Herpes simplex virus: a new era?

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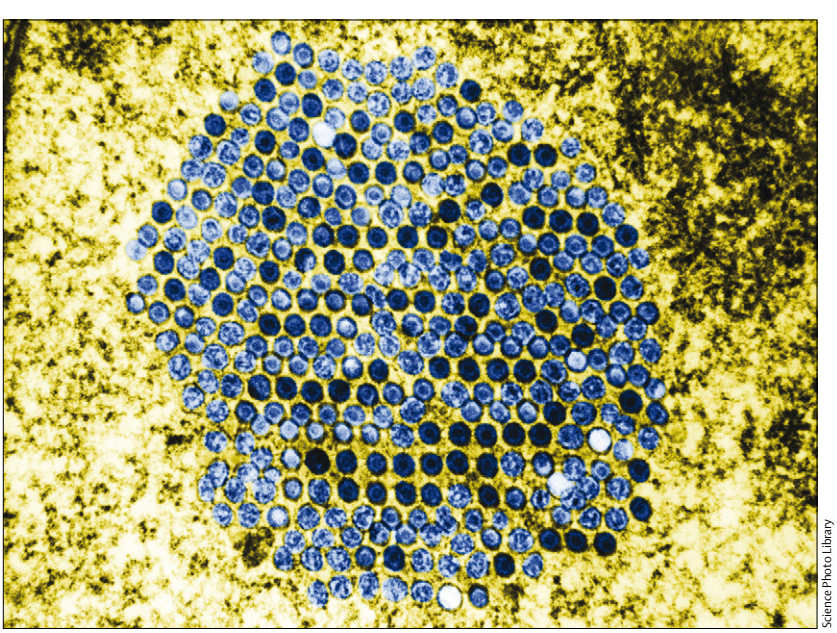
Herpes simplex virus type 2 (HSV-2) causes life-long infection with episodic reactivation. For decades, antiviral drugs, such as guanosine analogues (aciclovir and its prodrug valaciclovir), have been used to treat or prevent frequent and painful episodes.[1] One outstanding question about HSV is why transmission is not stopped by these suppressive treatments.[2]

In *The Lancet*, Christine Johnston and co-workers[3] provide some clues with three clinical trials (cross-over studies) that assessed the effect of antiherpes drugs on HSV-2 genital shedding. Various doses of antiviral drugs were tested for their effects on asymptomatic, frequent, short (a few hours), breakthrough episodes of HSV reactivation in 90 patients, who collected genital swabs four times daily. In the first trial, the investigators compared low-dose aciclovir with no medication in symptomatic and asymptomatic HSV-2 seropositive patients. The second trial compared standard-dose valaciclovir with high-dose aciclovir, and the third study compared standard-dose valaciclovir with high-dose valaciclovir, in patients with four or more genital herpes recurrences per year. In trial 1, standard-dose aciclovir reduced HSV-2 shedding, although rare shedding episodes still occurred. The shedding rate was not correlated with drug adherence, which makes it unlikely that shedding was caused by missed doses of antiviral therapy. By contrast, aciclovir or valaciclovir, irrespective of dose, had less effect on HSV-2 genital shedding in patients with frequent reactivations. Although high-dose valaciclovir reduced the HSV shedding rate by about 50% compared with standard-dose valaciclovir, HSV was still detected on 3·3% of swabs, and the number of breakthrough shedding episodes was the same for both standard-dose and high-dose antiviral medication. Overall, no antiviral regimen fully suppressed short subclinical reactivations of HSV.

The finding that treatment cannot fully prevent transmission should encourage patients to use condoms and adopt safe sex practices, especially since increase of the treatment dose would not further reduce the risk of transmission to patients' partners. Furthermore, the study prompts reconsideration of the nature of latency and reactivation of chronic HSV. Chronic HSV-2 infection is characterised by symptomatic reactivations at mucosal sites and by short, frequent breakthrough shedding episodes.[4] Mathematical modelling suggests that HSV replication, instead of being characterised by periods of replicative silence (latency) separated by viral bursts (reactivations), probably occurs almost constantly.[5] According to this model, HSV is continuously released—albeit slowly—by infected neurons in sensory ganglia; about 40–90 virions are produced every day.[5] This release is followed by rapid spread of HSV-2 within the genital tissues, with secondary plaques forming because of cell-free particle propagation. In the model, viral replication and propagation is controlled in situ by CD8 cells with highly localised activity and is probably the major factor for duration and severity of reactivations at mucosal sites;[6] cell density is 70% lower 1 cm away from the lesion. The so-called hide and seek interplay between the virus and its host[7] is not only theoretical; low-level viral replication substantially increases transmission risk and is not easily suppressed by antiherpetic therapies. The complex interactions between herpes viruses and HIV[7,8] and the conflicting results from trials of the effectiveness of interventions to reduce HIV transmission by HSV suppression should be revisited.[9,10]

What should be done to address the ineffectiveness of antiherpetic therapies for suppression of viral replication? The development of new antiherpetic drugs such as helicase–primase inhibitors is important.[11]



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Human cell infected with HSV-2

However, even if such antiviral drugs could stop HSV shedding, and thereby transmission, their use would need good coverage and satisfactory long-term adherence to affect HSV dynamics substantially. These needs are unlikely to be met because about 20% of the general population is infected with HSV-2 in the USA and Europe, most of whom have no clinical need for antiherpetic therapy.[12] Alternative control tools, such as immunotherapeutic strategies (therapeutic vaccines),[13] are in preclinical development, but they are hampered by the absence of an adequate animal model[14] and the lack of commitment from pharmaceutical companies and the public sector.

Philippe Van de Perre, Nicolas Nagot
INSERM U 1058, Montpellier, France (PVdP, NN); Université Montpellier 1, Montpellier, France (PVdP, NN); and CHU Montpellier, Département de Bactériologie-Virologie et Département d'Information Médicale, 34295 Montpellier Cedex 5, France (PVdP, NN)
p-van_de_perre@chu-montpellier.fr

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1 Fiddian AP, Halsos AM, Kinge BR, Nilsen AE, Wikstrom K. Oral acyclovir in the treatment of genital herpes. Preliminary report of a multicenter trial. *Am J Med* 1982; **73:** 335–37.
2 Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004; **350:** 11–20.
3 Johnston C, Saracino M, Kuntz S, et al. Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials. *Lancet* 2012; published online Jan 5. DOI:10.1016/S0140-6736(11)61750-9.
4 Tronstein E, Johnston C, Huang ML, et al. Genital shedding of herpes simplex virus among symptomatic and asymptomatic persons with HSV-2 infection. *JAMA* 2011; **305:** 1441–49.
5 Schiffer J, Swan D, Magaret A, et al. Rapid spread of herpes simplex virus-2 in the human genital tract. *Sex Transm Infect* 2011; **87:** A84–85.
6 Schiffer JT, Abu-Raddad L, Mark KE, et al. Mucosal host immune response predicts the severity and duration of herpes simplex virus-2 genital tract shedding episodes. *Proc Natl Acad Sci USA* 2010; **107:** 18973–78.
7 Van de Perre P, Segondy M, Foulongne V, et al. Herpes simplex virus and HIV-1: deciphering viral synergy. *Lancet Infect Dis* 2008; **8:** 490–97.
8 Rubbo PA, Tuaillon E, Nagot N, et al. HIV-1 infection impairs HSV-specific CD4+ and CD8+ T cell response by reducing Th1 cytokines and CCR5 ligand secretion. *J Acquir Immune Defic Syndr* 2011; **58:** 9–17.
9 Nagot N, Ouédraogo A, Foulongne V, et al; ANRS 1285 Study Group. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med* 2007; **356:** 790–99.
10 Celum C, Wald A, Lingappa JR, et al; Partners in Prevention HSV/HIV Transmission Study Team. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med* 2010; **362:** 427–39.
11 Chono K, Katsumata K, Kontani T. ASP2151, a novel helicase–primase inhibitor, possesses antiviral activity against varicella-zoster virus and herpes simplex virus types 1 and 2. *J Antimicrob Chemother* 2010; **65:** 1733–41.
12 Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. *J Infect Dis* 2002; **186** (suppl 1)**:** S3–28.
13 Dasgupta G, Nesburn AB, Wechsler SL, BenMohamed L. Developing an asymptomatic mucosal herpes vaccine: the present and the future. *Future Microbiol* 2010; **5:** 1–4.
14 Dasgupta G, Benmohamed L. Of mice and not humans: how reliable are animal models for evaluation of herpes CD8(+)-T cell-epitopes-based immunotherapeutic vaccine candidates? *Vaccine* 2011; **29:** 5824–36.