HSV-2 treatment may work to reduce HIV transmission

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Why HSV-2 treatment will work to prevent HIV transmission

- Epidemiologic observations
  - Increased risk of HIV acquisition & transmission due to HSV-2 after adjustment for behavior
  - High Population Attributable Fraction of incident HIV due to HSV-2
- Biologic data
- Mathematical modeling
- Data from initial proof-of-concept trials

HSV-2 and HIV: Early Epidemiologic and Biological Observations

- HSV-2 associated with increased risk for HIV acquisition among MSM in Seattle (Stamm 1988)
- GUD was strong risk factor for HIV acquisition among men who had sex with a prostitute in Nairobi (Simonsen 1988)
- HIV isolated from genital ulcers in Nairobi prostitutes (Kreiss 1989)
- Frequent recovery (25 of 26) of HIV from HSV-2 lesions in MSM (Schacker 1998)
  - Titers of HIV in genital lesions > 10,000 c/mL in 75%
  - Seen in men with low and high plasma HIV levels

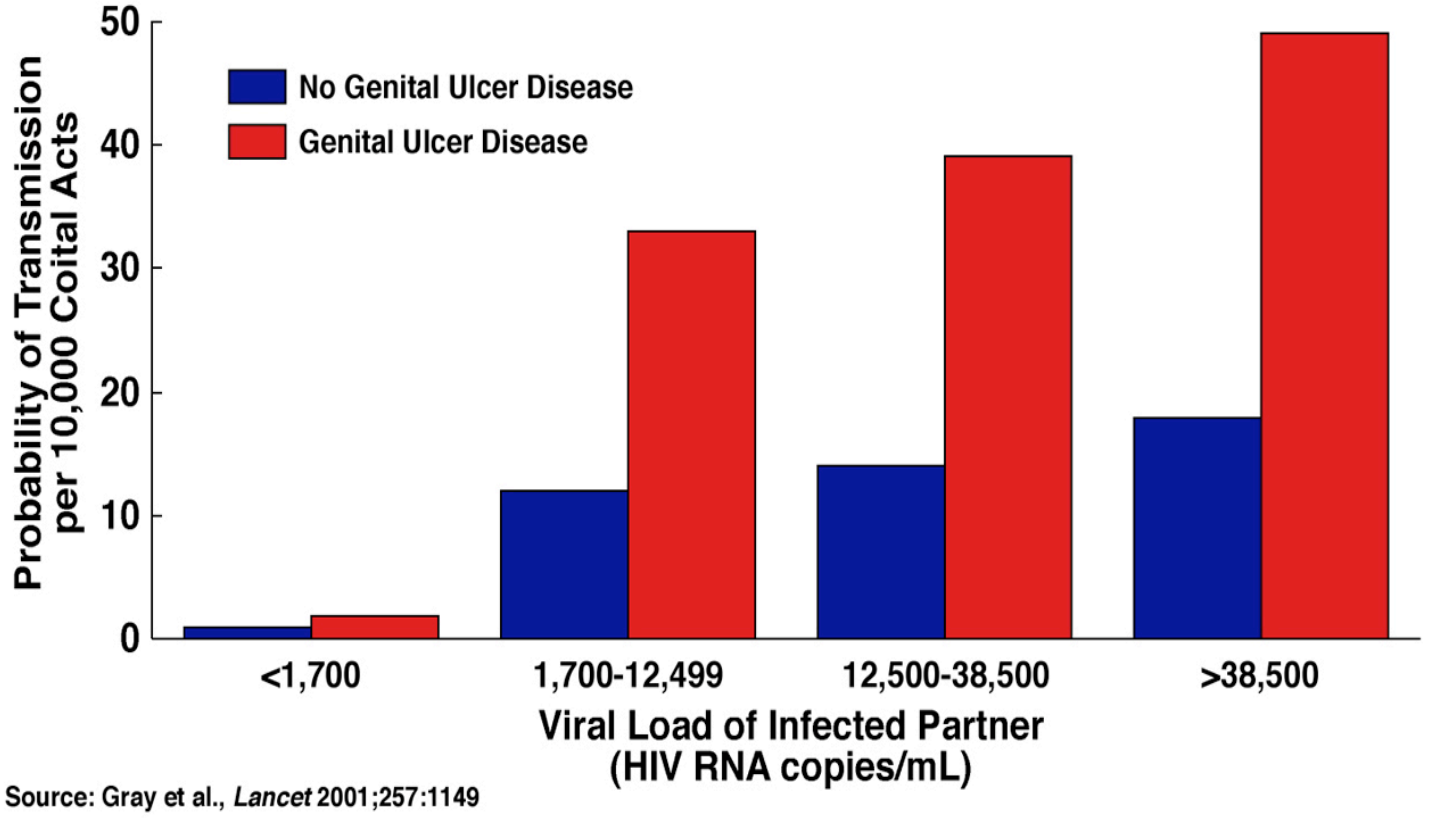
Systematic Review: HSV-2 & HIV Acquisition

- 18 longitudinal studies, which adjusted for age & sexual behavior
- Prevalent HSV-2 infection and HIV acquisition:
  - Heterosexual men: odds ratio [OR[2.7 (95% confidence interval [CI] 1.9-3.9)
  - Women: OR 3.1 (95% CI 1.7-5.6)
  - MSM: OR 1.7 (95% CI 1.2-2.4)
- Incident HSV-2 & HIV acquisition: relative risk [RR] 1.8-6.0
- Potentially 38% to 69% of new HIV infections in ♀ and 8% to 49% in ♂ due to prevalent HSV-2 infection

Freeman, AIDS 2006

Genital Ulcers & HIV Transmission

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



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

HIV Acquisition & Transmission: Mechanisms by Which HSV-2 Increases Risk

- Mucosal or epithelial break
  - Portal of entry or exit during HSV-2 reactivation
  - Can be small, typically unnoticed
- HIV target cells (activated CD4+ cells) in herpes lesions (Koelle 2001)
- Upregulation of HIV replication in HSV-coinfected cells
  - Intermediate cell proteins & *HIV LTR*

    (Mosca 1987, Schafer 1996, Moriuchi 2000)

HSV-2 and HIV: Natural History

- HSV-2 reactivation: ↑ genital & plasma HIV levels (Schacker 1998, 2002; Mole 2000)
- Mortality benefit in HIV-positive persons on acyclovir in HAART era (Ioannidis 1998)
- HSV-2 & GUD: ↑ HIV serum levels in early & chronic HIV infection (Gray, 2003)
- ↑ frequency of HSV-2 reactivation in HIV-positive persons (Corey 2004)
- HAART: ⇓ symptomatic, not subclinical HSV-2 reactivation (Posavad 2004)

Mathematical modeling:
Kisumu: A tale of 2 viruses in a Kenyan city

Back of the envelope calculation

- Male circumcision:
  - ~ 0.4 is RR of acquisition (only in males)
  - ~ 0.7 is RR of transmission per coital act (male to female)

- HSV-2:
  - ~ 2-3 is RR of HIV acquisition
  - ~ 2 is RR of transmission per coital act during HSV-2 activation

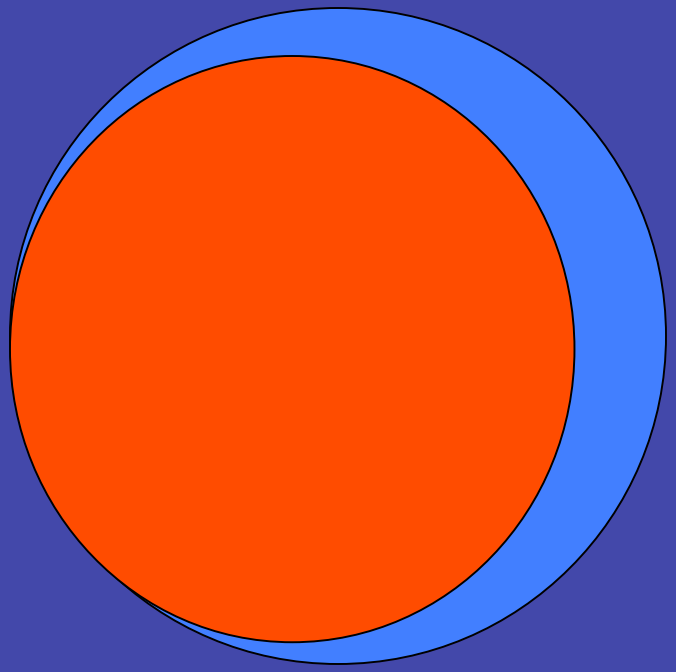
  Intuitively, the impact of HSV-2 is *twice* that of circumcision. HSV-2 may explain up to 2/3 of the difference between high and low HIV prevalence cities.

Another implication: Population attributable fraction of HIV due to HSV-2

Core group of transmitters (CGT)

Core group of transmitters (CGT): HSV-2

For HSV-2, the CGT is the population with ρ > 0.5 effective partners per year



Effect of HSV-2 Suppression on Plasma and Genital HIV Levels

- ANRS 1285a Trial: 140 HIV/HSV-2-coinfected women in Burkina Faso.
  - Median CD4+ cell count 440 cells/mcL,
  - plasma viral load (PVL) 4.5 $\log_{10}$ copies/mL
- 75 days baseline observation
- Randomized to placebo or valacyclovir 1000 mg once daily for 75 days
- HIV-1 RNA in plasma & cervicovaginal lavage q 2 wks

Nagot. CROI 2006; LB33.

Summary: Impact of Valacyclovir on Genital and Plasma HIV-1 RNA

	Baseline Phase Log_{10} Copies/mL		Treatment Phase Log_{10} Copies/mL		*P* Value
	Placebo	VACV	Placebo	VACV	
Mean genital HIV-1 RNA	2.63	2.41	2.72	2.15	- - -
Difference 2 phases (Δ)	- - -		+0.09	-0.26	.003
Mean plasma HIV-1 RNA	4.65	4.17	4.81	3.79	- - -
Difference 2 phases (Δ)	- - -		+0.12	-0.39	.001

- **Mean ↓ in plasma HIV-1 RNA: 0.58 log_{10} copies/mL**
- **Mean ↓ in genital HIV-1 RNA: 0.3 log_{10} copies/mL**

Nagot. CROI 2006; LB33.

Summary: HSV-2 & HIV Interactions

- HSV-2 is highly prevalent in HIV-infected persons
- Strong epidemiologic & biologic data:
  - HSV-2 increases HIV susceptibility & infectiousness
- Large proof-of-concept study: ↓ HIV in plasma & genital tract
- Complimentary HSV-2 suppression studies:
  - HIV acquisition & HIV transmission
  - Acyclovir & HAART, ACV in GUD management
- HSV-2 provides a needed prevention strategy while developing HIV vaccines, microbicides, new interventions