Have sex workers revealed a connection between semen exposure and HIV resistance?

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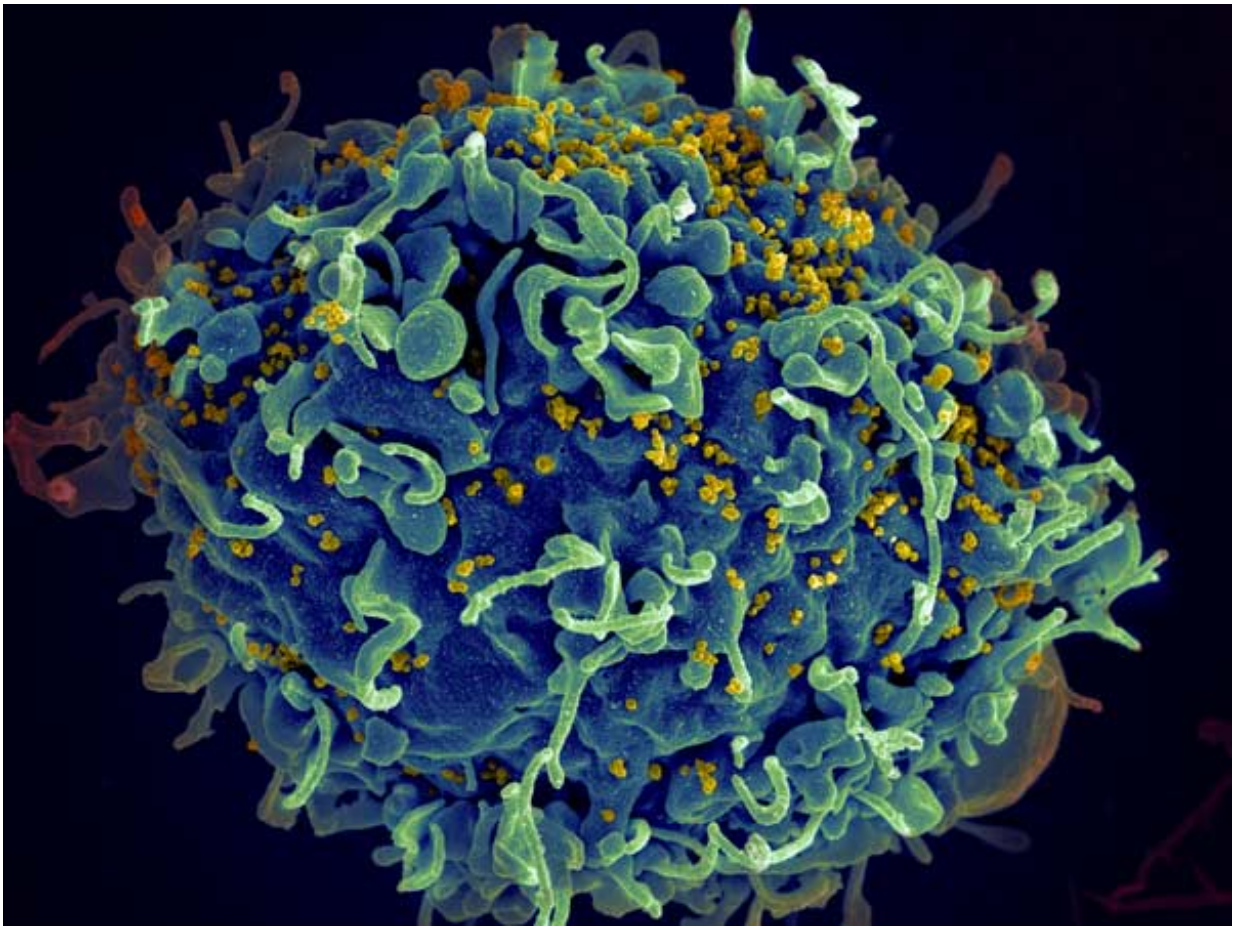

HIV (yellow) infecting a human immune cell. Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, National Institute of Allergy and Infectious Diseases, National Institutes of Health

More than half of all people infected by the HIV-1 virus worldwide are women. Commercial sex workers, who are at increased risk of contracting HIV because of repeated exposure to the virus, have long been studied to test preventive behavioral and vaccine approaches aimed at decreasing the number of infections. In some areas of the world where HIV prevalence is higher, a small number of female sex workers continue to test negative for the infection despite repeated sexual activity and low rates of condom use. However, the reason as to why these women are protected from HIV infection has eluded scientists, since they seem to have none of the known immune responses against HIV itself.

Scientists at The Wistar Institute have now hypothesized that these women experienced changes in their tissues as well as alterations in how their immune systems responded that are different from the type of responses that vaccines generate. Now, newly published data shows that continued semen exposure in these sex workers sustains changes in the cervical and vaginal microenvironment that may actually increase HIV-1 resistance. This information may lead the way to better preventative strategies that block the transmission of the virus and improved designs for future HIV vaccine studies that can monitor the described changes when recruiting sex workers into vaccine trials.

The results of the study were published in the November issue of the journal *Mucosal Immunology*.

"Making the link between sex work, changes in immune state and semen exposure gives us an important piece of information that will hopefully help us establish whether or not chronic semen exposure and its effects on to the female reproductive tract can contribute to HIV resistance in sex workers that remain uninfected despite low condom use," said Luis J. Montaner, D.V.M., D.Phil., the Herbert Kean, M.D., Family Professor at The Wistar Institute, director of Wistar's HIV-1 Immunopathogenesis

Laboratory, and lead author of the study. "It also clearly indicates that women are equipped to activate mechanisms of resistance due to sex itself, which we did not expect to find at the start of this research."

Prior studies have shown that long-term sex work does not always result in infection. For example, groups of long-term female sex workers in Africa have consistently remained uninfected despite the fact that condom use among these women is low, therefore subjecting these women to chronic exposure to both semen and HIV-1. Even though female sex workers in San Juan, Puerto Rico are within an area that has 5-10 times lower HIV-1 prevalence than Africa, the Wistar team was able to address how long-term sex work, frequency of intercourse and condom use may change the immune and female reproductive areas exposed to virus.

Wistar's team collaborated with investigators from the University of Puerto Rico Maternal Infant Studies Center and analyzed a cohort of long-term female sex workers in San Juan who tested negative for the HIV-1 virus and compared them with a group of women with self-reported low semen exposure recruited in the same area. Among the sex workers in the cohort, the median age was 35.50 years and they had been working in the trade for at least three years. The groups were also compared based on rates of unprotected sex, what types of contraceptives were used (if any) and excluded sex workers who had any active sexually transmitted infections such as chlamydia or syphilis.

The researchers identified three distinct mechanisms that may contribute to the decreased rate of infection among these sex workers.

First, they observed lower rates of immune activation in the blood and mucosal tissue of these women. This is an important observation because the HIV virus actually thrives in activated immune systems, with the activation actually helping the virus achieve infection and spread once it

has been transmitted. Second, these women had enhanced expression of interferon ε in epithelial cells, which are signaling proteins responsible for protecting the female reproductive tract from viral and bacterial infections. The researchers also showed that levels of interferon ε were associated with the number of condomless sex acts and that semen could increase the expression of this protein in cervical cell lines grown in the laboratory. Third, factors in this mucosal tissue that the HIV virus needs to infect were expressed at lower levels in these women. Genes like CD4 and Nucleoporin 153 are critical for HIV to survive and spread, so lower levels of these and other similar genes keep the virus at bay.

"It is important to note that the study does not make a case for sexual intercourse without a condom, as doing so will increase the overall risk of HIV infection and other sexually transmitted diseases," Montaner said. "Instead, this study identifies unexpected effects that long-term semen exposure may have on the cervix and vagina that may lower but not remove the likelihood of infection."

"This work could provide insight into why cohorts of women at risk recruited for preventive trials in the United States have demonstrated lower sero-conversion rates than expected based on community prevalence," said Carmen D. Zorrilla, M.D., professor of obstetrics and gynecology at the University of Puerto Rico and one of the authors of the study. Zorrilla was one of the investigators in a cohort study of 799 participants, including sex workers with sustained condomless sex, that did not have high enough HIV incidence to pursue a prevention study even though the researchers used geography and sexual network characteristics that would normally warrant further study.

More information: S A Abdulhaqq et al. HIV-1-negative female sex workers sustain high cervical IFNε, low immune activation, and low expression of HIV-1-required host genes, *Mucosal Immunology* (2015). DOI: 10.1038/mi.2015.116

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