Herpes simplex vaccine development: Pipeline and possibilities

STI vaccines: Advancing the global agenda
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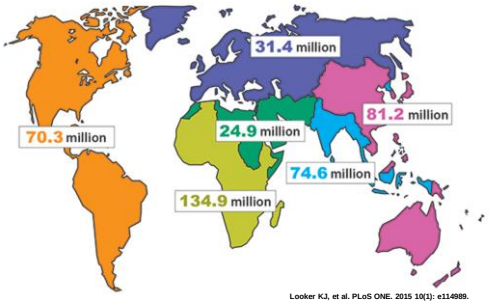
417 million people worldwide are infected with HSV-2 (2012 estimate)



Looker KJ, et al. PLoS ONE. 2015 10(1): e114989.

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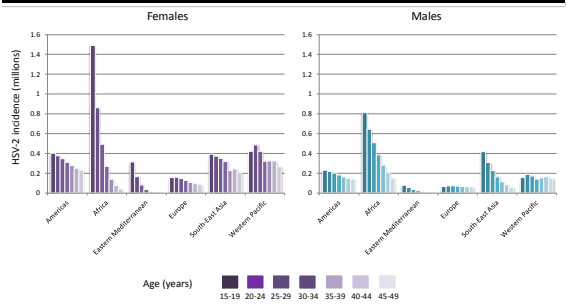
19 million incident HSV-2 cases worldwide (2012)



Adapted from Looker KJ, et al. PLoS ONE. 2015 10(1): e114989.

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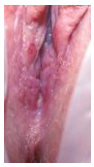
Impact of genital herpes: The case for a vaccine

Leading cause of genital ulcer disease worldwide



Habif. Clinical Dermatology, 3rd ed., Copyright © 1996 Mosby-Year Book, Inc

311,600 years lived with disability (YLD) in 2013

Neonatal Herpes

Rare, high morbidity and mortality

Global Burden of Disease, Lancet 2015

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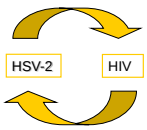
Impact of HSV-2 on HIV epidemic



HSV-2 increases the risk of HIV-1 acquisition 2-3 fold

Genital ulcer disease increases risk of HIV-1 transmission

25%-50% of HIV infections attributable to HSV-2 in high prevalence settings

Modeling studies: a prophylactic vaccine that reduced HSV-2 acquisition by 75% would also decrease HIV incidence by 30-40% after 20 years

Freeman AIDS 2006
Gray Lancet 2001
Masese AIDS 2015
Freeman Vaccine 2009

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Genital HSV-1: a new epidemic

- Now most common cause of first episode genital herpes in women and MSM < 25 years old in USA, Australia, Europe
- May be due to decreasing HSV-1 seroprevalence
  - First exposure to HSV-1 at initiation of sexual activity
- Estimated 140 million cases genital HSV-1 worldwide
- Leading cause of neonatal herpes

Ryder et al, STI 2009
Xu et al, JAMA 2006
Kropp Peds 2006

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HSV-2 prevention strategies

- Antiviral agents
  - Acyclovir, valacyclovir, famciclovir
    - Suppressive: Decreases risk of transmission (50%) among HIV-negative, HSV-2 discordant heterosexual couples in North America
- Male circumcision
  - Decreased risk of HSV-2 acquisition in men
  - Decreased risk of GUD in men and female partners
- Condoms
  - 30% decreased risk of transmission if used all of the time

These strategies are not highly efficacious, are not widely available, and are unlikely to interrupt HSV-2 epidemic

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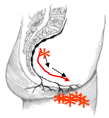
HSV Pathogenesis

Successful pathogen has evolved with us
Many immune evasion strategies



Wide clinical spectrum of infection
Most acquisition and transmission is asymptomatic

Genital HSV-2 shedding is frequent and often subclinical
HSV is detected from genital tract on 20% of days in persons with symptomatic infection

Shedding measured by HSV PCR from genital secretions is a sensitive marker of clinical disease and risk of transmission

Mertz Ann Int Med 1992
Langenberg NEJM 1999
Tronstein et al, JAMA 2011

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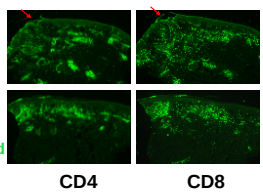
HSV-2 and genital tract inflammation

CD4+/CCR5+ and CXCR4+ cells and resident CD8+ T cells persist for 24 weeks

HSV-2 infection associated with increase in stromal inflammation in foreskin in both HIV+/HIV- men

Oligoclonal, activated CD8+ tissue resident memory T cells persist at sites of genital herpes recurrences

These responses may be required to prevent HSV-2 infection ("Prime-pull" strategy in mice)



Zhu Nat Med, 2009
Johnson, AIDS 2009
Johnson, JID 2011
Zhu, Nature 2013
Shin, Nature 2012

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Vaccine strategies: Prophylactic vs. Therapeutic

	Prophylactic	Therapeutic
Target Population	High risk HSV-2 seronegative	HSV-2 seropositive
Goal	Prevent infection –or- Reduce severity of disease	Reduce severity of disease and risk of transmission
Preferred endpoint	Infection (seroconversion) Incidence of genital herpes	Genital shedding and recurrences

Adapted from Johnston et al, JCI 2011

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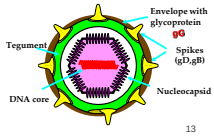
Clinical Trials of Prophylactic Vaccines

- Over 20,000 participants enrolled in prophylactic vaccine trials
- Most prophylactic vaccines have targeted glycoproteins (gD, gB)
  - Subunit vaccines
  - Elicit neutralizing antibody



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Herpevac Trial for Women — Prophylactic vaccine

- gD2t subunit vaccine with alum/MPL adjuvant
- Enrolled >8000 **HSV seronegative** women aged 18-30 in North America
  - Vaccine given at months 0, 1 and 6
  - Control vaccine: hepatitis A
- Primary endpoint: genital herpes disease
  - 70 cases of genital herpes observed
  - 32 HSV-1 and 38 HSV-2
- 286 seroconversions observed:
  - 179 HSV-1 and 108 HSV-2

Belshe et al, NEJM 2012

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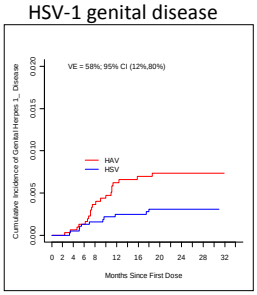
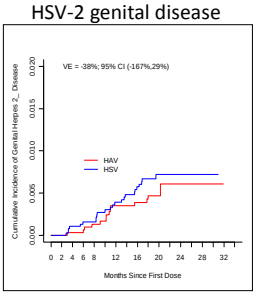
Genital HSV 1 / 2 Disease Cumulative Incidence Per Protocol Efficacy Cohort Months 2-20

HSV-1 genital disease



HSV-2 genital disease



Belshe, et al NEJM 2012

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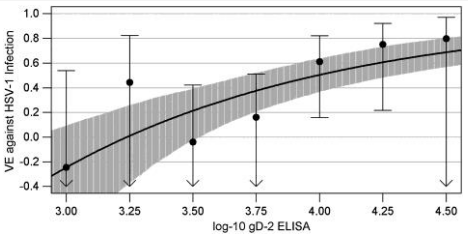
Vaccine efficacy as a function of ELISA titer: HSV-1



- First evidence for correlate of protection against HSV-1

Belshe et al, JID 2014

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Immune Correlates

- Magnitude of CD4+ T cell responses to gD2 not associated with prevention of infection
- CD8+ T cells responses were not detected

Belshe et al, JID 2014

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Lessons from Herpevac

- Goal: Vaccine to prevent HSV-1 and HSV-2?
  - Timing of vaccine series
  - Use in HSV-1 seropositive persons
- Immune Correlates
  - Neutralizing antibody is a correlate of protection against HSV-1 infection
    - Is this relevant for HSV-2?
- Efficiency
  - Phase III trial required large number of participants due to low attack rate -Cohorts with higher incidence are needed
- Endpoints:
  - Infection vs. Disease

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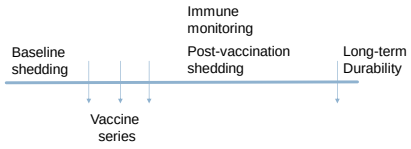
Testing therapeutic HSV-2 vaccines: A new paradigm



- Endpoint: Shedding rate pre/post vaccine
- Participant is compared to themselves

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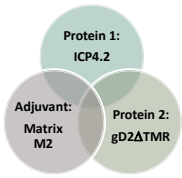
Therapeutic vaccine example: GEN-003 Phase 1B results



Treatment Group	N	Mean Baseline Rate	Mean Post-Treatment Rate	Mean Relative Change from Baseline	p-value
Placebo	28	11.8	13.2	12%	0.8
GEN003 (10 µg)	31	11.5	11.3	-2%	0.75
GEN003 (30 µg)	29	**13.5**	**6.6**	-51%	<0.001
GEN003 (100 µg)	27	**14.8**	**10.4**	-30%	<0.001

Preliminary results: Phase II - 55% reduction in shedding (60µg + 75µg adjuvant dose)

Wald, ICAAC, 2013

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HSV vaccines currently in clinical trials: The Pipeline

Vaccine	Platform	Adjuvant	Current Phase	Results
Admedus	DNA, gD2 codon optimized	Ubiquitin tagged	1B/II, prophylactic therapeutic	Elicited cellular responses in Phase 1
VCL-HB01	DNA gD2 +/- UL46	Vaxfectin	I/II POC therapeutic	Prelim results: Did not meet primary endpoint (decreased shedding)
GEN-003	Subunit gD2/ICP4	Matrix-M2	II, therapeutic	55% reduction in shedding
HerpV	32 35-mer peptides, complexed with heat shock protein	QS-21	II, therapeutic	15% reduction in shedding
HSV529	Replication deficient HSV-2 (deletion UL5/UL29)	NA	I, prophylactic therapeutic	Pending

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HSV Vaccines: Preclinical Pipeline

Candidate Name/Identifier	Replication competent	Replication deficient	Other
HSV-2 0ΔNLS-ICP0	X		
gE2-deletion	X		
HF10	X		
AD472 (HSV-2 mutated for g34.5, UL43.5, UL55-56, US10-12)	X		
ΔgD2		X	
CJ-2-gD2 HSV-2 gD dominant negative		X	
Prime-pull strategy			X
Inactivated HSV-2 in MPL/alum			X
HSV-1 glycoprotein B lentiviral vector			X
Recombinant HSV-1 gB intranasal			X
gD/gC/gE (Trivalent glycoprotein)			X

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HSV Vaccines: Cause for optimism

- Success of HPV and VZV vaccines
- Rich pipeline with novel candidates
  - Several platforms
  - Therapeutic vaccines rapidly moving forward
- New insights into importance of neutralizing antibody and cellular immune response
- Increased knowledge about lack of geographic diversity of virus
  - 0.4% maximum genetic divergence
- Extensive experience with optimizing clinical trials design (prophylactic and therapeutic)
  - Endpoints
  - Populations

Newman JVI 2015

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HSV Vaccines: Challenges

- Need additional data about immune correlates and what responses need to be stimulated
  - May be different for therapeutic and prophylactic vaccines
- Available animal models do not mimic human disease or immune system
- Lack of standardized assays
- Efficiency: Use of smaller, iterative clinical trials
- Must continue to pursue prophylactic vaccines
- Manufacture of select vaccines
- Improved public-private partnership

Knipe, Vaccine 2014

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