ABSTRACT

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 incidence and self-reported condom use was associated with an 80% reduction in per-contact risk, which is consistent with widely accepted estimates of condom effectiveness. 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. Per-contact risk of HIV-1 transmission in the absence of condoms was similar to that from other studies. Finally, high condom use in our population accompanied frequent couples counselling, and HIV-1 incidence was lower than in previous studies without such counselling.

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. 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 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. 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 consultation\textsuperscript{8} 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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