

Dynamics of Herpes Virus Reactivation in the Genital Tract

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An estimated 15 percent of individuals 14 - 49 years old in the United States and Canada are infected with herpes simplex virus-2 (HSV-2), the main cause of genital herpes (e.g., CDC, 2010). In this age group, prevalence of HSV-2 climbs to 30 - 60 percent in Asia, Africa, and Latin America (Looker *et al.*, 2008). After a person becomes initially infected with this sexually-transmitted virus, HSV-2 evades the immune system by persisting in a quiescent form in the cell bodies of sensory neurons that innervate the genital tract. When the viruses become reactivated episodically from their dormant state, they travel down the neurons, exit the sensory dendrites and infect keratinocytes, the most abundant cell type in the epidermis and genital mucosa. Some episodes of HSV-2 shedding result in painful genital ulcers and prolonged periods of viral replication. Other episodes are brief and asymptomatic, providing the opportunity for cryptic sexual transmission of the virus (Mark *et al.*, 2008; Schiffer *et al.*, 2009).

The high variability of HSV-2 shedding in infected individuals and the complex dynamics of prolonged shedding episodes are poorly understood, though such knowledge is needed to refine therapeutic approaches for treating HSV-2 infection and to eventually develop an effective HSV-2 vaccine. Dr. Joshua Schiffer and colleagues (Vaccine and Infectious Disease Division of the Fred Hutchinson Cancer Research Center and University of Washington School of Medicine) helped fill these gaps in our understanding of the biology of HSV-2 infection in a recent paper published in the journal *eLife*. The team of researchers did so by combining mathematical modeling with extremely thorough clinical sampling of HSV-2 loads at brief and protracted time intervals and across a variety of spatial scales in the genital tract.

The authors considered empirical data from five different immunocompetent cohorts of HSV-2-infected study participants, ranging from 2 - 531 participants per cohort and including genital tract swabbing frequencies ranging from every five minutes to once per day. Using these data, Schiffer *et al.* quantified several different kinetic features of HSV-2 reactivation within individual genital tract sites. These features included total HSV DNA copy number (measured at different time points during an HSV-2 episode using a quantitative PCR assay), rate of viral expansion during the episode, rate

of viral contraction due to immune containment, episode duration and total number of episodes per year. To help them gain insights into the biology of the highly heterogeneous shedding episodes that define chronic, untreated genital herpes, Schiffer *et al.* formulated different mathematical models of HSV-2 pathogenesis by building on models from their earlier work (Schiffer *et al.*, 2009; Schiffer *et al.*, 2010). Several new biological and spatial features describing genital herpes infection were added to the previous models (see figure). The authors then tested the fit of their different models to the empirical data to evaluate different hypotheses about HSV-2 infection.

The research team found that infected individuals experience episodes approximately twice per month. While most episodes are asymptomatic and rapidly cleared within hours, others persist for more than ten days and are associated with painful crops of genital ulcers. Results of the authors' modeling support the prediction that viral expansion occurs extremely rapidly within a single genital tract micro-environment, which is visible clinically as a single genital ulcer. Within this environment, HSV-2 infection typically spreads from one infected keratinocyte to thousands of others in less than twelve hours. However, host immune responses generally completely eliminate infected cells in the same micro-environment within 24 hours. This immune containment is mediated primarily by tissue resident CD8⁺ (*i.e.*, cytotoxic) T-cells. For example, Schiffer *et al.* (2010) previously found that a higher density of CD8⁺ T cells at a site of viral reactivation reduces the severity of an HSV-2 episode.

Given this rapid containment of HSV-2 by CD8⁺ T cells within a single micro-environment, what accounts for the authors' observation that HSV-2 episodes – asymptomatic or otherwise – commonly last several days? According to Dr. Schiffer, the team's empirical findings and modeling results support the hypothesis that "complex episodes with multiple peaks and valleys occur due to concurrent viral expansion and decay in multiple regions." After reactivation of the virus at the beginning of an episode, secondary ulcers often form in new regions of genital skin or mucosa due to the spread of cell-free viruses. These secondary ulcers can further seed additional sites, prolonging total episode duration for ten days or more across the genital tract (see figure).

The findings of Schiffer *et al.* are significant in several ways. Their results suggest that the mucosal immune system is primed to rapidly clear HSV-2 infected cells. Yet, the virus also appears to have evolved mechanisms for spreading through the genital tract during a single HSV-2 episode, prolonging the period of shedding and the probability of infecting other individuals. Related to these findings, Dr. Schiffer points out that "a useful genital herpes vaccine will need to enhance containment within a single micro-environment, while limiting spread to new genital regions."

[Schiffer JT, Swan D, Al Sallaq R, Magaret A, Johnston C, Mark KE, Selke S, Ocbamichael N, Kuntz S, Zhu J, Robinson B, Huang ML, Jerome KR, Wald A, Corey L](#). 2013. Rapid localized spread and immunologic containment define Herpes simplex virus-2 reactivation in the human genital tract. *eLife* 2:e00288.

Also see: [Centers for Disease Control and Prevention \(CDC\)](#). 2010. Seroprevalence of herpes simplex virus type 2 among persons aged 14 - 49 years – United States, 2005-2008. *MMWR Morb. Mortal. Wkly. Rep.* 59:456-59.

[Looker KJ, Garnett GP, Schmid GP](#). 2008. An estimate of the global prevalence and incidence of herpes simplex virus type 2 infection. *Bull. World Health Org.* 86:805-12.

[Mark KE, Wald A, Magaret AS, Selke S, Olin L, Huang ML, Corey L](#). 2008. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. *J. Infect. Dis.* 198:1141-49.

[Schiffer JT, Abu-Raddad L, Mark KE, Zhu J, Selke S, Magaret A, Wald A, Corey L](#). 2009. Frequent release of low amounts of herpes simplex virus from neurons: results of a mathematical model. *Sci. Transl. Med.* 1:7ra16.

[Schiffer JT, Abu-Raddad L, Mark KE, Zhu J, Selke S, Koelle DM, Wald A, Corey L](#). 2010. Mucosal host immune response predicts the severity and duration of herpes simplex virus-2 genital tract shedding episodes. *Proc. Natl. Acad. Sci. USA* 107:18973-78.

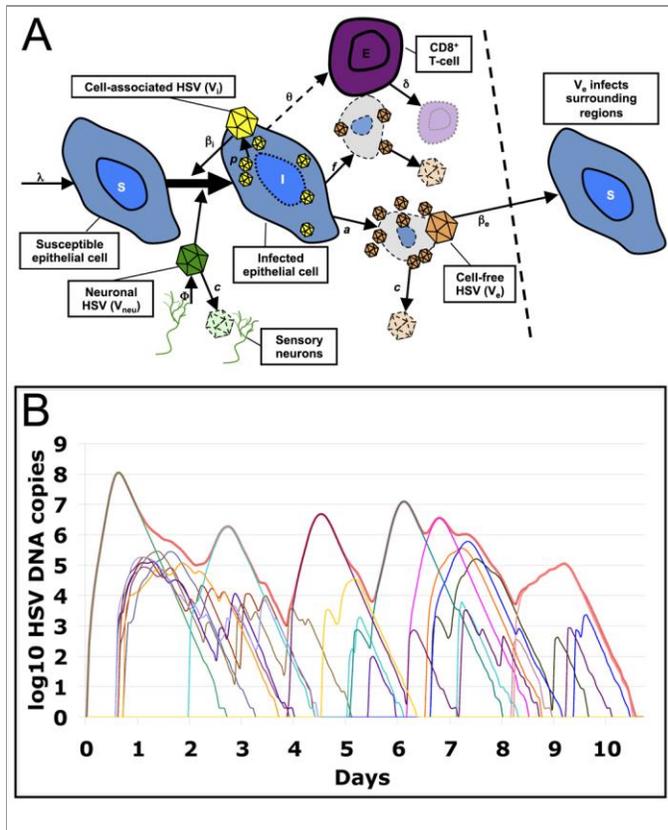


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The authors' model of HSV-2 infection within a single genital tract micro-environment and an example of some of their modeling results. (A) Equations in the model of Schiffer et al. describe: the seeding of susceptible epithelial cells, 'S', via sensory neurons, the cell bodies of which serve as the dormant reservoir of genital herpes in the sacral ganglia; replication of HSV-2 in infected epithelial cells, 'I'; viral transmission to other susceptible cells (e.g., in surrounding regions of epithelium); response of cytotoxic CD8-positive T cells to infected cells; transition of cell-associated HSV-2 to cell-free HSV-2 upon lysis of infected cells; and elimination of infected skin cells and cell-free virions. New model features include: separate terms for cell-associated and cell-free virus particles; an allowance for multiple, concurrent viral plaques to serve as sources for seeding adjacent regions and prolonging individual episodes; and a more realistic two-dimensional spatial array of epithelial micro-regions. (B) Profile of total cell-free HSV-2 virus particles produced over a ten-day simulation (wide red line along the top of the profile) shows a saw-toothed pattern of prolonged virus production. This saw-toothed pattern is the summed result of HSV-2 virions produced by single genital tract micro-environments or individual ulcers (thin lines of different colors). Note that the occurrence of secondary ulcers, which arise after the first ulcer at the beginning of the simulation, prolongs total episode duration.