Herpes Simplex Virus Type 2 and HIV-1: The Dialogue between the 2 Organisms Continues

Lawrence Corey
Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, and Departments of Medicine and Laboratory Medicine, University of Washington, Seattle

(See the articles by Kapiga et al., on pages 1260–9, and Cachay et al., on pages 1270–7.)

This issue of the Journal continues the dialogue on the interaction between HIV and herpes simplex virus type 2 (HSV-2). Two articles in this issue, one by Kapiga et al. [1], describing a cohort of women in Tanzania, and the other by Cachay et al. [2], describing a cohort of largely men who have sex with men (MSM) in San Diego, are devoted to the interaction between the 2 agents. Each of the studies evaluates very different regions in the spatial and temporal dynamics between the 2 organisms [3]. Superficial reading of these articles suggests an even draw: one showing and the other not showing a significant interaction between the 2 infections.

The article by Kapiga et al. continues to strengthen the burgeoning number of studies indicating that both past and recently acquired HSV-2 infection are major factors, on both a population and individual basis, for increasing the risk of HIV acquisition. Since initially reported by our group and other researchers in San Francisco in cohorts of highly sexually active MSM studied in the early 1980s [4, 5], >35 studies detailed in 2 separate meta analyses have shown that prevalent HSV-2 increases the risk of HIV-1 [6, 7]. The study by Kapiga et al. adds to this body of work, showing that this association is relevant in sub-Saharan African women and that the risk is marked by HSV-2 infection itself and not whether there is recognizable genital ulcer disease. The underlying biological mechanisms by which HSV-2 is a plausible factor for an increased risk of HIV-1 acquisition has been strengthened considerably in the past several years by studies that indicated that subclinical genital mucosal reactivations occur in ~90% of HSV-2–seropositive women and 80% of seropositive men, that such reactivations are common (20% of days with daily sampling), and that these “shedding episodes” are associated with microscopic ulcerations and the influx of activated CD4+ T cells to the ulcerative region [8–16]. The even higher risk between incident HSV-2 and HIV acquisition, as shown by Kapiga et al. in the present issue and by Reynolds et al. in a prior issue of the Journal [17], can be explained by the even higher rates of subclinical reactivation (35%–40% of days) in early versus more-chronic HSV-2 infection [8, 18, 19]. What makes for epidemiological/population-based concern about the interaction between these 2 agents versus those of other genital ulcer diseases is the much higher prevalence of HSV-2 versus that of Treponema pallidum or Haemophilus ducreyi in most populations throughout the world [20–22]. HSV-2 appears to be rapidly acquired after coital activity in sub-Saharan Africa, especially in young women, and the seroprevalence of HSV-2 is >50% in most high-risk populations throughout the world [23–25]. A map delineating the seroprevalence in women of child-bearing age throughout the world is shown in figure 1. The high HSV-2 seroprevalence, coupled with the high frequency of reactivation in the HSV-2–seropositive person, creates frequent mucosal disruption that can influence the acquisition of a sexually transmitted disease (STD) such as HIV infection, even one that has relatively low rates of transmission on a per-sexual-contact basis [26]. Thus, the epidemiological evidence and biological plausibility of a significant interaction between these 2 agents in the area of HIV acquisition are overwhelming.

The critical issue is: can we mitigate this interaction? Would more-aggressive treatment of prevalent HSV-2 infection with daily antiviral therapy such as acyclovir reduce the likelihood of HIV acquisition [3, 24]? Generic acyclovir is readily available and relatively inexpensive (3–10 cents/capsule or tablet). Although the yearly cost
Prevalence of HSV-2 in women throughout the world (pregnant or sexually active adult women)

Figure 1. Prevalence of herpes simplex virus type 2 (HSV-2) in women of childbearing age. Uncolored areas indicate regions where no sex/age-specific seroprevalence data are available. Nos. represent the percentage of subjects with HSV-2-specific antibodies.

of $30 is still expensive for many areas of the world, the potential utility of such an approach, if effective, would merit discussion. A trial (HIV Prevention Trials Network [HTTPN] Protocol 039) to evaluate whether 400 mg of acyclovir twice daily would reduce the frequency of HIV infection among high-risk HSV-2–seropositive persons is currently nearing completion. One issue of discussion in designing this trial was whether the dose of acyclovir would provide enough pharmacological coverage to optimally reduce subclinical shedding of HSV. With once-daily sampling of adults, 400 mg of generic acyclovir twice daily has been shown to reduce HSV reactivation rates by 70% [11]. More recently, it has been shown that shedding episodes of HSV-2 may be even shorter and more frequent than is appreciated [27]. Whether this means higher or more frequent dosing of antivirals may be required to effectively reduce HSV-2 reactivation is unclear. We must await the results of the HPTN trial to determine whether antiviral therapy with twice-daily generic acyclovir produces any measurable benefit.

Most studies of genital HSV-2 and HIV have shown that the risk is unrelated to the appearance of overt genital ulcers [6, 7]. HIV is shed in genital ulcers, including those caused by HSV-2 [28, 29]. Effective treatment of the ulcers reduces the ability to isolate HIV from the lesions; however, 4–5 days of anti–HSV-2 therapy are required to reduce HIV shedding from genital lesions effectively [29]. Thus, it appears unlikely to this author that episodic therapy of HSV for genital ulcer disease will significantly alter the role of HSV-2 in HIV acquisition on a population basis.

The article by Cachay et al. focuses on another part of the HSV-2/HIV conundrum. Does chronic HSV-2 infection provide a measurably important component to viral load measurements in HIV-positive persons? Several studies have suggested that HIV/HSV-2–positive persons appear to have somewhat higher plasma HIV loads (0.33–1 log) than those who are HIV positive but HSV negative [17, 30–32]. This increase in viral load has been seen to be clinically significant in other settings and to lead to increased disease progression [33]. Schacker et al. [29] demonstrated that a strain of HIV-1 isolated from a genital lesion subsequently became the prevalent strain in plasma, which suggests that genital HSV-2 reactivation could be a reservoir for HIV replication in the host. That study was performed in untreated persons with low CD4+ T cell counts.

Cachay et al. performed a detailed analysis of the dynamics of early HIV replication among MSM with primary HIV-1
infection and showed no effect of HSV-2 on HIV load. How does one reconcile past and present studies? Perhaps the best answer is—we don’t know. We do know that the major reservoir for HIV in early infection is in the gastrointestinal tract [34, 35]. As such, other areas in which the virus is found and compartmentalized may not play a significantly discernible role in up-regulating T cell replication and dissemination until this reservoir is “burned out.” Whether this is the explanation for the discrepancies between the results of Ca-chay et al.’s study and those of other trials remains to be determined. What is clear is that the complex biological interactions between these 2 unrelated pathogens that can occupy the same ecological “space” but pursue their chronicity by different mechanisms continues to intrigue physician scientists and yet dismays the public health efforts to control these viral STDs. The answer is simple—effective vaccines are needed for both HIV and HSV-2. Defining the solution is easy; solving the scientific reality of these issues is, however, proving difficult.

References


