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The Interplay between Sexually Transmitted Infections and HIV: An Evolving Story

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It is recognized that persons with sexually transmitted infections (STIs) are at increased risk for acquisition of HIV. Early studies primarily linked this association to high-risk sexual behaviors that placed persons at risk for both STIs and HIV. However, continuing research has elegantly revealed that independent of behavioral factors, the presence of an STI, especially ulcerative types (e.g., herpes simplex virus 2 (HSV-2), primary syphilis), appears to be associated with a higher risk for subsequent HIV acquisition [1,2]. The mechanisms for this heightened risk include the disruption of the mucosal epithelial lining of the genital tract, together with the local recruitment and influx of immature dendritic and CD4 cells, as part of the local inflammatory process. These cells contain the CCR5 receptor, the primary target for the entry of HIV into the body.

Although the initial findings of increased acquisition focused on ulcerative STIs, recent evidence has demonstrated the importance of non-ulcerative STIs (e.g., gonorrhea, Chlamydia), as reviewed by Naresh et al. [3]. In addition to these traditional non-ulcerative STIs, data just released indicate that human papillomavirus (HPV) infections are also a risk factor for HIV acquisition among both heterosexual men and men who have sex with men (MSM), as described in studies done in South Africa [4] and the United States [5], respectively. Of note, multiple and “high-risk” HPV types appear to convey the highest risk [4,5]. In addition to the heightened risk for HIV acquisition, the presence of an STI may increase the transmission of HIV from infected persons to their partners as the result of higher plasma HIV viral load and via disruption of the normal mucosal barriers, with elevated genital HIV viral load shedding at the site of the coexisting infection. Collectively, these data suggest that STIs have had a dramatic worldwide impact on the HIV epidemic through the interplay between STIs and the increased risk of HIV acquisition and transmission.

What should we do with these findings? Intuitively, it would seem that STI prevention and treatment programs should be implemented where needed and reinforced where ongoing in an effort to reduce the number of incident HIV infections. Several community-based studies - largely within Africa - have examined the impact of STI treatment on reducing the incidence of HIV infections. As described by Naresh et al. (Table 3) [3], to date, many of these studies have revealed surprisingly little to no benefit from such interventions [6]. Potential reasons for

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the lack of efficacy are explored by Naresh et al. including that STIs may play a smaller role in a more advanced HIV epidemic, that the antibiotic utilized in some studies had a suboptimal effect against many of the prevalent STIs in the community, and of course, the possibility that control of bacterial STIs may not be an effective means of preventing HIV-1 infection [3].

Of major interest is the possibility of suppressing HSV-2 as a method of reducing incident HIV infections, as HSV-2 is arguably the most prevalent ulcerative STI in the world. The importance of HSV-2 in HIV transmission was highlighted in a recent publication, which, using deterministic models, suggested that genital herpes has played a more important role than any other STI in driving HIV prevalence in Africa and may have accounted for >25% of new HIV infections in some countries [7].

Research has demonstrated that HSV-2 suppression (with acyclovir or valacyclovir) reduces the plasma and genital HIV RNA levels, key components of HIV transmission, as well as the occurrence of clinical lesions [8–11]. Given these supportive preliminary data suggesting that HSV-2 suppression may reduce HIV transmission [12], three published randomized clinical studies have since evaluated this strategy among HSV-2/HIV-1 positive persons and the subsequent HIV incidence rates among their partners. These studies have shown no significant benefit of anti-HSV-2 suppressive therapy in preventing HIV transmission [13–15]. In addition, a recent investigation conducted by Celum et al. concluded that after studying 3,408 heterosexual HIV-discordant couples at 14 African sites, acyclovir at 400 mg twice daily had no appreciable benefit (rate of new HIV infections in the acyclovir and placebo groups were 2.8 vs. 1.8/100 person-years, respectively; HR 0.92, $p=0.70$) [16].

We now need to reflect upon the reasons why these clinical trials did not show benefit. Perhaps multiple interventions (including methods to more effectively reduce risky behavior and suppress HSV-2 in combination) are in order. Associations between HSV-2 and HIV may be driven by residual confounding of higher risk sexual behaviors, suggesting that these factors may need to be addressed concurrently in clinical trials. Perhaps the dose of acyclovir was inadequate. Whether higher doses of acyclovir or the use of valacyclovir would result in greater reductions in HIV RNA plasma and genital levels, and, in turn, significantly reduce HIV transmission, requires further study. Finally, HSV-2 suppression in the setting of a prevalent infection may not mechanistically work. A recent report suggested that HIV receptor-positive inflammatory cells may persist in the genital area after the resolution of HSV-2 reactivation and the healing of lesions, perhaps explaining the inability of anti-HSV-2 therapy to reduce HIV acquisition [17]. Careful consideration of all these methodological possibilities is critical in the planning of future trials. Also on the horizon is the possibility of an HSV-2 vaccine that could have a substantial population-level impact on HIV incident infections [18]; further efforts to develop an effective HSV-2 vaccine should be undertaken.

Important interactions between STIs and HIV may extend beyond the public health arena to the health of the individual HIV-infected person. There are several reasons to encourage HIV-infected persons to engage in safer sex practices to avoid acquiring STIs. As described by Naresh et al., the occurrence of STIs in this population may result in more severe clinical disease, multiple episodes of recurrence, and/or more treatment failures compared to immunocompetent hosts [3]. Additionally, acquisition of another STI during HIV infection may be associated with transient reductions in the CD4 cell counts and elevations in HIV RNA levels. Not only is this a public health concern, since this may increase the transmissibility of HIV (as plasma and genital viral load levels are major factors in HIV transmissibility) [19], but it may also impact the immunologic and virologic status of the individual. Several studies have shown that acute STIs, such as syphilis, lead to adverse effects on the CD4 counts and viral loads [20–22]; whether these effects are simply transient or have a long-term impact (especially in the setting of repeated STIs on HIV progression) requires further study. The role

of HSV-2 suppression on HIV disease progression among dually infected persons was examined in a 2009 study by Lingappa et al. [23]. In this investigation, which took place in Africa among HIV patients with a CD4>250 who were not receiving antiretroviral therapy, acyclovir reduced the rate of both CD4 decline and mortality [23]. For now, whether HIV-infected persons who already have a non-curable STI (e.g., HSV-2 or HPV) will benefit from strategies to suppress these viral co-infections requires further data and will likely be a major focus of future research. All in all, these data suggest that the avoidance of acquiring an STI (“Prevention in Positives”) benefits both HIV-infected persons and the public health arena.

What should we as clinicians do with current findings? We should continue to explore evidence-based methods to reduce the occurrence of STIs among both HIV-infected and uninfected persons in an attempt to reduce new HIV infections. We should educate the public and our patients on the important interrelatedness between the acquisition of STIs and HIV. Finally, we should use these data to promote efforts in reducing high-risk behaviors among all persons, including among individuals already infected with HIV. With these interventions and further studies on the bidirectional interactions between HIV and STIs, a future with fewer incident HIV infections and ultimately control of the HIV epidemic will hopefully be closer at hand.

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