

4. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006;28:1245-57.
5. Tillie-Leblond I, Marquette C-H, Perez T, et al. Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med* 2006;144:390-6.
6. Sevenoaks MJ, Stockley RA. Chronic obstructive pulmonary disease, inflammation and co-morbidity — a common inflammatory phenotype? *Respir Res* 2006;7:70-8.
7. Calverley P, Pauwels R, Vestbo J, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;361:449-56. [*Lancet* 2003;361:1660.]
8. Sin DD, Wu L, Anderson JA, et al. Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. *Thorax* 2005;60:992-7.
9. Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:842-6.
10. *Idem*. Inhaled steroids and mortality in COPD: bias from unaccounted immortal time. *Eur Respir J* 2004;23:391-5.
11. Huiart L, Ernst P, Ranouil X, Suissa S. Low-dose inhaled corticosteroids and the risk of acute myocardial infarction in COPD. *Eur Respir J* 2005;25:634-9.
12. Parimon T, Chien JW, Bryson CL, McDonnell MB, Udris EM, Au DH. Inhaled corticosteroids and risk of lung cancer among patients with COPD. *Am J Respir Crit Care Med* (in press).
13. Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775-89.
14. Vestbo J, TORCH Study Group. The TORCH (TOwards a Revolution in COPD Health) survival study protocol. *Eur Respir J* 2004;24:206-10.
15. Carroll L. *Alice's adventures in wonderland*. London: Macmillan, 1865.
16. Decramer M, Celli B, Tashkin DP, et al. Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial. *COPD* 2004;1:303-12.

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Synergistic Copathogens — HIV-1 and HSV-2

Lawrence Corey, M.D.

The variability in both the clinical progression and transmission of human immunodeficiency virus (HIV) infection has prompted a search for cofactors influencing replication of the virus. Although it is clear that host immune and genetic factors, as well as the replication kinetics of particular viral strains, influence the progression of HIV disease, a variety of exogenously acquired infectious agents also appear to influence the pace of HIV replication, the destruction of CD4+ T cells, and HIV transmission to infants and sexual partners. Transient bursts of HIV replication occur after vaccination and during episodes of acute systemic infection. More persistent elevations in plasma HIV levels have been seen in patients with chronic infections (such as those with *Mycobacterium tuberculosis* and herpes and hepatitis viruses), and such coinfecting patients have a more rapid loss of CD4+ T cells and an increased rate of progression to AIDS and death.¹

HIV replication is compartmentalized in anatomic sites of the body, and the interactions between HIV type 1 (HIV-1) and microbes occupying these anatomic sites influence the amount and strain of HIV-1 in these regions. Interactions between the gut flora with HIV in gut lymphoid tissue and between sexually acquired pathogens and HIV-1 in the genital tract are perhaps the two areas of greatest importance in influencing the progression of disease and viral transmission. Localized infections of the genital tract with sex-

ually acquired bacterial infections such as *Neisseria gonorrhoeae* and, to a lesser extent, *Chlamydia trachomatis* are associated with higher amounts of HIV in genital secretions; treatment of these infections with antimicrobial agents is associated with a lowering of the HIV load in these secretions.² Thus, the identification and treatment of such infections have been important parts of the medical care of patients with HIV infection.

The clinical management of herpes simplex virus type 2 (HSV-2) in patients with HIV infection has lagged seriously behind the large body of medical literature on the importance of the interaction between these two pathogens.³ Persistent HSV-2 infection was one of the original opportunistic infections that resulted in the identification of HIV. Since the initial reports in 1988 studying men who have sex with men, many additional studies have shown the association between prevalent and incident HSV-2 infection and the risk of HIV acquisition.^{4,5} In this issue of the *Journal*, a study by Nagot et al.⁶ underlines the association of HSV-2 with significantly higher amounts of HIV-1 in plasma and in genital secretions in women with sexually acquired HIV-1. This finding has direct clinical implications, suggesting that HIV-1 replication can be reduced with antiviral therapy directed solely at HSV-2, since acyclovir has no direct antiviral activity against HIV.⁷

The conceptual importance of this observation is high. HSV-2 is acquired rapidly after the onset

of coitus in sub-Saharan Africa. Among patients with HIV infection, HSV-2 infection is also present in 30 to 70% of those in Europe and 50 to 90% of those in Africa.³ As Nagot et al. show with sampling every two weeks, 50% of patients who are coinfecting with HSV-2 and HIV-1 shed HSV-2 virus asymptomatically; with daily sampling, 75 to 95% of such patients shed HSV-2 virus in the genital tract, and the mean frequency of shedding is 40% of days. More than 85% of shedding episodes are subclinical, and highly active antiretroviral therapy (HAART) has little influence on either the frequency or titer level of mucosal HSV-2 shedding.⁸ Thus, most people worldwide with sexually acquired HIV have virologically active HSV-2 infection. HIV-1 is shed from genital ulcers caused by HSV-2; viral variants of HIV-1 that arise from these ulcers can appear and persist in plasma,⁹ and most important, these frequent subclinical episodes of HSV-2 reactivation are associated with both a higher frequency and a higher amount of HIV-1 in genital secretions.⁶ Both clinical and subclinical reactivations of HSV-2 are associated with the influx of activated CD4+ T cells into the genital mucosa and skin, and several HSV-2 proteins are capable of reactivating latent HIV infection. These interactions appear to account for the higher titers of HIV-1 in plasma in coinfecting patients.

Multiple studies have shown that a persistent increase of 0.5 log₁₀ copy per milliliter in the plasma HIV-1 level is associated with a clinically shortened time for progression to AIDS.¹⁰ The demonstration that daily anti-HSV-2 therapy can reduce the viral load by this amount is thus of direct importance for treatment. The study by Nagot et al. underlines the findings of a 1989 study showing that zidovudine plus acyclovir was associated with prolonged survival, as compared with zidovudine alone.¹¹ The recent studies evaluating the effect of antiviral therapy for HSV-2 among patients with HIV-1 infection have used relatively short courses of anti-HSV-2 therapy (3 to 4 months). Although this duration of anti-HSV-2 therapy has been sufficient to demonstrate the importance of HSV-2 in influencing HIV replication, the results do not provide clinicians with definitive findings to quantitate the benefit and to guide clinical management. Will the HSV-2 suppression in patients with HIV-1 infection who have not undergone antiretroviral therapy delay the loss of CD4+ T cells and prolong the time

until the initiation of antiretroviral therapy? Will prolonged suppression of HSV-2 among patients receiving antiretroviral therapy delay the emergence of resistant HIV strains and recurrent HIV viremia? Trials of a longer duration of therapy that includes measurement of these clinical end points of progression of HIV-1 disease are needed.

As described by Nagot et al., the reduction of 0.5 log₁₀ copy per milliliter in plasma HIV levels with anti-HSV-2 therapy is large enough to provide a potential clinical benefit. However, it is less clear whether such a reduction in mucosal genital HIV with anti-HSV-2 therapy is consistent enough to influence the role of transmission of HIV-1 to sexual partners. At present, sexual transmission of HIV-1 has a stronger correlation with plasma HIV levels than with the mucosal viral load.¹² This finding may be related to the variability in collection and the accuracy of measurement in mucosal sampling, as compared with plasma sampling. Since systemic anti-HSV-2 therapy lowers both types of virus, the real question is whether routine use of anti-HSV-2 therapy will provide benefit both to patients by reducing the progression of HIV-1 and to the community by reducing transmission to others.

The interconnections between HSV-2 and HIV-1 are well documented; the vast majority of patients with sexually acquired HIV — whether they are women or men or live in Europe, North America, Africa, or Asia — also have HSV-2 infection. The study by Nagot et al. highlights the potential benefit that screening and treating subclinical HSV-2 infection may offer to patients with HIV infection. Many questions about the interaction between these two organisms remain, and larger studies with defined clinical end points are needed to move the medical literature on this interaction into more effective clinical and population-based management. In the meantime, clinicians may want to incorporate more routine HSV-2 testing into the initial evaluation of HIV-seropositive patients.

Dr. Corey is director of the University of Washington Virology Division, which has received grant support from GlaxoSmithKline and Novartis, two companies that make antiviral drugs for the treatment of HSV-2. However, he receives no salary support from these studies. Dr. Corey reports serving as a paid expert in a legal dispute over a valacyclovir patent and receiving consulting fees from Antigenics, which is developing an HSV-2 vaccine. No other potential conflict of interest relevant to this article was reported.

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1. Toossi Z, Mayanja-Kizza H, Hirsch CS, et al. Impact of tuberculosis (TB) on HIV-1 activity in dually infected patients. *Clin Exp Immunol* 2001;123:233-8.
2. Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet* 1997;349:1868-73.
3. Corey L, Wald A, Celum CL, Quinn TC. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. *J Acquir Immune Defic Syndr* 2004; 35:435-45.
4. Stamm WE, Handsfield HH, Rompalo AM, Ashley RL, Roberts PL, Corey L. The association between genital ulcer disease with acquisition of HIV infection in homosexual men. *JAMA* 1988;260:1429-33.
5. Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS* 2006;20:73-83.
6. Nagot N, Ouedraogo A, Foulongne V, et al. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med* 2007;356:790-9.
7. Smith MS, Pagano JS. Inhibition of human immunodeficiency virus type 1 replication by guanosine analogues and lack of synergistic antiviral effect of acyclovir with 3'-axido 3'-deoxythymidine. *Antivir Chem Chemother* 1991;2:29-34.
8. Posavad CM, Wald A, Kuntz S, et al. Frequent reactivation of herpes simplex virus among HIV-1-infected patients treated with highly active antiretroviral therapy. *J Infect Dis* 2004;190: 693-6.
9. Schacker T, Ryncarz AJ, Goddard J, Diem K, Shaughnessy M, Corey L. Frequent recovery of HIV-1 from genital herpes simplex virus lesions in HIV-1 infected men. *JAMA* 1998;280:61-6.
10. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997;126:946-54.
11. Cooper DA, Pehrson PO, Pedersen C, et al. The efficacy and safety of zidovudine alone or as cotherapy with acyclovir for the treatment of patients with AIDS and AIDS-related complex: a double-blind randomized trial. *AIDS* 1993;7:197-207.
12. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *N Engl J Med* 2000;342:921-9.

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Educational Continuity in Clinical Clerkships

David M. Irby, Ph.D.

Continuity in medical-student clerkships is becoming a thing of the past. There is little continuity between students and teachers, between students and patients, and between specialty-based components of the curriculum. Although block rotations in clerkships have been used for more than 100 years, in Abraham Flexner's day, patients, teachers, and students were together in the hospital for extended periods on medicine, obstetrics, and surgery services, which provided excellent opportunities to learn in a relatively relaxed and longitudinally mentored environment. Not so today.

Faculty members struggle to meet clinical productivity quotas while maintaining teaching and research responsibilities. Attending physicians are on service for shorter and more intense periods of time, so there is much less opportunity to get to know students and residents. Most faculty members have even less time for substantive involvement in curriculum development and implementation. As a result, mentoring relationships either are fragile or do not exist, and the progressive advancement of student competencies is not well guided across the curriculum.

Students complain about having to start all over again with each new specialty-specific rotation. The constant churning of people and sites

leaves students feeling overwhelmed by what they do not know about each specialty and struggling to understand their new roles, new tasks, and new coworkers. Unfortunately, we chronically underestimate the powerful influence of these changing contexts on learners' thoughts, actions, and values.¹ Context matters, because learning from experience accrues from being immersed in and acculturated to a community of practice,² and experiential learning is strongly influenced by issues such as the patient census, time sensitivity in the environment, and multiple and conflicting commitments of participants.³

Discontinuity creates an inefficient and disjunctive system that produces great frustration and anxiety in learners and great challenges for teachers. Perhaps it is time to return to the best aspects of our past and create new models of apprenticeship that offer greater continuity and provide faculty members with protected time for teaching and mentoring.⁴

In this issue of the *Journal*, Hirsh and colleagues describe various forms of continuity in clinical education, advancing our understanding of the strengths and challenges of longitudinal relationships in clinical settings.⁵ They identify key components of educational continuity (con-

CORRECTION

Synergistic Copathogens — HIV-1 and HSV-2

Synergistic Copathogens — HIV-1 and HSV-2 . The fourth sentence of the fourth paragraph (page 855) should have read “As Nagot et al. show with sampling every 2 weeks, 50% of patients who are coinfecting with HSV-2 and HIV-1 shed HSV-2 virus asymptotically” rather than “with once-weekly sampling.” The text has been corrected on the *Journal's* Web site at www.nejm.org.