Left out but not forgotten: Should closer attention be paid to co-infection with herpes simplex virus type 1 and HIV?

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Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are among the most common co-infections seen in individuals infected with HIV-1. Most research on HSV-HIV co-infection has focused on HSV-2, and in particular, on its impact on HIV transmission. HSV-2 is associated with micro- and macro-ulcerations in genital mucosal surfaces, increased numbers of HIV target cells in genital mucosal tissue and increases in plasma HIV viral load of up to 0.5 log10 copies/mL, such that HSV-2 infection increases the risk of both HIV acquisition and transmission. Because plasma HIV RNA levels are a major determinant of rates of CD4 cell decline, HSV-2 co-infection may also adversely affect the progression of HIV disease. Anti-HSV medications have in fact been associated with reciprocal decreases in HIV viral load in short-term studies. These findings have led to the development of several clinical trials of HSV-2 suppression as strategies for preventing HIV transmission and slowing the rate of HIV disease progression. HSV-1 co-infection has largely been ignored from this growing body of research, yet there are several reasons that this co-infection remains an important issue for study. First, the seroprevalence of HSV-1 is consistently higher than that of HSV-2 among both HIV-infected and HIV-uninfected populations, underscoring the relevance of HSV-1 co-infection to the majority of HIV-infected persons. Second, pre-existing HSV-1 antibodies in individuals may modulate the course of subsequently acquired HSV-2 infection; the implications of such changes on HSV-HIV co-infection remain unexplored. Third, HSV-1 and HSV-2 are closely related viruses that share 83% genetic homology. Their virological and pathobiological similarities suggest that their implications on HIV pathogenesis may be similar as well. Finally, HSV-1 is becoming increasingly relevant because the incidence of genital HSV-1 has risen. Although genital herpes is traditionally associated with HSV-2, recent studies have shown that the majority of serologically confirmed primary genital herpes in some settings is attributable to HSV-1. Because the genital tract is an important site of biological interaction between HSV and HIV, this epidemiological change may be clinically important.

Key Words: Coinfection; Genital herpes; HIV; HSV; Orolabial herpes

Mise de côté sans être oubliée : Faut-il porter davantage attention à la co-infection par le VHS-1 et le VIH?

Les virus de l’herpès simplex de type 1 (VHS-1) et de type 2 (VHS-2) causent certaines des co-infections les plus souvent observées chez les sujets VIH-1 positifs. La majeure partie des recherches qui ont porté sur la co-infection VHS-VIH se sont attardées au VHS-2 et plus particulièrement à son impact sur la transmission du VIH. Le VHS-2 est associé à des micro- et des macro-ulcération de la muqueuse génitale, à un nombre accru de cellules cibles du VIH dans les tissus de la muqueuse génitale et à des augmentations de la charge virale plasmatique du VIH jusqu’à 0,5 log10 copie/mL, de sorte que l’infection au VHS-2 accroît le risque de contracter et de transmettre le VIH. Étant donné que le taux d’ARN du VIH est un important facteur déterminant du déclin des lymphocytes CD4, la co-infection par le VHS-2 peut aussi accélérer la progression de la maladie au VIH. Les médicaments anti-VHS ont en fait été associés à des baisses réciproques de la charge virale du VIH lors d’études à court terme. Ces résultats ont conduit à la mise au point de plusieurs études cliniques sur la suppression du VHS-2 comme stratégie pour prévenir la transmission du VIH et ralentir la progression de la maladie qu’il cause. La co-infection par le VHS-1 a pour une bonne part été ignorée de ce corpus de recherche croissant et pourtant, à plusieurs points de vue, cette co-infection demeure une importante question à explorer. Tout d’abord, la séroprévalence du VHS-1 est toujours plus élevée que celle du VHS-2, tant chez les populations infectées par le VIH que chez les populations indemnes, ce qui rappelle la portée de la co-infection par le VHS-1 chez la majorité des personnes infectées par le VIH. Ensuite, la préexistence d’anticorps anti-VHS-1 chez les sujets pourrait influer sur l’évolution de l’infection au VHS-2 acquise par la suite. Les implications de ces changements sur la co-infection VHS-VIH restent méconnues. Troisièmement, le VHS-1 et le VHS-2 sont des virus étroitement apparentés qui partagent 83 % d’homologie génétique. L’ensemble de ces données suggère que leurs implications dans la pathogenèse du VIH pourraient également être similaires. En terminant, le VHS-1 est de plus en plus pertinent en raison de l’augmentation de l’incidence du VHS-1 génital. Bien que l’herpès génital ait traditionnellement été associé au VHS-2, de récentes études ont montré que dans certains milieux, la majorité des cas d’herpès génital primaire confirmés par des analyses sérologiques est causée par le VHS-1. Étant donné que les voies génitales sont un important siège d’interaction biologique entre le VHS et le VIH, cette variation epidemiologique pourrait revêtir une importance clinique certaine.
in the absence of active herpes lesions (12-14). The frequency of asymptomatic shedding may partially explain why up to 90% of persons with serological evidence of HSV-2 deny any history of herpes symptoms (15).

The lifelong, often asymptomatic nature, and the high prevalence and incidence of HSV infection in HIV-positive individuals imply that any adverse impact of HSV on the natural history of HIV infection could have considerable clinical and public health significance. To date, most research on HSV-HIV coinfection has focused on HSV-2, and in particular, on its impact on HIV transmission. HSV-1 coinfection has been largely ignored from this growing body of research, yet there are several reasons that this coinfection remains an important issue for study, including the high seroprevalence of HSV-1 relative to HSV-2, the modular impact of pre-existing HSV-1 antibodies on subsequent HSV-2 infection, the virological and pathophysiological similarities between the two viruses, and the increasing proportion of genital herpes that is caused by HSV-1. The relatively recent advent of type-specific serological assays that can distinguish between HSV-1 and HSV-2 has provided a timely technological advance that makes the conduct of such studies feasible. These assays detect human immunoglobulin G (IgG) antibodies to glycoprotein G-1 (in HSV-1) or G-2 (in HSV-2) – the major proteins that evoke type-specific responses. In cohorts of pregnant women and sexually active adults, the often-used HerpeSelect 1 and 2 ELISA IgG (Focus Diagnostics, USA) and HerpeSelect 1 and 2 Immunoblot IgG (Focus Diagnostics, USA) have shown sensitivities of 91% to 100% and 89% to 100% for HSV-1 and HSV-2, respectively, and specificities of 92% to 95% and 94% to 98%, respectively, compared with Western blot (16-18). The present paper reviews current evidence regarding the significance of HSV-2 in the transmission and pathogenesis of HIV infection, outlines the reasons that HSV-1 coinfection warrants increased attention in this area and identifies future areas for research.

HOW HSV-2 MAY FUEL THE HIV EPIDEMIC

It has long been recognized that ‘classic’ sexually transmitted infections (STIs) may be important cofactors in the propagation of HIV infection, and several randomized controlled trials of various STI management strategies for preventing HIV have been previously reported (19-22). These studies met with mixed success, and a number of plausible explanations have been advanced to explain the differences in their results, most notably, the important epidemiological differences among the HIV epidemics in the trial settings (23,24). Importantly, however, these trials focused largely on bacterial STIs; the high burden of untreated HSV-2 infection in the study cohorts may have been another important reason that some trials failed to impact on HIV transmission rates. Since that time, a large number of studies have shown that HSV-2 seropositivity increases the risk of HIV acquisition, with one systematic review (25) showing an RR of 2.1 (95% CI 1.4 to 3.2). Similar results were obtained in another, more recent meta-analysis (26), in which the RR of HIV associated with HSV-2 infection was considered separately for men (summary adjusted RR 2.7, 95% CI 1.9 to 3.9), women (RR 3.1, 95% CI 1.7 to 5.6) and among men who have sex with men (MSM) RR 1.7, 95% CI 1.2 to 2.4).

The mechanisms through which HSV-2 may drive the amplification of HIV transmission are multiple (27). First, both symptomatic and asymptomatic HSV-2 infections may result in the disruption of the epithelial barrier of genital mucosal surfaces, providing increased portals of entry for HIV into the HSV-2-infected person during sexual contact. Second, HSV-2 infection results in increased recruitment of HIV target cells, such as CD4/CCR5 T lymphocytes and dendritic cells harbouring the lectin dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin, even in the absence of clinical symptoms or asymptomatic viral shedding (28). Higher numbers of target cells likely contribute to the increased HIV susceptibility observed in HSV-2-infected persons. Finally, among individuals who become HSV-2-HIV coinfected, HSV-2 has been associated with increases in HIV viral load in both plasma and genital secretions of up to $0.5 \log_{10} \text{copies/mL}$ (12,29-32), thus increasing the likelihood of secondary HIV transmission to HIV-uninfected partners. Taken together, these findings provide a strong epidemiological and pathophysiological rationale for studying pharmacological HSV-2 suppression as a therapeutic strategy for preventing HIV acquisition. However, two recent randomized controlled trials (33,34) conducted in HIV-endemic settings in East Africa have shown that acyclovir 400 mg administered twice a day, compared against placebo, does not protect against HIV acquisition among HSV-2-seropositive individuals. These surprising findings are further discussed below.

EVIDENCE THAT HSV-2 INFECTON MAY IMPACT ON HIV PROGNOSIS

In addition to the role of HSV-2 in fuelling HIV transmission, it has more recently been recognized that HSV-2 may also have important adverse impacts on HIV disease progression for coinfection persons themselves. As mentioned above, both symptomatic and asymptomatic episodes of HSV-2 reactivation are associated with increases in HIV viral load of up to $0.5 \log_{10} \text{copies/mL}$, which is recognized as a clinically significant amount (35). HSV-2 is believed to be the cause, not the effect, of increased HIV viral load, for several reasons. First, in vitro research shows that HSV gene products, such as infected cell protein (ICP)-0, ICP-4, ICP-27 and Us11, directly upregulate HIV replication (36-39), and that HSV increases expression of HIV in infected macrophages through stimulation of the nuclear factor-kappa B pathway (40). The release of pro-inflammatory cytokines from HSV-infected cells could similarly stimulate HIV expression, as has been observed for other herpesviruses (41). Second, HSV coinfection may result in the effective expansion of HIV cell tropism by modulating the expression of either CD4 or CCR5/CXCR4 coreceptors on their surfaces, as has been observed for human herpesvirus-6 (42,43). Simultaneous infection of host cells by both HIV and HSV could also expand and enhance the range of HIV-susceptible cells by producing viral ‘pseudotypes’ in which HIV genomes are encapsulated by HSV glycoproteins, resulting in productive HIV infection of CD4-negative cells (39). Indeed, this has been demonstrated for HSV-1; skin biopsy specimens coinfected with HSV-1, and HIV obtained from AIDS patients, have revealed HIV virions within keratinocytes – a cell type that is normally incapable of being infected by HIV due to the lack of CD4 receptors (44). Third, both the
broad and magnitude of HIV-specific CD8+ T cell proliferative and interferon-gamma responses are reduced in HSV-2-HIV-coinfected persons, suggesting a potential mechanism through which this coinfection impairs the immune response to HIV and facilitates ongoing viral replication (45). Furthermore, the severity of symptomatic HSV disease in the setting of HIV infection is known to correlate with immune dysregulation (ie, low CD4 counts) rather than with HIV virulence (12,46). Finally, treatment with anti-HSV medications, such as the acyclovir prodrug, valacyclovir, has been associated with reciprocal decreases in HIV viral load of 0.33 log_{10} copies/mL to 0.53 log_{10} copies/mL in small, randomized clinical trials (47,48) with short periods of follow-up.

This causal relationship between HSV-2 and increased HIV viral load is important because plasma HIV viral load is the principal driver of immune depletion (as measured by CD4 cell decline) and HIV disease progression (49-51), such that patients with higher viral loads have faster rates of progression to AIDS and death. It follows that HSV-2 coinfection may be associated with more rapid progression of HIV disease, but this question has yet not been directly studied.

HSV-1: AN UNJUSTLY IGNORED COPATHOGEN?

HSV-1 is capable of causing severe morbidity and mortality, both in the setting of advanced HIV disease (52) and in immunocompetent hosts. Furthermore, HIV has been shown to be independently associated with both HSV-1 (OR 1.10, 95% CI 1.02 to 1.1) and HSV-2 (OR 1.50, 95% CI 1.37 to 1.68) infections in large cohort studies (53). Studies have also shown a trend toward more subclinical shedding of HSV-1 in HIV-infected versus HIV-uninfected persons (12). Yet, current research into HSV-HIV coinfection has all but ignored HSV-1, in part because it is generally understood to cause less frequent and less severe herpes reactivations than HSV-2 (54,55). In addition, because coinfection with HSV-1 and HSV-2 is common, it may be difficult to separate the impact of HSV-1 coinfection with HIV from that of HSV-2 coinfection. Nevertheless, the frequency of HSV-1, its impact on subsequent HSV-2, its biological similarities to HSV-2 and the proportion of genital herpes caused by HSV-1 all suggest its potential importance both with regard to the transmission of HIV to HIV-susceptible persons and the pathogenesis of HIV disease in HIV-infected persons.

HSV-1 is common

The seroprevalence of HSV-1 is consistently higher than that of HSV-2 worldwide, because the acquisition of this infection generally occurs in childhood through direct person-to-person contact. Roughly 50% to 70% of individuals in most industrialized world settings, and up to 99% to 100% in adult Sub-Saharan African populations have been infected with this ubiquitous virus (9). In the setting of HIV, the prevalence is still higher, underscoring the relevance of HSV-1 coinfection to the majority of HIV-infected persons. Paradoxically, the near-universal seroprevalence of HSV-1 in settings with high HIV endemicity is a major reason that this virus has been ignored in much of the literature to date; it becomes virtually impossible to accrue sufficient HSV-1-negative persons to serve as a control group in such settings.

In this regard, the later age of infection of HSV-1 and corresponding high serooccurrence of HSV-1 infection reported in HIV high-risk populations in some industrialized countries is an emerging phenomenon of epidemiological importance that may provide important opportunities to explore the significance of HSV-1-HIV coinfection. For instance, among participants in a large Australian cohort study (56) of MSM who were HIV-negative at baseline, the observed incidence rates for HSV-1 was 5.58 per 100 person-years, compared with 1.45 per 100 person-years for HSV-2. The HSV-1 incidence rate was highest among men younger than 25 years of age (11.48 per 100 person-years), but remained higher than the overall HSV-2 incidence rate even among those in the oldest age category studied (2.49 per 100 person-years for those older than 44 years of age) (56). Although the relationship between HSV and HIV incidence rates was not reported, these findings suggest that HIV prevention strategies targeting HSV coinfection must increasingly consider the impact of both prevalent and incident HSV-1.

An additional way in which the high prevalence of HSV-1 may be epidemiologically relevant to studies of HSV-HIV coinfection stems from the observation that the majority of persons with HSV-2 infection are coinfected with HSV-1. Studies (2,6,53,57) of HSV seroprevalence in HIV-positive or HIV-mixed status populations have shown remarkable consistency in the proportion of HSV-2-infected persons who harbour HSV-1 coinfection, at roughly 70% to 75% (Table 1). It is, therefore, conceivable that some of the reported adverse impact of HSV-2 coinfection among HIV-infected persons may be driven by or exacerbated by the presence of HSV-1 coinfection. It is unlikely that HSV-1 infection itself could explain these effects, because the HSV-2 seronegative control groups against whom HSV-2-infected persons are compared in such studies would be expected to have a high burden of HSV-1 infection. Nevertheless, the possibility that dual infection with both HSV types is at least in part responsible for the outcomes attributed to HSV-2 infection warrants further consideration.

HSV-1 may modulate the course of incident HSV-2 infection

A related reason that dual infection with HSV-1 and HSV-2 may be important is because pre-existing HSV-1 infections have been shown to modulate the course of HSV-2 infection. Studies have shown both decreases and increases in various measures of HSV-2 severity. For instance, although pre-existing antibodies against HSV-1 do not diminish the likelihood of

<table>
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<th>Reference</th>
<th>Setting</th>
<th>HIV status of cohort</th>
<th>HSV-1</th>
<th>HSV-2</th>
<th>HSV-1 and HSV-2</th>
<th>Proportion of HSV-2 positive with HSV-1 coinfection, %</th>
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<td>Europe</td>
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<td>54.5</td>
<td>42.1</td>
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<tr>
<td>Ameli et al. 2006 (57)</td>
<td>USA</td>
<td>Positive</td>
<td>95.5</td>
<td>94.6</td>
<td>70.2</td>
<td>74.2</td>
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<tr>
<td>Smit et al. 2007 (53)</td>
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acquiring HSV-2 infection, they do increase the likelihood that incident HSV-2 infection will be asymptomatic by a factor of 2.6 (P<0.001) (58). Conversely, compared with HSV-2 infection alone, dual infection with both HSV types has also been shown to result in increased HSV-2 shedding among HIV-infected persons, with an OR of 1.9 (95% CI 1.0 to 3.7) (12).

Such modulations of HSV-2 severity in those with pre-existing HSV-1 antibodies may be particularly important given the above-mentioned later age of HSV-1 seroincidence in some settings (56), because an increasing proportion of individuals may be expected to acquire primary HSV-2 infection (ie, incident HSV-2 in the absence of prior HSV-1 antibodies). One study (10) reported that incident HSV-2 infection in recently HIV-infected individuals was not associated with significant changes in HIV viral load or CD4 cell count levels, but pre-existing HSV-1 serology was not documented. Most incident cases of HSV-2 infection in that study likely had pre-existing HSV-1 antibodies, because nine of 10 cases were asymptomatic. The impact of primary incident HSV-2 infection on HIV pathogenesis and transmissibility thus remain understudied and, therefore, further attention to HSV-1 serological status in HSV-HIV-coinfection studies is needed.

**HSV-1 is similar to HSV-2**

Another reason that HSV-1 merits further attention is that HSV-1 and HSV-2 are closely related herpesviruses that share 83% genetic homology (59). Furthermore, most of their divergent nucleotide sequences occur in noncoding regions of their genomes (59). This high degree of genetic homology is mirrored by the pathophysiological similarities between HSV types, and together these observations suggest that the clinical implications of HSV-1 and HSV-2 on HIV pathogenesis may be similar as well (39).

In support of this possibility, numerous in vitro experiments have shown that HSV-1 gene products can upregulate HIV expression, as mentioned above (36-40,60). Indeed, in contrast to the clinical literature on HSV-HIV coinfection, the majority of basic science literature on the molecular mechanisms of HSV-HIV interactions has focused on HSV-1, largely because of a greater availability of HSV-1 laboratory strains and animal models. Nearly all HSV-1 genes have an HSV-2 homologue, such that these basic science findings regarding HSV-1 have been extrapolated to HSV-2 in the clinical setting. Thus, because of the close relatedness of the two virus types, both HSV-1 and HSV-2 have been shown to increase HIV replication. For instance, coinfection of peripheral blood mononuclear cells from HIV-infected donors with either HSV-1 or HSV-2 has been demonstrated to produce active HIV-1 replication (61). The mechanism of this effect is thought to be through both mitogenic stimulation of the HIV-infected cells as well as transactivation of proviral HIV by HSV gene products. Similarly, other investigators have shown that coinfection of resting CD4+ T cells from HIV-infected patients with supernatants from monocyte-derived macrophages that had been exposed to HSV-1 or HSV-2 virions results in HIV replication (62). This effect was not seen after treating resting CD4+ T cells with only HSV virions, nor with only the supernatants of unconditioned monocyte-derived macrophages.

**HSV-1 accounts for an increasing burden of genital herpes**

In general, genital shedding of HSV-2 is higher than that of HSV-1, and oral shedding of HSV-1 is higher than that of HSV-2 (63). However, the issue of HSV type is becoming especially relevant because the incidence of genital HSV-1 has increased. For instance, a Swedish study (64) showed that 44% of 97 patients presenting with culture-positive primary genital herpes have HSV-1 infection, and that 64% of serologically confirmed primary genital herpes was attributable to HSV-1. In Edinburgh, Scotland (United Kingdom), HSV-1 accounted for 42% and 62% of virologically confirmed first episode genital herpes outbreaks in men and women, respectively (65). Among American college students, the proportion of newly diagnosed genital herpes attributed to HSV-1 rose dramatically from 31% in 1993 to 78% in 2001 (P<0.001; linear trend P<0.001) (66). Similarly, high or rising rates of genital HSV-1 have been shown in other industrialized settings, including France (67), Finland (68), Holland (53) and the United States (69,70). In Northern Ireland, this shift has actually rendered HSV-1 the most common cause of recurrent genital ulcer disease among women attending genitourinary medicine clinics (71). As for HSV-2, asymptomatic shedding of genital HSV-1 has also been documented (72), and the impact of such shedding on HIV remains to be determined.

Because the genital tract is an important site of biological interaction between HSV and HIV, this epidemiological change may be clinically important. HSV-1-induced micro- and macroulceration of the genital mucosa would be expected to have similar implications for facilitating HIV transmission to those of HSV-2 lesions, as would the upregulation of HIV by HSV-1 through the molecular mechanisms described above. However, differences have been observed in the genital mucosal immune responses to HSV-1 and HSV-2 infections (73). For instance, HSV-1 productively infects mucosal dendritic cells and downregulates CD1a, CD40, ICAM-1, CD80 and CD86, potentially resulting in delayed T cell activation as a strategy of immune evasion (74). In contrast, HSV-2 induces activation of submucosal dendritic cells, which drain to local lymph nodes and stimulate T cell priming and interferon-gamma release by presenting viral peptides in the context of major histocompatibility complex class II molecules (75). The significance of such nuances in what is known about the immune responses to HSV-1 versus HSV-2 for HIV coinfection remain largely unexplored. One may speculate that different degrees of recruitment of HIV target cells to the genital tract may produce clinical variation in HSV-induced HIV susceptibility and pathogenesis. However, because symptomatic genital HSV-1 recurs less frequently than HSV-2 (one versus four times a year) (54,55), the overall impact of this epidemiological shift remains to be determined.

**IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH**

HSV-HIV coinfection may yield practical implications because the availability of safe, affordable anti-HSV medications (acyclovir, valacyclovir and famciclovir) makes this infection a potential locus for clinical and public health interventions. But there remain important unanswered questions regarding the ways in which emerging knowledge on HSV-1 and HSV-2 infection could inform clinical practice and public health policy.

In the clinical care of HIV-infected persons, highly active antiretroviral therapy (HAART) has drastically reduced the
HSV-1 and HSV-2 (79), the potential synergy between these contraceptives, have been shown to increase shedding of both because modifiable risk factors, such as the use of hormonal tings in which such efforts will be most realistic. In addition, the more moderate seroprevalence and the relatively setting are further considered. In addition, based on the high seroprevalence of HSV-1, analogy to HSV-2 and emerging infection among men who have sex with men in Peru. The prevalence of HSV-1 among HIV-infected and HIV-uninfected persons will be of value. Published recommendations for type-specific HSV sero-

Indeed, previous trials in which clinically important effects of herpesvirus suppression were seen in HIV-coinfected persons used either much higher doses of acyclovir, or the acyclovir produg valacyclovir. For instance, more than 3200 mg of acyclovir taken per day was associated with improved survival in a meta-analysis of studies among advanced AIDS patients in the pre-HAART era (80), and 800 mg of acyclovir taken twice daily produced decreases in cervicovaginal HIV shedding in HSV-2-HIV-coinfected women in Thailand (81). Valacyclovir may be preferable to study over acyclovir due to its improved bioavailability (54.5% versus 15% to 30%) and significantly decreased pill burden (82); indeed, among women in Burkina Faso (Africa) and MSM in Peru, 500 mg of valacyclovir taken twice daily was associated with reductions in plasma HIV RNA levels of up to 0.53 log_{10} copies/mL (47,48). Furthermore, the finding that HSV-2-specific immune responses persist in genital skin long after resolution of clinical symptoms suggests that prolonged doses of such high-potency drugs may be required to fully suppress the effects of HSV-2 infection (83).

**CONCLUSION**

HSV-2-HIV coinfection has garnered appropriate attention in both HIV prevention and treatment, because of the well-documented virological, clinical and epidemiological syner-
gisms between these two viruses. However, more information on their interactions with HSV-1 is clearly needed to identify promising strategies for decreasing HIV transmission and attenuating HIV disease progression. In particular, increased attention to the significance of incident and prevalent HSV-1 infection on HIV pathogenesis, pre-existing HSV-1 antibodies in HIV-infected persons with incident HSV-2 infection, and the emergence of symptomatic and asymptomatic genital HSV-1 among HIV-infected and HIV-uninfected persons will be of value.

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