

Genital Herpes: Framing the Problem, Diagnosing the Disease

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Herpes Simplex Virus

- Mucocutaneous infection, retrograde infection of sensory nerves, continuous slow replication (with clinical latency) in cranial or spinal ganglia and peripheral nerve endings, mucocutaneous recurrences
- HSV-1
 - Mostly orolabial (cold sores, fever blisters)
 - 20%-50% of initial genital herpes in North America and western Europe
- HSV-2
 - Almost entirely genital; oral infection uncommon
 - >90% of recurrent genital herpes

Prevalence of Genital HSV Infection in Adults in the United States

- HSV-2, NHANES-II (1978) 16% (15M age 15-49)
- HSV-2, NHANES-III (1991) 22% (24M age 15-49)
- HSV-2, NHANES 1999-2004 17% (27M age 15-49)
- HSV-2 NHANES 2005-2010 15.3% (27 M age 15-49)
- Genital HSV-1 infection 10 million (??)

- TOTAL >20% >30 million

*Fanfair et al. *Sex Transm Dis.* 2013;40:860-864

Xu F et al. *JAMA.* 2006;296:964-973.

Bradley et al. *JID* 2014;209:325-333

Change in HSV-2 Seroprevalence

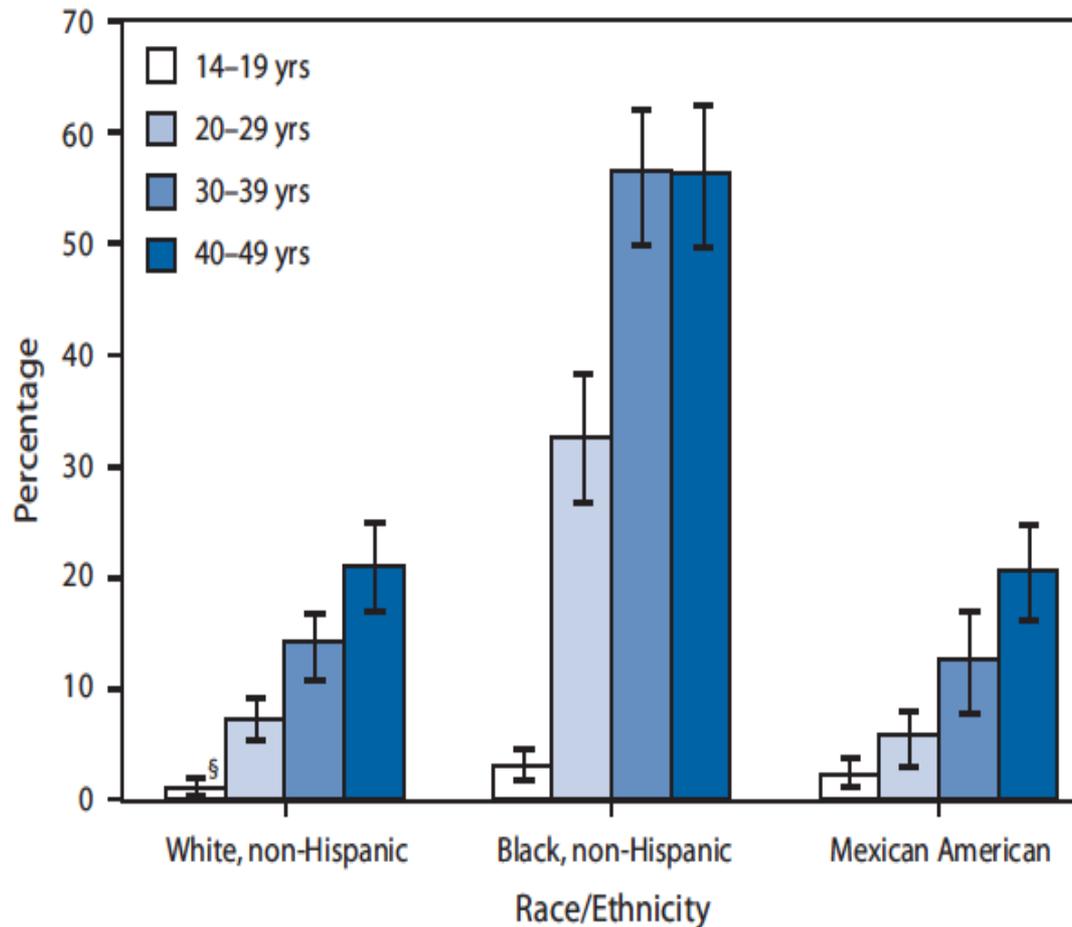
Table 2. Weighted Herpes Simplex Virus Type 2 Seroprevalence by Age Among Men and Women Aged 14–49 Years: NHANES, 1999–2004 and 2005–2010

Age Group, y	1999–2004			2005–2010			% Change	(95% CI)
	Sample Size	HSV-2 Seroprevalence		Sample Size	HSV-2 Seroprevalence			
		%	(95% CI)		%	(95% CI)		
14–19	4650	1.6	(1.2, 1.9)	3180	1.2	(0.8, 1.5)	–24.0	(–47.2, 9.3)
20–29	2412	10.6	(8.8, 12.3)	2658	9.9	(8.7, 11.1)	–6.2	(–23.7, 15.3)
30–39	2251	22.1	(20.1, 24.1)	2592	19.3	(17.1, 21.5)	–12.8	(–24.7, 1.0)
40–49	2195	26.3	(24.1, 28.5)	2670	25.6	(23.1, 28.2)	–2.6	(–14.4, 10.8)
Total	11 508	17.2	(15.8, 18.6)	11 100	15.7	(14.6, 16.8)	–8.5	(–17.6, 1.8)

Abbreviations: CI, confidence interval; HSV-2, herpes simplex virus type 2; NHANES, National Health and Nutrition Examination Survey.

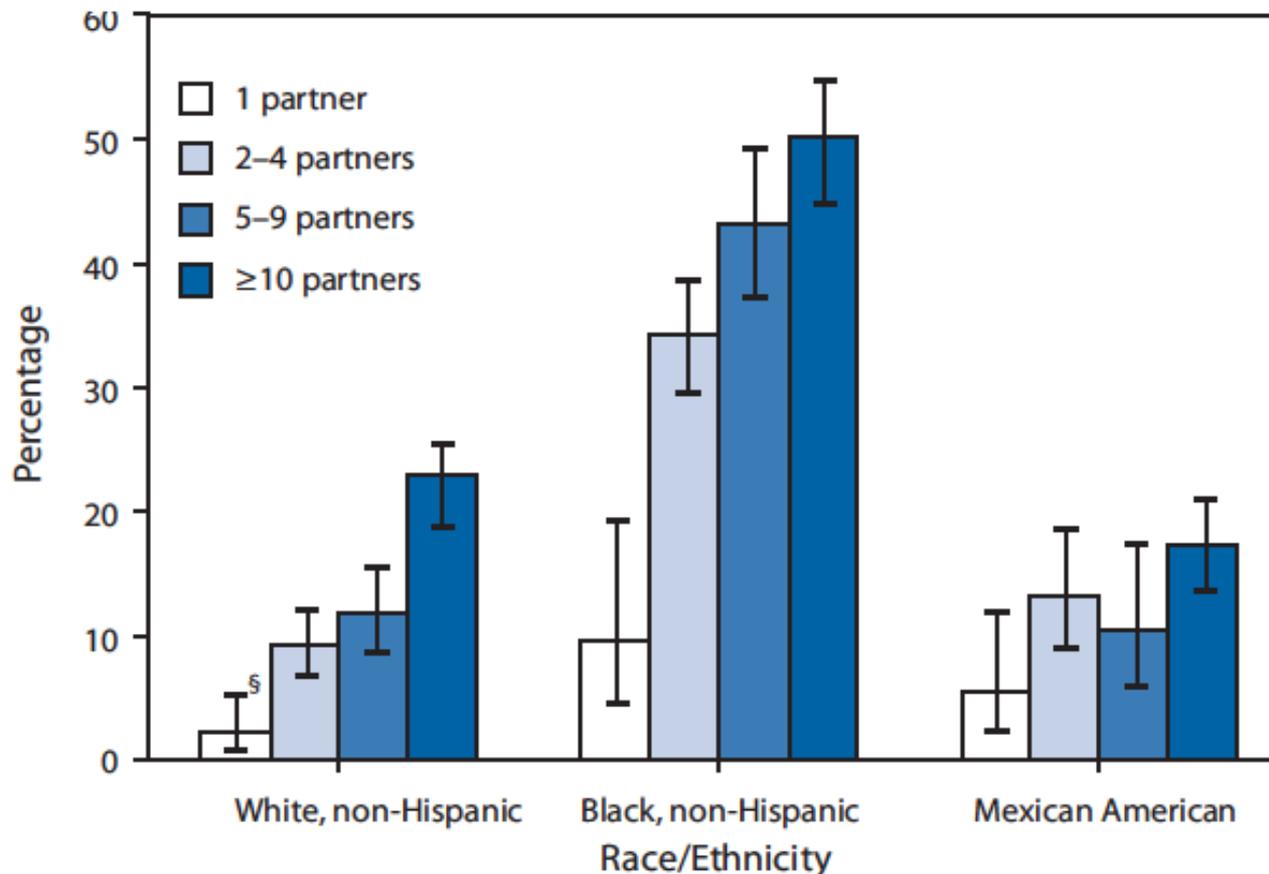
HSV is a Health Inequity Issue

FIGURE 1. Herpes simplex virus type 2 seroprevalence* among persons aged 14–49 years, by age group and race/ethnicity† — National Health and Nutrition Examination Survey, United States, 2005–2008



Network matters more than Number of Partners

FIGURE 2. Herpes simplex virus type 2 seroprevalence* among persons aged 14–49 years who reported having had sex, by number of lifetime sex partners and race/ethnicity† — National Health and Nutrition Examination Survey, United States, 2005–2008



Decreasing Prevalence of HSV-1 Infection

Table 1. Weighted Herpes Simplex Virus Type 1 Seroprevalence by Age Among Men and Women Aged 14–49 Years: NHANES, 1999–2004 and 2005–2010

Age Group, y	1999–2004			2005–2010			% Change	(95% CI)
	Sample Size	HSV-1 Seroprevalence		Sample Size	HSV-1 Seroprevalence			
		%	(95% CI)		%	(95% CI)		
14–19	4650	39.0	(36.7, 41.2)	3180	30.1	(27.3, 32.8)	–22.9	(–30.7, –14.2)**
20–29	2412	54.4	(51.8, 57.0)	2658	49.5	(46.0, 52.9)	–9.1	(–16.4, –1.1)*
30–39	2251	63.5	(60.7, 66.3)	2592	61.8	(58.6, 65.0)	–2.7	(–9.1, 4.1)
40–49	2195	65.3	(62.6, 67.9)	2670	63.6	(60.4, 66.7)	–2.6	(–8.6, 3.8)
Total	11 508	57.9	(56.1, 59.6)	11 100	53.9	(51.6, 56.1)	–6.9	(–11.6, –2.0)**

Abbreviations: CI, confidence interval; HSV-1, herpes simplex virus type 1; NHANES, National Health and Nutrition Examination Survey.

* $P \leq .05$.

** $P \leq .01$.

Asymptomatic acquisition of Genital Herpes

HSV-seronegative women, aged 18–30 years, who were in the control arm of the HERPEVAC Trial for Women were followed for 20 months for primary HSV infections.

Results :

3438 evaluable participants

183 became infected with HSV:

HSV-1: 127 (3.7%)

HSV-2: and 56(1.6%)

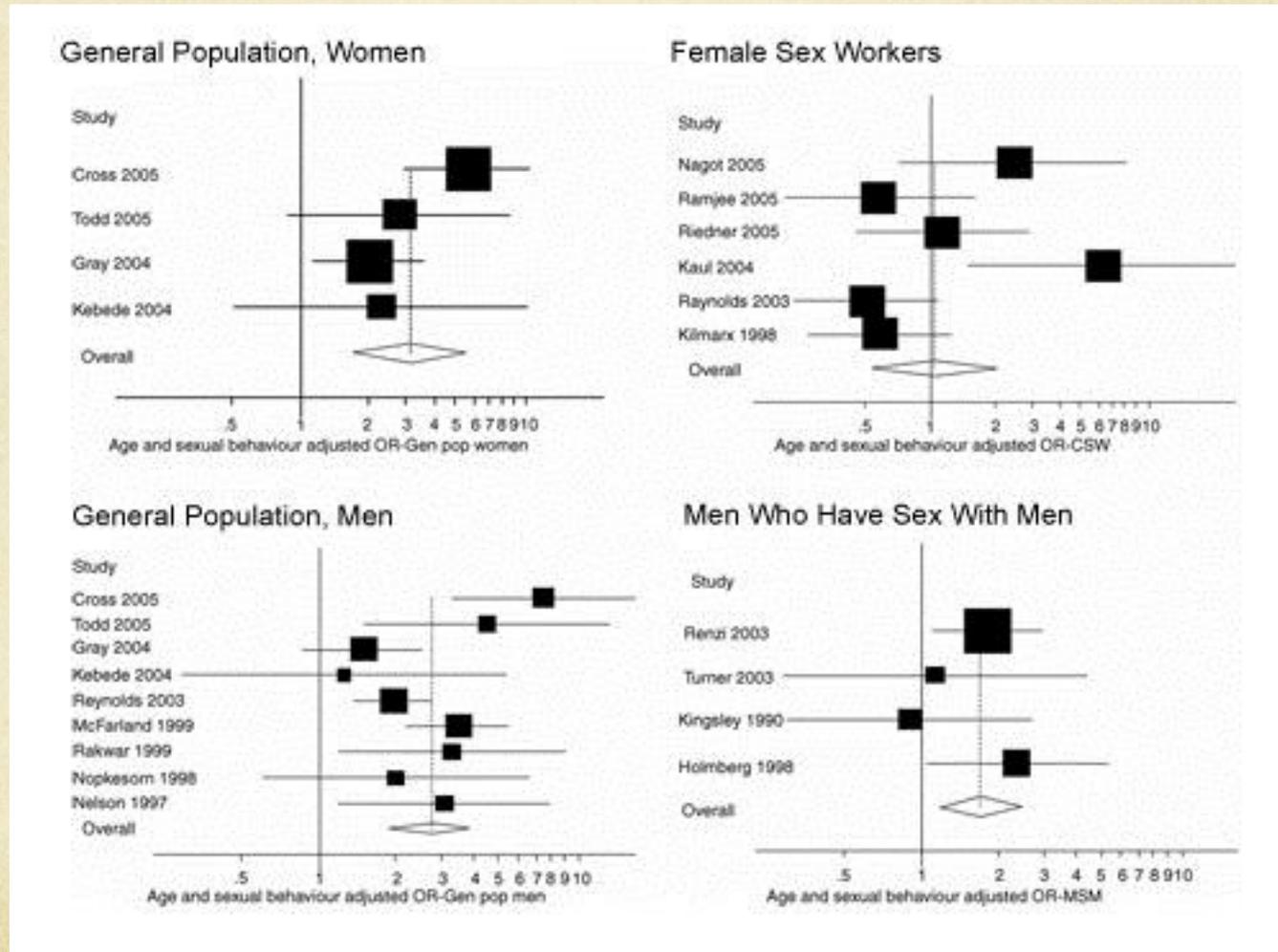
The rate of infection for HSV-1 (2.5 per 100 person-years) was more than twice that for HSV-2 (1.1 per 100 person-years). **Most infections (74% of HSV-1 and 63% of HSV-2) occurred without recognized signs or symptoms of herpes disease.**

**Bernstein *et al.* CID
2013;56;344-351**

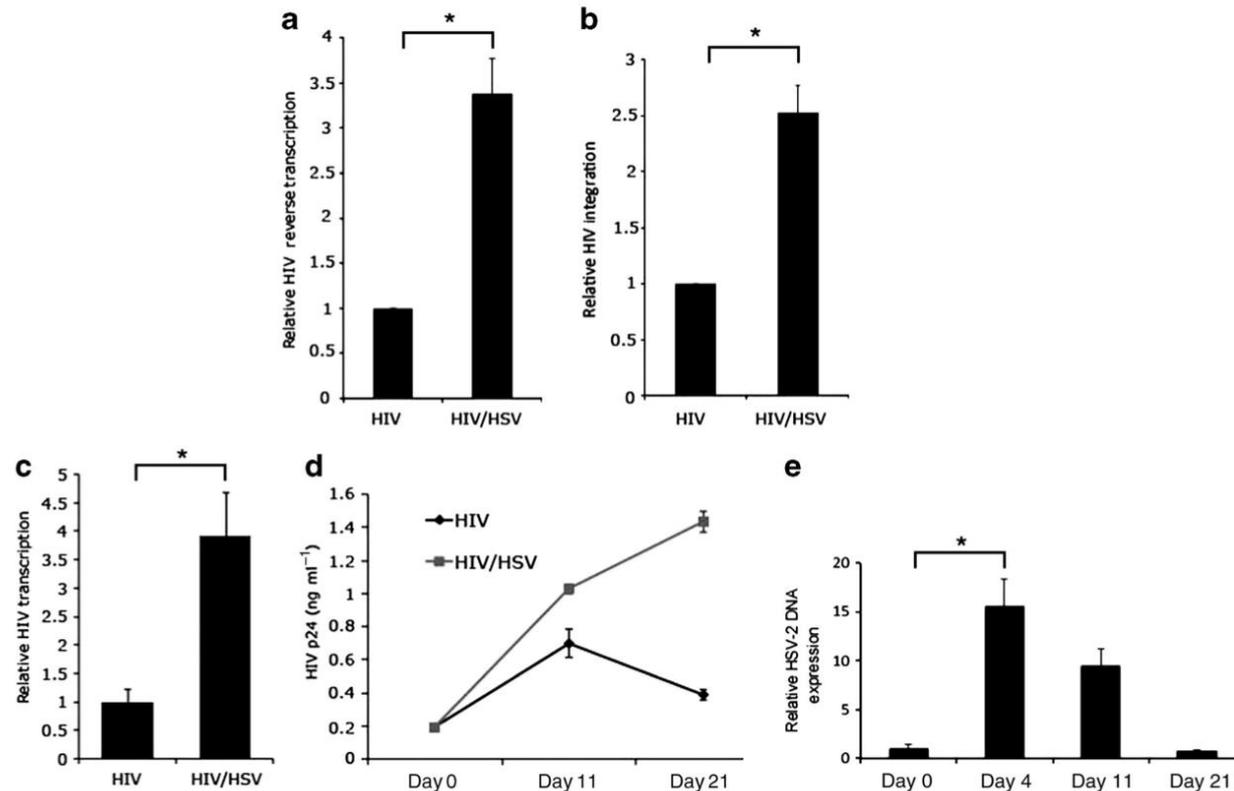
Genital Herpes and HIV Transmission

- HSV-2 infection is an important STD in enhancing HIV transmission efficiency; may account for up to half of all HIV infections
- HSV-2 infected persons have 2–4x increased chance of sexual acquisition of HIV
- Dual HIV and genital HSV-2 infection increases HIV transmission. HSV reactivation increases seminal HIV levels
- Consider HSV-2 serologic screening persons with HIV or at high risk for HIV (MSM, intravenous drug users, and their partners)

Relative Risk of HIV Acquisition in HSV-2 Positive vs HSV-2 Negative Persons

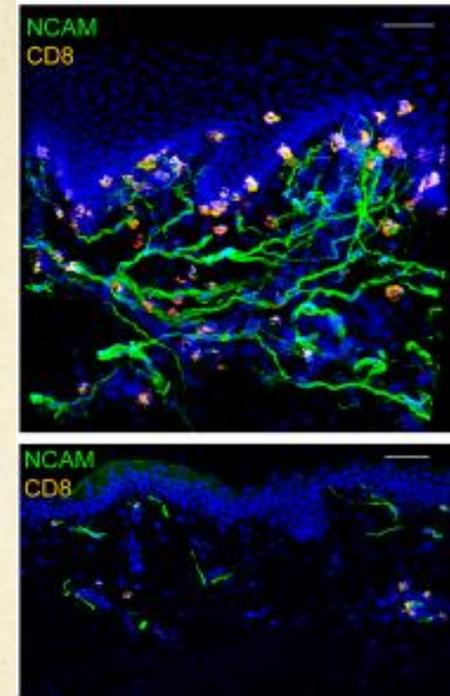
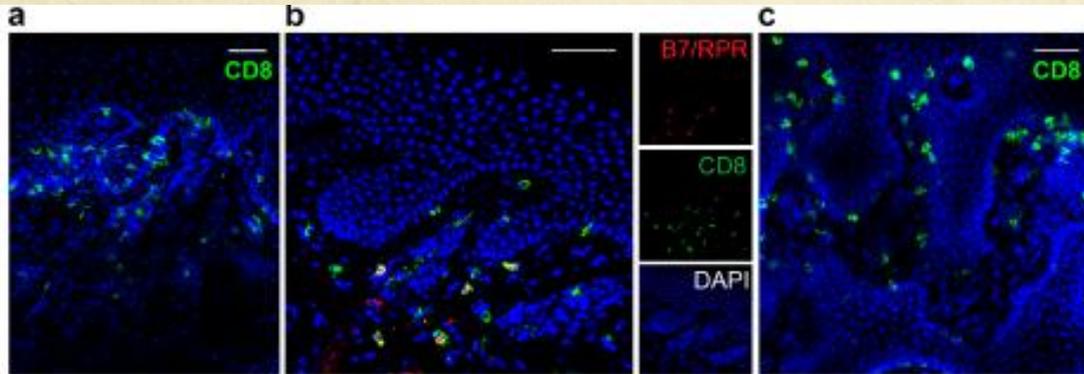


HSV-2 increases HIV expression in ectocervical tissue



Rollenhagen et.al.Nature 2014

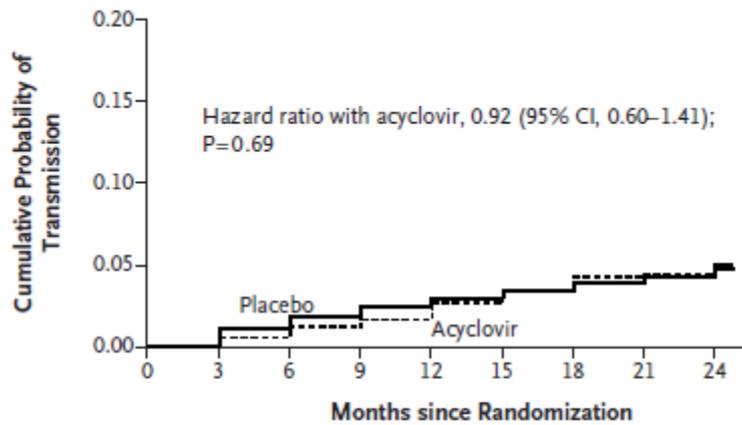
CD8 and HSV-2 and CD4



HSV-2 increases the risk of HIV acquisition, possibly due to increased CD4 β T-cell activation in the cervix and an increased expression of HIV susceptibility markers, CCR5 and a4b7.

**Zhu, J et al JEM 2007
Martinelli, E. et al. PLoS Pathog. 2011
McKinnon, L.R. Curr. Opin. HIV AIDS 2012**

No Effect of HSV-2 suppression on HIV Transmission or Acquisition



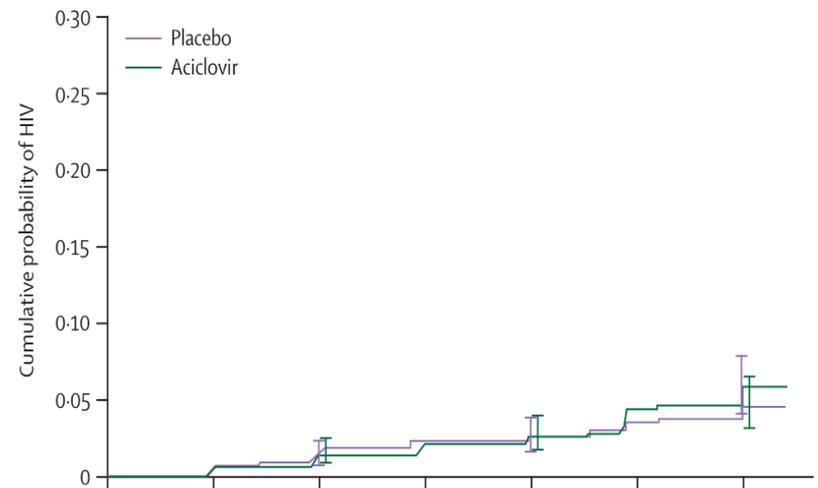
No. at Risk

Placebo	1654	1654	1610	1550	1434	1208	1021	760	570
Acyclovir	1640	1640	1577	1514	1389	1175	1000	761	565

Figure 3. Kaplan–Meier Curves for the Modified Intention-to-Treat Analysis.

The cumulative probability of genetically linked transmission of HIV-1 is shown for the two study groups.

A Overall



Number at risk

Placebo	1591	1526	1496	1441	1104	1016	934
Aciclovir	1581	1509	1467	1423	1174	983	930

HSV is a Spectrum Disease

- Infection results in latency
- Latency  reactivation
- Reactivation = shedding
- Shedding varies in frequency and quantity
- Balance of immune clearance and shedding determines subclinical/disease state

Genital Herpes Clinical Spectrum

- First episode infection
 - Primary: First infection with HSV-1 or -2 (~20%)
 - Nonprimary first episode: Prior infection with the opposite HSV type (~40%)
 - First recognized episode of longstanding infection (~40%)
- Recurrent infection: Second or subsequent outbreak (HSV-2 >> HSV-1)
- Subclinical infection: ~60%–90% of infections
 - Truly asymptomatic
 - Unrecognized















Outbreak Revurrences

- Mean recurrence rate in first year after initial genital HSV-2 infection (N = 457, median FU 391 days)
 - Men 5.2 episodes/yr
 - Women 4.0 episodes/yr
- ≥ 6 recurrences in first year 38%
- ≥ 10 recurrences in first year 20%
- Rate gradually declines over several years
- Recurrence after initial genital HSV-1 (N = 83)
 - Mean recurrences 1.3 yr 1, 0.7 yr 2, & beyond
 - 38% had no recurrences

What Triggers Recurrent Outbreaks?

- Oral HSV-1
 - Other infections ('cold sore,' 'fever blister')
 - Actinic/ultraviolet injury
 - Other local trauma (eg, surgery)
- Genital HSV-2
 - *No clearly documented triggers*
 - No good data support stress, diet, menstruation, sex, etc, despite anecdotal reports and strongly held beliefs to the contrary

Asymptomatic Viral Shedding in Transmission and Acquisition of HSV-2

Key Facts for genital HSV-2

- Transmission occurs frequently between outbreaks^[1]
- Nearly all shed virus asymptomatically^{*[2]}
- Patients cannot predict when AVS will occur^[3]
- All are at risk for AVS, regardless of outbreak frequency^[3]
- Shedding is a nearly continuous process
- Safer sex practices should be used
 - Even with safer sex , it is still possible to transmit HSV
 - Condoms cannot provide 100% protection against transmission, they do not cover all potential sites of HSV shedding

*Shedding in the absence of lesions

1. Corey L, Wald A. *Sex Transm Dis.* 1999;285-312.

2. Wald A, et al. *N Engl J Med.* 1995;333:770-775.

3. Mertz GJ, et al. *Ann Intern Med.* 1992;116:197-202.

Asymptomatic Viral Shedding

- Asymptomatic viral shedding (AVS) is the presence of HSV on the surface of the skin/mucosa in the absence of signs and symptoms^[1-3]

1. Corey L, Wald A. *Sex Transm Dis*. 1999;285-312.

2. Wald A, et al. *N Engl J Med*. 1995;333:770-775.

3. Mertz GJ, et al. *Ann Intern Med*. 1992;116:197-202.

Asymptomatic Viral Shedding Is Common and Can Occur Frequently

- Most GH patients experience asymptomatic shedding*
- PCR has a ~3-4 times higher detection rate than culture

Asymptomatic Shedding	Via Culture†	Via PCR†
% of patients with ≥ 1 day	51%-61%	72%-88%
% of days	2.0%- 6.6%	7.8%- 27%

PCR = polymerase chain reaction; *shedding in the absence of lesions; †shedding rates can vary based upon time since diagnosis, frequency of recurrences, method of detection, frequency/site of sampling

Gupta R, et al. *J Infect Dis.* 2004;190:1374-1381.

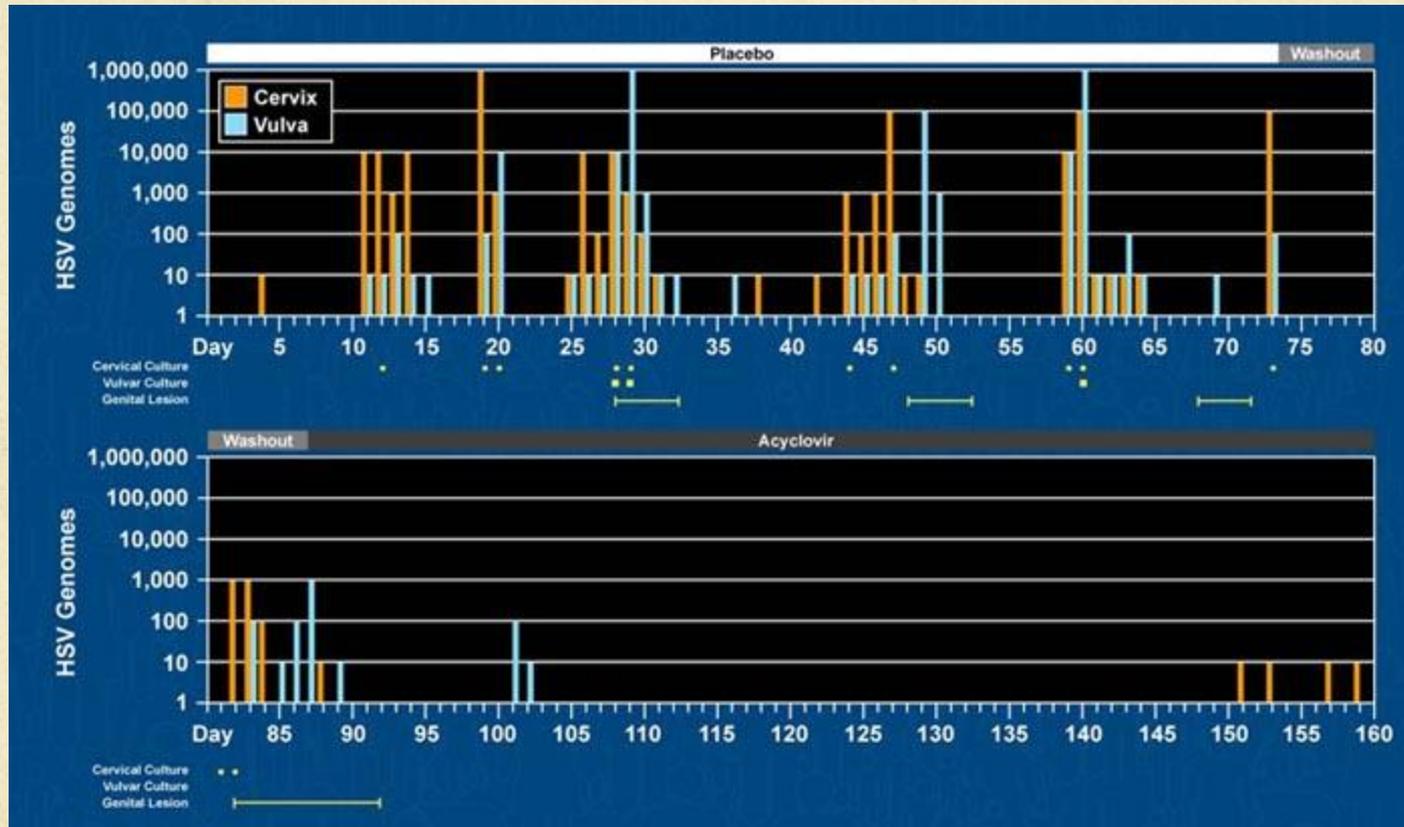
Wald A, et al. *N Engl J Med.* 1995;333:770-775.

Corey L, et al. *N Engl J Med.* 2004;350:11-20.

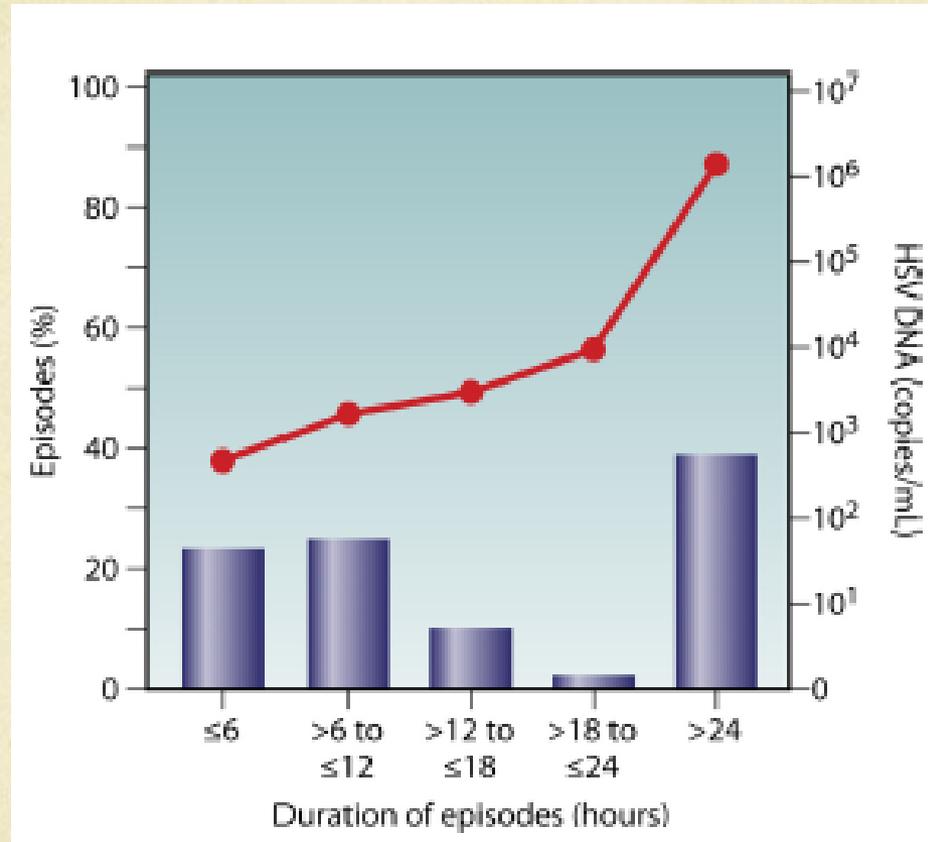
HSV-2 Shedding and Frequency of Outbreaks

- Those with symptomatic hx detected on **20.1%** of day; (18.3%-22.0%) vs. **10.2%** (7.7%-13.6%) asymptomatic infection ($P < .001$).
- Subclinical shedding rates were higher in persons with symptomatic infection compared with asymptomatic infection **13.1%** (11.5%-14.6%) vs. **8.8%** (6.3%-11.5%) ($P < .001$)
- No difference in amount of subclinical shedding detected similar
- Difference in shedding mostly due to lesions

Viral Shedding Patterns Are Unpredictable and Influenced by Therapy



AVS Duration



Mark KE, et al. JID 2008

HSV-2 transmission probability estimates

- Predict transmission is unlikely at viral loads less than 10^4 HSV DNA copies.
- Most transmissions occur during prolonged episodes with high viral copy numbers.
- Many shedding episodes that result in transmission do not reach the threshold of clinical detection

**Schiffer, et.al;
J. R. Soc. Interface. 2014 11 95 2014 (26 March
2014)**

Up to 70% of Transmission May Occur During Asymptomatic Viral Shedding

- 9.7% of patients infected their partner (14/144)
- Transmission frequently occurs between outbreaks

Transmission during asymptomatic viral shedding



Transmission during symptomatic outbreaks

Summary of Asymptomatic Viral Shedding

- Infection = Shedding
- Asymptomatic viral shedding (AVS) is frequent and difficult to predict when and where
- AVS does decrease with time but remains high over time. Most of the decrease in shedding occurs within the 1st 6-12 mo of infection
- AVS driving force for transmission

Genital Herpes: Diagnosis

Diagnosis of Genital Herpes

- Test all genital ulcers for HSV, including clinically obvious genital herpes
 - Clinical diagnosis insensitive and nonspecific
 - Virus type determines clinical prognosis, transmission, and counseling
- Virologic tests
 - PCR is test of choice
 - Culture : less sensitive after ulceration
 - Direct FA: Some don't provide virus type
 - Cytology (Tzanck prep): Insensitive, no virus type; do not use
- Serologic testing: Use only glycoprotein G (gG)-based assays

Uses of Type-Specific HSV Serology

Definite Indications

- Diagnosis of GUD, recurrent symptoms, etc
- Management of sex partners of persons with herpes
- Persons with or at risk for HIV acquisition

Other Uses

- Selected (all?) pregnant women and their partners
- Patient request
 - Request to test for herpes
 - Comprehensive STD evaluation

Screen All Sexually Active Persons (controversial)?

Type-Specific HSV Serologic Tests

Antibody to HSV-1 or -2 glycoprotein G (gG-1 or gG-2)

- Western blot
 - The gold standard but expensive and need reference lab
- *HerpeSelect* HSV-1 and HSV-2 ELISA
 - Sensitivity for HSV-2 ~90%, specificity ~98%
 - Insensitive for HSV-1
 - HSV-2 may be falsely positive at low index values (1.1-3.5). Such low values should be confirmed with another test, such as Biokit or the Western blot
- *HerpeSelect* HSV-1 and HSV-2 Differentiation Immunoblot
 - Same antigen as ELISA, probably similar performance
- *biokitHSV2*
 - Point of care
 - HSV-2 only

Interpreting HSV-2 *HerpeSelect*

- The numerical value is the ratio between the test optical density (OD) and control, *not a titer*
 - <0.9 Negative
 - $0.9-1.1$ Equivocal
 - $1.1-3.5$ Positive, but influenced by HSV-1
 - >3.5 Unequivocally positive
- Notes
 - Varying values below 0.9 are meaningless
 - Some values $1.1-3.5$ are false positive if HSV-1 antibody is present

HSV IgM Testing is Not Clinically Useful

- Not type specific
- Does not distinguish early from late infection
- False-positive results common
- There is no valid indication for use in adults

Options for Confirmatory Testing of the HSV-2 ELISA

- BioKit Assay
- Western blot
- Immunoblot
- ELISA avidity assay
- Repeat/convalescent testing

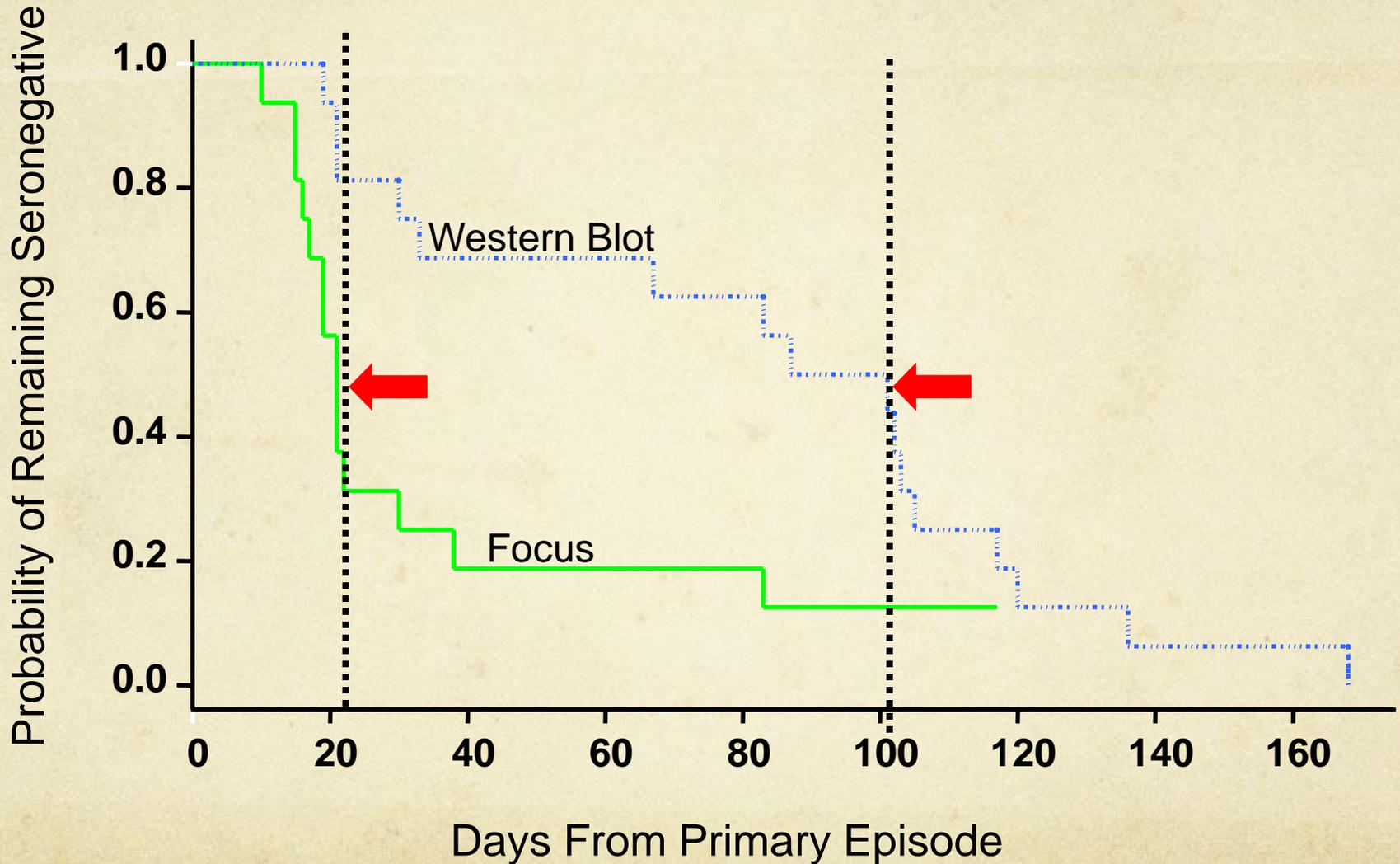
Workowski KA, et al. 2015. MMWR Recommen Rep 64(RR-3):1–137.

Wald A, et al. 2002. Clin Infect Dis 35:S173–182.

Golden MR, et al. 2005. Sex Transm Dis 32:771–777.

Morrow RA, et al. 2005. BMC Infect Dis 5:84.

Time to HSV-2 Seroconversion



Prevention and Available and Emerging Treatments for HSV-2 Infection

Interventions for HSV

- Beneficial
 - oral antiviral therapy in first episodes (Statistically and clinically significant for disease but not transmission)
 - oral antiviral therapy at a start of recurrence (Statistically significant but not clinically significant for disease or transmission)
 - daily antiviral therapy significant to control disease and/or reduce risk of transmission

Transmission Reduction: *What Can Be Done?*

- Advise patients to avoid sexual contact during outbreaks

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- Offer suppressive therapy

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- Advise patients to avoid sexual contact during outbreaks
- Inform patients about transmission risk during periods of asymptomatic shedding
- Offer suppressive therapy
- Condoms

Condom Sense

- Condoms appear ~ 30% protective against HSV-2 acquisition in men and in women.
- Evidence for condoms' efficacy will always be measured indirectly

Wald A, et al. *Ann Intern Med* 2005;143:707-713.

Wald A, et al. *JAMA* 2001;285:3100-3106.

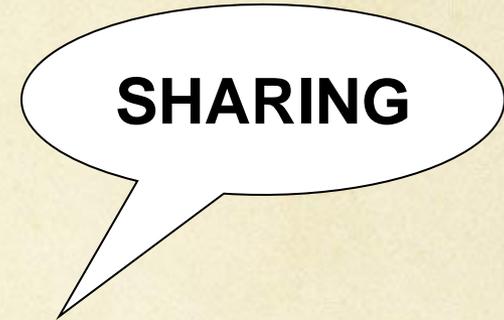
Gottlieb SL, et al. *J Infect Dis* 2004;190:1059-1067.

Transmission Reduction: Disclosure to Sexual Partners

- A recent study found that a strong protective factor against genital HSV-2 acquisition was partner disclosure of genital herpes
- Median time to transmission
nondisclosers: 60 days

vs

disclosers: 270 days $P = .03$



Suppressive Antiviral Therapy to Reduce Transmission Risk

CDC Sexually Transmitted Diseases Treatment Guidelines and ACOG Recommend Daily Therapy

- **CDC:** Discordant couples should be encouraged to consider suppressive antiviral therapy as a part of a strategy to prevent transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences
- **ACOG:** For couples in which 1 partner has HSV-2 infection, suppressive* antiviral therapy should be recommended for the partner with HSV-2 to reduce the rate of transmission

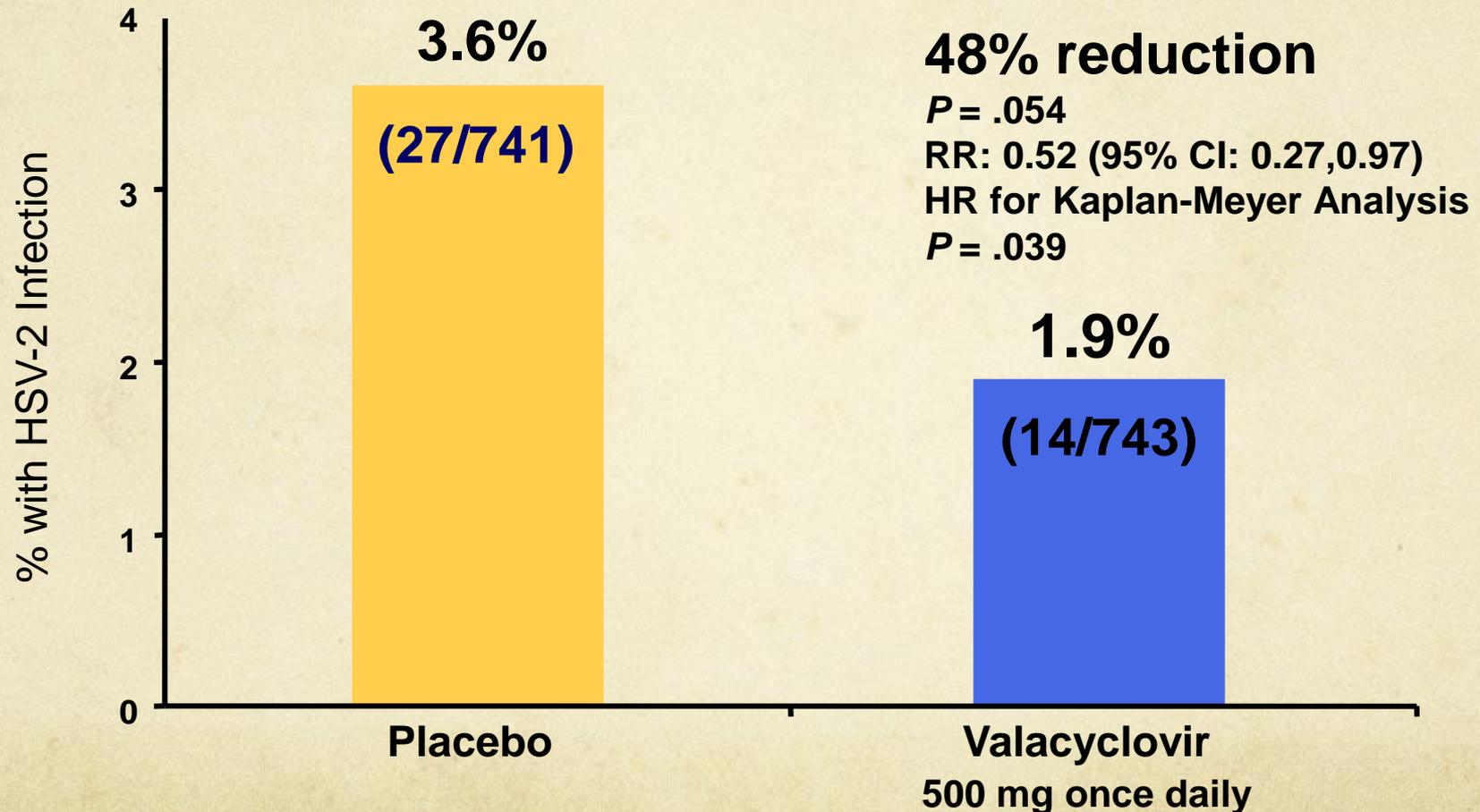
Centers for Disease Control and Prevention. *MMWR Recomm Rep.* 2006;55(R-11):1-94.

***ACOG recommends valacyclovir 500-1000 mg daily for suppressive therapy.**

ACOG Practice Bulletin. *Obstet Gynecol.* 2004;104:1111-1117.

Workowski KA, et al. 2015. MMWR Recommen Rep 64(RR-3):1-137.

Proportion of Susceptible Partners With Overall Acquisition of HSV-2 Infection



Initial Episode

- **Acyclovir**
- 400 mg t.i.d. or 200 mg 5 times/d for 7 to 10 days

- **Famciclovir**
- 250 mg t.i.d. for 7 to 10 days

- **Valacyclovir**
- 1 g b.i.d. for 7 to 10 days

Treatment Options: Episodic Therapy

	5-Day Regimens	Shorter Regimens
Acyclovir	400 mg t.i.d. 800 mg b.i.d.	800 mg t.i.d. for 2 days
Famciclovir	125 mg b.i.d.	1 g b.i.d. for 1 day
Valacyclovir	1 g q.d.	500 mg b.i.d. for 3 days

Treatment Options: Suppressive Therapy

Possible dosing regimens¹:

–**Acyclovir**

400 mg b.i.d.

–**Famciclovir**

250 mg b.i.d.

–**Valacyclovir**

500 mg q.d. or (for >10 occurrences/year)

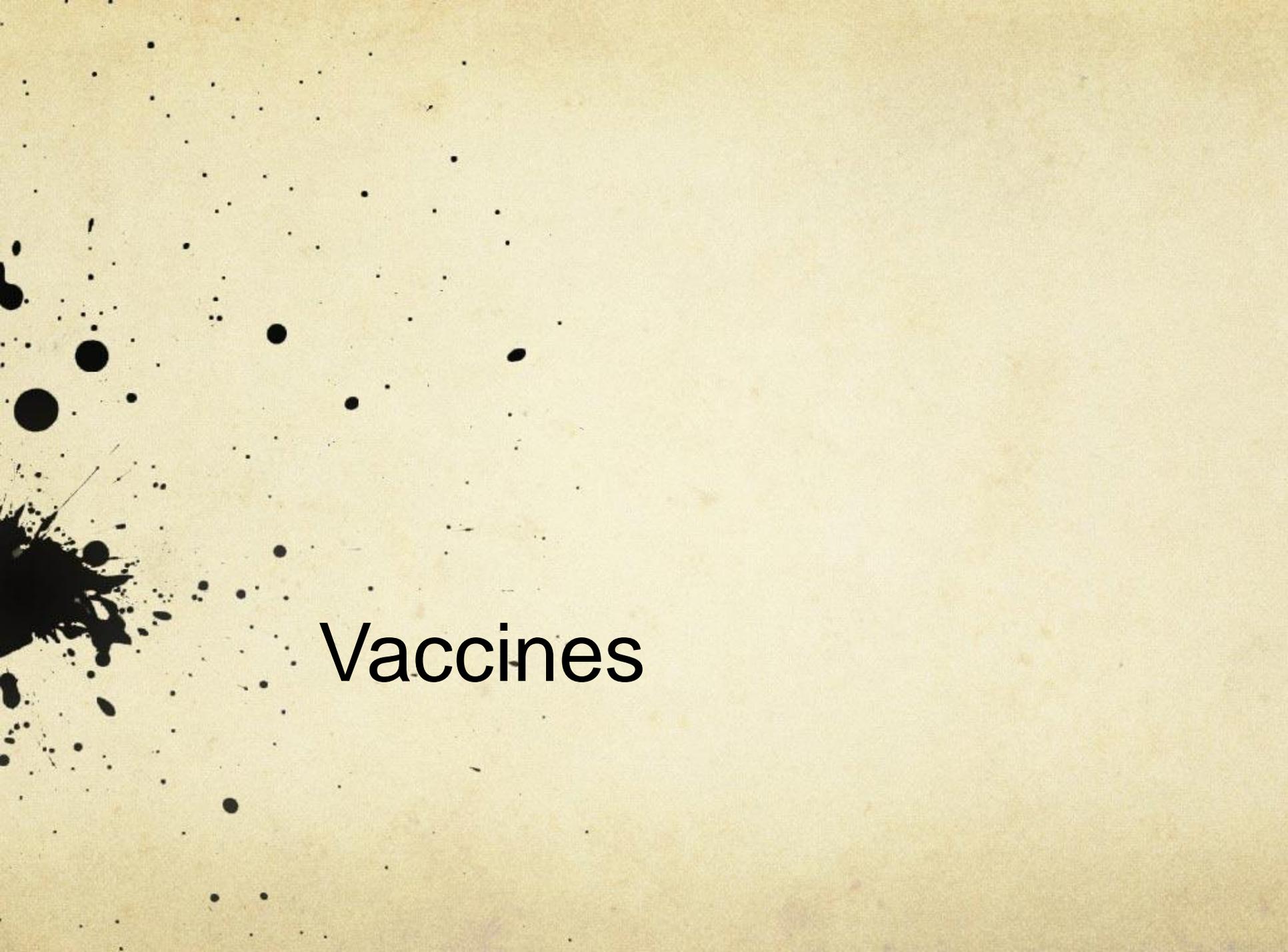
1 g q.d.

Candidates for Antiviral Suppressive Therapy

In HSV 2-Infected Patients	Use Antiviral Suppressive Therapy Primarily to	
	Control Disease	Reduce Transmission
With new infection	√	√
With bothersome outbreaks	√	
Who are immunocompromised	√	
Who are in late pregnancy	√	
Who are distressed by the diagnosis	√	
With a sexual partner who is uninfected or has an unknown HSV status		√
With multiple sexual partners		√

Acyclovir resistance

- Suspect if lesions persist or recur while on antiviral treatment,
- Obtain viral isolate for sensitivity testing
- All acyclovir-resistant strains are resistant to valacyclovir, and the majority are resistant to famciclovir.
- Treatment options:
 - Foscarnet, 40-80 mg/kg IV q 8 hours until clinical resolution
 - IV cidofovir 5 mg/kg once weekly
 - Imiquimod topical alternative , as is topical cidofovir gel 1%, however cidofovir must be compounded at a pharmacy. These should be applied to the lesions once daily for 5 consecutive days.



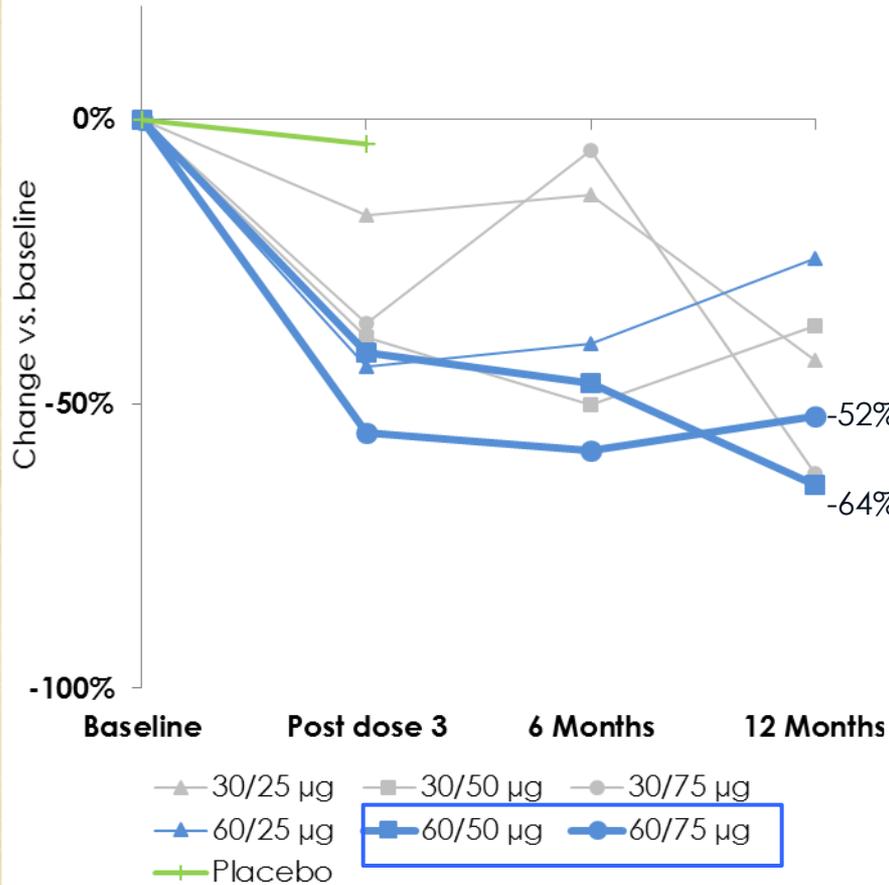
Vaccines

Vaccines

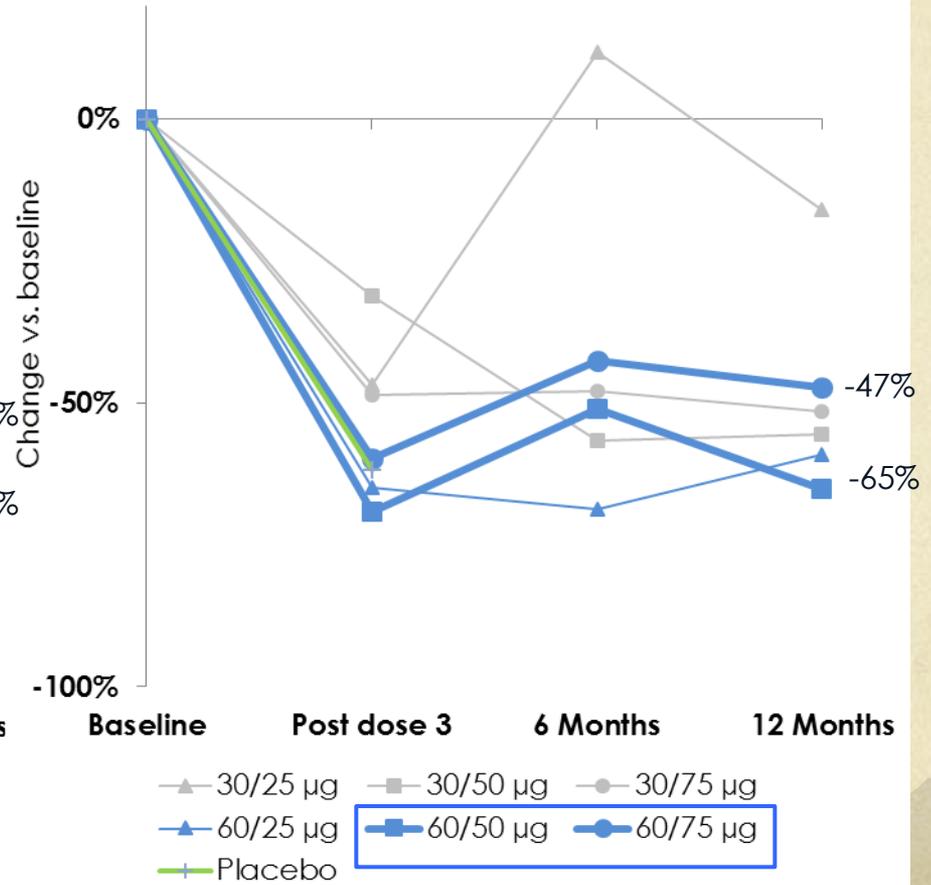
- Prophylactic – failed; primarily glycoprotein based
- Therapeutic: several in trials
 - GEN-003- gD2 and ICP4 with matrix M adjuvant
 - HerpV – 32 HSV Ag complexed with human hsp70 and with QS-21
 - Vical DNA vaccine - vaxfectin liposomes

Sustained Responses at 12m for Both Shedding and Lesion Rates

Shedding Rates

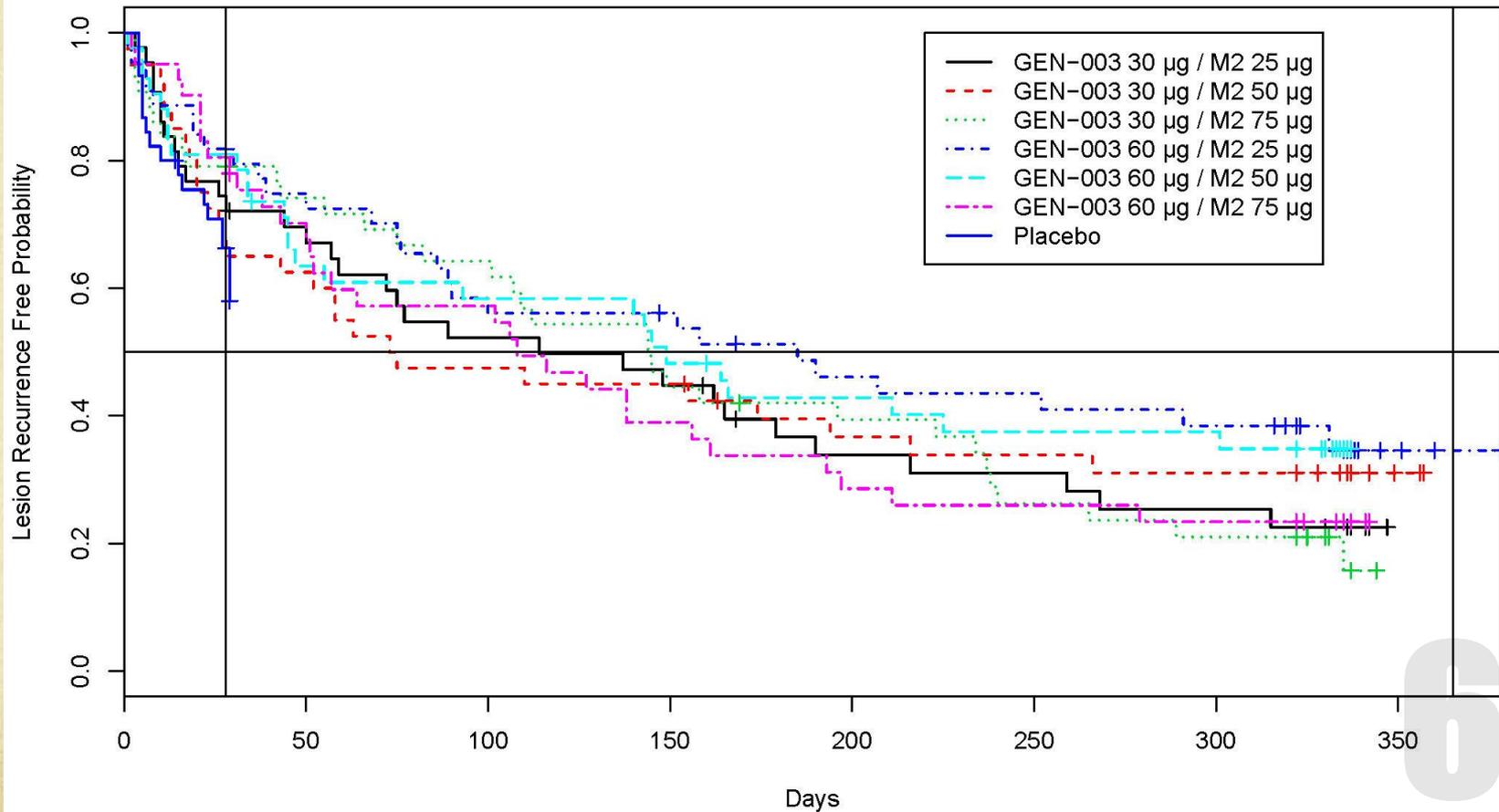


Lesion Rates



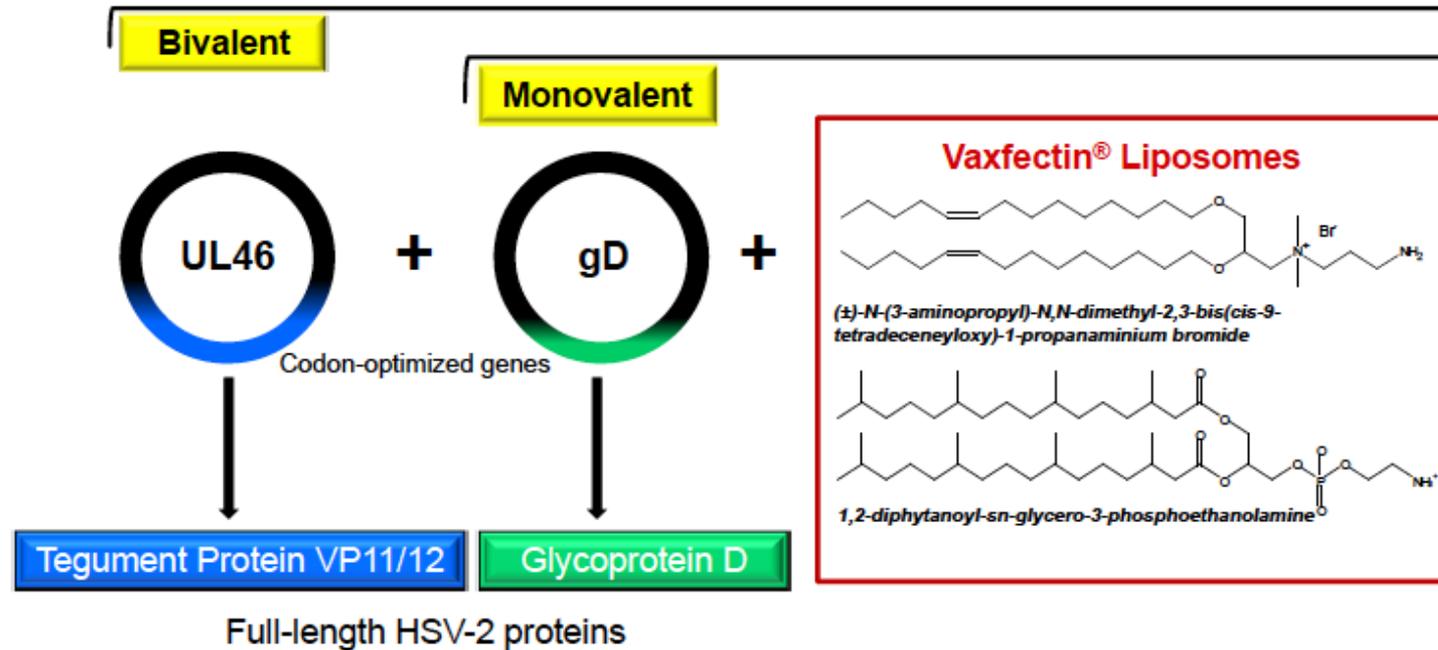
KM Graph – 20-30% lesion free at 12m (Historical comparison: Valtrex 34%, Placebo 4%)

GEN003-002: 12 Month Lesion Recurrence Free Probability



Vical HSV DNA Vaccine

HSV-2 Vaccine Candidates



Vical

Secondary Endpoint – Lesion Rate

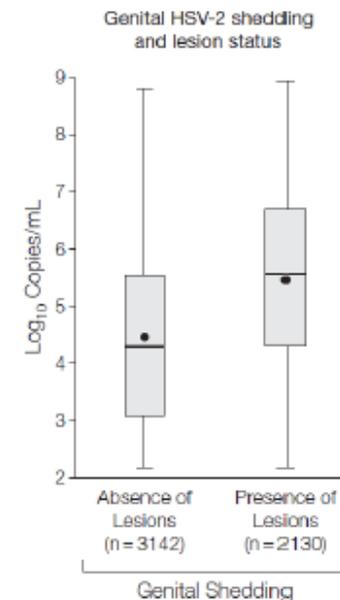
Treatment Group (N)	Prevaccine Lesion Rate [CI]	1 st Postvaccine Lesion Rate [CI]	Rate Ratio [CI]	P-value
Bivalent (56)	6.0 [5.3, 6.9]	2.9 [2.4, 3.6]	0.49 [0.31, 0.79]	0.0037
Monovalent (54)	6.0 [5.3, 6.9]	6.2 [5.4, 7.1]	1.03 [0.70, 1.51]	0.8759
Placebo (21)	6.4 [5.2, 7.9]	3.5 [2.6, 4.6]	0.54 [0.26, 1.09]	0.0850

Vical

What Viral Load is Clinically Meaningful?

- Higher viral loads in presence vs absence of lesions¹
- > 90% of episodes with viral loads > 10,000 copies/mL are associated with lesions
 - 1,000 shedding episodes among 386 subjects²:

Viral Load (copies/mL)	% of Total Shedding Episodes	% of Episodes Associated with Lesions
≤ 10,000	41	9
> 10,000	59	91



Conclusions

- Genital herpes is common and under-recognized
- Shedding is the norm
- Treat to control disease and/or transmission
- Therapeutic vaccines on the horizon