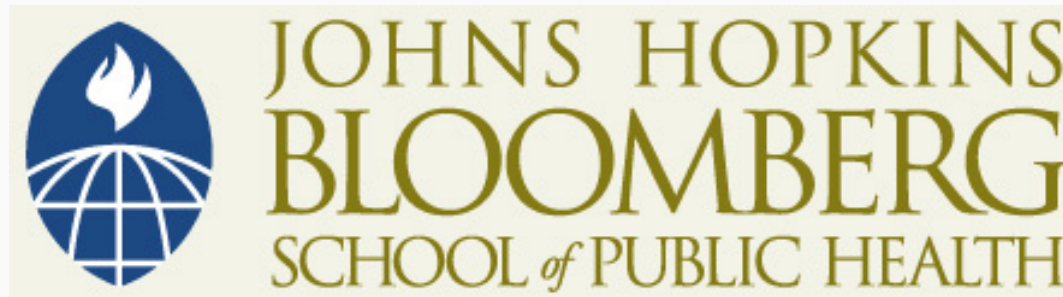


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Update on Genital Herpes

Anne Rompalo, MD, ScM
Johns Hopkins University

- Genital herpes is recurrent, incurable
- HSV is rarely fatal
- There are two serotypes—HSV-1, HSV-2
- Most recurrent genital herpes are HSV-2
- At least 50 million are infected in U.S.
- Most HSV-2 infected are not diagnosed
 - They have mild or unrecognized infections
 - But they shed intermittently from the genital tract
- Most transmission occurs during asymptomatic shedding episodes

- More is known about . . .
 - “A-typical” presentations
 - Asymptomatic shedding
 - Genital HSV-1
- New serologic tests are FDA approved and available
 - Proper use of these diagnostics may decrease neonatal HSV transmission
- No new approved drugs (but shorter regimens can be used) and new drugs are in development
- Suppressive therapy prevents transmission
- NIH has vaccine trial underway



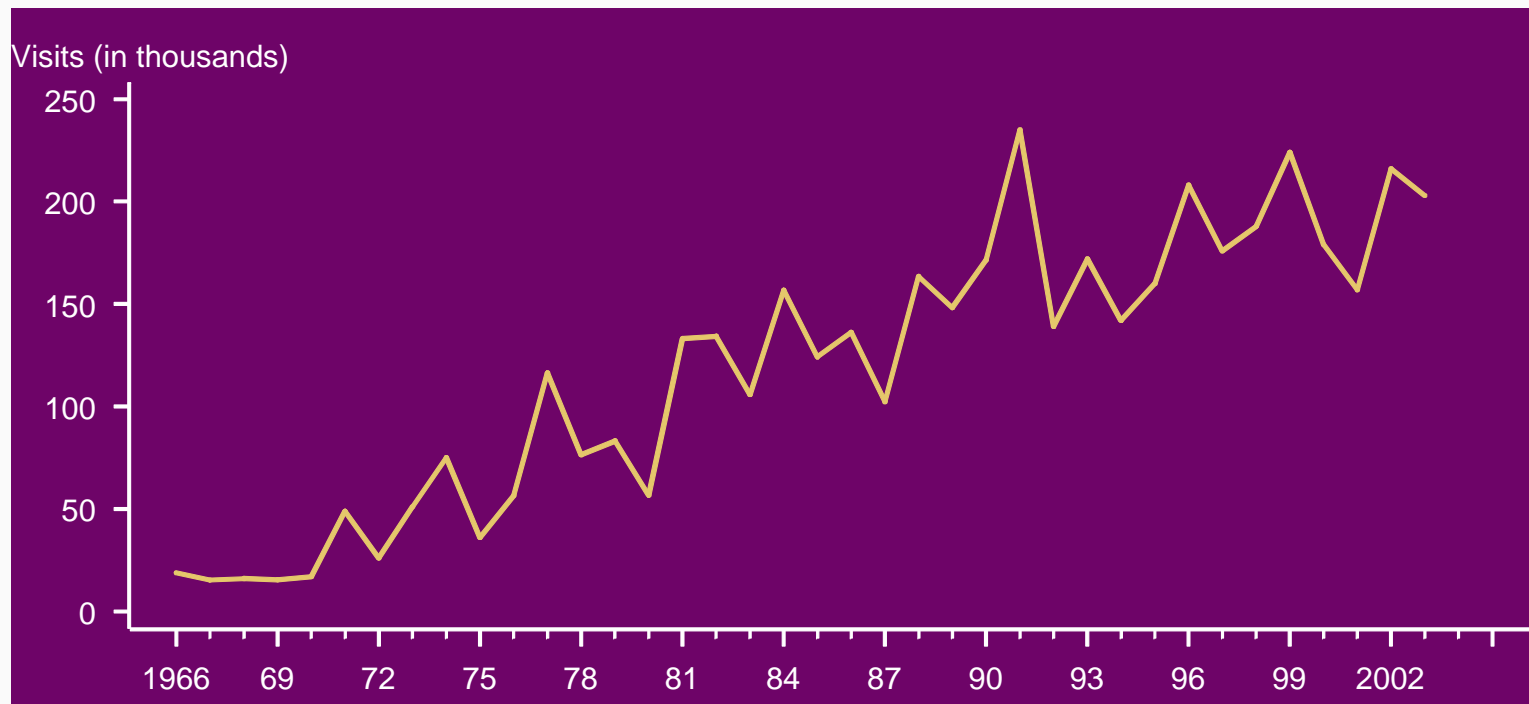
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Section A:

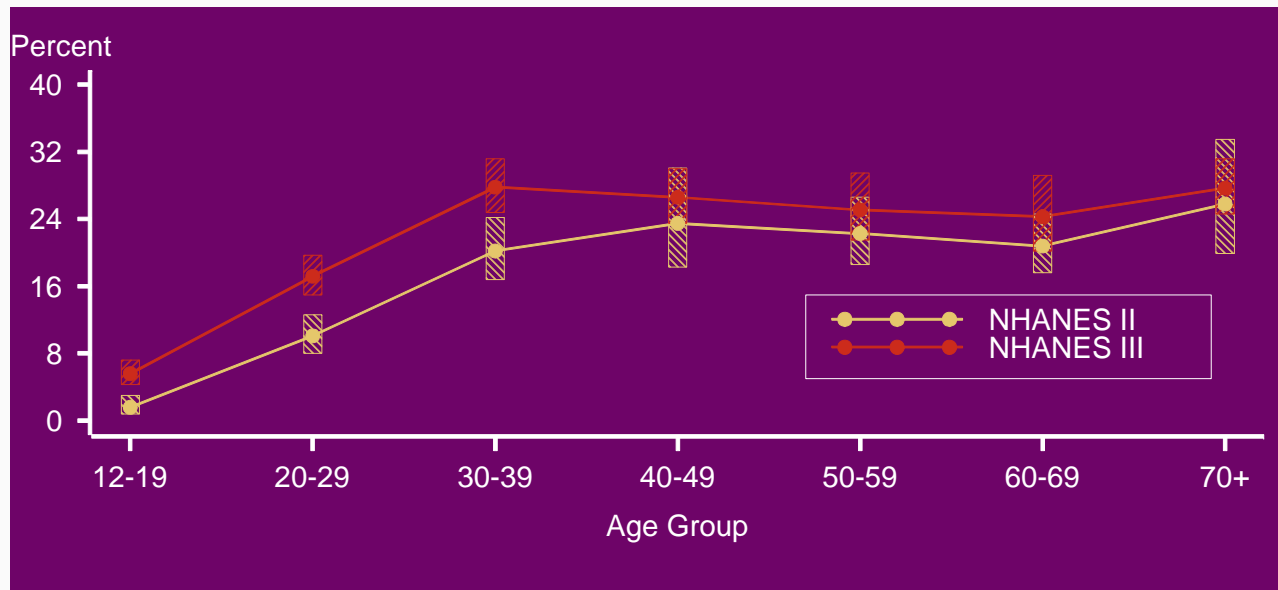
Epidemiology

Genital Herpes—Initial Visits to Physicians' Offices:

United States, 1966–2003

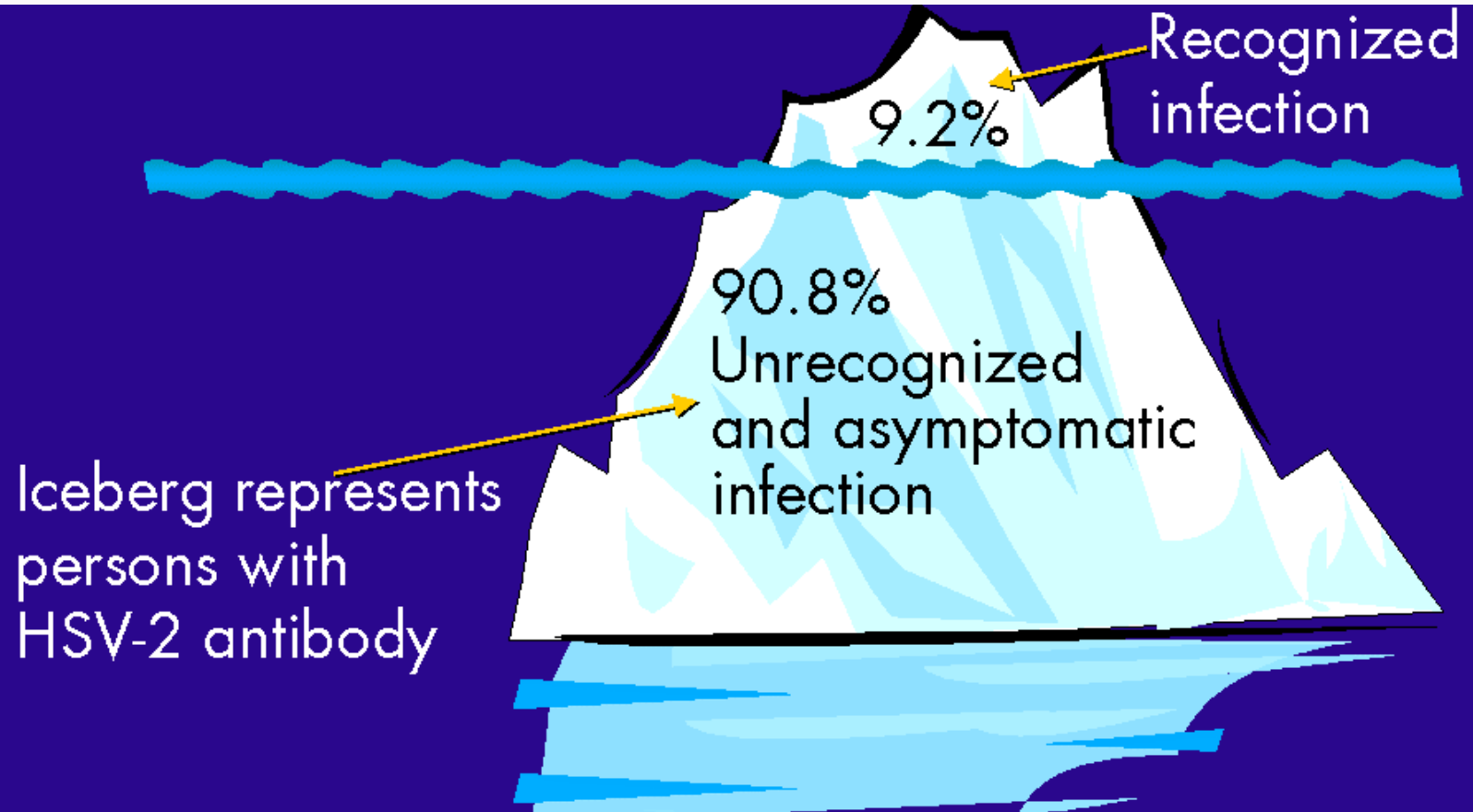


- From 1988 to 1994, the overall seroprevalence of HSV-2 was 21.9%
- Compared to '76-80, the age-adjusted seroprevalence increased 30%, with the greatest relative increase among young whites
- Women were 45% more likely than men to be infected with HSV-2



Comparing NHANES III (1988-1994, N=9165) to NHANES (1999-2000 N=3590)

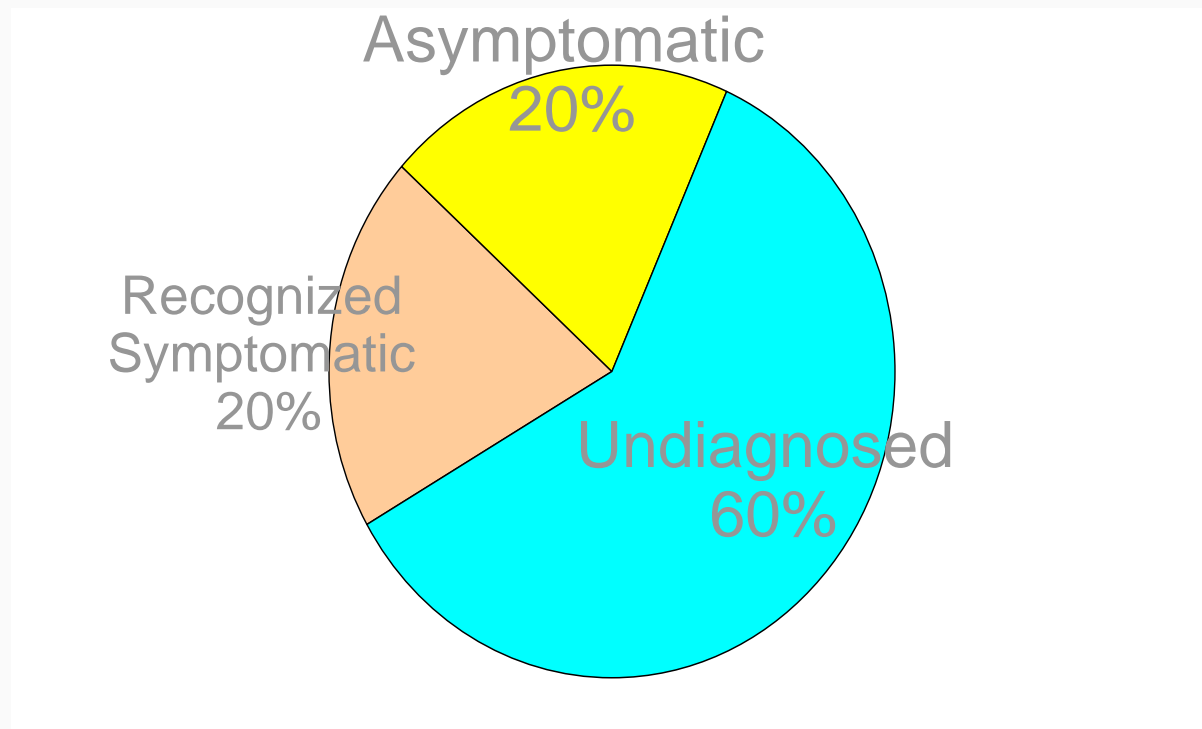
- Seroprevalence = 21.3% versus 17.6%; a decrease of 17%
- Largest decreases were in ...
 - ▶ Younger age groups
 - 74% in 14-19 yr olds (From 5.8% to 1.5%)
 - 48% in 20-29 yr olds (From 17.2% to 8.9%)
 - 35% for Males (from 17.2% to 11.2%)
 - 46% in Mexican Americans (from 22.5% to 12.1%)



Fleming DT, et al. *N Engl J Med.* 1997;337:1105-1111.

The Clinical Spectrum of HSV-2

- Up to 80-90% of HSV-2 seropositive patients have no clinical history of genital HSV outbreaks
- Most have mild unrecognized disease
- Probably all shed intermittently



Data from University of Wisconsin Health Services

- Retrospective review of HSV isolated collected over a nine-year period
- HSV-1 accounted for 78% of all genital herpes isolated in 2001 compared to 31% in 1993
- HSV-1 was more common in persons aged 16 to 21 compared to 22 or older

HSV-2 Incidence/Prevalence

- Most HSV-2 is acquired in third decade of life
- BUT recent studies show earlier acquisition
 - Rates quintupled in white teens and doubled in young adults
- Among teens
 - Seroprevalence is > 5% (4.5% white; 9% in black students)
- Among college students
 - Seroprevalence is 1–9% with high yearly seroconversion

- High prevalence of HSV-2 in most sexually experienced populations
- Most genital herpes is unrecognized
- HSV-1 accounts for increasing proportion of first genital herpes episodes



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Section B

Pathogenesis

- Need mucosal inoculation
- Virus is transported via peripheral nerve axon to nerve cell bodies in dorsal root ganglia
- Virus may remain latent indefinitely in paraspiinous ganglia
- Reactivation, viral replication, centrifugal migration to mucosal surfaces, focal cell necrosis

- Histopathologic changes
 - Focal necrosis
 - Ballooning degeneration of cells
 - Production of multi-nucleated giant epithelial cells
 - Eosinophilic intra-nuclear inclusions called Cowdry type A bodies



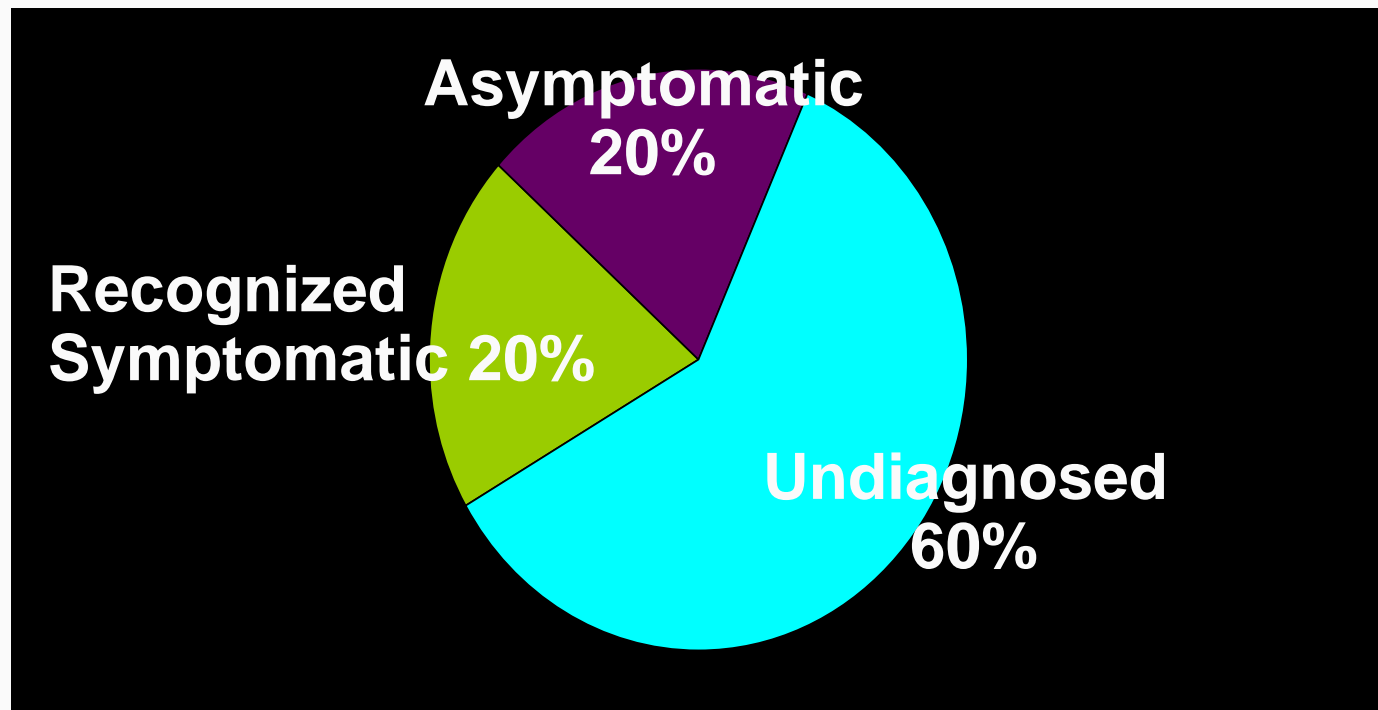
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Section C

Clinical Manifestations

The Clinical Spectrum of HSV-2

- Up to 80-90% of HSV-2 sero-positive patients have no clinical history of genital HSV outbreaks
- Most have mild unrecognized disease
- Probably all shed intermittently



- First clinical episode (primary)
 - No infection ever
 - No serum antibody when symptoms appear; serum antibody appears in convalescence
 - Clinically more severe

- First clinical episode (non-primary)
 - First clinically apparent episode with HSV-1 or HSV-2 in person previous seropositive to other virus type
 - Clinically milder
 - 25% with HSV-2 have had a prior asymptomatic primary infection

- Recurrent or first recognized
 - Antibody is present when symptoms occur although patient may not be aware of previous episodes
 - Generally, there is no or little change in antibody titer in convalescence
 - Disease is mild and short in duration

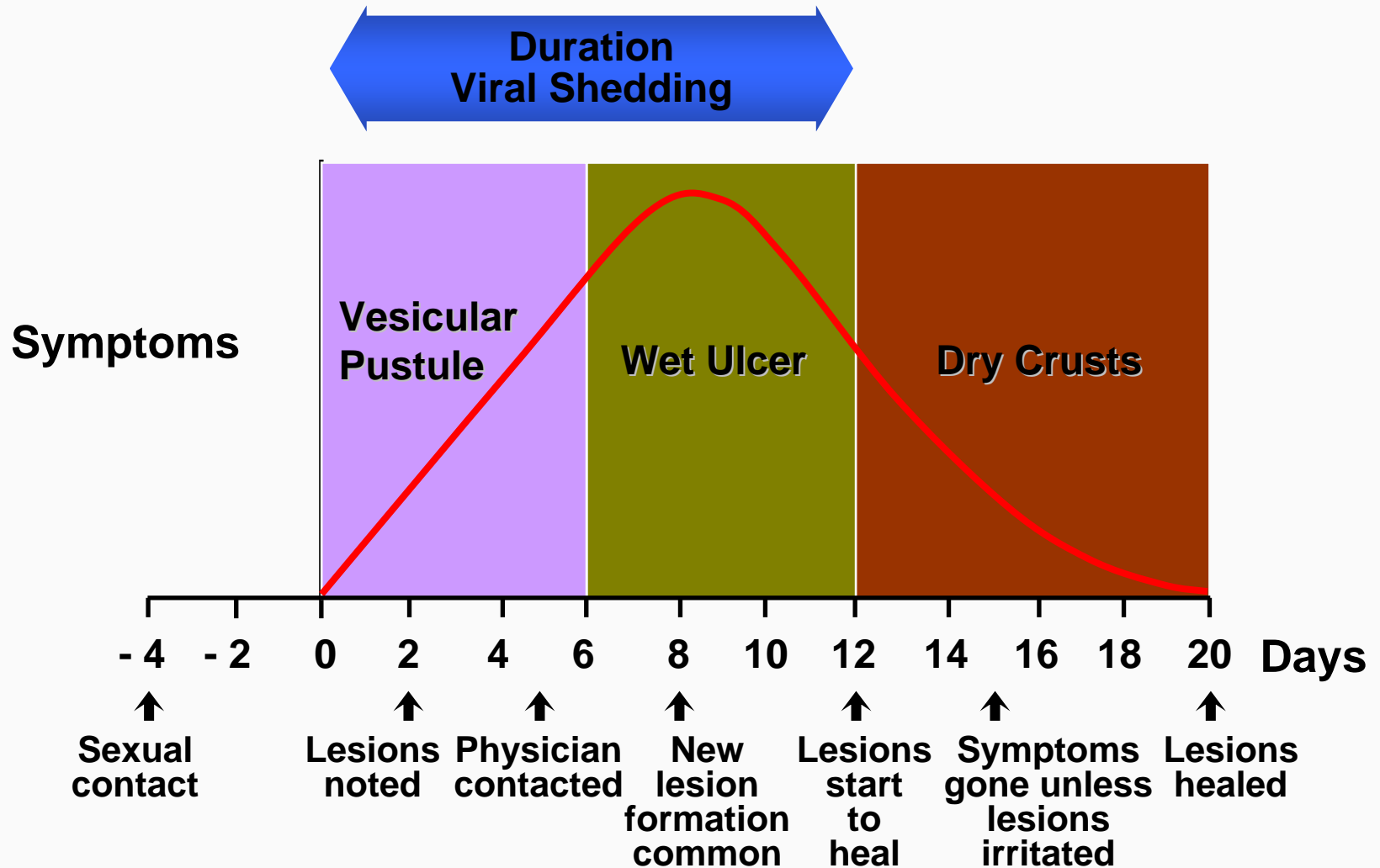
- Asymptomatic infection
 - Serum antibody is present
 - No known history of outbreaks
 - Up to 66% with identified asymptomatic HSV-2 can be taught to recognize clinical signs and symptoms of genital outbreaks

Type Specific Antibody at Time of Presentation

Infection Type	Lesions/Symptoms	HSV-1	HSV-2
1st episode primary (Type 1 or 2)	+/- severe, bilateral	-	-
First episode non-primary (Type 2)	+/- moderate	+	-
First episode recurrence (Type 2)	+/- mild	+/-	+
Symptomatic recurrence (Type 2)	+/- mild, unilateral	+/-	+
Asymptomatic infection (Type 2)	-	+/-	+

- Macule
- Papule
- Vesicle
- Ulcer
- Crusted lesions
- Healed lesion

Clinical Course of Initial Herpes Virus Infection



- Often have systemic symptoms
 - Fever, headache, malaise, myalgias (40% men; 70% women)
 - 10% women have urinary retention
 - Symptoms peak within 3–4 days of lesion onset and recede over the next 3–4 days

- Local symptoms
 - Pain (95%), itching, dysuria (60%), vaginal (85%), urethral (30%) discharge, tender lymphadenopathy (80%)
 - Lesions are numerous and bilateral; last 11–12 days; full healing takes average of 17–20 days

- Median duration of viral shedding is about 12 days and correlates well with the time from vesicles to crusting
- Inguinal adenopathy peaks in week 2–3 and is often last finding to resolve
- Lymph nodes are firm, nonfluctuant, and tender to palpation

- Primary HSV cervicitis occurs in ~90% of primary HSV-2 and ~70% of HSV-1
- It may present as mucopurulent cervicitis, or may be asymptomatic
- Cervix will often appear abnormal with ulcerative lesions, erythema, or friability
- Exo- and endocervix may be involved

- Following the initial genital infection
 - HSV becomes latent in the sacral nerve ganglia and can reactivate
 - About 85% of women and nearly all men with symptomatic acquisition of genital HSV-2 will have a recurrence within the first year (average 4–5 bouts/year)

- Following the initial genital infection
 - Recurrent episodes are shorter and more localized (may be chronic and unpredictable)

- Triggers for reactivation may or may not be known (trauma, fever, UVL, stress)
- Prodromal symptoms (50%) begin 12–24 hours before lesions and sometimes without lesions
- Duration is shorter (painful lesions last four to six days); shedding is shorter (four days)

- Lesions tend to be unilateral
- Average of 2–6 recurrences/year—but highly variable
- Recurrence probability increases if ...
 - Primary is HSV-2
 - Primary is severe/prolonged (>30 days)

- HSV will recur more frequently and after shorter period in men
- Rate of cervical virus shedding in women is 12–20%

Asymptomatic Viral Shedding

- Has been documented in almost all HSV-2 seropositive persons studied
- Most HSV-2 is transmitted during asymptomatic shedding
- Shedding rates are similar in patients with no reported history of genital HSV (2.7%) compared to those with a history (3.0%)

- Most common shedding sites
 - Women—vulva and perianal areas
 - Men—penile skin
- Shedding rates are greater with HSV-2 than HSV-1

In Asymptomatic Seropositive Persons

- Prospective study of 53 HSV-2 antibody positive patients with no history of genital HSV versus 90 patients with symptomatic HSV-2
- Genital secretions were sampled daily and cultured for HSV for median 94 days

In Asymptomatic Seropositive Persons

- Of 53 asymptomatic patients, HSV was detected in 38 (72%) by culture and by PCR in an additional four (85%); 33 (62%) subsequently reported typical HSV lesions
- Rate of subclinical shedding was similar in both groups (3.0% of symptomatic patients vs. 2.7% of patients with no reported symptoms)

In Asymptomatic Seropositive Persons

- Among asymptomatic persons
 - Duration of recurrences was shorter vs. symptomatic persons (median three vs. five days, $p < 0.001$)
 - Frequency of recurrences was lower (3.0 per year vs. 8.2 per year, $p < 0.001$)
 - Shedding was similar comparing men to women

Diary: No Relationship of Symptoms to Shedding

Symptoms and Signs	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
No symptoms	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X
Itching, burning, tingling											G																				
Localized redness or sore spots																															
Sores, blisters, ulcers, crusts																			G												
Abrasion, skin splits, scratches, fissures																															
Urethral pain or burning																															
Abnormal vaginal discharge											G						X	X													
Thigh or buttock pain or sensitivity											X																				
Swollen groin or lymph nodes																															
HSV culture	2	2	2	2	2																							2	2		

- Aseptic meningitis
 - More common in primary than in recurrent infection
 - More common with HSV-2 than HSV-1
 - More common in women than in men (35% vs. 11% with primary disease)

- Aseptic meningitis
 - May be severe and require hospitalization
 - Usually no neurologic sequelae
 - Recent data suggest that benign recurrent meningitis (Mollaret's meningitis) is usually caused by HSV-2

- Stomatitis and pharyngitis
- Radicular pain, sacral paresthesias
- Transverse myelitis
- Autonomic dysfunction—hyperesthesias, neurogenic bladder, constipation, impotence

- Disseminated (viremic) infection—occasional in patients with atopic eczema, pregnant women, impaired CMI, neonates
 - High mortality
 - Fulminant hepatitis
- Ocular involvement
 - More common with HSV-1
- Herpetic whitlow
 - More common with HSV-1

Why Is Genital HSV Increasing?

- Frequency of misdiagnosis
- Lack of awareness with unintended spread
- Chronicity of condition with lifelong infectivity
- Occurrence of symptomatic viral shedding
- Lack of cure
- High rate of recurrence—90% recur at least once in first year (60% have four or more)

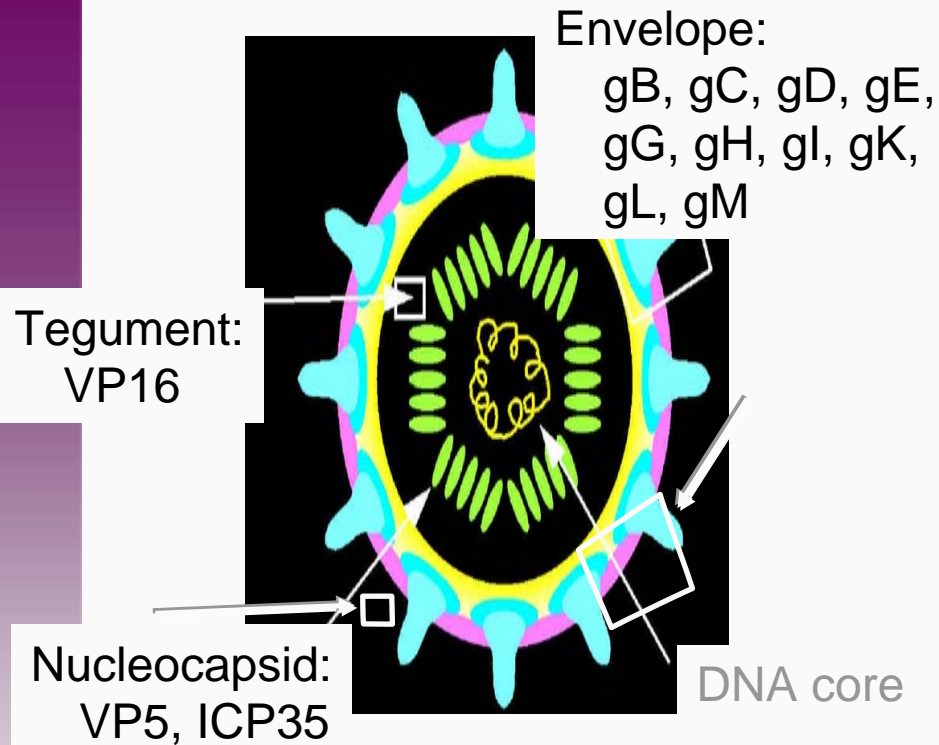


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Section D

Herpes: Diagnosis

- Isolation of virus in culture
- Modified culture techniques
 - Shell vial or spin amplification methods
 - ELVIS™ (Enzyme-Linked Virus-Inducible System)
- Antigen detection
 - Direct fluorescent antibody (FA)
 - EIA (Herpcheck)
- DNA amplification methods
 - Polymerase chain reaction (PCR)
 - TaqMan, LightCycler



Glycoprotein gG tests

Western blot

gG ELISA

gG-membrane tests

gG immunoblot

Table 1. Commercial Type-Specific gG-Based Serology Kits*

	Manufacturer	HSV Type
FDA Approved		
HerpeSelect® ELISA	Focus	HSV-1, HSV-2
HerpeSelect® Immunoblot	Focus	HSV-1, HSV-2
POCkit® HSV-2 Off the market	Diagnology	HSV-2
Premier™ ELISA Off the market	Meridian	
Not FDA Approved		
Cobas®-HSV-2	Roche	HSV-2
QuickVue® HSV-2	Quidel	HSV-1, HSV-2

* The Western blot assay, which is considered the gold standard, is not commercially available. HSV indicates herpes simplex virus; FDA, Food and Drug Administration; ELISA, enzyme-linked immunosorbent assay.

Limitations of gG-Based tests

- Antibodies to gG arise relatively late—first appearing two to three months after infection in 60–70% of newly infected persons
- Therefore, Western blot detects seroconversion more quickly (not a commercially available test)
- Type specific IgM tests are under development

- The sensitivities of these assays for detection of HSV-2 range from 80-98% (false negative results may occur)
- Specificities are high (>96%), but false-positive results can occur, especially in patients with low likelihood of infection
- Therefore, repeat or confirmatory testing may be indicated

Role of Serology in Clinical Management

- Symptomatic—supplements virus detection efforts
 - When lesions are negative for virus
 - When lesions cannot be sampled for virus
 - When lesions are healed or not present
- Subclinical—high-risk patients
 - Partner has genital herpes
 - Sexual history
 - Symptoms suggestive of atypical or undiagnosed herpes



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Section E

Herpes: Treatment

Recommended Regimen for First Clinical HSV Episode

- Acyclovir 400 mg PO TID
- Acyclovir 200 mg PO 5 x/day
- Famcyclovir 250 mg PO TID
- Valacyclovir 1 g PO BID

for 7-10 days or until clinical resolution

Recommended Regimen for Episodic Recurrent HSV

- Acyclovir 400 mg PO TID
- Acyclovir 200 mg PO five times daily
- Acyclovir 800 mg PO BID
- Famciclovir 125 mg PO BID
- Valacyclovir 1 gm QD for five days
- Valacyclovir 500 mg PO BID for three to five days

- Among patients with frequent recurrences (> 6 per year), reduces frequency by up to 93%
- Safe and efficacious
- Discontinue periodically (once a year) and reassess

Recommended Regimens for Daily Suppression of HSV

- Acyclovir 400 mg PO BID
- Famciclovir 250 mg PO BID
- Valacyclovir 500 mg PO once a day
- Valacyclovir 1.0 g QD if recurrence > 10 per year

Does Suppressive Therapy Decrease Subclinical Shedding?

- Wald, A., et al. (1996). *Ann Intern Med*; 124: 8-15
 - Double-blind, placebo-controlled, crossover clinical trial comparing acyclovir 400 mg BID for 70 days, followed by a 14 days washout period, then placebo or in reverse order
 - 34 women with HSV 2 of less than two years' duration
 - Daily samples of vulvar cervicovaginal and perianal areas, diary of symptoms
 - Sub-clinical shedding occurred on 83 or 1439 days with placebo (5.8%) vs. six of 1611 days on acyclovir (0.37%)
 - A 94% reduction

Mechanism of DNA Synthesis Inhibition of Acyclovir and New Drugs

- Helicase-primase complex unwinds HSV-DNA at the replication fork and primes both lagging and leading strands
- New drugs bind to this complex and inhibit its activity at a different site than acyclovir



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Section F

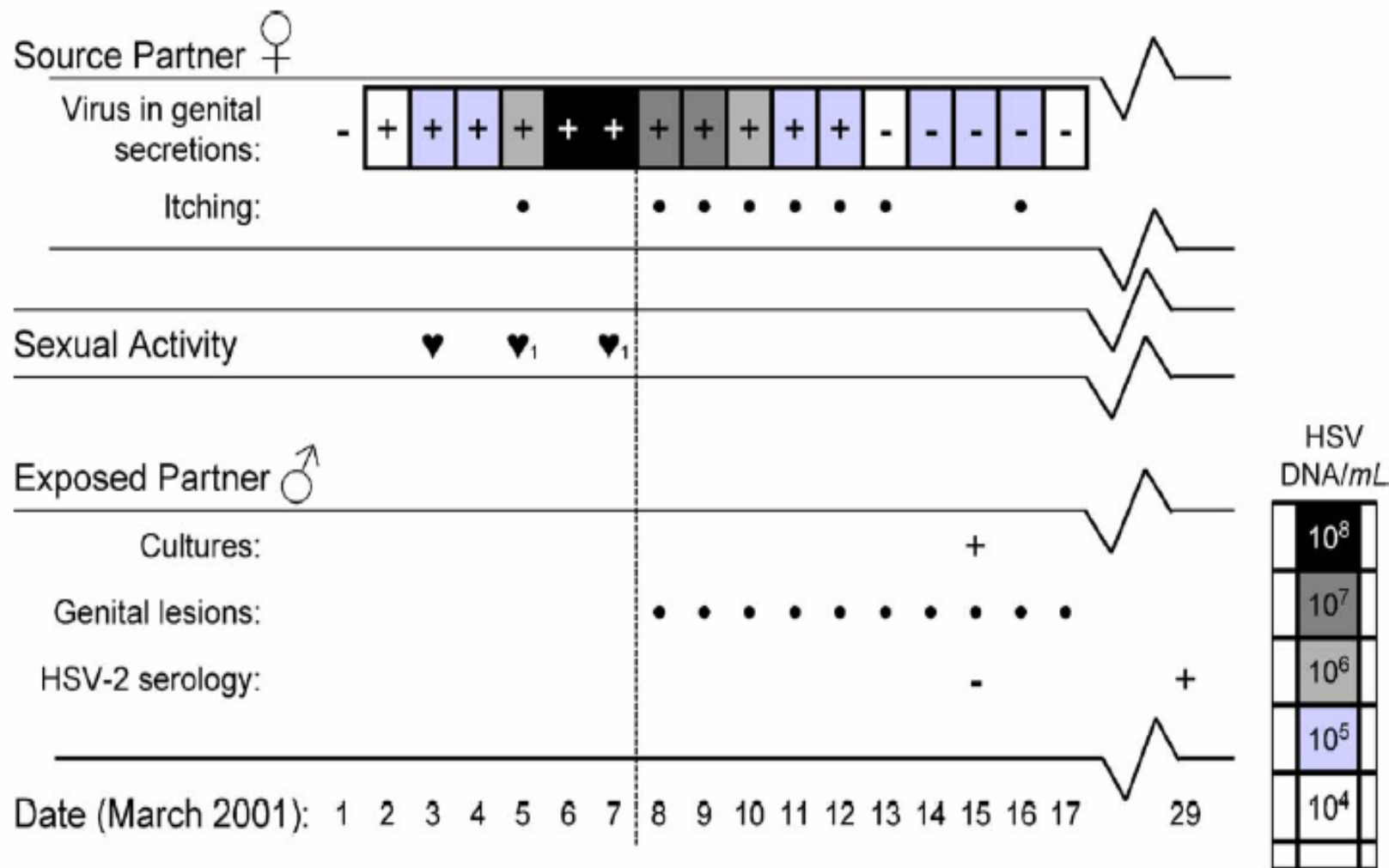
Herpes: Prevention

- Effect of condoms on reducing the transmission of Herpes Simplex Virus Type 2 from men to women
- Reduction from 8.5% to 0.9% incidence in discordant couples (men → women)
- No protective effect seen in women → men

Risk of HSV-2 Acquisition in a Prospective Study (N=528)

Risk	Hazard Ratio
Each additional sex act per week	1.16
Condom use >25% vs. ≤ 25%	0.38
Sex with lesions vs. no sex w/ lesions	2.01
Acyclovir use by source partner	0.64

Transmission of HSV-2 in a Discordant Couple

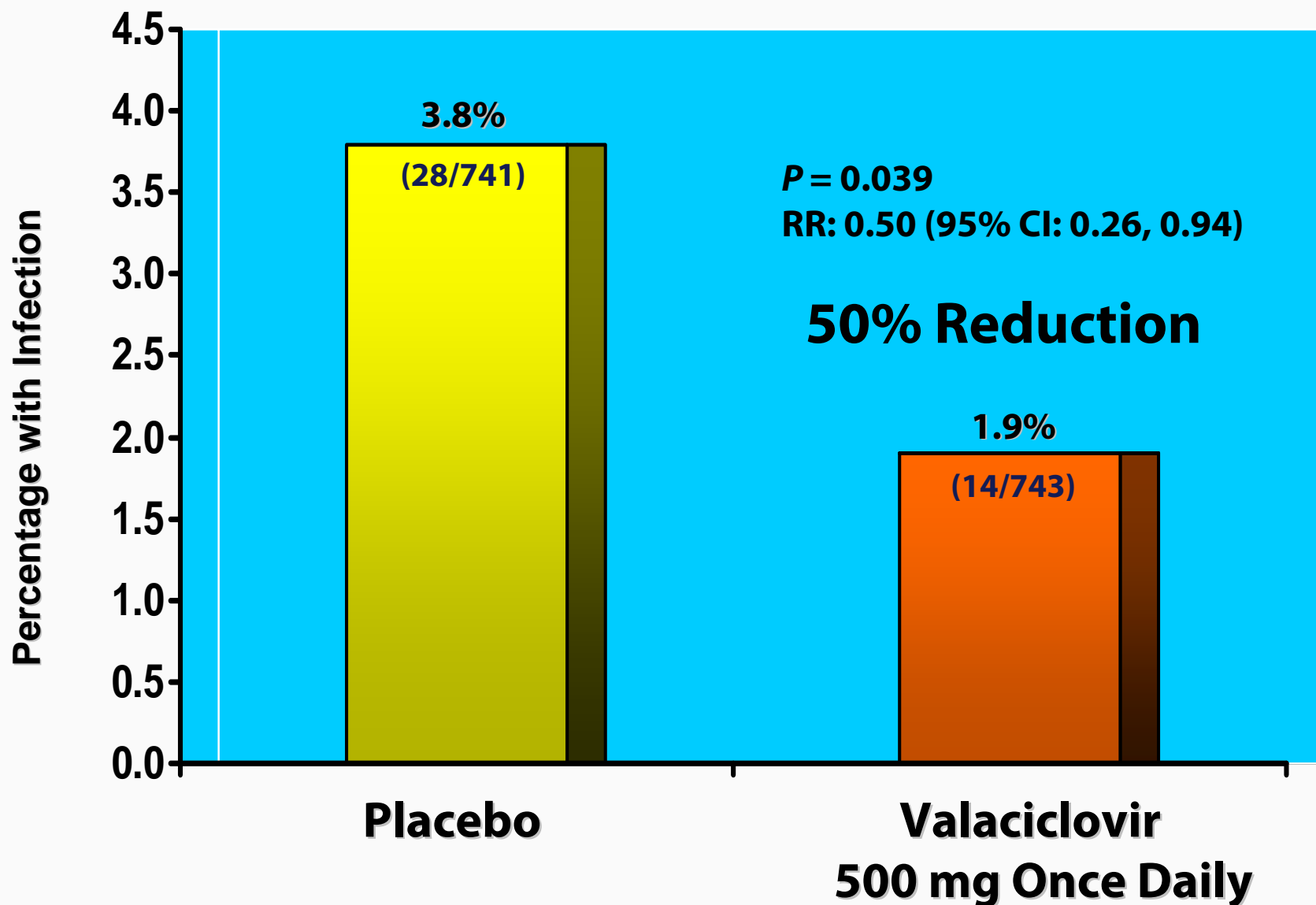


¹Source partner reports irritation during sexual intercourse

Once Daily Valaciclovir Reduces Transmission of Genital Herpes

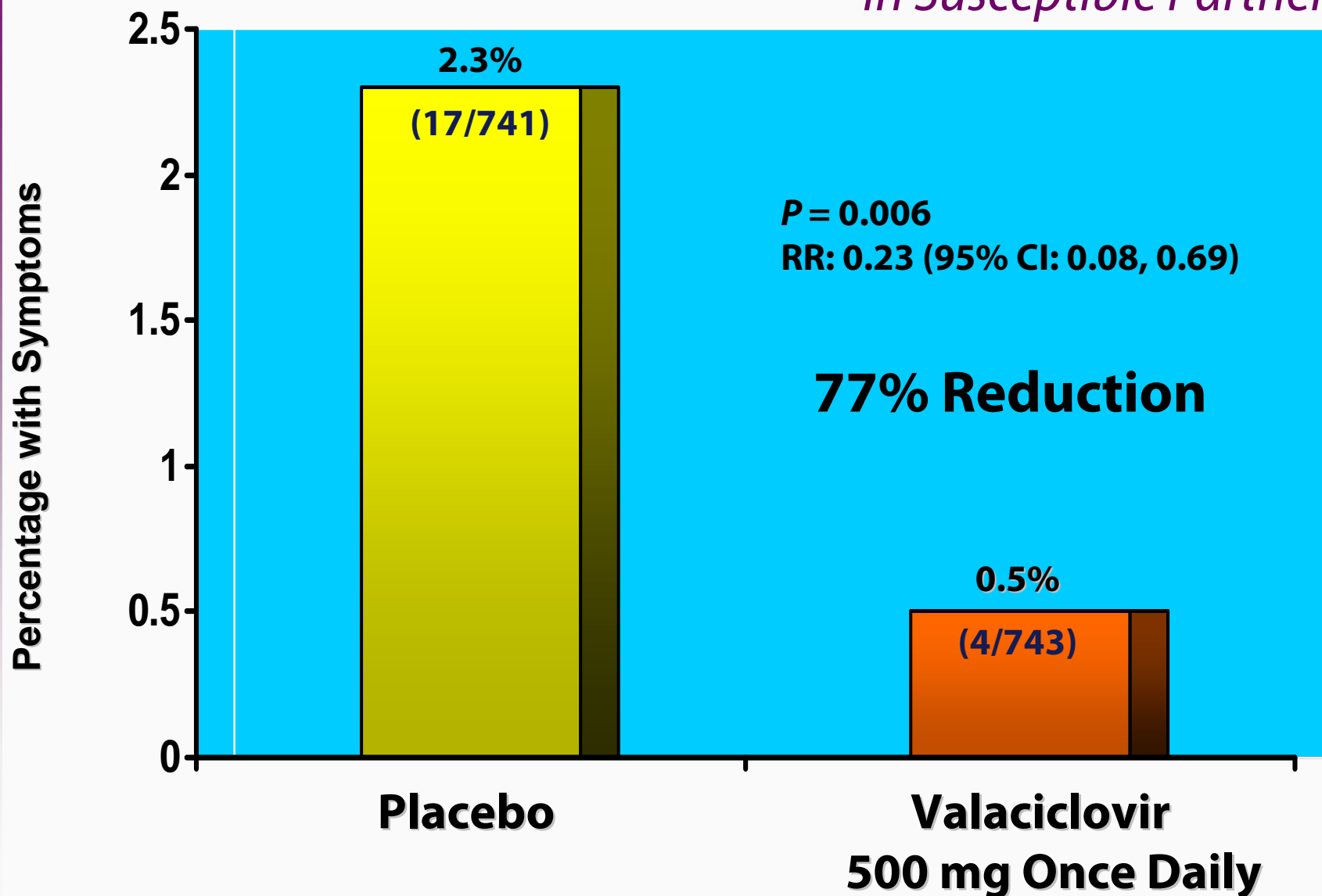
- L. Corey, S. Tyring, K. Beutner, T. Warren, S. Sacks, R. Patel, A. Wald, G. Mertz, J. Paavonen, and the International Valaciclovir Study Group
- *NEJM* 2004; 350:11-20

Proportion of Susceptible Partners with HSV-2 Infection



Frequency of Clinically Symptomatic Genital Herpes

in Susceptible Partners



Conclusions: Valaciclovir 500 mg Once Daily

- Suppressive therapy significantly reduced the rate of transmission of . . .
 - Symptomatic genital herpes by 77%
 - HSV-2 infection by 50%
 - Total HSV acquisitions by 61%

- HSV-2gD plus adjuvant—Smith Kline, in Phase 3 trials, maybe data next year
 - Information: www.herpevac.com
 - 1-866-HERP-VAC
- HSV-2 DISC—Paired mutants, single replication cycle
- HSV-2gD—Nucleic acid vaccine



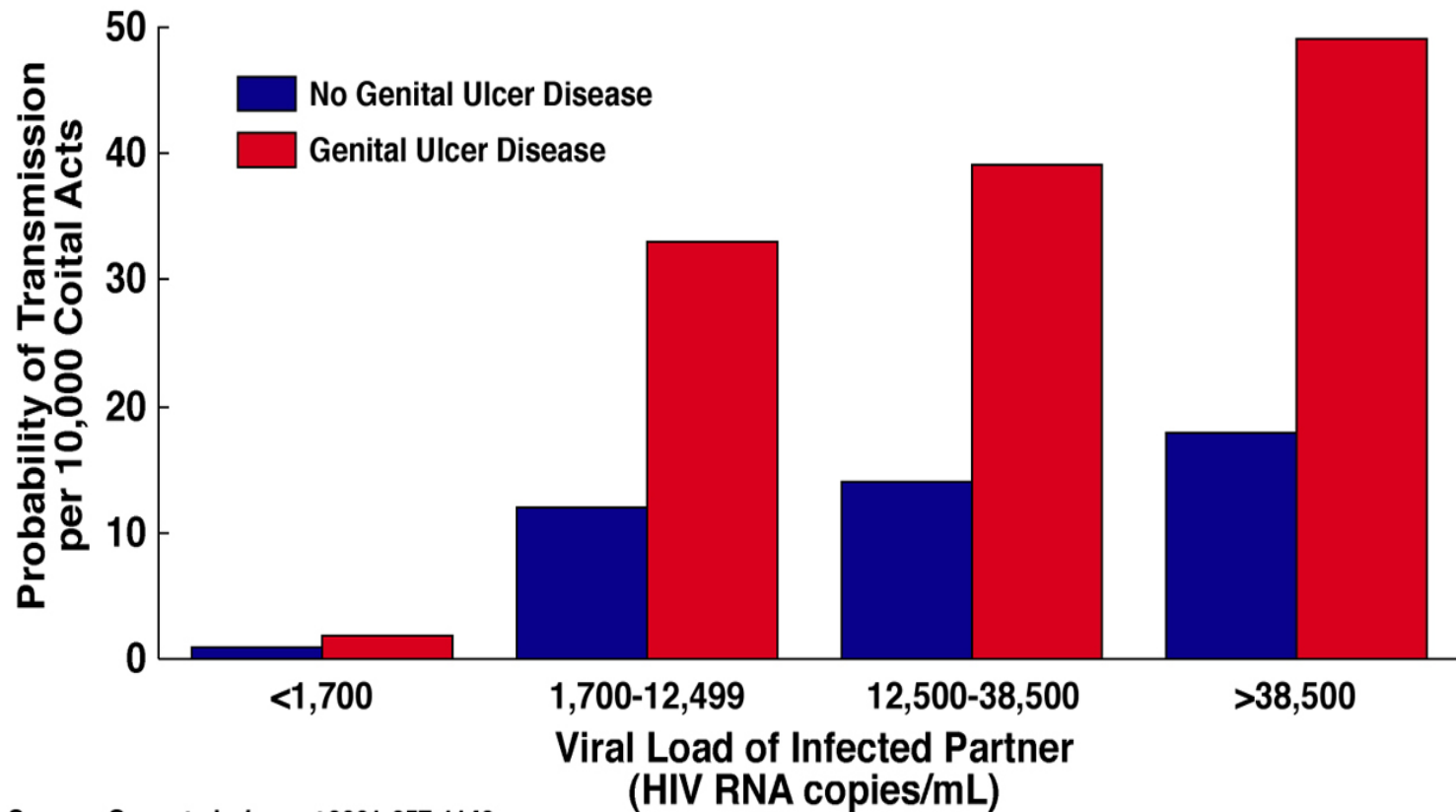
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Section G

HSV and HIV: Relations and Affectations

- Clinically can be more severe
- Requires higher doses of therapy for longer duration
 - Acyclovir 400 mg PO 3-5 x daily
 - Famciclovir 500 mg BID
 - Valacyclovir 1.0 gram PO BID for 5-10 days

Probability of HIV Transmission per Coital Act in Monogamous, Heterosexual, HIV-Discordant Couples in Rakai, Uganda



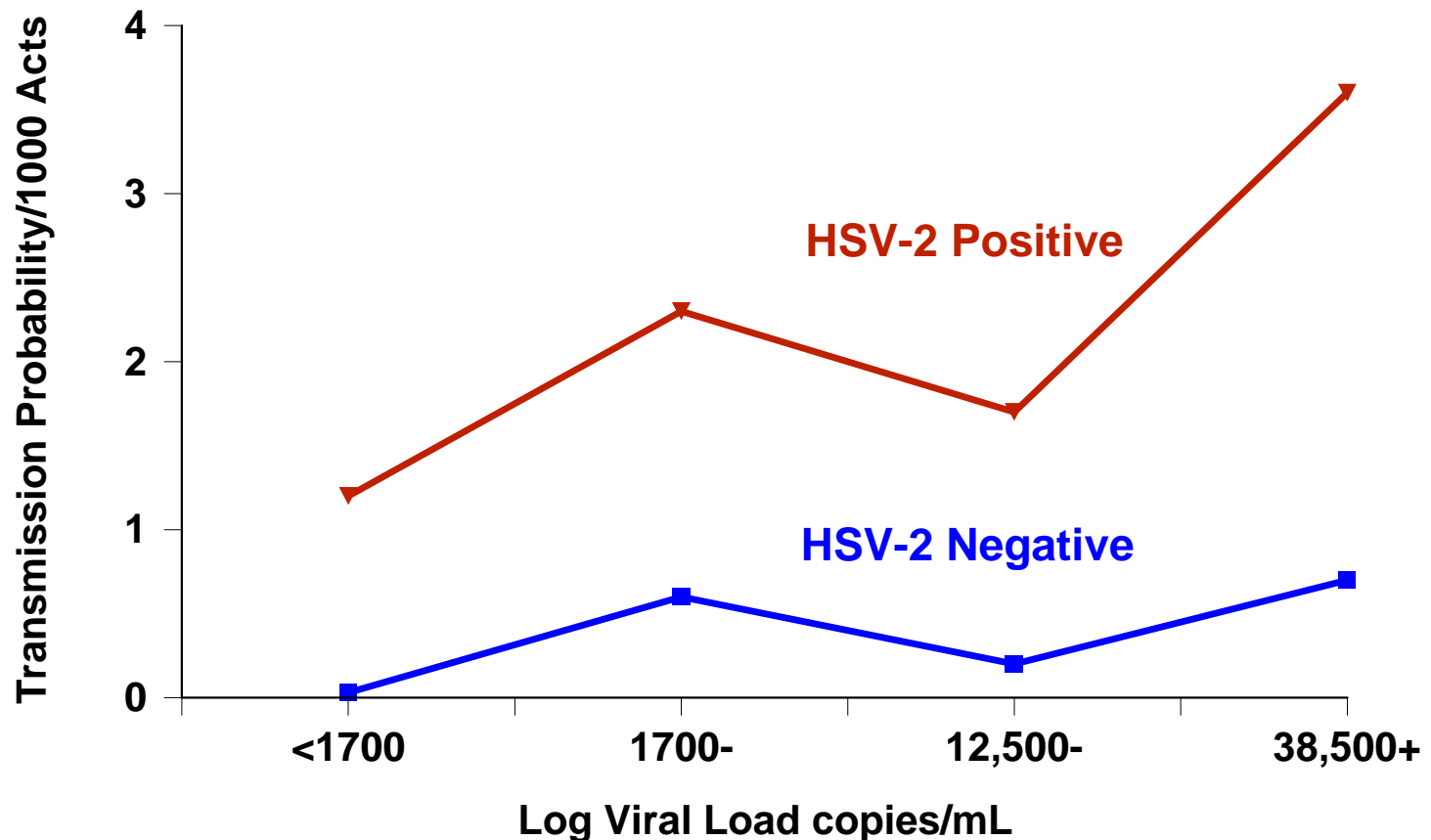
Source: Gray et al., *Lancet* 2001;257:1149

Acquisition Probabilities per Act

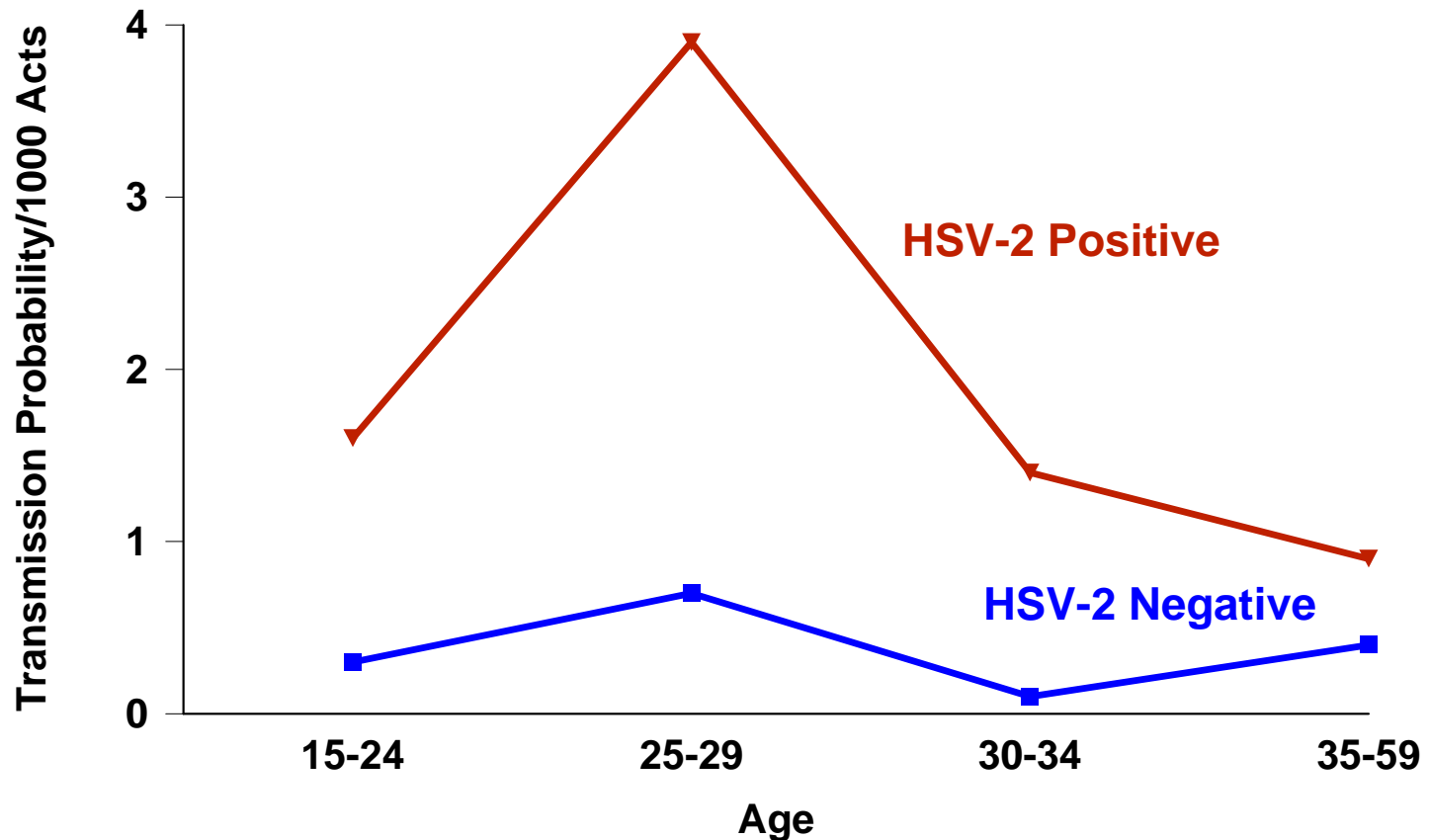
by HSV-2 Status of HIV-Negative Partner

	Acquisition Probabilities per Act
HSV-2 Positive	0.0020**
HSV-2 Negative	0.0004
P = 0.01	

Probability of HIV Acquisition per Sex Act by HSV-2 in HIV-Negative Partner and Viral Load of the HIV-Positive Partner



Probability of HIV Acquisition per Sex Act by HSV-2 Serostatus and Age of HIV-Negative Partner

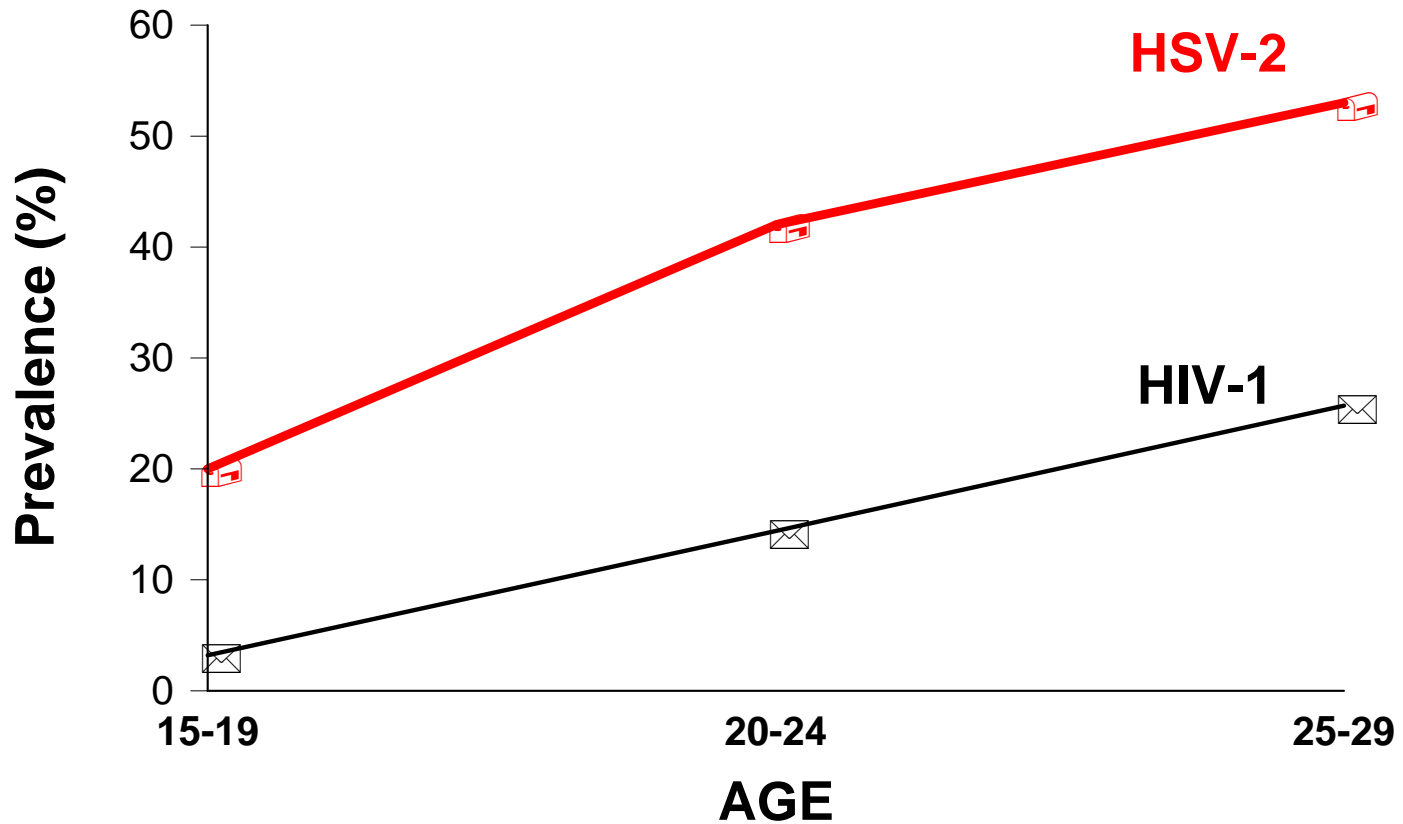


Acquisition Probabilities per Act

by GUD and HSV in HIV-Negative Partner

	Acquisition Probabilities per Act
GUD+/HSV+	0.0031
GUD-/HSV+	0.0019
GUD-/HSV-	0.0004*

Prevalence of HSV-2 and HIV



- GUD risk factor for HIV acquisition (RR~3.0)
- 45% of GUDs are due to HSV-2 (Multiplex PCR)
- Age and sex-specific prevalence of HSV-2 mirrors that of HIV