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The Effects of Herpes Simplex Virus-2 on HIV-1 Acquisition and Transmission: A Review of Two Overlapping Epidemics

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Abstract

Abstract: Increasing evidence demonstrates a substantial link between the epidemics of sexually transmitted HIV-1 and herpes simplex virus (HSV)-2 infection. More than 30 epidemiologic studies have demonstrated that prevalent HSV-2 is associated with a 2- to 4-fold increased risk of HIV-1 acquisition. Per-sexual contact transmission rates among couples from Rakai, Uganda indicate that at all levels of plasma HIV-1 RNA in the source partner, HSV-2-seropositive HIV-1-susceptible persons have a 5-fold greater risk of acquiring HIV-1 compared with HSV-2-negative persons. In vitro and in vivo studies suggest that mucosal HIV-1 shedding is more frequent and in greater amounts during mucocutaneous HSV-2 replication, including subclinical mucosal reactivations. Most HIV-1-infected persons are coinfecting with HSV-2, and most experience frequent subclinical and clinical reactivations of HSV-2. Subclinical HSV reactivation

elevates serum HIV-1 RNA levels, and daily therapy with acyclovir appears to reduce plasma HIV-1 RNA. These data show that greater attention to the diagnosis and treatment of HSV-2 among HIV-1-infected persons is warranted, especially those who continue to be sexually active, those not on antiretroviral therapy, or those whose disease is not well suppressed by antiretrovirals.

Over the past 5 years, data from Africa, Asia, and the Americas have highlighted the parallel and intersecting epidemics of HIV-1 and herpes simplex virus (HSV)-2, with growing understanding about the impact of genital HSV infection on increased risk of HIV-1 acquisition. Of all the sexually transmitted diseases (STDs), there appears to be true “epidemiologic synergy” between these 2 viruses, 1 in that HIV-1 incidence is increased in parallel with HSV-2 prevalence among HIV-1-negative and -positive persons, and HIV-1 prevalence increases HSV-2 incidence. Furthermore, HIV-1 infection changes the natural history of HSV-2 infection, and HSV infection may alter the course of HIV-1 disease.

Sexual transmission of HIV-1 continues throughout Africa, Asia, and Eastern Europe, with the rate of new HIV-1 infections again increasing in the United States and Europe after a decade of decline. An even more silent epidemic of HSV-2 is also occurring throughout all regions of the world, including the United States; 1 in 4 sexually active adults in the United States has HSV-2 infection, with a 31% increase in HSV-2 prevalence between 1978 and 1990. 2 In the United States, 40-60% of attendees in STD clinics have already acquired genital herpes, 3-5 and 20-35% of pregnant women are HSV-2 seropositive. 6-8 Mathematical models derived from HSV-2 seroprevalence studies estimate that 1.6 million new HSV-2 infections occur yearly in the United States. 9 In the United States, African American persons, especially African American women, account for a disproportionate burden of both HSV-2 and heterosexually transmitted HIV-1 infection. 2,10,11

Seroprevalence of HSV-2 in Western European countries, including France, Germany, the Netherlands, Italy, and Switzerland, now approaches that of the United States (Table 1). In South America, HSV-2 prevalence rates are similar to or higher than the United States, in both heterosexual and homosexual populations. Household serosurveys of women in Costa Rica and Brazil and serosurveys of pregnant women in Latin America show HSV-2 prevalence rates >30%. 12,13 HSV-2 infection is comparably high among men who have sex with men (MSM) in Latin America with 60-70% of HIV-1-seronegative MSM and >85% of HIV-1-seropositive MSM in Peru infected with HSV-2. 14 Comparably high HSV-2 rates have been observed in sub-Saharan Africa, where HIV prevalence is the highest. HSV-2 acquisition rates among South African teenagers are estimated to be 10-20% per year after sexual debut, and 20% of HIV-1-seronegative and 80% of HIV-1-seropositive teenagers are HSV-2 seropositive. 15 HSV-2 seroprevalence is >40% among antenatal attendees in Africa, 16 and ranges from 60% to 95% among female sex workers in sub-Saharan Africa. 16-18

Graphic TABLE 1. HSV-2 Seroprevalence in Selected Populations

Graphic TABLE 1. (continued) HSV-2 Seroprevalence in Selected Populations

HSV is now is the major cause of genital ulcer disease (GUD) in both developed 19 and developing countries. 20-22 In South Africa, where the etiology of GUD has been studied for 3 decades, HSV was demonstrated to be the cause of GUD in 1.3% of male gold miners with GUD in 1986, increasing to 10% in 1994 and 24% in 1998. 23 Similar trends over the past 2 decades have been observed in Harare, Zimbabwe, where the proportion of GUD diagnosed as herpes increased from <25% in the 1980s to 73% in 1999. 24 Recent studies have shown HSV to be the predominant cause of genital lesions in Thailand (82%) and India (50%). 25,26 In all of these studies, HSV-2 infections were substantially more frequent than other etiologies of genital ulcers. This shift likely reflects several factors, including successful treatment of syphilis and chancroid through the World Health Organization Syndromic Management Guidelines for GUD; patients with HIV-1-associated immunodeficiency have more persistent HSV-2 ulcerations and thus present for care more frequently than immunocompetent persons; and the increasing use of polymerase chain reaction (PCR)-based methods to detect HSV DNA in ulcers—a technology that is 4 times more sensitive for detecting HSV on mucosal surfaces than viral isolation, and less subject to collection and transport problems. 27,28

Given the recent number of studies documenting epidemiologic, clinical, and biologic interactions between HSV-2 and HIV-1, we undertook a systematic review of the literature. This article reviews the data suggesting that HSV-2 increases the risk of HIV-1 acquisition; HSV-2 increases the risk of HIV-1 transmission; HIV-1 alters the natural history of HSV-2; HSV-2 accelerates HIV-1 disease progression; and why this accumulating evidence warrants greater attention and new approaches from clinicians, epidemiologists, and public health leaders.

METHODS

We searched MEDLINE from 1968-2002 using the terms HIV-1 or AIDS and HSV or genital herpes. In addition, we reviewed abstracts from pertinent infectious disease and HIV-1 conferences, examined the bibliographies of relevant articles, and contacted directors of laboratories performing type-specific serologies. For each issue addressed, we present the available data and discuss the quality of evidence.

RESULTS

Epidemiologic Associations Between HSV and HIV-1 Acquisition

A recent meta-analysis of the association between HSV-2 infection and risk of HIV-1 acquisition reviewed 31 studies, involving >25,000 persons. ²⁹ When this review was performed, the risk estimate from 9 cohort and nested case-control studies that documented HSV-2 infection prior to HIV-1 acquisition was 2.1 (95% CI 1.4, 3.2). The risk estimate from 22 case-control and cross-sectional studies was 3.9 (95% CI 3.1-5.1). The risk of HIV-1 infection in HSV-2-seropositive persons was elevated in all subgroups examined: women (odds ratio [OR] = 4.5, 95% CI 3.8-7.4), MSM (OR = 4.3, 95% CI 2.4-7.6), heterosexual men (OR = 5.1, 95% CI 3.2-8.4), developed countries (OR = 2.9, 95% CI 1.7-4.7), and developing countries (OR = 5.3, 95% CI 3.8-7.4). Most studies adjusted the estimate for the relationship between HSV-2 and HIV for sexual behavior, and the relationship remained significant. Although unmeasured confounding by high-risk sexual behavior is possible, observational studies cannot show causality, therefore the association between HSV-2 and HIV in wide geographic regions in populations with diverse sexual behavior suggests that the association is unlikely to be solely an "epiphenomenon of behavioral risk." In one of the largest studies, Weiss et al. ^{30,31} evaluated factors that could distinguish between 2 cities with high HIV-1 prevalence in central Africa (Kisumu, Kenya, and Ndola, Zambia, both with HIV-1 seroprevalence of 30-32%) and 2 cities with low HIV-1 prevalence (Cotonou, Benin, and Yaounde, Cameroon, with HIV-1 seroprevalence of 3-8%). The frequency of HSV-2 infection and lack of circumcision were identified as 2 central determinants of HIV-1 prevalence. ³¹

Three recent studies have indicated that recent acquisition of HSV-2 increases the risk for HIV-1 acquisition even more than prevalent HSV-2 infection. In a study of 763 adults in rural Tanzania, HSV-2 increased the risk of HIV-1 acquisition among persons who seroconverted to HSV-2 in the prior 2 years (OR = 13.2, 95% CI 5.0-34.9 for men and OR = 2.4, 95% CI 0.8-6.8 for women), which was greater than the risk of prevalent HSV-2 infection (OR = 5.8, 95% CI 2.4-13.9 and OR = 1.3, 95% CI 0.6-2.8 among men and women, respectively). ³² Similarly, in a study of 2260 male STD clients and 463 female STD clinic patients and sex workers in Pune, India, persons recently infected with HSV-2 had a 3.8-fold increased risk of HIV-1 acquisition compared with 1.7-fold increased risk for those with prevalent HSV-2 infection. ³³ Incident HSV-2 infection was also associated with several-fold increased risk of HIV-1 acquisition among MSM in Peru. ³⁴ In a nested case-control study of 116 MSM who seroconverted to HIV-1 and 342 matched HIV-negative MSM controls in the United States, there was a trend toward a higher risk of HIV acquisition among those with incident HSV-2 (adjusted OR = 2.8; 95% CI 0.8-10.1) than prevalent HSV-2 infection (adjusted OR = 1.8, 95% CI 1.1-2.9). ³⁵ Although sexual behavior may be one factor in the higher risk of HIV infection among those with incident than prevalent HSV-2 infection, these observations also have a biologic explanation in that both clinical and subclinical HSV reactivation is substantially more frequent in the first year after acquisition of HSV-2 than later. ^{36,37}

HSV-2 Increases the Per-Contact Transmission Rate of HIV-1

The most compelling observational data about the relative effects of HSV-2 infection on HIV-1 acquisition and transmission come from recent analyses of data from the Rakai community STD intervention trial. ³⁸ HSV-2 is prevalent in this rural district of Uganda; HSV-2 antibodies were detected in 61% of 15- to 29-year-old women and 31% of 15- to 29-year-old men, and HSV was detected in 87% of ulcers with a confirmed etiology. ³⁹ Data from a cohort of monogamous HIV-1-discordant couples from Rakai have helped define the per-contact rate of HIV-1 acquisition and transmission in the context of other risk factors such as HIV-1 RNA of the HIV-1-infected partner. ⁴⁰ Symptoms of urethritis and laboratory-confirmed STD diagnoses, including gonorrhea, *Chlamydia* infection, and trichomoniasis, did not increase the per-contact risk of HIV-1 acquisition, which averaged 0.0011. ⁴¹ However, as shown in [Table 2](#), the per-contact probability of HIV-1 infection was 5-fold higher if the susceptible partner was HSV-2 seropositive than HSV-2 seronegative (0.002 vs. 0.0004 per-contact, $P = 0.01$), an association that was observed for both men and women. In addition, if the HSV-2-seropositive susceptible partner reported symptomatic GUD, the probability of acquisition per coital act was 0.0031. However,

the risk of HIV acquisition was also increased with asymptomatic HSV-2 (probability per act = 0.0019), suggesting that subclinical HSV-2 infection is almost as important as clinically recognized lesions in increasing susceptibility to HIV. [41](#) Notably, the per-contact HIV-1 acquisition rate of an HSV-2-seropositive person with a partner who has plasma HIV-1 RNA <1700 copies/mL was similar to that of an HSV-2-seronegative with a partner with HIV-1 RNA of 12,000 to 39,000 copies/mL ([Table 3](#)). Although this study was conducted among persons not receiving highly active antiretroviral therapy (HAART), these findings highlight the potential role of HSV-2 in increasing risk of HIV transmission in the setting of viral transmission on HAART.

Graphic

TABLE 2. Per-Contact Probability of HIV-1 Acquisition in HIV-1-Discordant Couples by HSV-2 Serology

Graphic

TABLE 3. Per-Contact Probability of HIV-1 Acquisition, Stratified by Plasma HIV-1 RNA in HIV-1-Seropositive Partner and HSV Serostatus in the Susceptible Partner*

In summary, a review of >35 studies conducted over the past decade in 4 continents (Europe, Africa, Asia, and South and North America), which includes heterosexual men, women, and MSM, consistently shows at least 2-fold increased risk of HIV-1 acquisition in persons with HSV-2 infection. The data from HIV-1-serodiscordant couples indicate that the risk for HIV-1 acquisition conferred by HSV-2 was demonstrated at all levels of plasma HIV-1 RNA of the source partner. Thus, preventing, recognizing, and treating early HSV-2 infection may be an important component of any strategy focusing on reducing the synergistic interaction between the 2 viruses. Mathematical modeling suggests the influence of HSV-2 fueling the HIV-1 epidemic may be greatest in the early periods of HIV-1 introduction into a community, before HIV-1 prevalence rates become high; an effect that has been posited for other STDs as well. [42](#) Suppressive antiviral therapy will be tested for efficacy in preventing HIV-1 acquisition among HSV-2-seropositive persons at high risk of HIV-1 acquisition as a "proof of concept" in a National Institutes of Health-funded multicenter trial (HIV Prevent Trials Network [HPTN] Protocol 039).

Biologic Interactions Between HSV and HIV-1: Implications for Acquisition

The biology of herpetic infections supports the epidemiologic observations regarding an association between HSV-2 and HIV-1 acquisition. In experimental animal models, mucosal disruption leads to increased susceptibility to HIV-1, as measured by infection occurring at a lower inoculation of simian retrovirus infection. [43](#) In addition to mucosal disruption, herpetic ulcerations are associated with an influx of large numbers of activated CD4-bearing lymphocytes, [44,45](#) providing increased numbers of target cells for HIV-1 attachment and entry in the genital tract during HSV-2 reactivation. Both mucosal disruption and the presence of increased numbers of activated CD4 cells increase the likelihood that any potential exposure to HIV-1 will result in infection of the exposed host.

Several HSV proteins (ICPO, ICP27, Us11, and others) increase expression of HIV-1, [46-49](#) and HSV infects and replicates in activated CD4 cells and macrophages. [50](#) Both heat-inactivated and infectious HSV-1 and HSV-2 virions have been shown to increase HIV-1 expression in macrophages, likely through stimulation of nuclear factor (NF)- κ B activity. [51](#) Biopsy samples have demonstrated viruses in both keratinocytes and macrophages by electron microscopy. [52](#) Schacker et al. [53](#) demonstrated HIV-1 RNA in 25 of 26 genital herpes lesions. HIV-1 RNA often exceeded 10,000 copies/mL of swab fluid and the quantity of HIV-1 in genital samples often exceeded HIV-1 RNA levels in blood. Similar findings were reported by investigators in India that demonstrated HIV-1 in genital ulcers in 34% of consecutive HIV-1-seropositive patients with GUD. [54](#)

Several studies have shown that subclinical HSV reactivation is also associated with increased replication of HIV-1 on mucosal surfaces. This is of great importance epidemiologically in that most HSV-2 reactivation in the genital tract is clinically inapparent but associated with the same mucosal destruction and lymphocytic infiltration as overt genital herpetic lesions; HSV is released from mucosal lesions into the submucosa and small ulcerations precede the development of subclinical reactivation. [55](#) Mbopi Keou et al. [56](#) studied HSV-2 DNA and HIV-1 RNA in cervicovaginal secretions of women without genital lesions. The amount of HSV DNA measured in genital secretions correlated with amount of HIV-1 in genital secretions ($r = 0.47$, $P = 0.02$). McClelland et al. [57](#) also found that quantity of HSV DNA in cervical and vaginal secretions correlated with cervical HIV RNA and proviral DNA levels in those secretions.

Does HSV-2 Infection Enhance HIV-1 Transmission?

These data on the mucosal interactions of HIV and HSV-2 suggest that HIV-1-seropositive, HSV-2-seropositive persons may transmit HIV infection more frequently than HIV-1-seropositive persons who are HSV-2 seronegative. A study of HIV-discordant couples in Uganda found similar probabilities of HIV transmission irrespective of whether the HIV-positive partner was HSV-2 seropositive or seronegative. ⁵⁸ However, the high prevalence of HSV-2 antibodies in HIV-positive persons (~85%) limited the power to detect an effect. It is noteworthy that the presence of recent symptomatic genital ulceration in the HIV-positive source partner significantly increased the transmission probability per act (0.0041) when compared with no ulceration (0.0011). ³⁹ Because HSV-2 is the most common cause of genital ulceration in this population, it suggested that HSV-2 may enhance transmission of HIV from symptomatic dually infected persons.

Prospective studies of transmission of sexually transmitted infections are challenging, particularly because in most HIV-1-discordant couples in whom the HIV-1-infected partner has HSV-2 infection, the susceptible partner is also HSV-2 seropositive and thus it is difficult to disentangle acquisition and transmission effects. Thus, the central issue of whether control of HSV-2 reactivation can control HIV-1 transmission remains to be tested. The recent demonstration that daily antiviral therapy with valacyclovir can reduce HSV-2 transmission among HSV-2-discordant heterosexual couples supports the concept that antiviral therapy can reduce transmission of a viral STD. ⁵⁹ The strong biologic plausibility that HSV-2 amplifies HIV-1 transmission indicates that an intervention study is warranted to evaluate whether treating HSV-2 among HIV-1-infected persons will reduce HIV-1 transmission.

HIV-1 Is Fueling the HSV-2 Epidemic

HIV-1 infection also appears to be fueling the HSV-2 epidemic. Studies of male factory workers in Zimbabwe and men and women in rural Rakai have shown markedly higher acquisition rates for HSV-2 in HIV-1-seropositive compared with HIV-1-seronegative persons, with relative risks of 4.7 and 3.7, respectively. ^{60,61} HIV-1-infected persons appear to have an increased risk of acquisition of HSV-2, although it is not known whether these observations represent increased susceptibility to HSV-2 infection or are a marker for sexual exposure to HIV-1 and HSV-2 coinfecting persons who shed HSV from mucosal surfaces more frequently than HIV-1-seronegative persons with HSV-2 infection.

HSV-2 Infection in the HIV-1-Positive Person

Although HSV was one of the initial opportunistic infections described in the original report of AIDS in 1981, ⁶² it is only recently that the natural history of this infection has been systematically studied in HIV-1-infected persons. In the setting of untreated, advanced HIV-1 disease, HSV ulcers are often large, deep, sometimes mimicking chancroid, slow to heal, often appear in "atypical" areas of the body, and can lead to scarring (Fig. 1). However, they represent only a minor part of the spectrum of genital herpes in the HIV-1-infected person and markedly underestimate the frequency of true mucosal reactivation of HSV-2 in the HIV-1-seropositive person.

Graphic

FIGURE 1. Clinical manifestations of HSV infection in HIV-infected persons. **A,** Patient who presented with persistent genital and perianal HSV-2 infection as his first manifestation of HIV infection. **B,** Patient with long-standing HIV infection and severe immunosuppression who presented with a mass behind the left ear. All work-up was negative but a viral culture yielded HSV-2. The lesion slowly resolved on acyclovir therapy (photo courtesy Dr. David Spach). Patient had a history of recurrent genital HSV-2 infection. He was not receiving ART at the time.

Similar to the natural history of HSV-2 among immunocompetent persons, most HSV-2 reactivation among HIV-positive persons is subclinical. ^{63,64} Figure 2 and Table 4 collate data from studies conducted in Seattle of HSV reactivation among HIV-1/HSV-2-seropositive men, as measured by viral isolation and HSV DNA PCR. HSV-2 reactivation is more frequent in HIV-seropositive vs. HIV-negative men; HSV-2 DNA was detected a median of 38% of days in HIV-1-seropositive MSM vs. 25% of days among HIV-1-seronegative MSM, and HSV was isolated in culture in 13 vs. 4% of days, respectively. Forty percent of days of HSV-2 reactivation as detected by culture and 59% of days by HSV DNA PCR was subclinical in HIV-seronegative men; the corresponding proportions were 54 and 66% in HIV-seropositive MSM, indicating the high frequency of subclinical disease in the immunocompromised populations. Both CD4 T-cell count and HIV-1 plasma RNA influence HSV-2 reactivation rates. A direct correlation is observed between days HSV is detected by culture or PCR and plasma HIV RNA levels and the negative correlation between CD4 count and HSV reactivation frequency. ⁶³ However, the variability in reactivation rates is high at all levels of CD4 count and many persons with CD4 T-cell counts >350 cell/mm³ have as frequent reactivation as those with CD4 counts of <100 cells/mm³. ^{63, 64}

Graphic

TABLE 4. HSV-2 Culture and HSV DNA PCR Positivity Rates Among HIV-1/HSV-2-Seropositive Persons, Stratified by CD4 Count and HIV-1 RNA

Graphic

FIGURE 2. Frequency of HSV isolation and HSV DNA detection in men, stratified by sexual orientation, HIV-1 status, and HAART. The HSV PCR assay detects both HSV-1 and HSV-2. More than 98% of genital samples are HSV-2 when typed by HSV-1- and HSV-2-specific primers. 96

Posavad et al. 65 recently followed a cohort of HSV-2- and HIV-infected persons receiving HAART. Although HAART therapy reduced the frequency of genital lesions, it had surprisingly little effect on reducing subclinical HSV reactivation as measured by either HSV culture or PCR. 65 Thus, HSV reactivation is still frequent among HAART-treated patients (Fig. 2). Whether these frequent episodes of subclinical HSV reactivation among patients on HAART are associated with the same increase in mucosal HIV-1 RNA shedding as previously seen among persons not on HAART is at present unknown. These data do, however, suggest the interaction between HSV-2 and HIV remains of concern even among HIV-infected persons on HAART.

HIV-1 Replication Is Influenced by HSV

Several studies have evaluated the influence of HSV reactivation on plasma HIV-1 RNA. 66 Some have shown a rise in plasma HIV-1 RNA in association with genital lesions, whereas others have not. 67,68 Some studies used genital lesions as a marker of HSV reactivation, which, as discussed here, underestimates the frequency in which mucosal HSV infection occurs by approximately 2-fold and ignores the observation that subclinical HSV-2 reactivation influences mucosal HIV-1 replication. Two recent studies that evaluate subclinical HSV shedding suggest that HSV-2 significantly influences the replication of HIV-1. Gray et al. 67 have shown that in newly infected HIV-1-seropositive men and women in Rakai, HSV-2/HIV-1-coinfected persons have HIV-1 RNA titers that are a half log higher than HSV-2-seronegative HIV-1-seropositive persons. Schacker et al. 68 directly studied the influence of HSV infection on HIV-1 replication in vivo by administering chronic daily therapy with acyclovir to HIV/HSV-2-coinfected persons and measuring plasma HIV-1 RNA levels before and after administration of acyclovir. Acyclovir reduced plasma RNA levels by an average of one-third of a log; a reduction in plasma HIV RNA levels was observed in 11 of 12 persons, and HIV-1 RNA levels returned to previous baseline upon discontinuation of therapy. These studies may provide some explanation of the older studies with zidovudine monotherapy that showed increased survival with concomitant acyclovir use. 69 Whether the addition of daily antiviral therapy for HSV-2 infection would enhance the durability of HIV suppression on HAART therapy is unknown.

Treatment of Genital Herpes in the HIV-1-Seropositive Person

Nucleoside analogues for the treatment of HSV have been available for >2 decades. 70 All 3 licensed compounds—acyclovir, famciclovir, valacyclovir—have been shown to be effective for episodic, and, more importantly, chronic daily therapy for HSV-2 infection in HIV-positive men and women. 71-75 The data from these studies are summarized in Table 5 and illustrate the safety and efficacy of all 3 medications for reducing clinical and subclinical reactivation of HSV infection in HIV-infected men and women. Thrombotic microangiopathy was observed in early studies of valacyclovir in doses of 8 g per day for prevention of cytomegalovirus disease in HIV-1-infected patients but has not been observed among patients with HIV-1 treated with lower doses of valacyclovir appropriate for HSV infections (e.g., 1-1.5 g/d). 76 Oral antiviral medications for HSV lack significant drug interactions with antiretroviral therapies.

Graphic

TABLE 5. Results of Clinical Trials of Treatment of Genital Herpes Among Persons With HIV-1 Infection

Decreased susceptibility of HSV isolates to acyclovir was initially described in immunocompromised patients, and acyclovir-resistant HSV became an important management issue early in the HIV-1 epidemic. 77 Three mechanisms of HSV resistance to acyclovir

have been described. 78,79 By far, the most common is deficiency of thymidine kinase, which renders acyclovir ineffective as the drug requires viral thymidine kinase for initial phosphorylation. 80 Other, less commonly found mutants, include strains with altered thymidine kinase and DNA polymerase mutations. 81,82 Strains resistant to acyclovir are almost always resistant to penciclovir (the active form of famciclovir). Isolates with in vitro resistance to acyclovir may be found in lesions that respond to therapy. 83-85 In general, poor clinical response to the nucleosides is associated with high-level resistance to acyclovir (>10 µg/mL). Treatment of acyclovir-resistant HSV is beyond the scope of this review; success has been achieved with foscarnet, topical trifluoridine, and topical cidofovir. 86,87 Little is known of antiviral resistance to HSV infections in the developing world and antiviral monitoring of acyclovir resistance among HIV-seropositive persons should be maintained, as nucleoside treatment of genital herpes continues to increase worldwide. 88,89 If increasing chronic suppressive use results in increasing rates of resistance, then recommendations will need to be refocused on select groups at greatest benefit and with the lowest risk of acyclovir-resistant herpes.

The frequency of acyclovir-resistant HSV infection in the United States and Western Europe appears to have stabilized and even decreased, perhaps coincident with the widespread use of HAART. A recent survey of HIV-positive persons attending STD clinics in the United States showed that 3-5% of HIV-infected persons harbored HSV-2 isolates with reduced (>2 µg/mL) susceptibility to acyclovir in vitro, which is only slightly higher than the 1% observed among HIV-negative persons recruited from the same sites 88; none of these persons displayed clinically evident, symptomatic acyclovir-resistant herpes. Anecdotal evidence suggests that frequency of acyclovir-resistant herpes declined with the introduction of HAART.

Despite the data on the clinical utility of these medications on HSV reactivation in HIV-positive populations, definitive guidelines on the use of the nucleoside analogues for HSV are not available. We recommend that genital herpes be treated to reduce the duration and severity of clinical reactivation anogenital herpes. Given the high HSV-2 seroprevalence among HIV-infected persons, treatment of HSV-2 could potentially have a substantial public health impact on HIV transmission, which has led to intervention studies to determine what degree HSV-2 suppression reduces HIV transmission. Similarly, no data are available to indicate whether anti-HSV therapy further prolongs survival among HAART-treated patients, as it did with zidovudine monotherapy. 90

What should clinicians do now pending these data? There are no definitive answers and resource allocations appear to drive current practice. We believe the weight of the data support more frequent use of type-specific serologies to identify HIV-infected persons with unrecognized genital herpes and daily anti-HSV therapy for HIV-infected persons. HIV-seropositive persons whose disease is poorly controlled on ART and who have frequent HSV reactivation should be considered for chronic suppressive therapy. In addition, HIV- and HSV-2-coinfected persons who are sexually active should be advised of the association between HSV-2 reactivation and mucosal HIV-1 shedding, and such persons should be considered for daily suppressive anti-HSV therapy.

DIAGNOSIS OF HSV-2 INFECTION IN THE HIV-POSITIVE PERSON

Studies have indicated that >95% of HSV-2-seropositive persons reactivate HSV-2 on mucosal surfaces and hence provide support for the concept that serologic testing for HSV-2 infection identifies persons at risk for mucosal reactivation. 91 In the United States and Western Europe, 40-80% of HIV-infected persons are coinfecting with HSV-2, and, as such, serologic screening for HSV-2 would identify persons at high risk of frequent mucosal HSV-2 reactivation and enhanced shedding of mucosal HIV-1. Type-specific serologic assays for antibodies to HSV-2 have been approved for clinical use by the US Food and Drug Administration and are licensed throughout Europe. These assays detect antibodies to the HSV-1 and HSV-2 glycoproteins gG1 and gG2 and have been used in a wide variety of settings involving HIV-seropositive men and women. Their utility in some areas of central Africa is still being debated, but they have had extensive use in serosurveys and clinical management in the United States and Europe. 91-93 In addition to these serologic assays, laboratory assays such as viral culture, or, preferably, HSV DNA PCR should be used to define the etiology of genital lesions in HIV-seropositive persons. 94,95 Clinical diagnosis of GUD in HIV-seropositive persons is often unreliable, and infection with multiple pathogens is common. 94 HSV DNA PCR is the assay with the greatest sensitivity for detecting HSV in genital lesions. Ballard et al. 23 have shown that the appropriate treatment of genital lesions due to HSV-2 results in reduced amount of HIV-1 shed in such lesions.

In North America and Europe, we believe that data are sufficient to urge routine serologic testing for HSV-2 among persons with HIV-1 infection. Identifying the 50-60% of HIV-infected persons who are HSV-2 seropositive provides important information about the high likelihood of intermittent perianal and genitourinary symptoms from HSV-2 reactivation and the potential that such reactivation may lead to increases in plasma HIV-1 RNA elevations. 68,96 Moreover, such persons should have anti-HSV medications included for the empiric treatment of genital ulcerations or to consider HSV as a likely co-infecting pathogen if other causes of GUD are suspected.

We believe that HSV-2 serologic assays are unlikely to be necessary to define prevalent HSV-2 infection in populations where such

coinfection is nearly universal (e.g., commercial sex workers in Africa). Such persons should be considered to be coinfecting and increased awareness of the high prevalence of HSV as a sole or copathogen of genital ulcers in such persons is important. More systematic surveys of the prevalence of HSV-2 in African, Caribbean, and Asian HIV-infected people should be performed.

CONCLUSION

New approaches to reducing the transmission of HSV-2 and HIV-1 are needed. The increasing number of HSV-2- and HIV-1-seropositive persons with CD4 T-cell counts of >350 cells/mm³ who are not on HAART is of concern regarding the influence HSV-2 will continue to play in promulgating the HIV-1 epidemic in North America and Europe. Although use of antivirals for episodic therapy would be less costly and easier to implement as an HIV-1 prevention strategy, episodic treatment is also likely to be less effective in preventing HIV-1 acquisition or transmission than daily suppressive therapy, given the high proportion of subclinical HSV-2 reactivation. Lastly, recent consideration by the World Health Organization to include antiviral therapy for the syndromic treatment of GUD will lead toward providing more appropriate therapy for genital ulcers in the developing world. The tight epidemiologic and clinical association between HSV-2 and HIV-1 also provide an impetus to speed development of a vaccine to prevent HSV-2 acquisition or reactivation. From both clinical and public health perspectives, there is a clear imperative to test different approaches to interrupting the synergistic link between herpes and HIV-1.

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