HSV-2 Mathematical Model Explains Partial Effectiveness of Antiviral Drugs

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Infection with herpes simplex virus 2 (HSV-2) induces frequent episodes of symptomatic genital lesions and asymptomatic viral shedding even during treatment with currently available antiviral medication. A recent paper by Dr. Joshua Schiffer and colleagues from the Vaccine and Infectious Disease Division reports the use of a mathematical model of viral replication and spread to analyze virologic data supplied by clinical trials for two antiviral medications. The model, when combined with available pharmacokinetics and pharmacodynamics data for these drugs, correctly predicted key aspects of viral outbreak episodes both on and off treatment. Model simulations found that even during twice-daily administration of a drug, frequent episodes of viral shedding occur, and these episodes are the result of the rapid decline in plasma drug levels leading to sub-therapeutic drug levels for nearly half of the time during the dosing cycle.

Genital herpes is caused by HSV-2, which infects epithelial cells in the genital mucosa. The virus then infects peripheral neurons and migrates along the cell axon to the neuronal cell body in the dorsal root ganglia, a clump of nerve cells at the base of the spine. This is where HSV-2 establishes a lifelong latent infection during which replication is mostly quiescent. However, latency is characterized by recurrent reactivation flare-ups during which the virus undergoes replication and retrograde transport back to the periphery, causing symptomatic genital lesions and viral shedding, which in turn causes infection of new epithelial cells and transmission to other hosts during sexual contact. The current antiviral medications for genital herpes function by reducing viral replication and are effective in decreasing rates of viral shedding and lesions in the genital tract. However, despite administration of these drugs at high doses, patients still experience symptoms and transmission still occurs.

"For many years, a fundamental mystery in the field of genital herpes therapeutics is that breakthrough shedding of virus occurs despite the availability of potent antiviral treatments. This is clinically important because breakthrough shedding can result in development of genital lesions, as well as transmission to sexual partners," explains Dr. Schiffer. "The mechanism for incomplete antiviral therapy effectiveness for most viral infections is drug resistance. However, drug resistance is not the cause of breakthrough genital shedding in the vast majority of patients infected with HSV-2."

To explore causes of breakthrough shedding other than drug resistance, Dr. Schiffer and colleagues, developed their mathematical model to incorporate multiple aspects of HSV-2 infection, replication and spread. This highly complex model was derived using all the relevant parameters in the HSV-2 life cycle including the different cell types and anatomical regions, viral replication rates, cell-to-cell transmission, and immune control of the virus via HSV-2 specific CD8+ T-cells. In order to predict the effects of therapy on the viral life cycle, and especially rates of viral shedding, additional variables describing the drug characteristics, such as dosage and dosing frequency, drug half-life and other pharmacokinetic/pharmacodynamic parameters were added to the model. The final outcome from multiple simulations using the model was to pinpoint key aspects of the system to explain the observed characteristics of viral spread during treatment.

Dr. Schiffer explained that, "our paper utilizes detailed analysis of clinical trial data and mathematical modeling to demonstrate that two factors contribute to breakthrough HSV-2 reactivations [during] treatment: the extremely rapid expansion rate of HSV-2 and the short half-life of available antiviral agents. Based on these two factors, drug levels dip below a therapeutic level for periods of hours," (see figure showing the level of the drug acyclovir (blue line)). "[This] is adequate time for HSV-2 to replicate extensively and spread to other cells."

The data generated by the simulations also revealed that the viral reactivation episode intensity and duration were interestingly more affected by local CD8+ T-cell density than by drug concentration at episode onset. However, the most conspicuous result was the importance of drug half-life on the treatment's failure to prevent the reactivation episodes. Schiffer concludes, "this finding is exciting because several novel agents directed against HSV-2 have longer half-lives. Our hope is that our model can be utilized to arrive at optimal dosing regimens in future clinical trials."

Schiffer JT, Swan D, Corey L, Wald A. 2013. Rapid viral expansion and short drug half-life explain the incomplete effectiveness of current Herpes Simplex Virus-2 directed antiviral agents. *Antimicrob Agents Chemother* 57(12):5820-5829.

Also see: 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.

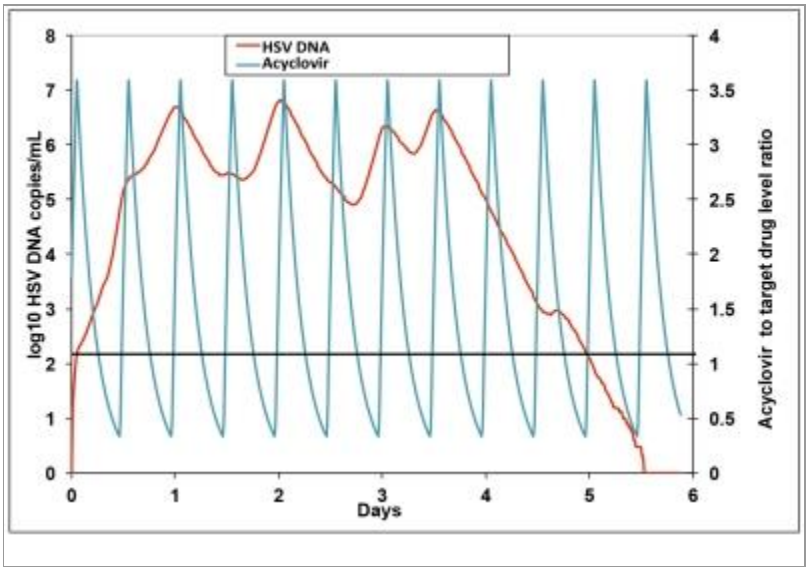

Image provided by Dr. Joshua Schiffer.

Model simulations of HSV-2 dynamics and drug levels during twice-daily treatment with the antiviral acyclovir. The rapid drug decay results in substantial periods when drug levels fall below the target therapeutic amount (black line). Viral expansions allowing breakthrough viral shedding occur during periods when the drug is below the target level.