

Heffron and Authors respond to attacks

Heffron and colleagues¹ finding that use of injectable hormones for birth control increases women's risk of acquiring and transmitting HIV presents an opportunity for HIV prevention and challenges researchers to better characterise risks with alternative birth control methods.

HIV-negative women changing from injectable hormones to no hormonal contraception reduce their risk of HIV by 54% (1-1/2-19), and HIV-positive women reduce transmission to HIV-negative partners by 67% (1-1/3-01). Therefore, women changing from injectable hormones to no hormonal contraception reduce their contribution to a complete cycle of male-to-female-to-male transmission by 84% (1-[1/2-19] [1/3-01]). Although Heffron and colleagues and Morrison and Nanda² cite other studies linking injectable hormones to HIV risk, they overlook a study³ in Malawi in which the risk for HIV incidence was 10.4 times greater in women using injected hormones than in those who did not. From these data, facilitation of women to change from injectable hormones to other birth control methods might be a promising HIV prevention intervention.

Even without official warnings, many women will be afraid to use injectable hormones and will want to use other methods that do not increase their risk of HIV. These women urgently need good information about HIV risks with oral hormones, implants, intrauterine devices, diaphragms, and other birth-control methods. To expedite dissemination of evidence-based information about HIV risks with various birth-control methods, organisations that fund HIV research in Africa could ask study teams for all completed studies of risks for HIV incidence in adults to make public all unpublished data for these methods and for HIV incidence.

In 24 years, 44 randomised controlled trials of interventions for

HIV prevention in adults in Africa have followed up more than 78 000 women and noted more than 3000 incident infections in women.⁴ Many other studies of risks for HIV incidence have additional data. Many if not most studies provided routine medical care or collected information about drugs taken, and so have information about women's birth control practices. Morrison and Nanda propose a randomised trial of hormonal birth-control methods as risks for HIV; however, this trial would take time, and might not be needed or even ethical if the proposed review of available data shows what methods are or are not risks for HIV.

I declare that I have no conflicts of interest.

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Authors' reply

We acknowledge the limitations of self-reported sexual behaviour; however, findings from several supplementary analyses suggest that incomplete statistical control for sexual behaviour does not explain our findings. First, self-reported unprotected sex was strongly associated with HIV-1 risk in our multivariate models (adjusted hazard ratio [HR] 2.82, 95% CI 1.62-4.92; $p=0.0002$ for HIV-1 acquisition in women and 2.57, 1.38-4.77; $p=0.003$ for HIV-1 transmission from women to men). Second, unprotected sex strongly

correlated with increased pregnancy incidence¹ and self-reported condom use was associated with an 80% reduction in per-contact risk,⁷ which is consistent with widely accepted estimates of condom effectiveness.³ Third, Gray and Shelton argue that reported condom use was too high for our reported HIV-1 incidence in women, but their calculations do not account for substantially increased risk of HIV-1 in periods with no condom use, high concentrations of plasma HIV-1 RNA in male partners that increased risk for some couples, and transmissions to women from other sexual partners with whom condom use was uncommon.⁴ Per-contact risk of HIV-1 transmission in the absence of condoms was similar to that from other studies.⁷ Finally, high condom use in our population accompanied frequent couples counselling, and HIV-1 incidence was lower than in previous studies without such counselling.^{5,6}

Addition of the total number of unprotected sex acts to our model, as suggested by Hubacher, and van Leeuwen and de Vries, did not substantially change our findings—eg, for the relation between injectable contraception and HIV-1 acquisition in women the adjusted HR was 2.04 (95% CI 1.03–4.04; $p=0.04$) compared with that of 1.98 (1.06–3.68; $p=0.03$) in our primary analysis. When the woman's report of unprotected sex was replaced with her partner's report (his report was probably not affected by her contraceptive use) the results were similar (HR 2.03, 95% CI 0.95–4.32; $p=0.06$).

Investigators of future observational studies could benefit from gathering biological samples (eg, vaginal swabs to assess for semen exposure) to estimate rates of behavioural misreporting. However, while scientific interest continues in isolation of a biological effect of injectable contraception on HIV-1 risk, a public health approach might focus on the total effects,

because a new HIV-1 infection that is potentially related to contraceptive use is compelling, irrespective of whether it is biologically mediated or because of reduced condom use.

We agree with Beksinska and colleagues that studies should separately assess the injectable contraceptives depot medroxyprogesterone acetate (DMPA) and norethisterone enanthate, which is used in South Africa. In our study, women from outside South Africa who consistently used injectable contraceptives—ie, consistent DMPA users—had high HIV-1 risk (adjusted HR 3.93, 95% CI 1.38–11.22; $p=0.01$).

Shelton argues against biological plausibility, but the potential biological mechanisms by which hormonal contraceptives could increase HIV-1 risk have been reviewed extensively.⁷ We postulated that moderately increased concentrations of genital HIV-1 could partly explain increased transmission from women to men, in conjunction with other mechanisms. We measured cervical concentrations of HIV-1 RNA per swab (not per volume of mucus), which would account for reduced mucus production from injectable progestin use.

A WHO consultation⁸ concluded that data associating HIV-1 risk with injectable contraceptive use are insufficient to mandate policy change to restrict use of such methods, but recommended that women at risk of HIV-1 who use progestogen-only injectables should be counselled to use condoms consistently. Furthermore, a call was made for expansion of the contraceptive method mix and for more research into this important question. Future observational analyses should be done with rigorous statistical consideration, including several techniques and sensitivity analyses, and avoiding of overadjustment for mediating factors. The alternative risks results biased towards the null; a potentially reassuring finding, but one that would not serve the health of women and

their partners. A randomised trial could overcome some limitations of observational analyses, but it should be done so that contraceptive switching and loss to follow-up do not undermine the benefits of randomisation.

Our hope is that our results have stimulated important global discussions about contraceptive options, the interface of HIV-1 prevention and contraception, and the need for development of novel strategies to dually protect against HIV-1 and pregnancy.

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