Comment on 'Effects of injectable progestogen contraception versus the copper intrauterine device on HIV acquisition: sub-study of a pragmatic randomised controlled trial'

Hofmeyr *et al.* reported no significant differences in HIV acquisition in their randomised controlled trial (RCT) among South African women using injectable progestogens or copper intrauterine contraceptive devices (Cu-IUDs) for pregnancy prevention.[1] Acknowledging their longitudinal study of 1290 HIV-negative women (with time from enrolment to follow-up HIV testing of about 20 months) was underpowered to identify modest differences in HIV risk, they concluded that larger RCTs will more definitively define the effect of specific contraceptives on HIV susceptibility. They also noted their trial was halted early because of plans to conduct a larger and more comprehensive RCT. This Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study was designed to compare HIV acquisition in women from sub-Saharan Africa randomly allocated depot medroxyprogesterone acetate (DMPA) injection, levonorgestrel-releasing subcutaneous implant, or Cu-IUD.

While the ECHO Study may eventually identify one of these contraceptives as more appropriate for at-risk populations, Hofmeyr *et al.*'s results highlight the need to perform basic research in conjunction with clinical trials to more effectively broaden available options for safe and effective contraception. The authors reported 25% and 27% losses to follow-up in the injectable progestogens and Cu-IUD arms, respectively, an observation that reduced the study's ability to identify either method as a significant HIV risk factor. Similar random losses to follow-up, in addition to participants switching contraceptives, would lessen the capacity of any RCT to define the connections between HIV transmission and contraceptive use. In addition, the unacceptability of randomly allocating women to receive no contraception makes identification of suitable contraceptive methods by RCT dependent on differential outcomes. For example, if DMPA, progestogen implants and Cu-IUDs comparably affect HIV susceptibility, the ability of the ECHO Study to define precisely the risks associated with an individual contraceptive would be impaired.

This is relevant to the ECHO Study because while DMPA likely represents an important risk factor for HIV acquisition,[2 3] data from clinical studies on the effects of progestogen implants or Cu-IUDs are extremely limited. In mice, we showed that systemic treatment with DMPA or levonorgestrel (LNG), the progestogen released by commercially available subcutaneous implants and LNG-releasing intrauterine systems (LNG-IUSs), comparably increased genital mucosal permeability and susceptibility to herpes simplex virus type 2 (HSV-2) infection.[4] This indicated that enhanced genital infection susceptibility is a class effect of exogenous progestogens, not unique to DMPA. Examining ectocervical biopsy tissue from women before and 1 month after initiating DMPA or LNG-IUS use, we found these progestogens analogously induced increased genital mucosal permeability.[4 5] This implied that unopposed progestogen, in the form of injection, implant, or IUS, may similarly weaken genital mucosal barrier protection and increase susceptibility to genital pathogens. It also highlights that while LNG-IUSs and Cu-IUDs may represent better contraceptive choices than DMPA in high-risk populations, their effect on susceptibility to HIV is essentially unexplored.

Conversely, we also used the mouse to show that combined administration of exogenous progestogen and estrogen restored genital mucosal integrity and abolished susceptibility to genital HSV-2 infection.[4] Whether similar approaches in women would deliver contraception less compromising of genital mucosal barrier function than unopposed progestogens is uncertain. However, our results make plain that identifying efficacious and cost-effective choices for contraception in populations at high risk for HIV will require continued contributions from basic research that both capture data unattainable in clinical research and inform clinical study design.

Nirk Ericson Quispe Calla

Department of Comparative Medicine, Stanford University School of Medicine, Stanford, California, USA; nirk.quispe@stanford.edu

Rodolfo D Vicetti Miguel

Department of Comparative Medicine, Stanford University School of Medicine, Stanford, California, USA; vicettimiguel1@stanford.edu

Thomas L Cherpes

Department of Comparative Medicine, Stanford University School of Medicine, Stanford, California, USA; cherpes1@stanford.edu

***Corresponding author**

Contributors NEQC, RDVM, and TLC contributed equally to this letter.

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