



**Title: Misreporting contraceptive use and the association of peak study progestin levels with weight and BMI among women randomized to the progestin-only injectable contraceptives DMPA-IM and NET-EN**

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## **Abstract:**

Progestin-only injectable contraceptives, mainly depo-medroxyprogesterone acetate intramuscular (DMPA-IM), are the most widely used contraceptive methods in sub-Saharan Africa. The pharmacokinetic profile of injectable contraceptives shows an initial peak concentration within the first few weeks post-injection, followed by a decline to steady-state levels that maintain contraceptive efficacy until the next dose. While previous studies on levonorgestrel (LNG) and etonogestrel implants have shown decreased progestin concentrations with increased weight and/or BMI, no such data from a highly powered randomized study on DMPA-IM and NET-EN are available. Determining the concentrations of serum progestins is important for several reasons. Progestins may elicit dose-dependent biological side-effects such as increased risk of sexually transmitted infections, decreased bone density and weight change. Systematic reviews suggest a 32-40% lower risk of HIV acquisition among participants using NET-EN versus DMPA-IM, stimulating interest and urgency in obtaining data on the relative effects of DMPA-IM and NET-EN on health outcomes. However, insufficient robust data on their peak serum concentrations limit understanding of reported outcomes in contraception trials.

The Women's Health, Injectable Contraception and HIV (WHICH) clinical trial randomized HIV-negative women to DMPA-IM (n=262) or NET-EN (n=259) at two South African sites. We measured serum concentrations of study and non-study progestins at initiation (D0) and peak serum levels, one week after the 24-week injection [25 weeks (25W)] and investigated associations between progestin levels, and participants' BMI and weight.

Peak median serum concentrations were 6.59 nM for medroxyprogesterone (MPA) (n=161) and 13.6 nM for norethisterone (NET) (n=155). At D0, MPA was the most common non-study progestin (54%), followed by NET (29%) and LNG (6.9%), while other progestins were quantifiable in  $\leq 14$  participants. MPA and NET concentrations were negatively associated with weight and BMI and significantly higher peak serum progestin concentrations were detected in normal weight versus obese women.

Reported contraceptive-related health outcomes are likely confounded by MPA, more so than NET, with DMPA-IM effects likely underestimated, at sites where DMPA-IM is widely used, due to misreporting of contraceptive use. Peak serum levels of MPA and NET are negatively associated with BMI and weight, suggesting a potential increase in side-effects for normal weight versus overweight and obese women. While peak MPA concentrations were lower than those of NET, published data on steroid receptor affinity and activity suggest that peak concentrations of MPA, but not NET, could be sufficient to result in glucocorticoid receptor-mediated side-effects in select cells/tissues, particularly in the female genital tract.

## **Biography:**

Chanel Avenant, PhD, is a Research Officer in the Department of Molecular and Cell Biology at the University of Cape Town. Early in her career, Chanel's main area of research focused on gene regulation and intracellular signaling via steroid receptors. Of particular interest was to determine how different hormones (including those commonly used in contraception) can elicit differential responses via steroid receptors. This research was conducted in the broad context of reproduction, inflammation and contraception. Since 2010, her research has been

expanded to include regulation of HIV-1 infection by different progestins and endogenous hormones, particularly those involved in the female reproduction pathway.