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The role of HSV-2 suppressive therapy for HIV prevention

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Herpes simplex virus type 2 (HSV-2) is one of the most common sexually transmitted infections globally with seroprevalence rates as high as 90% reported from HIV-infected persons in sub-Saharan Africa.[1;2] The epidemiologic and biologic association between HSV-2 and HIV has been the subject of numerous studies over the past two decades with strong evidence supporting the hypothesis that HSV-2 increases the risk of acquisition among HSV-2 infected HIV negative individuals.[3-5] The biological plausibility of this association is explained in part by the portal of entry created during the time of genital ulceration among HSV-2 infected persons and also in part by the influx of HIV target cells which occurs during episodes of HSV-2 reactivation.[6;7] Among individuals co-infected with HIV and HSV-2, considerable evidence exists to support the hypothesis that HSV-2 also increases the risk of transmission of HIV to uninfected partners because of increase in HIV plasma viral load, and increased HIV shedding from genital ulcers and from the genital tract.[2;8-10] This biological synergy between these two viruses has lead researchers to consider HSV-2 suppressive treatment as a biomedical prevention strategy to reduce the risk of HIV transmission.

The apparent synergy between HSV-2 and HIV acquisition prompted researchers to embark on randomized, clinical trials of HSV-2 suppressive therapy with the hopes of adding another biomedical HIV prevention strategy to the current prevention options. Two randomized, controlled trials were initiated in 2006 in various sites across sub-Saharan Africa, the United States and Peru to evaluate the impact of HSV-2 suppressive therapy on the risk of HIV acquisition. One trial conducted at a single site in Tanzania enrolled 821 high risk HIV negative women who were treated with 400mg acyclovir twice daily and followed for a minimum of 12 months. This study unfortunately showed no difference in HIV incidence between the study arms after 2 years of follow-up (RR 1.08;95% CI, 0.64-1.83).[11] A second study conducted among 1814 men who have sex with men in the United States and Peru and 1358 women in South Africa, Zambia, and Zimbabwe also failed to show any impact on the risk of HIV acquisition despite high levels of adherence to acyclovir (HR 1.16; 95% CI, 0.83-1.62).[12] Given the strength of association observed in the epidemiological studies and the supporting biological evidence suggesting an increased risk of HIV acquisition among HSV-2 infected individuals, what could explain the negative findings of these well conducted clinical trials? Adherence in both studies as measured by self-report was high although the Tanzanian study subsequently investigated drug levels among participants which suggested the possibility of a lower rate of adherence than measured by self-report as only 55% of urine samples from women randomized to the acyclovir arms of the study had detectable acyclovir.[13] The negative results emerging from these two clinical trials has prompted investigators to return to the cellular level to understand the immunobiology of HSV-2 recurrences which will be discussed later in this article.

More disappointing results emerged recently from a large, multi-center, randomized controlled trial involving 3408 HIV-serodiscordant couples where one partner is HIV infected and one is

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not. In this trial the HIV/HSV-2 co-infected partner was treated with acyclovir 400mg twice daily to evaluate the impact on infectiousness to the HIV uninfected partner. The results of this trial known as the partners in prevention study were presented at the International AIDS Society meeting last July and revealed no reduction in HIV transmission despite good adherence to acyclovir among treated partners.[14] Despite the disappointing results from this study from the prevention standpoint, interesting data was presented on the role of acyclovir on HIV disease progression among HSV-2/HIV co-infected individuals. The partners in prevention study found that 400mg of acyclovir twice daily delayed disease progression (defined as CD4<250, death due to AIDS or ART initiation other than for prevention of mother to child transmission) by 17%. Although the delay in disease progression may be viewed as modest, given the current demand for ART and limited resources in sub-Saharan Africa, this finding may have a role in the pre-ART care of HIV infected patients which chronic HSV-2. A second study investigating the role of suppressive acyclovir on HIV disease progression in Rakai, Uganda will be completed in September 2010 and will add additional information on the impact of suppressive acyclovir on HIV disease progression.

How can one interpret the disappointing results of these clinical trials in light of the strong epidemiologic and biologic evidence that HSV-2 increases both acquisition and transmission of HIV? Research done at the University of Washington has shed some important light on explaining the clinical trial findings by understanding the complexity of what is going on at the cellular level during episodes of HSV-2 reactivation. To understand the immunobiology occurring during periods of HSV-2 reactivation, eight healthy HIV-negative individuals with culture-proven recurrent symptomatic HSV-2 were studied. [15] Punch biopsies were taken during the time of clinically symptomatic ulcerative lesions, at resolution and then at 2, 4, and 8 weeks after healing. Four individuals were then treated with acyclovir 400mg twice daily at the start of an acute episode and treated for 20 weeks. Biopsies of these individuals were taken again during the acute episode, at resolution and at 2, 4, 8, 12, 16 and 20 weeks. The researchers found evidence of an acute inflammatory response with CD4+ and CD8+ influx in the epidermis and dermis which persisted for months despite healing of the lesions. Acyclovir treatment was not found to significantly alter this intense inflammatory response even after 20 weeks of therapy. These data help explain why the clinical trials may have failed to interrupt the association between HSV-2 and HIV. Without the ability to diminish the chronic inflammatory milieu resulting from HSV-2 the intervention (acyclovir 400mg twice daily) may not have been capable of interrupting the biologic interplay between these two viruses.

So what does all this body of evidence leave for the HIV research community looking for ways to stem the current HIV epidemic? Clearly better ways to suppress HSV-2 reactivation and the influx of HIV target cells will need to be developed if this strategy is to have any effect on reducing the risk of HIV acquisition and transmission. Ideally an effective HSV-2 vaccine could still have a major impact on reducing HIV transmission given the burden of HSV-2 disease in countries most affected by HIV/AIDS. Until the time when such a vaccine is developed, combination prevention efforts using evidence based strategies, tailored to the dynamics of individual epidemics will remain the cornerstone of HIV prevention.

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