# End of the debate on hormonal contraception and HIV risk?

Contraceptives are life-saving interventions because they prevent maternal and neonatal mortality from unwanted pregnancies. Worldwide, birth control (all forms) is estimated to reduce maternal deaths by 44% (272 000 deaths averted in 2008), and could prevent an additional 29% of such deaths if the full demand for contraception was met. Since their introduction in 1960, hormonal contraceptive methods have revolutionised the lives of many millions of women of child-bearing age, allowing them to take control of their own fertility. However, unlike barrier methods such as condoms, hormonal contraceptives do not protect against sexually transmitted infections such as HIV. Indeed, whether hormonal contraceptives might actually increase the risk of HIV acquisition has been debated since the early 1990s. Concern focuses particularly on the injectable drugs depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN).

In an Article in this issue, Lauren Ralph and colleagues attempt to resolve the debate with a meta-analysis of observational studies of hormonal contraceptive use and women's risk of HIV acquisition. The researchers identified 12 relevant studies with a total of almost 40 000 women. Compared with non-hormonal or no contraception, DMPA use was associated with a 40% increased risk of HIV acquisition (hazard ratio 1·40, 95% CI 1·16–1·69). The risk was lower (1·31, 1·10–1·57) when only the general population was considered, after exclusion of women in high-risk groups such as sex workers and those in serodiscordant partnerships. No increased risk of HIV acquisition was found in women using oral contraceptive pills (1·00, 0·86–1·16) or NET-EN (1·10, 0·88–1·37).

Do Ralph and colleagues' findings close the debate on whether hormonal contraceptives increase the risk of HIV acquisition? Many experts will argue that a definitive answer is impossible when the available data come from observational studies. Despite the best efforts of investigators to minimise confounding, the results of observational studies are prone to bias introduced by unmeasured variables that differ between groups. For example, women using DMPA might have more frequent sexual intercourse or be less likely to use condoms than women using other contraceptive methods, both of which would increase the risk of HIV infection irrespective of any specific effect of DMPA.

Because of such uncertainty in the data, the debate around whether hormonal contraception increases risk of HIV acquisition has become polarised and heated, as pointed out by Christopher Colvin and Abigail Harrison in the Comment that accompanies the Article by Ralph and colleagues. A randomised controlled trial, usually regarded as providing the highest level evidence, appears to be the best way of getting a definitive answer. Indeed, the ECHO consortium is planning a trial that will randomise 7800 women in sub-Saharan Africa to receive contraception by either DMPA, progestin implant, or non-hormonal copper intrauterine device.

The very idea of the ECHO trial has faced substantial criticism. Critics question whether it is ethical to conduct a trial for which the primary outcome is harm in the form of HIV infection. Furthermore, they argue that because the available data show that DMPA increases the risk of HIV acquisition, the trial groups would not be in equipose at the point of randomisation. Trial participants could not be masked to contraceptive method, so another concern relates to whether women would be compliant with their allocated method. Whether the findings of the trial would lead to a change in practice has been questioned, because modelling analyses suggest that even if a doubling of risk was found, the benefits of DMPA in terms of maternal mortality would still outweigh the increased number of HIV infections. Writing in *The Lancet* last year, Gollub and Stein said: "A randomised trial appears to be a high-risk (for failure) venture for marginal gain." At present, the start of the ECHO trial has been delayed by problems in finding sufficient funding.

In sub-Saharan Africa, injectable hormonal contraceptives (particularly DMPA) are among the most widely used forms of birth control. Irrespective of whether a randomised trial eventually provides conclusive evidence on the risk of HIV acquisition related to this form of contraception, women will still need access to effective control over their fertility. Alternative—and more effective—methods, such as hormonal implants and intrauterine devices, already exist. Any moves to withdraw DMPA must go hand in hand with roll-out of alternative contraceptive methods. ■ *The Lancet Infectious Diseases*

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