Next steps for research on hormonal contraception and HIV

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Despite decades of observational research, uncertainty remains about whether use of hormonal contraception, especially the injectables depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN), increases a woman's risk of acquiring HIV.[1] Because of concerns that the increased risk in observational studies is an artifact of confounding and selection bias, a randomised controlled trial has been proposed.[2] One potential design includes four groups: DMPA, NET-EN, Jadelle implant, or a copper intrauterine device comparison group. With perfect method adherence, measurement, and power, this study could clarify the association between use of DMPA and NET-EN and the risk of HIV in women. The study could also offer crucial new data about the effect of implants. However, the apparent usefulness and policy relevance of results from such a trial must be tempered by consideration of the ethical and methodological issues that constrain real-world research.

In view of the potential increased risk of HIV acquisition in women using DMPA and NET-EN in some high-quality observational studies,[3] whether equipoise would be violated by random assignment is unclear. Further, because informed and voluntary choice in contraceptive decision making is the central tenet of successful family planning programmes worldwide,[4] women might not comply with random assignment. For example, 44% of women who were approached about participation in a hypothetical study on the association between hormonal contraception and sexually transmitted infections were unwilling to be randomly assigned to use either intrauterine devices or DMPA.[5] In two studies that randomly assigned women to use DMPA or intrauterine devices,[6,7] initial participation rates among eligible women were roughly 65% and a further third of women were lost to follow-up during the study. Such low participation and retention rates raise substantial concerns about the external validity of findings from randomised clinical trials of contraceptive methods.

If randomly assigning women is ethical and feasible, low rates of method adherence and method switching might quickly neutralise the benefits of randomisation that are central to causal inference. To minimise these issues, eligibility criteria would probably specify that women indicate that they do not intend to become pregnant during the trial. However, previous studies, including HIV prevention trials, have shown that women's pregnancy intentions and contraceptive preferences are dynamic. For example, one in five women in the Methods for Improving Reproductive Health in Africa (MIRA) trial became pregnant over the 2-year study although they had initially stated no intention of getting pregnant in that time-frame, and half the women switched methods.[8] Although adherence to longacting methods such as implants and intrauterine devices will be higher than injectables, it will still be imperfect; 1-year discontinuation rates for these methods are 8% (implants) and 18% (intrauterine devices) in sub-Saharan Africa.[9,10] Non-compliance to the randomised treatment group results in outcomes similar to those reported from observational studies in which only post-hoc analytic approaches can be used to address causality.[11,12] Moreover, the ability to measure key confounders such as condom use, coital frequency, and new partner acquisition accurately is just as restricted in a randomised clinical trial as it is in an observational study. Finally, without enormous resources from funders and communities, a study with four groups would probably have insufficient power to detect the effect size estimated (risk ratio [RR] <1·5), which would leave doubts on the role of hormonal contraception on risk of HIV infection.

In view of these methodological concerns, and the time it takes for results of randomised clinical trials to become available—at least 4 years—the available data on this topic should not be overlooked. A recent meta-analysis

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of high quality studies found a modest increase in the risk of HIV acquisition among DMPA users (RR 1·35, 95% CI 1·14–1·61) (unpublished). In modelling studies,[13,14] this slightly raised risk would neither be sufficient to merit complete withdrawal of DMPA (in view of the burden of unintended pregnancy on women and infants' morbidity and mortality[15]), nor would it change WHO guidance that women at risk of HIV be encouraged to use condoms.[1] More confidence should also be placed in these observational studies because misreporting of condom use could not fully account for the increased risk of HIV acquisition reported in the study by Heffron and colleagues of serodiscordant partners (hazard ratio ~2).[16,17] Further secondary analyses with existing datasets could answer key questions related to the effects of cumulative hormonal contraception exposure and the role of bias.

Finally, perhaps more important than a trial is to prioritise strategies with continuing research and programmes to broaden women's contraceptive options, including identification of barriers to uptake of highly effective but underutilised methods such as intrauterine devices and the development of dual prevention methods. For example, a study that examines comparative methods of promotion (eg, provider or user incentives, social media advertising, or e-health) would be a fraction of the cost and time of the proposed trial. Considering the limitations of a randomised clinical trial, such approaches might represent a more useful allocation of scarce resources.

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