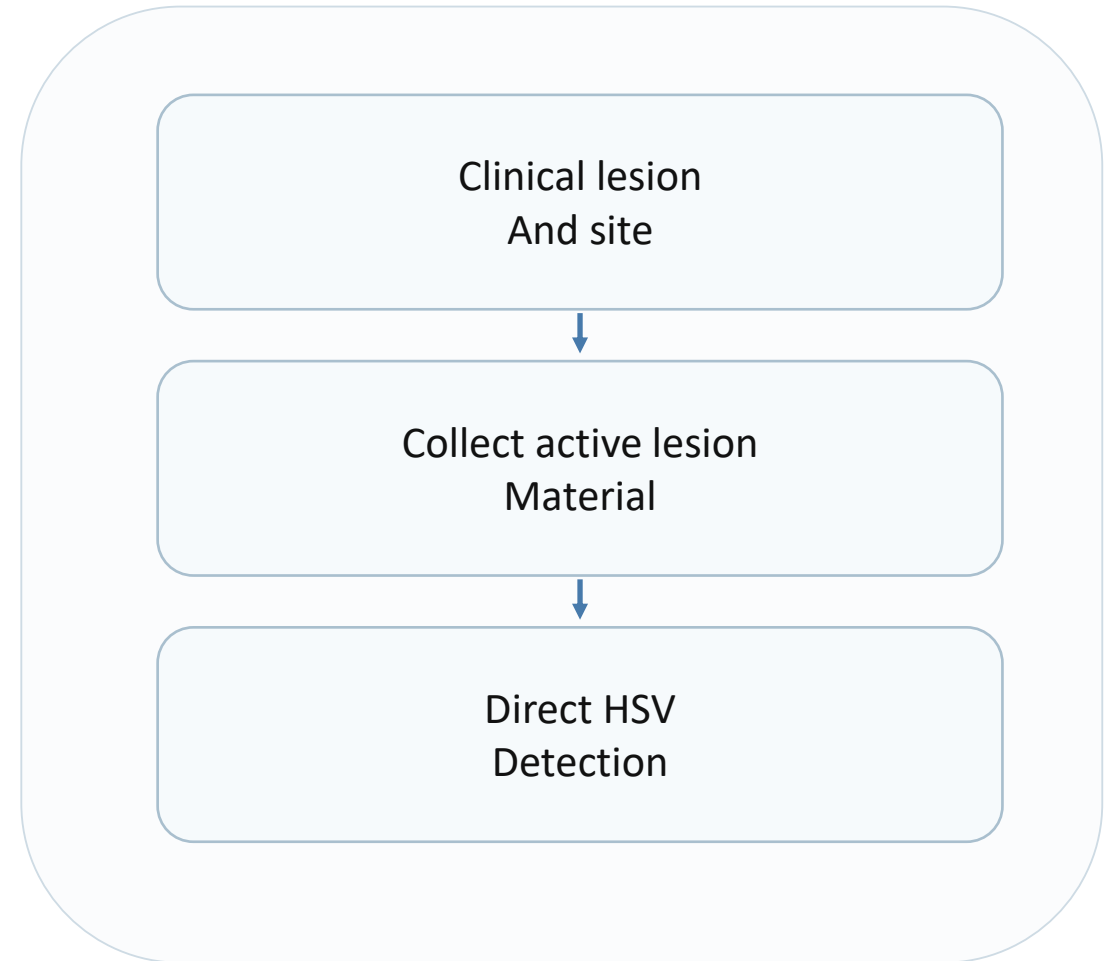
Diagnostic assessment begins with the lesion

- Clinical morphology and anatomic distribution guide suspicion
- HSV detection from active lesions is important for confirmation
- Morphology is useful but cannot substitute for all organism-specific tests



Laboratory detection of HSV

- The genital-tract chapter describes viral culture from lesional secretion
- PCR assays offer a more sensitive method of detecting HSV
- Immunofluorescence and other antigen-based assays are also discussed



Serology and direct viral detection answer different questions

Method	Primary question
Lesion PCR	Is HSV DNA present in sampled lesion?
Viral culture	Is infectious virus recoverable?
Type-specific serology	Evidence of HSV-type exposure

Why HSV cytology is suggestive, not site-specific

Morphologic element	Interpretive significance
Ballooning + vesicle	Lytic epithelial injury
Cowdry type A inclusion	Intranuclear viral replication material
Multinucleation	Cell fusion / syncytial cytopathic effect

Comparing the two forms of herpetic keratitis

Epithelial keratitis	Stromal keratitis
Direct viral cytolysis	Immune-mediated tissue injury
Surface epithelial damage	Mononuclear inflammation
Epithelial lesion	Neovascularization / opacity / scar

Case: Recurrent perioral vesicles

- A patient develops grouped vesicles around the lip after a previous similar episode
- The eruption is bilateral rather than limited to one dermatome
- Explain the site of viral latency and the route back to epithelium

Discuss

Mechanism → lesion → tissue injury

What observation makes the diagnosis plausible?

Case: Painful genital ulceration

- A patient presents with clusters of painful vulvar ulcers and inguinal tenderness
- A cervical smear shows multinucleated squamous cells with abnormal nuclei
- Identify the likely infection and the most useful route to viral confirmation

Discuss

Mechanism → lesion → tissue injury

What observation makes the diagnosis plausible?

Case: Altered behavior and seizures

- A young adult develops acute altered behavior and memory disturbance with seizures
- A lesion predominantly involves the temporal lobe
- Explain why HSV-1 is an important infectious diagnostic consideration

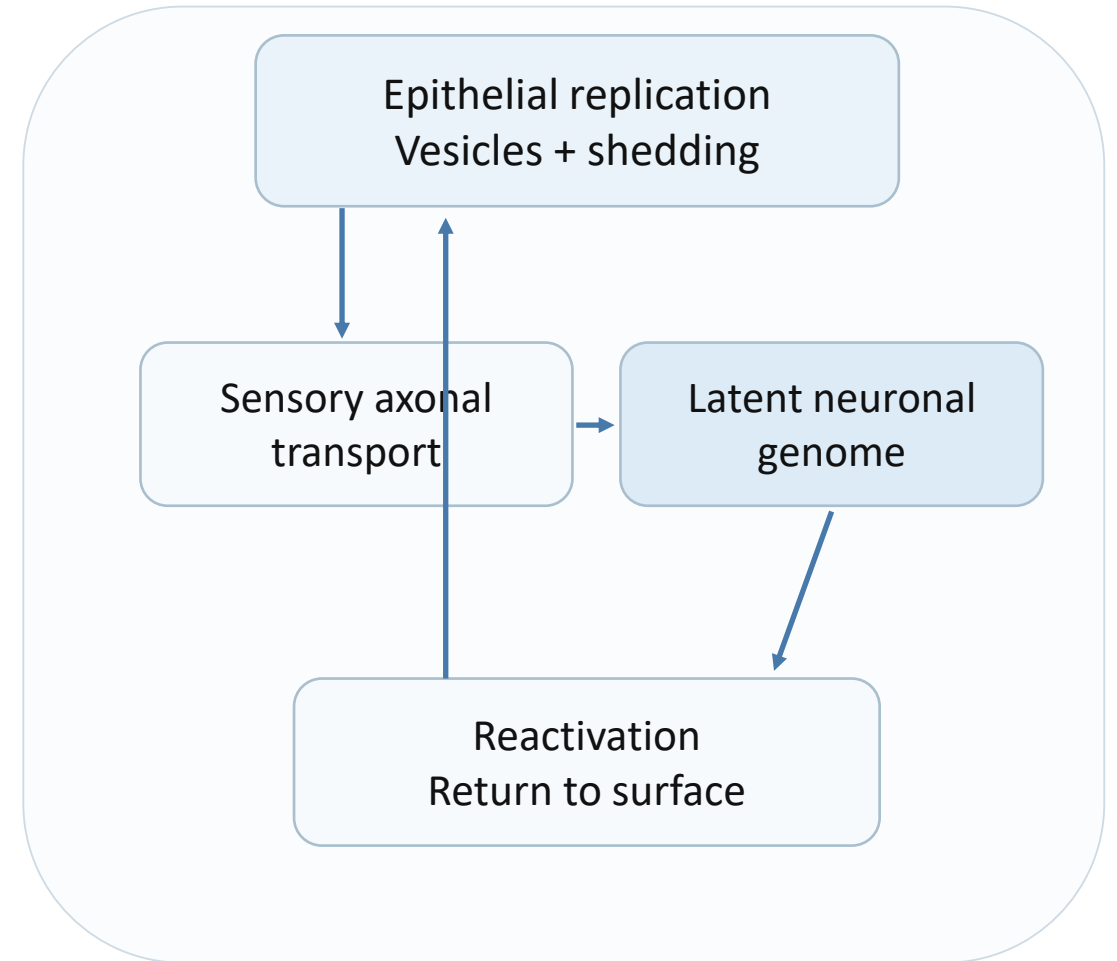
Discuss

Mechanism → lesion → tissue injury

What observation makes the diagnosis plausible?

Mechanism-to-morphology synthesis

- Epithelial viral replication produces ballooning, vesicles and ulcers
- Neuronal latency preserves infection after visible recovery
- Reactivation recreates epithelial injury, and immune evasion favors persistence

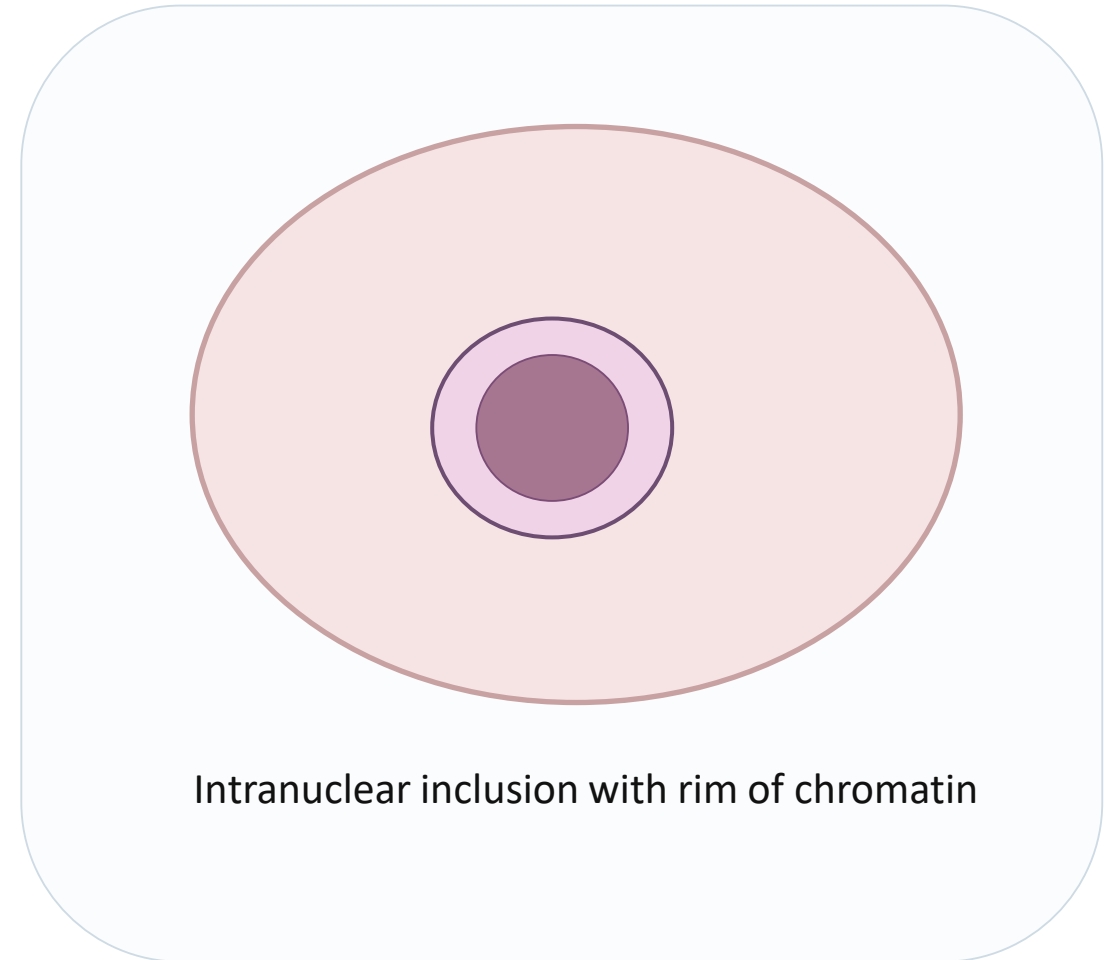


Organ injury: Three different mechanisms

Site	Principal pathology
Skin / mucosa	Cytolysis; vesicles / ulcers
Corneal stroma	Immune-mediated scarring
Brain / viscera	Necrotizing tissue injury

Essential morphologic recognition points

- Intraepithelial vesiculation follows ballooning degeneration
- Cowdry type A intranuclear inclusions displace peripheral chromatin
- Cell fusion produces multinucleated inclusion-bearing syncytia



Schematic — not a clinical or histologic specimen

References

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Chapter 8: Infectious Diseases, pp. 320–322
- Cross-referenced sections: Chapter 16 (oral HSV); Chapter 22 (genital HSV); Chapter 28 (CNS HSV)
- Schematic illustrations were constructed as editable PowerPoint shapes; they are not histologic specimens