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Increased HIV-1 acquisition by Depo-Provera unlike Nur-Isterate involves increased HIV-1 replication and CCR5 co-receptor levels

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Epidemiological data show a significant association between usage of the progestin-only injectable contraceptive depo-medroxyprogesterone acetate (DMPA, Depo-Provera) and increased HIV-1 acquisition. No such association is shown for the progestin-only injectable contraceptive norethisterone (NET) enanthate (Nur-Isterate). Whether this association for DMPA is due to confounding factors inherent in clinical studies is highly controversial and a critical issue for women's health, especially in developing countries with high DMPA usage and high HIV-1 prevalence and incidence. Using novel receptor and cell biology approaches to this clinical problem, we investigated the direct actions of these progestins on tissue and cellular models *ex vivo*, towards elucidation of biological mechanisms to explain the clinical data. We show for the first time that MPA, unlike NET, significantly increases HIV-1 replication in human cervical explant tissue at concentrations detected in the serum of DMPA users. These results together with results in peripheral blood mononuclear cells and an indicator cell line support a mechanism whereby MPA, acting via the glucocorticoid receptor (GR), increases HIV-1 replication in genital tract tissue. We discuss the mechanisms of this effect. Our data offer novel insights and a plausible biological mechanism for more informed choice of contraception for women at high risk of HIV-1 infection with significant potential impact on contraception policy and HIV-1 prevention.

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