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Exogenous Estrogen Therapy Increases HIV Target Cell Frequencies in Male Rhesus Macaques

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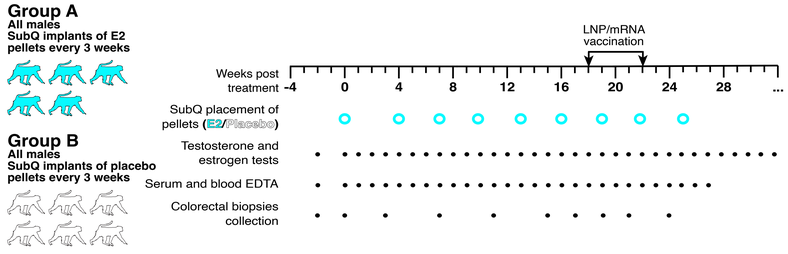
Background

Transgender women (TGW) share a disproportionate burden of HIV infection, with a global prevalence of 19% and a 66-fold higher odds ratio of acquiring HIV than individuals over 15. Considering TGW's high risk of acquiring HIV, they stand to benefit greatly from anti-HIV therapeutics, though little work has been devoted to understanding the immuno-modulatory effect of feminizing hormone therapy (FHT). To relieve gender dysphoria and take steps toward gender affirmation, many TGW utilize FHT, which includes exogenous estrogens, primarily 17-β estradiol, to facilitate physical feminization and bring estrogen levels closer to those of cisgender women. It is well established that estrogen can influence T-cell development and associated with higher immune responsiveness to infection and vaccination in women versus men. Importantly, estrogen has been associated with increases in CCR5+ CD4+ T-cells, which are the primary targets of early HIV-1 infection. Importantly, high frequencies of CCR5+ CD4+ T-cells have been linked to increased susceptibility to mucosal simian immunodeficiency virus transmission in rhesus macaques. Based on the immune-enhancing properties of estrogen, we postulate that FHT predisposes TGW to HIV infection through amplification of target cell populations. Hence, to advance our understanding of the immunomodulatory effects of cross-sex estrogen therapy, we set out to model FHT in male rhesus macaques.

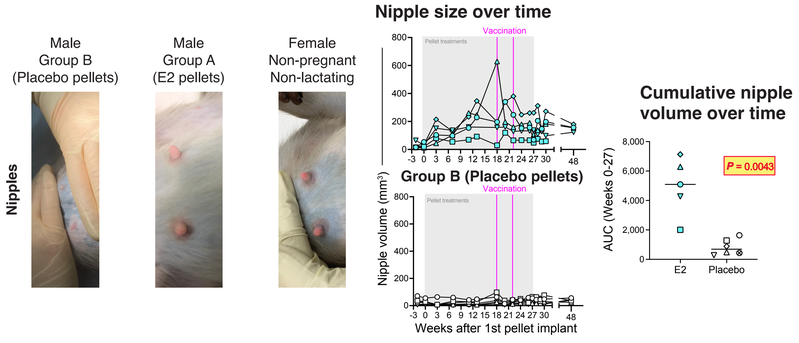
Experimental Layout

To achieve sustained delivery of 17-β estradiol (E2) *in vivo*, five male rhesus macaques aged 3-4 years (Group A) received slow-release E2 pellets (0.3 mg/kg) every 3-4 weeks. Six age-matched males received placebo pellets in parallel and served as controls (Group B). To uncover potential FHT-induced immune differences, all monkeys in both groups received LNP/mRNA vaccinations at weeks 18 and 22.



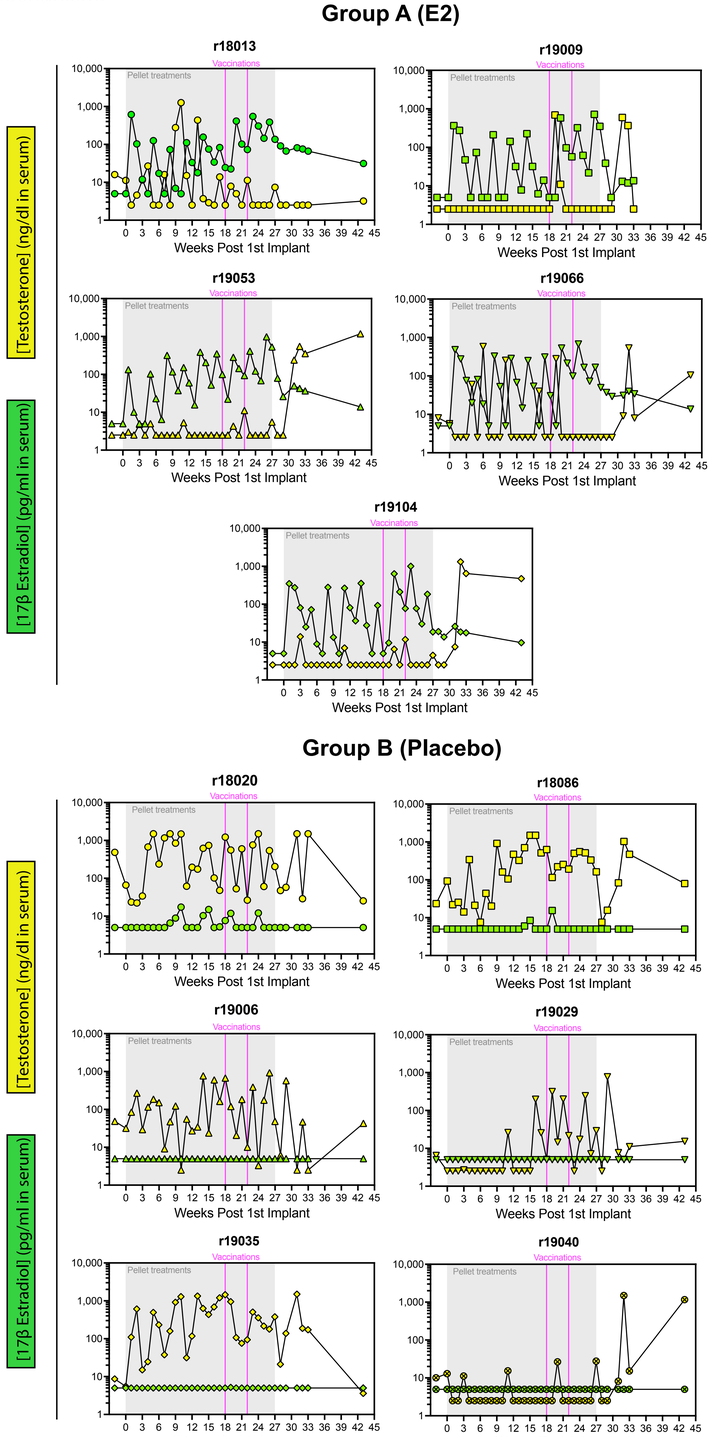
Physical Feminization

Consistent with the ability of E2 to induce feminine physical traits, the Group A males, but not the Group B ones, developed significantly larger nipples throughout the pellet regimen.



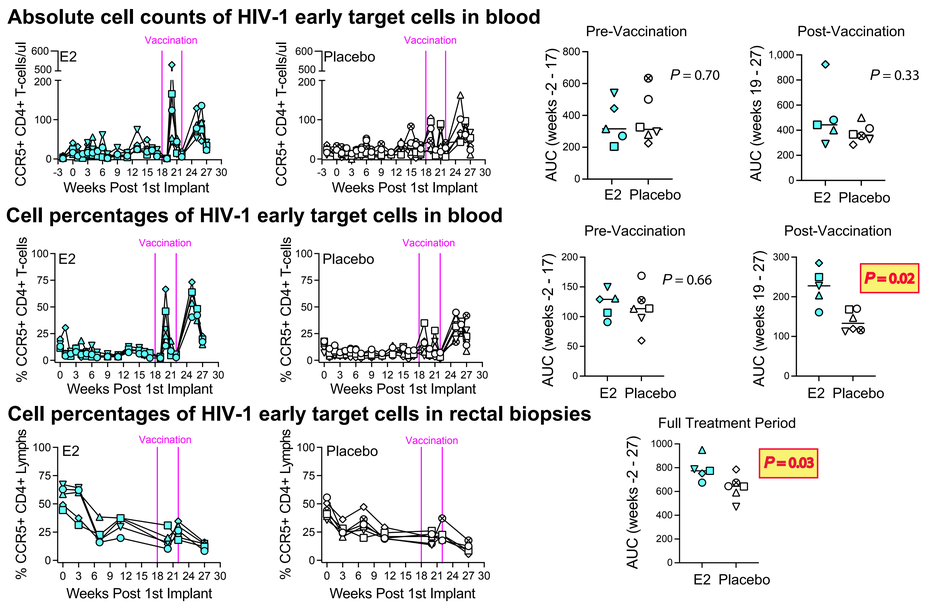
Hormone Measurements

The E2 regimen increased serum concentrations of 17-β estradiol in Group A and suppressed endogenous testosterone production, consistent with the ability of E2 to inhibit androgen synthesis through a central feedback mechanism.



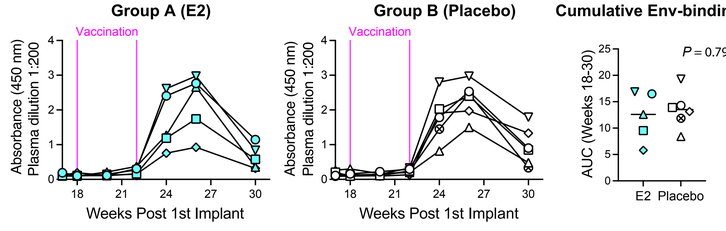
Dynamics of CCR5+ CD4+ T Cells Throughout Pellet Regimens

E2 treatment was associated with marginal, albeit statistically significant, increases in CCR5+ CD4+ T cells in PBMC and rectal biopsies, especially after the LNP/mRNA vaccinations.



Outcome of LNP/mRNA Vaccinations

To test if FHT could amplify vaccine-induced immune responses in biological males, all macaques in Groups A and B were primed and and then boosted with LNP/mRNA vaccine encoding a membrane anchored chimeric 16055 SOSIP antigen at study weeks 18 and 22. Both groups developed similar levels of Env-binding IgG antibodies, indicating that FHT did not significantly affect the immunogenicity of the LNP/mRNA vaccine.



Conclusions

Not only did FHT induce physical feminization (i.e. increased nipple sizes), but it also triggered significant increases in CCR5+ CD4+ T-cells in the blood and rectal mucosa of male macaques. It is important to highlight that CCR5+ CD4+ T-cells are the main targets for HIV replication and that the rectal mucosa is the primary portal of HIV acquisition in TGW. Whether this E2-mediated immune activation translates to increased susceptibility to rectal acquisition of immunodeficiency virus remains to be tested.

In sum, this work provides a new clinically relevant *in vivo* system to investigate the immune consequences of feminizing hormone therapy in transgender women.

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