The Impact of Sex Hormones on HIV infection

Sex hormones play a critical role mediating differences observed during HIV infection between males and females. Despite being more susceptible to HIV-1, women present lower viral loads during acute and chronic infection, yet progress faster to AIDS at the same level of viremia (*Quinn and Overbaugh, Science 2005; Addo and Altfeld, J Infect Dis. 2014*). Differences remain even under antiretroviral treatment (ART), affecting viral reservoir dynamics and pointing at a direct role for sex hormones in latency maintenance and HIV-1 reactivation (*Das et al., PNAS 2018; Scully, Curr HIV/AIDS Rep 2018*).

The female reproductive tract (FRT) is a unique compartment with a strong hormonal control of the immunological microenvironment to limit incoming pathogens while tolerating the presence of allogeneic spermatozoa and a successful pregnancy. Sex hormones estradiol and progesterone influence tissue environment through cytokines, chemokines and growth factors to enhance and suppress essential components of the humoral, cell-mediated and innate immune systems along the FRT (*Wira et al., Am J Reprod Immunol 2014*). While other critical factors such as the vaginal microbiome contribute to this modulation, it has been postulated that there is a particularly susceptible immune environment, referred as the "window of vulnerability", when hormonal changes that optimize conditions for a successful fertilization may lower the threshold for HIV-1 acquisition (*Patel et al., Current Immunology Reviews 2019*). This time-frame, which lasts from ovulation into the secretory stage of the menstrual cycle, includes suppression of certain immune responses and potential increases in the number of target cells (*Quinn and Overbaugh, Science 2005*). Further, once infected, HIV-positive women display increased levels of immune activation. Enhanced activation may be a central mechanism accounting for sex differences observed in the speed of HIV-1 disease progression and the risk of comorbidities. Part of these observations are linked to biological sex differences in innate immunity responses such as the higher expression of interferon-stimulated genes in women (*Addo and Altfeld, J Infect Dis 2014*). However, women are more likely to spontaneously control HIV, even after treatment interruption, since they are over represented in the post-treatment controllers *(Scully, Curr HIV/AIDS Rep 2018*). While the stronger antiviral responses reported in women may influence viremia and spontaneous control, multiple factors may contribute and confound the effect of sex hormones.

While basic research studies have strongly suggested that hormones are likely to affect immunity in ways that could plausibly have an influence on HIV acquisition risk, the impact of exogenous hormones for contraception in HIV transmission has been somewhat controversial (*Wira and Veronese, Am J Reprod Immunol 2016*). Still, enhanced risk of infection has been associated with the use of depot medroxyprogesterone (DMPA) hormonal contraception *(Scully, Curr HIV/AIDS Rep 2018*). Thus, the effects associated with hormone exposure on HIV infection, which also impact the vaginal microbiome, need to be considered and further dissected. Another important hormonally-influenced event affecting women is menopause, which is characterized by the absence of cyclic changes in hormone levels and lower levels of estradiol and progesterone in comparison to premenopausal women. Several immunological parameters are modified with menopause, which may affect the

susceptibility of $CD4^+$ T cells to HIV-infection in the FRT (*Rodriguez-Garcia, Mucosal Immunol 2014*) and potentially modulate the reservoir dynamics. In this sense, current strategies to reduce the viral reservoir and achieve a functional cure are often based on immunotherapies and, thus, need to account for sex-based differences on immune modulation or on drug metabolism. Unfortunately, underrepresentation of women in studies relevant to cure strongly limit conclusions in this regard *(Scully, Curr HIV/AIDS Rep 2018*). However, a recent report underscores that women have lower inducible HIV-1 RNA reservoirs than men and that reactivation of the HIV-1 reservoir is potently inhibited by estrogen (*Das et al., PNAS 2018*). Based on these findings, a Clinical Trial to evaluate "Selective Estrogen Receptor Modulators to Enhance the Efficacy of Viral Reactivation" (*ClinicalTrials.gov Identifier: NCT03382834*) is ongoing. Still, more studies will be necessary to fully understand the effect of hormones on reservoir establishment and maintenance, considering that resident memory populations from the FRT represent a potential long-lived reservoir for HIV-1 (*Cantero-Pérez et al., Nat Com 2019*).

In summary, sex hormones regulate the immune system and the response to infectious diseases, including HIV-1. Better assessment of sex-specific differences and hormonal influence affecting various aspects of HIV-1 infection, as well as more inclusion of women on research studies and clinical trials, will help guide therapeutic strategies for prevention, treatment and, ultimately, a cure for HIV-1 infection.

Meritxell Genescà

Infectious Disease Department, Hospital Universitari Vall d'Hebron

Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain.

Contact: meritxell.genesca@vhir.org