

# Gray, Shelton and Hubacher attack Heffron, et al.

## Use of hormonal contraceptives and risk of HIV-1 transmission

Renee Heffron and colleagues<sup>1</sup> finding of an association between hormonal contraceptive use and acquisition and transmission of HIV-1 has profound implications for policies on family planning in countries with high HIV risk, such as sub-Saharan Africa. Therefore, potential problems should be considered in the interpretation of this observational study. All observational studies of contraception and risk of HIV and sexually transmitted infections are open to potential bias and confounding because women choosing hormonal contraception might have higher HIV risk behaviours than do those not using these methods. Furthermore, because condoms can protect from HIV, the inclusion of condom users in the comparison group could cause an artifactual increase in the apparent risk associated with hormonal contraception.

The HIV-1-serodiscordant couples in the study received couples counselling and disclosure of HIV test results. These couples had extremely high self-reported rates of protected intercourse (more than 90% if the man was infected and almost 90% if the woman was infected). Such rates are inconsistent with pregnancy during 16% of the follow-up intervals in non-hormonal users, particularly considering this group included women who had had a hysterectomy or tubal ligation. The HIV acquisition rate of 3.8 per 100 person-years in users of non-hormonal contraceptive methods is likewise higher than expected. A European study<sup>2</sup> of discordant couples reported no HIV infections in consistent condom users. This finding suggests over-reporting of protected intercourse, possibly because of

social desirability bias, because the couples had been counselled to use condoms. Concurrent use of condoms and a highly effective contraceptive is uncommon in Africa, and non-users of hormonal contraception might be motivated to use condoms consistently if they rely on this method for both pregnancy and HIV prevention. Such increased consistency of condom use for dual pregnancy and prevention of HIV and sexually transmitted infections has been previously reported.<sup>3</sup> Thus, general over-reporting of condom use, and the possibility for unmeasured differential consistency in actual condom use, could inflate the apparent risk associated with hormonal contraception, despite attempts to statistically adjust for unprotected sex. The only way to resolve this issue is to exclude condom users from both groups, but because only about 10% of individuals reported no condom use in the past month, the study has insufficient power to assess this comparison.

In summary, the study's findings cannot determine whether hormonal contraception affects the risks of HIV acquisition and transmission because of evidence of inaccurate reporting of condoms, and a likelihood that this bias might differ between users and non-users of hormonal contraception.

I declare that I have no conflicts of interest.

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- 1 Heffron R, Donnell D, Rees H, et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis* 2012; **12**: 19–26.
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What credible mechanisms might explain Heffron and colleagues' disparate findings for HIV and hormonal contraception? The investigators found the same two-times increased risk associated with injectable contraception for two very different biological processes: risk of women contracting HIV by using injectables, and risk of them transmitting the infection to their partners. Moreover, they found a similar (albeit not statistically significant) two-times increased risk for both acquisition and transmission with oral contraceptives, which act somewhat differently biologically from progestin-only injectables because they contain both oestrogen and progestin. Poor biological plausibility, specifically for transmission to partners, calls all of Heffron and colleagues' findings into serious question.

Concentrations of genital HIV-1 RNA were increased by 0.19 log<sub>10</sub> copies per swab in women using injectable hormones, which Heffron and colleagues offer as an explanation of the doubling in transmission risk. However, this increase is insufficient according to analysis from broadly the same population,<sup>2</sup> which quantified the positive relation of genital shedding to transmission and noted that 1.0 log<sub>10</sub> copies per swab generated only a 67% increase in transmission. Because progestins reduce volume of cervical mucus, use of cervical swabs to collect genital secretions might artifactually increase viral concentration for injectables. By contrast, cervicovaginal lavage methodology has indicated that hormonal contraception does not increase viral RNA shedding.<sup>3</sup> Moreover, Heffron and colleagues noted no increase in viral shedding with oral contraceptives, despite the increased point estimates for transmission.

A plausible alternative explanation for the findings for acquisition and transmission is bias from lower HIV exposure in the non-hormonal

contraceptive users in view of the likelihood of more consistent condom use<sup>4</sup> and possibly lower coital frequency in this group than in those using hormonal contraception. The investigators attempted to control for unprotected sex and reported that its frequency was slightly increased for HIV-positive users of hormonal contraception. However, unprotected sex must be highly under-reported in this trial setting, with about only 10% of individuals reporting any unprotected sex in the past month. For acquisition, a calculation with transmission of 0.00072 per coital act,<sup>5</sup> reported coital frequency of three per month for 12 months, and 8% reported exposure to any unprotected sex yields an expected annual infection rate of 0.21%, which is 20 times less than the acquisition rate of 4.09 per 100 person years in Heffron and colleagues' study.

Explaining the same two-times increased risk for transmission and acquisition for injectables and oral contraceptives is daunting, especially because their biological effects often differ. The seemingly necessary mechanism for transmission of genital viral shedding seems untenable; therefore, systematic bias might well underlie both the transmission and acquisition findings. Applying Occam's razor, the simplest explanation for all four increased findings is systematic bias (and residual confounding) from increased consistent condom use in individuals using non-hormonal contraception.

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Coital frequency could be the real reason for Heffron and colleagues' findings<sup>1</sup> that hormonal contraception increases risk of HIV acquisition. Although the investigators examined and dismissed the possibility that more sexual activity in hormonal contraceptive users than non-users was to blame, the veracity of self-reports about sex has always been questionable. Could women not using contraception or using only condoms have the same level of sexual activity as those using hormonal contraception? Women are probably likely to choose effective birth control, such as hormonal contraception, when the risks of unintended pregnancy are high. When sexual activity is sporadic or absent, risk of HIV acquisition is low, as is motivation to use hormonal contraception. Nevertheless, non-users might have overstated their sexual activity because of study requirements for participation. However, in the final relative risk analysis, hormonal contraception could be falsely implicated for the noted increase in risk of HIV acquisition.

Misreported condom use is the other possible confounder. The investigators concluded that condom use did not skew the findings; however, self-reports of this topic are notoriously inaccurate<sup>2</sup> and can substantially affect research. Reported condom use was balanced at roughly 91%. If those using hormonal contraception overstated condom use to avoid a lecture about safe sex, non-use of condoms combined with high sexual activity would put them at significant risk of HIV acquisition. Consequently, the raw data show that the comparison groups were equally

protected by condoms, which could falsely leave hormonal contraception as the risk factor for HIV acquisition. Marginal structural models cannot salvage the truth from potentially biased data.

In summary, the results of this and similar studies are built on shaky ground; far more evidence exists that self-reported coital frequency and condom use are poor scientific variables. However, at the margins these factors can be easily obscured, thus distorting the risk estimates for a primary exposure. In the published report, only 13 women on hormonal contraception seroconverted. Epidemiology often fails to prove causation. New approaches are needed to answer the important question of whether hormonal contraception increases risk of HIV acquisition.<sup>3</sup>

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