Hormonal contraception and HIV: an unanswered question

Published Online
October 4, 2011
DOI:10.1016/S1473-3099(11)70254-7
See Online/Articles
DOI:10.1016/S1473-3099(11)70247-X

Most of the 16 million women currently living with HIV are in sub-Saharan Africa, where 60% of HIV infections occur in women.[1] A high proportion of women in this region also use hormonal contraception, especially injectable depot-medroxyprogesterone acetate (DMPA).[2] Since the first report of increased HIV acquisition in women taking oral contraceptives,[3] whether hormonal contraception increases the risk of HIV acquisition remains a crucial unanswered question.

In *The Lancet Infectious Diseases*, Renee Heffron and colleagues[4] report, from a study of nearly 3800 HIV-1 serodiscordant couples from seven African countries, that women using hormonal contraception, primarily DMPA, had a two-times increased risk of acquiring HIV. Women who were HIV-infected at the beginning of the study and using injectable contraception were also twice as likely to transmit the infection to their uninfected male partners and had higher genital HIV RNA concentrations, a potential mechanism for increased HIV transmission.[4] This study adds to the growing body of observational evidence that DMPA might increase women's risk of acquiring and transmitting HIV.

The main strength of the study is that exposure to HIV was known. The study population consisted of HIV-serodiscordant couples, and analysis was limited to HIV infections genetically linked to the index partner. As such, the study was able to provide direct data on the risk of HIV-infected women using hormonal contraception transmitting the virus to their male partner. By contrast with many other studies, self-reported condom use was similar between hormonal and non-hormonal groups. Finally, the investigators used sophisticated analytical techniques and were able to adjust analyses for the plasma viral load of the infected partner.

However, similar to all observational studies, this study was open to aetiological pitfalls. Potential selection bias and confounding could have distorted interpretation. Furthermore, like all but two studies on this topic, this study was a secondary analysis of an HIV-prevention trial—not specifically designed to examine hormonal contraception and HIV risk. Few women used hormonal contraceptives (only 196·6 [11%] of the total person-years of follow-up were among hormonal-contraceptive users) and few HIV infections (ten for DMPA and three for oral contraceptive users) occurred in these users. Contraceptive use was self-reported and not confirmed by clinical records, and contraception was not provided at all of the 14 sites. Switching of contraceptive methods was common: almost half of women who used hormonal contraceptives were also non-hormonal users at some point. Switching between visits was not accounted for in analyses. Condom use was also self-reported and of unknown accuracy, and thus analytical adjustment for condom use might be insufficient. Finally, whether the increased risk associated with DMPA use is consistent across sites is unclear, because site-specific effect estimates were not provided.

12 published prospective observational studies have assessed DMPA use and HIV acquisition;[4–7] five (including several of the strongest studies) reported increased risks of HIV acquisition with DMPA use.[4,6,8] These human data are supported by data from macaques, suggesting that DMPA increases both the risk of simian immundeficiency virus and levels of viraemia after infection.[9,10] Although theoretical biological mechanisms for an increased risk of HIV with hormonal contraception exist (including changes to the vaginal–cervical epithelium, local immunological changes, a direct influence of sex hormones on HIV virulence), exact mechanisms remain unclear.[4,5,11,12] A previous study that directly measured the association between women's use of hormonal contraception with HIV transmission showed no increase in transmission risk to the uninfected male partner.[13]

Any potential increase in HIV risk with hormonal contraception must be considered in context. A separate analysis by the same study team suggests that pregnancy itself might increase risk of HIV transmission.[14] Furthermore, as the authors correctly point out, use of effective contraception to prevent unintended pregnancies has unequivocal benefits: reducing maternal mortality and morbidity, increasing the socioeconomic status of women, and improving the health of children through birth spacing. WHO Medical Eligibility Criteria for Contraceptive Use[15] currently recommend that the benefits of hormonal contraceptive use outweigh any potential harm for women at high risk of and living with HIV.

The question of hormonal contraceptive use and risk of HIV acquisition remains unanswered after more than two decades. Active promotion of DMPA in areas with high HIV incidence could be contributing to the

HIV epidemic in sub-Saharan Africa, which would be tragic. Conversely, limiting one of the most highly used effective methods of contraception in sub-Saharan Africa would probably contribute to increased maternal mortality and morbidity and more low birthweight babies and orphans—an equally tragic result. The time to provide a more definitive answer to this crucial public health question is now; the donor community should support a randomised trial of hormonal contraception and HIV acquisition.

Charles S Morrison, Kavita Nanda
Clinical Sciences, FHI 360, Durham, NC, USA (C S Morrison, K Nanda)
cmorrison@fhi360.org

We declare that we have no conflicts of interest.

1 Joint UN Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic 2010. Geneva: UNAIDS, 2010.
2 UN Department of Economic and Social Affairs, Population Division. Population and HIV/AIDS 2007. (Wall chart). New York: UN, 2008.
3 Plummer FA, Simonsen JN, Cameron DW, et al. Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. *J Infect Dis* 1991; **163:** 233–39.
4 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* 2011; pubished online Oct 4, 2011. DOI:10.1016/S1473-3099(11)70247-X.
5 Morrison CS, Turner AN, Jones LB. Highly effective contraception and acquisition of HIV and other sexually transmitted infections. *Best Pract Res Clin Obstet Gynaecol* 2009; **23:** 263–84.
6 Morrison CS, Chen PL, Kwok C, et al. Hormonal contraception and HIV acquisition: reanalysis using marginal structural modeling. *AIDS* 2010; **24:** 1778–81.
7 Watson-Jones D, Baisley K, Weiss HA, et al. Risk factors for HIV incidence in women participating in an HSV suppressive treatment trial in Tanzania. *AIDS* 2009; **23:** 415–22.
8 Baeten JM, Benki S, Chohan V, et al. Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women. *AIDS* 2007; **21:** 1771–77.
9 Marx PA, Spira AI, Gettie A, et al. Progesterone implants enhance SIV vaginal transmission and early virus load. *Nat Med* 1996; **2:** 1084–89.
10 Trunova N, Tsai L, Tung S, et al. Progestin-based contraceptive suppresses cellular immune responses in SHIV-infected rhesus macaques. *Virology* 2006; **352:** 169–77.
11 Hel Z, Stringer E, Mestecky J. Sex steroid hormones, hormonal contraception, and the immunobiology of human immunodeficiency virus-1 infection. *Endocr Rev* 2010; **31:** 79–97.
12 Ghanem KG, Shah N, Klein RS, et al. Influence of sex hormones, HIV status, and concomitant sexually transmitted infection on cervicovaginal inflammation. *J Infect Dis* 2005; **191:** 358–66.
13 European Study Group on Heterosexual Transmission of HIV. Comparison of female to male and male to female transmission of HIV in 563 stable couples. *BMJ* 1992; **304:** 809–13.
14 Mugo NR, Heffron R, Donnell D, et al. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1-serodiscordant couples. *AIDS* 2011; **25:** 1887–95.
15 WHO Department of Reproductive Health. Medical Eligibility Criteria for Contraceptive Use, 4th edn. Geneva: WHO, 2010.