

Cyclic Patterns of Inflammatory Cytokines in HIV-Infected Women

April 20, 2015

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Because the major route to HIV infection in women is heterosexual transmission, understanding HIV replication in the female genital tract (FGT) is critical, and could have implications for HIV prevention. Hormonal changes that occur during the menstrual cycle (MC) could have significant impacts on mucosal immunity and HIV shedding, but the mechanism is poorly understood. Cytokines are a diverse group of small proteins that act as important signaling molecules in various organ systems, particularly the immune system. Accordingly, cytokines are known to be involved in the etiology of many diseases, including HIV infection, yet the complexity of cytokine kinetics during HIV infection is only beginning to be elucidated.

Previous studies that examined FGT cytokine levels at weekly intervals found elevated levels of proinflammatory cytokines during the MC that correlated with HIV shedding. However, it has remained unclear whether shedding was regulated by the observed cyclic pattern of cytokines, or by the MC itself. A new Fred Hutch study led by former graduate student Dr. Valerie Cortez in the lab of Dr. Julie Overbaugh (Human Biology Division), published in *Open Forum Infectious Diseases*, confirmed and extended these observations by examining the daily levels of 26 vaginal cytokines in 15 women infected with HIV-1 from Mombasa, Kenya.

The women enrolled in the study attended daily clinics for a full cycle (median of 27 days) and cytokine concentrations were obtained from vaginal swabs. The data points were centered around the surge of luteinizing hormone (LH). The majority of cytokines exhibited a common pattern; they decreased during the follicular phase and subsequently increased steadily during the luteal phase, consistent with previous studies of mucosal immunity. After controlling for behavioral factors and coexisting sexually transmitted infections, levels of macrophage inflammatory protein (MIP)-1 α , interleukin (IL)-6, tumor necrosis factor (TNF)- α , interferon (IFN)- α 2 and IL-7 were all found to be significantly linked to cervical, but not vaginal, HIV shedding. However, this association no longer held up after controlling for the number of days that had elapsed since the LH surge. Next, the authors used linear mixed-effect models to evaluate the connection between hormone levels and cytokine concentrations, and found that progesterone positively correlated with IL-1 α and inversely correlated with granulocyte colony stimulating factor (G-CSF) and monocyte chemoattractant protein (MCP)-1. No significant correlations were found when estrogen was queried.

Overall, daily examination of cytokine levels in the FGT of women with chronic HIV-1 infections enabled the researchers to unmask several cytokines with cyclical patterns. This study also demonstrated that the connection between proinflammatory cytokines and viral shedding is likely to be mediated by the hormonal changes that drive the MC. "Our findings highlight the need for future longitudinal studies to further define the effects of hormonal changes on the complex immune environment in the female genital tract in women, irrespective of HIV status," concluded Dr. Cortez.

[Cortez V, Odem-Davis K, Lehman DA, Mabuka J, Overbaugh J. 2014.](#) Quotidian changes of genital tract cytokines in human immunodeficiency virus-1-infected women during the menstrual cycle. *Open forum infectious diseases*, 1(1), ofu002.

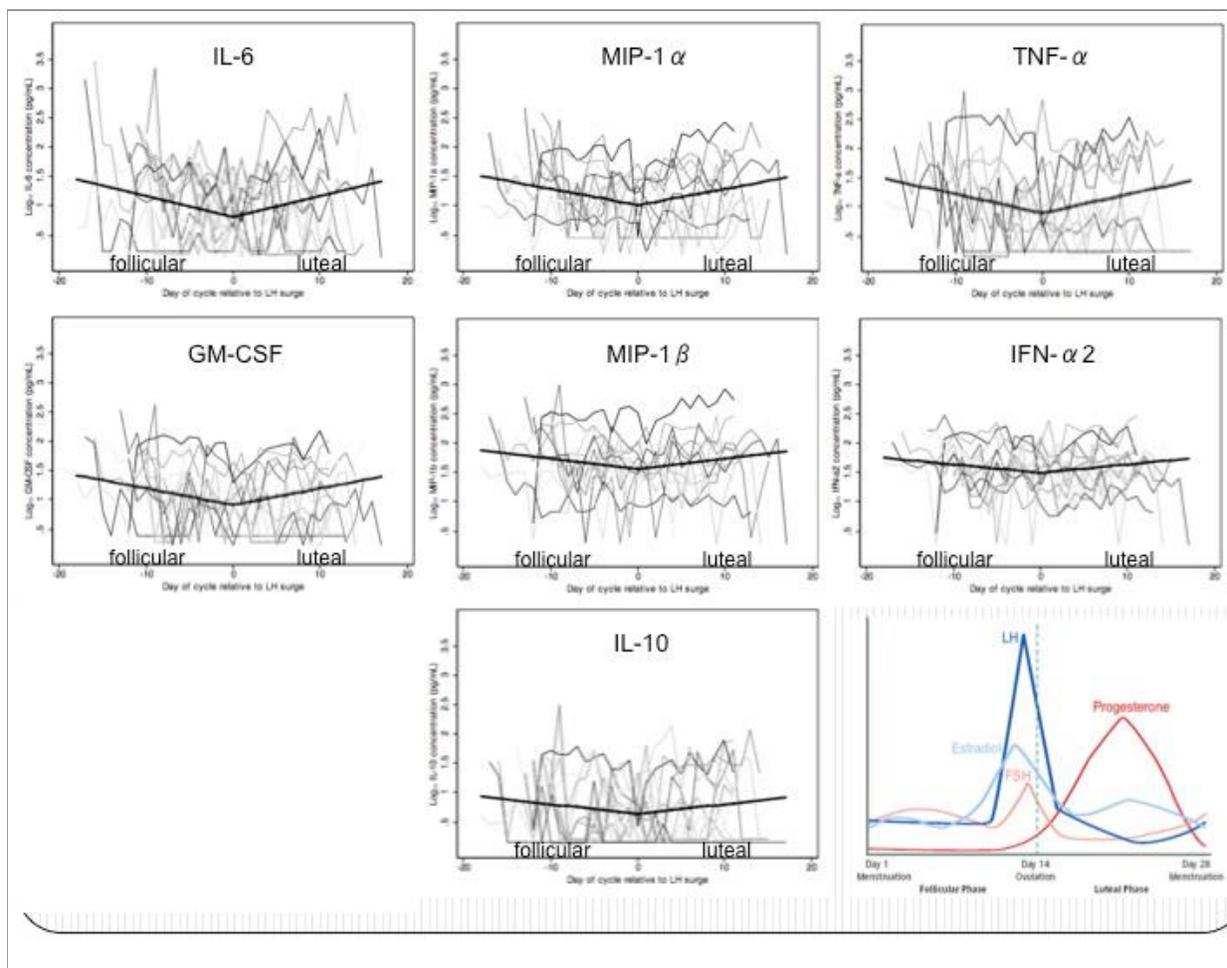


Image provided by Dr. Dara Lehman

Pattern of cytokine and chemokine levels across the menstrual cycle, centered on the luteinizing hormone (LH) surge. The graphs show log₁₀ concentrations of cytokines (pg/ml) that were significantly associated with days since the luteinizing hormone surge, after adjusting for menstruation in a linear mixed effect model. Each of the grayed lines represents one participant, with the dark bolded line denoting the averaged trend across the cycle. Hormonal changes during the menstrual cycle are shown in the final panel for reference.