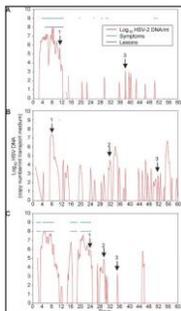




Increased Herpes Simplex Virus-2 Shedding in HIV-1 Infected Persons is due to Poor Immunologic Control in both Ganglia and Genital Mucosa

Joshua T. Schiffer, MD, MSc

HSV-2 genital shedding is frequent, episodic and heterogeneous

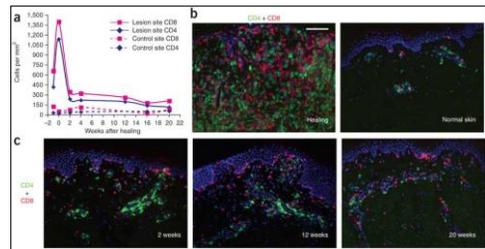


Mark KE, *JID*, 2008.
Schiffer JT, *Sci Trans Med*, 2009.

Study questions

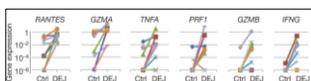
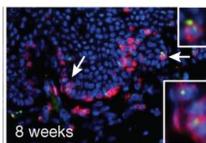
- HIV infected persons with low CD4+ T-cell count shed HSV-2 at higher rates and are more likely to develop persistent genital ulcer disease
- In which anatomic site is anti-HSV-2 immunity decreased in patients with HIV (ganglia and / or mucosa)?
 - In mucosa, is immune deficiency due to impaired clearance of infected cells, or impaired clearance of free virus?

HSV-2 ulcers are associated with an intense, highly-localized & persistent CD4+ / CD8+ response



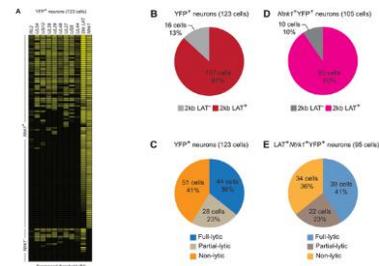
Zhu J, *Nat Med*, 2009.
Zhu J, *JEM*, 2007.

CD8 α (+) T cells display a memory effector phenotype weeks after lesion healing



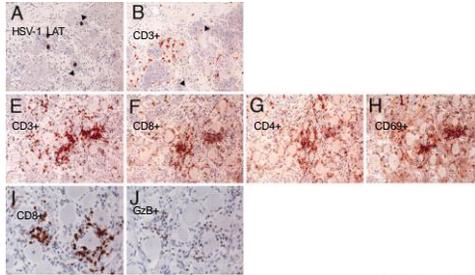
Peng T, *JV*, 2012.
Zhu J, *Nature*, 2013.

Ganglionic reactivation occurs frequently



Mu JZ, Russell TA, Spelman T, Carbone FR, Tscharke DC (2014) Lytic Gene Expression Is Frequent in HSV-1 Latent Infection and Correlates with the Engagement of a Cell-Intrinsic Transcriptional Response. *PLoS Pathog* 10(7): e1004237. doi:10.1371/journal.ppat.1004237
<http://dx.doi.org/10.1371/journal.ppat.1004237>

There are high numbers of activated CD8+ effector memory cells directed against HSV-1 in trigeminal ganglia



Verjans G M G M et al. PNAS 2007.

Which site of immunity is decreased in HIV infected patients?

- 4 cohorts of HSV-2 seropositive men:
 - HIV negative (n=98)
 - HIV positive, CD4>500 (n=34)
 - HIV positive, CD4=200-499 (n=43)
 - HIV positive, CD4<200 (n=21)
- Daily swabs x 60 days for HSV qPCR

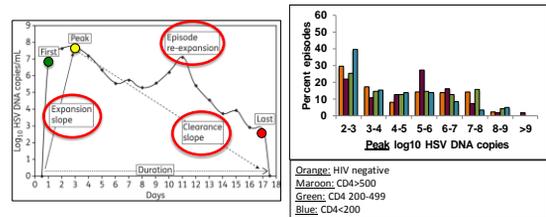
Shedding rate, episode rate & episode duration increase with decreasing CD4 count

	HIV negative	CD4>500	CD4 200-499	CD4<200
Total Swabs	6448	1960	2495	1556
Shedding rate	15%	19%***	21%***	31%***
Episode rate / year (95% CI) ¹	13 (11-16)	13 (10-18)	17 (13-22)*	20 (14-26)**
Median episode duration (days)	3.7	4.6	4.1	5.5**

* p<0.1, ** p<0.05, *** p<0.001

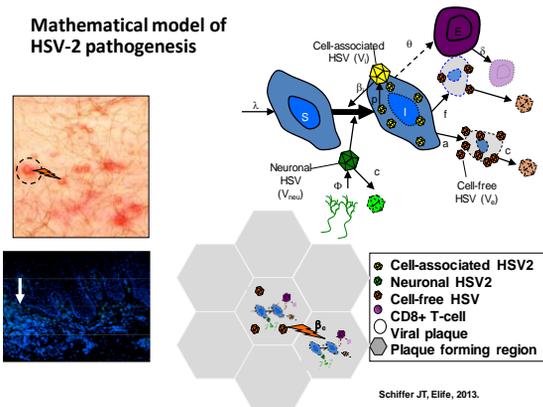
1. Episode rate is underestimated with daily sampling.

Kinetics features of episodes are surprisingly equivalent across all CD4 strata



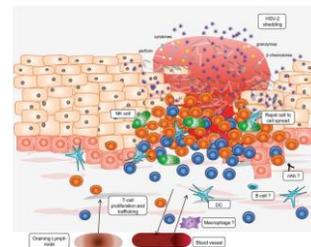
Schiffer JT et al. JID. 2012
Schiffer JT et al JAC, 2012.

Mathematical model of HSV-2 pathogenesis



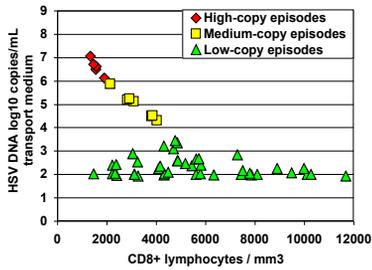
Schiffer JT, Elife, 2013.

The model's most important limitation is oversimplification of immunity



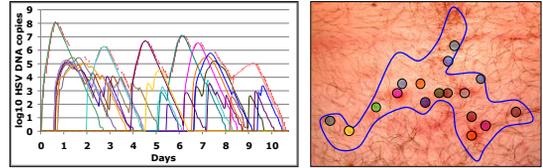
Schiffer and Corey, Nat Med. 2013 Mar; 19(3): 280-290.

The model predicts that mucosal T-cell density determines episode heterogeneity



Schiffer JT, PNAS, 2010.

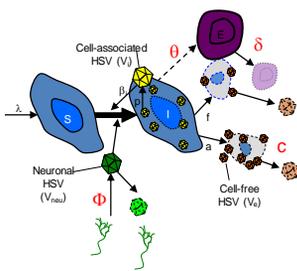
The model predicts extremely rapid HSV-2 containment within single ulcers



FRED HUTCH
40 YEARS OF CURES 1975-2015

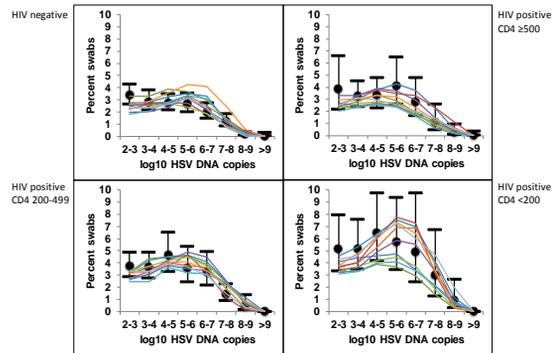
Schiffer JT, Elife, 2013.

Model fit to HIV (-) & (+) data



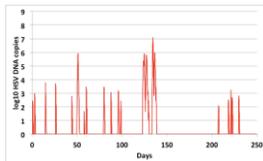
Varied parameters
 Θ = mucosal CD8+ expansion rate
 r = Number of HSV infected cells prior to CD8+ expansion
 δ = mucosal CD8+ decay rate
 c = Free viral decay rate
 Φ = Neuronal HSV drip rate

Model fit to HIV (-) & (+) data

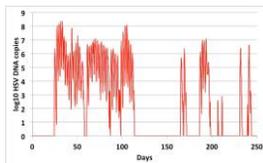


The model also reproduces shedding episode rate and kinetic characteristics

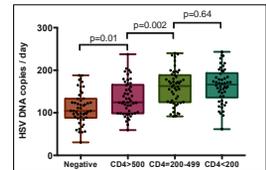
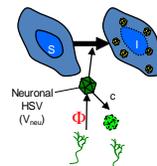
Simulated HIV negative shedding



Simulated HIV positive CD4<200 shedding

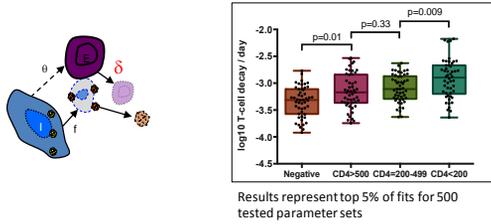


Neuronal release rate of HSV increases as CD4 decreases

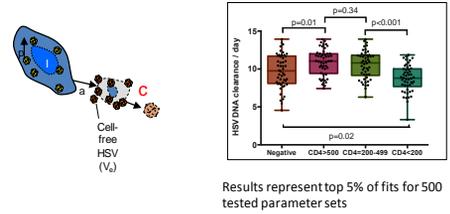


Results represent top 5% of fits for 500 tested parameter sets

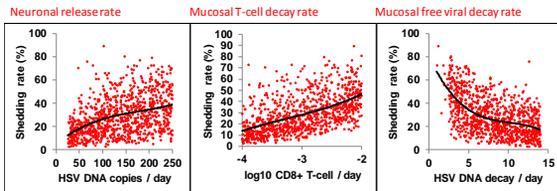
T-cell mucosal decay rate increases when CD4<200



Viral clearance rate decreases when CD4<200



Each parameter is only weakly predictive of increased shedding rate: immune dysfunction is therefore likely to be multifactorial



Implications

- Three broad areas of immunodeficiency in HIV patients:
 1. Decreased ganglionic immune protection against reactivation
 2. Decreased lifespan of mucosal T-cells
 3. Decreased clearance of cell-free HSV-2 in genital mucosa
- Enhancement of these parameters may be a key feature of a therapeutic vaccine

Thank you!



- VRC clinicians
- Study Participants
- NIH / NIAID

