Herpes simplex virus (HSV) and HIV have certain common features, including persistence, stigma, and treatment that effectively decreases viral replication but cannot achieve cure. There has been continuing interest in these 2 viruses and their interrelationship since disease caused by HIV was first reported in 1981 and acyclovir was approved by the US Food and Drug Administration in 1982. At one time, it was thought that acyclovir might be useful in treatment of HIV infection because of evidence that it slowed disease progression [1], an observation that is now hypothesized to be attributable to suppression of CD4+ cell activation by persistent HSV coinfection. Views of the relationship between HIV and HSV have now taken a different direction, but one that has substantial support in clinical observations and biology, the importance of HSV in facilitating HIV transmission. This comes at a time of renewed attention to prevention of HIV infection, with the publication of new guidelines from the US Public Health Service [2], although the specific issue of HSV coinfection is barely mentioned.

Management of HSV is particularly important in HIV-positive persons, who may experience severe and prolonged outbreaks. Recurrences may be more frequent or chronic and may become nearly continuous as immunosuppression progresses. Episodic or suppressive therapy with oral antiviral agents is often beneficial in the management of HSV disease in HIV-infected persons [3]. Acyclovir, famciclovir, and valacyclovir suppressive therapy have all been studied in HIV-immunocompromised persons [4–6]. The newer antiviral agents offer increased convenience over acyclovir, and valacyclovir may offer superior efficacy, compared with acyclovir [7]. The choice of treatment regimen is subjective and may be driven by cost, frequency and severity of the HSV outbreak, and patient preference for episodic or (daily) suppressive therapy.

One of the most important studies relevant to the role of HSV in HIV transmission is the report by Reynolds et al. [8]. The study involved a cohort of 2732 HIV-negative patients attending 3 sexually transmitted disease clinics and a reproductive tract infection clinic in Pune, India. The participants were screened for HSV-2–specific antibody and were followed prospectively to determine seroconversion to HSV and HIV. The prevalence of HSV-2 at baseline was 43%, the incidence of HSV-2 was 11.4 cases/100 person-years, and the incidence of HIV was 5.8 cases/100 person-years. The risk of HIV acquisition was 3.6% for those who were HSV-seronegative, 7.5% for those with positive HSV-2 serology at baseline, and 22.6% for those with HSV seroconversion within the past 6 months. The authors concluded that HSV represents a risk for HIV transmission and that recent HSV acquisition represents a particularly high risk.

The biological explanation of this observation is uncomplicated. HSV ulcerations harbor activated CD4+ cells that are easily infected with HIV [9], thus rendering the HSV-infected patient uniquely susceptible. The message of this observation is intuitively obvious to health care providers, who routinely advocate sexual abstinence in the presence of overt genital lesions. Perhaps less obvious is the high frequency of subclinical HSV-2 activation, since HSV shedding can be detected on 10%–25% of days, even in the absence of any obvious genital lesions [10, 11]. This frequency is substantially higher during the 6 months after initial infection, which may explain the high risk associated with recent HSV seroconversion noted by Reynolds et al. [8] and others [11, 12].

What is the magnitude of this issue? PCR technology has been an important advance in detection of herpesviruses at infected sites, and availability of type-specific herpes simplex virus serology has been an important advance in identifying persons who are infected [13, 14]. Use of this technology has made it clear that HSV is the most frequent cause of genital ulcers worldwide [15, 16]. Serological tests detect HSV-2 infections in 20%–30% of healthy persons aged 15–29 years, and this rate

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increases to 60% by age 60 years [14]. The frequency of HSV-2 seropositivity in commercial sex workers is substantially higher [8]. Most infected persons either are not aware of their infection or do not report it [17]. Public health awareness campaigns and preventive measures, such as safer sex practices and condom use, have had little impact on the HSV epidemic, although administration of valacyclovir, in combination with safer sex practices, has established efficacy in prevention of HSV transmission [18, 19]. Valacyclovir has established efficacy in significant reduction of HSV shedding as well.

Given the data showing that HSV-2–infected patients are twice as likely to acquire HIV, the obvious question is whether suppressive therapy with valacyclovir or acyclovir can play an important role in protecting the patient with HSV from infection with HIV. The presumed answer is “yes,” but supporting evidence from clinical trials is not yet available. The most obvious method to seek proof is a therapeutic trial of HSV suppressive treatment for subjects who are seronegative for HIV and seropositive for HSV-2 and who have partners with HIV. Under the assumption that this study would yield positive results, the next obvious question is to whom antiviral agents should be administered—all persons with HSV infection or a subset identified as at high risk for HIV? Three persons with HSV infection or a subset of viral agents should be administered—all the next obvious question is to whom antiviral therapy for the partner with both HIV and HSV.

One of the great curiosities about the observations summarized above is that the connections between genital ulcer disease and HIV transmission and the ability to suppress HSV relapses have been known for 15 years. The infrequent development of resistance despite chronic use of acyclovir by immunocompetent patients and the safety of this drug when used in this fashion have also been well established for at least a decade. The US experience has been that HIV prevention efforts have had minimal clear impact, with an estimated 40,000 new cases of HIV each year for the last decade, although the efforts have not attempted to focus on the use of suppressive antiviral therapy to prevent transmission. The issues for HIV prevention, especially in resource-limited countries, loom large on a global scale, and the message here may have an extraordinarily broad application [21].

Acyclovir and valacyclovir have established efficacy in prevention of symptomatic HSV infection and also in reduction of viral shedding. This benefit applies to both immunocompetent and immunosuppressed hosts, although resistance and severe relapses are more common with progressive declines in CD4+ cell count [6, 20]. Studies examining the potential utility of antiviral drugs to reduce the transmission of HIV are eagerly awaited.

References