Contraception and HIV: an exercise in clarity

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Twenty-eight years, hundreds of articles and more than half a dozen systematic reviews after the spectre of an association between the use of modern contraception and an increased risk of HIV acquisition was first raised, two systematic reviews[1 2] published in this Journal issue may, at last, close the debate. The reviews update the evidence on the association, and include the findings of a randomised controlled trial (RCT), the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial.[3] They were conducted to inform an expert meeting convened by the World Health Organization (WHO) to consider whether the updated evidence warranted changing the recommendations regarding the use of hormonal and intrauterine contraceptive methods by women at high risk of HIV.

First published in 1996, the WHO Medical Eligibility Criteria for Contraceptive Use (WHOMEC) guideline applies a four-category scale to indicate medical eligibility for use of all contraceptive methods in the presence of certain physiological or health conditions or risks, including women at high risk of HIV. Concern had first been raised by a Kenyan study reporting that prostitutes who used oral contraceptives were more likely to be HIV infected than those who did not.[4] Over the next two decades, increasing numbers of observational studies gradually focused concern on the effects of use of injectable depot medroxyprogesterone acetate (Depo-Provera, DMPA). Successive updates of WHOMEC reviewed the changing evidence. Concluding that there were no medical reasons to restrict any hormonal method, in three consecutive editions, high risk of HIV was a Category 1 condition for all hormonal contraceptives including DMPA. The use of intrauterine contraceptive devices (IUDs) was restricted, largely because the evidence suggested that sexually transmitted infections increased the risk of pelvic inflammatory disease (with significant morbidity and sequelae). In WHOMEC 2009, high risk of HIV was categorised as Category 2 (ie, the advantages of using the method generally outweigh the theoretical or proven risks, but extra consideration and counselling may be needed) for copper and progestogen-releasing IUDs.[5]

The research efforts continued and so did the systematic reviews. A review commissioned for updating WHOMEC in 2014[6] concluded that "uncertainty persists regarding the association between DMPA and HIV risk. Newly published analyses are in the direction of an elevated risk; taken together with prior evidence, the new data lead to a moderate increase in the consistency of estimates of the effect of DMPA on HIV risk". An expert panel agreed that the evidence still did not warrant changing the recommendations. As a compromise, however, in the fifth edition of WHOMEC (2015) an asterisk was added to the Category 1 grade, to highlight the accompanying clarification that women at risk "should be informed that progestogen-only injectables may or may not increase their risk of HIV acquisition".[7]

It was clear that such was the heterogeneity of the risk of confounding among the observational studies (particularly from the effects of condom use) that only an experimental design could resolve the question. Despite considerable discussion and disagreement as to the necessity and ethics of conducting an RCT,[8] the ECHO trial started recruitment at the end of 2015. Ultimately 7829 sero-negative women in 12 sites in sub-Saharan Africa were randomly assigned to use either DMPA-IM, the copper IUD or a levonorgestrel (LNG) contraceptive implant and followed up for 18 months.[3]

While the world waited for the results of the ECHO trial, the research – and the debate – continued. A meta-analysis of the observational data published in 2015 reviewed 12 studies involving almost 40 000 women, excluding the very high risk

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sex workers and sero-discordant couples, concluded that DMPA use was associated with an almost 40% increased risk of HIV acquisition compared with non-hormonal, or no contraception.[9] Another systematic review[10] concluded that "new information increases concerns about DMPA and HIV acquisition risk in women". It felt as though the evidence was getting stronger, and in 2017, persuaded that the controversial 1* recommendation for DMPA use among women at high risk of HIV had been "ineffective" in improving counselling, it was agreed that WHOMEC guidance for DMPA use should be elevated to Category 2 (ie, the benefits of use outweigh the risks).

In anticipation of the completion of the ECHO trial, a third expert meeting was convened in July 2019. The trial reported no substantial difference in HIV risk among the three methods evaluated (DMPA, IUD and LNG implant). After almost 3 days of discussion, the expert group, which included representatives from HIV-affected populations, concluded that women at risk of HIV could use any method of contraception without restriction (Category 1).[11]

Is this then really the end of the debate? It would seem not. In an editorial entitled 'Depot contraception and HIV: an exercise in obfuscation'[12] published within 3 months of the release of the new WHOMEC recommendations, the author accuses the expert group of a "lapse of scientific rigour" in its interpretation of the research, and demands that WHO's new guidance should be rejected until all data from the trial is (re) reviewed and reanalysed. A storm of correspondence supporting the author's position followed, much of it vitriolic. The systematic reviews[1 2] published in this Journal issue demonstrate that a well-conducted, adequately powered RCT trumps observational studies (although perhaps not passionately held beliefs) – but read the reviews and make up your own mind.

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