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Scientists learn why even treated genital herpes sores boost the risk of HIV infection

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New research helps explain why infection with herpes simplex virus-2 (HSV-2), which causes genital herpes, increases the risk for HIV infection even after successful treatment heals the genital skin sores and breaks that often result from HSV-2.

Scientists have uncovered details of an immune-cell environment conducive to HIV infection that persists at the location of HSV-2 genital skin lesions long after they have been treated with oral doses of the drug acyclovir and have healed and the skin appears normal. These findings are published in the advance online edition of *Nature Medicine* on Aug. 2.

Led by Lawrence Corey, M.D., and Jia Zhu, Ph.D., of the Fred Hutchinson Cancer Research Center and Anna Wald, M.D., M.P.H., of the University of Washington, both in Seattle, the study was funded mainly by the National Institute of Allergy and Infectious Diseases (NIAID) with support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, both part of the National Institutes of Health.

"The findings of this study mark an important step toward understanding why HSV-2 infection increases the risk of acquiring HIV and why acyclovir treatment does not reduce that risk," says NIAID Director Anthony S. Fauci, M.D. "Understanding that even treated HSV-2 infections provide a cellular environment conducive to HIV infection suggests new directions for HIV prevention research, including more

powerful anti-HSV therapies and ideally an HSV-2 vaccine."

One of the most common sexually transmitted infections worldwide, HSV-2 is associated with a two- to three-fold increased risk for HIV infection. Some HSV-2-infected people have recurring sores and breaks in genital skin, and it has been hypothesized that these lesions account for the higher risk of HIV acquisition. However, recent clinical trials, including an NIAID-funded study completed last year, demonstrated that successful treatment of such genital herpes lesions with the drug acyclovir does not reduce the risk of HIV infection posed by HSV-2. The current study sought to understand why this is so and to test an alternative theory.

"We hypothesized that sores and breaks in the skin from HSV-2 are associated with a long-lasting immune response at those locations, and that the response consists of an influx of cells that are a perfect storm for HIV infection," says Dr. Corey, co-director of the Vaccine and Infectious Diseases Institute at The Hutchinson Center and head of the Virology Division in the Department of Laboratory Medicine at the University of Washington. "We believe HIV gains access to these cells mainly through microscopic breaks in the skin that occur during sex."

The research team took biopsies of genital skin tissue from eight HIV-negative men and women who were infected with HSV-2. These biopsies were taken at multiple time points: when the patients had genital herpes sores and breaks in the skin, when these lesions had healed, and at two, four and eight weeks after healing. The researchers also took biopsies from four of the patients when herpes lesions reappeared and the patients underwent treatment with oral acyclovir. The scientists continued to take biopsies at regular intervals for 20 weeks after the lesions had healed. For comparison, the investigators also took biopsies from genital tissue that did not have herpes lesions from the same patients.

Previous research has demonstrated that immune cells involved in the body's response to infection remain at the site of genital herpes lesions even after they have healed. The scientists conducting the current study made several important findings about the nature of these immune cells. First, they found that CD4+ T cells—the cells that HIV primarily infects—populate tissue at the sites of healed genital HSV-2 lesions at concentrations 2 to 37 times greater than in unaffected genital skin. Treatment with acyclovir did not reduce this long-lasting, high concentration of HSV-2-specific CD4+ T cells at the sites of healed herpes lesions.

Second, the scientists discovered that a significant proportion of these CD4+ T cells carried CCR5 or CXCR4, the cell-surface proteins that HIV uses (in addition to CD4) to enter cells. The percentage of CD4+ T cells expressing CCR5 during acute HSV-2 infection and after healing of genital sores was twice as high in biopsies from the sites of these sores as from unaffected control skin. Moreover, the level of CCR5 expression in CD4+ T cells at the sites of healed genital herpes lesions was similar for patients who had been treated with acyclovir as for those who had not.

Third, the scientists found a significantly higher concentration of immune cells called dendritic cells with the surface protein called DC-SIGN at the sites of healed genital herpes lesions than in control tissue, whether or not the patient was treated with acyclovir. Dendritic cells with DC-SIGN ferry HIV particles to CD4+ T cells, which the virus infects. The DC-SIGN cells often were near CD4+ T cells at the sites of healed lesions—an ideal scenario for the rapid spread of HIV infection.

Finally, using biopsies from two study participants, the scientists found laboratory evidence that HIV replicates three to five times as quickly in cultured tissue from the sites of healed HSV-2 lesions than in cultured tissue from control sites.

All four of these findings help explain why people infected with HSV-2 are at greater risk of acquiring HIV than people who are not infected with HSV-2, even after successful acyclovir treatment of genital lesions.

"HSV-2 infection provides a wide surface area and long duration of time for allowing HIV access to more target cells, providing a greater chance for the initial 'spark' of infection," the authors write. This spark likely ignites once HIV penetrates tiny breaks in genital skin that commonly occur during sex. "Additionally," the authors continue, "the close proximity to DC-SIGN-expressing DCs [dendritic cells] is likely to fuel these embers and provide a mechanism for more efficient localized spread of initial infection."

The investigators conclude that reducing the HSV-2-associated risk of HIV infection will require diminishing or eliminating the long-lived immune-cell environment created by HSV-2 infection in the genital tract, ideally through an HSV vaccine. Further, they hypothesize that other sexually transmitted infections (STIs) may create similar cellular environments conducive to HIV infection, explaining why STIs in general are a risk factor for acquiring HIV.

More information:

J Zhu et al. Persistence of HIV-1 receptor-positive cells after HSV-2 reactivation is a potential mechanism for increased HIV-1 acquisition. *Nature Medicine* DOI: 10.1038/nm2006 (2009).

C Celum et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a ranDOI: 10.1016/S0140-6736placebo-controlled trial. *Lancet* DOI: 10.1016/S0140-6736(08)60920-4 (2008).

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