Published in final edited form as:

Lancet Infect Dis. 2015 February ; 15(2): 135–136. doi:10.1016/S1473-3099(14)71076-X.

Broadening the Debate over HIV and Hormonal Contraceptives

Christopher J. Colvin, PhD^{a,*} and Abigail Harrison, PhD^b

^aDivision of Social and Behavioural Sciences, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

^bSchool of Public Health and Population Studies and Training Center, Brown University, Providence, RI, USA

The debate over whether hormonal contraception (HC), and in particular Depo-Provera (DMPA), increases a woman's risk for acquiring HIV has been roiling ever since a potential association was first documented in 1991.¹ Subsequent observational studies also often found increased risk, though in many cases, data were drawn from secondary analyses in trials with different primary objectives. Prospective studies that focused on the HIV/DMPA link^{2–4} and systematic reviews of the existing observational data^{5,6} have lent weight to the view that DMPA use translates into a moderate contribution to HIV risk. This is especially true for women already at higher risk of contracting HIV, for whom the relative trade-offs of DMPA in terms of reduced maternal mortality and other pregnancy-related risks are less compelling. Efforts to synthesize the existing evidence, however, have confronted significant heterogeneity of findings as well as significant, uncontrolled risk of confounding of the HIV/DMPA relationship in many studies.^{5–7}

In *The Lancet Infectious Diseases*, Ralph and colleagues⁸ contribute to this debate by offering for the first time a pooled estimate of the association between DMPA and HIV acquisition, drawn from a meta-analysis of the most up-to-date observational evidence. They conclude that DMPA use increases a woman's chance of acquiring HIV by 40% (pooled relative risk: 1.4, CI: 1.16 – 1.69). Studies with women already at high risk of infection reported considerably higher effects of DMPA on HIV risk though heterogeneity prevented a pooled estimate. The authors also conducted a series of a priori secondary analyses that tested and supported the robustness of their pooled estimates.

These findings are certain to add an important new element in the longstanding debates over the HIV/DMPA link, and the calls for further evidence about its magnitude, mechanisms, and health impacts. Ralph and colleagues argue that their findings confirm previous studies and reviews that have found an elevated risk and further suggest that researchers and policymakers use these pooled estimates as soon as possible to guide decision-making about the use of DMPA in different local contexts.

*Corresponding Author. Christopher J. Colvin, PhD, MPH, Associate Professor and Head, Division of Social and Behavioural Sciences, School of Public Health and Family Medicine, Falmouth 3.46, Health Sciences Campus, University of Cape Town, Observatory 7925, Cape Town, South Africa, Phone: +27-21-406-6706, cj.colvin@uct.ac.za.

At the moment, debates over the HIV/DMPA link have crystallized into a narrow and increasingly fierce debate over whether a large RCT should be conducted to try and further clarify the link.⁷ Like many scientific controversies, lines have hardened, critiques have increasingly implied personal, financial or political agendas, and there has even been academic intrigue in the form of leaked copies of articles under peer review released to the public.⁹ Both sides in this debate have raised important and compelling arguments but the partisan character of this debate has also sometimes led to weaker argumentation and a restricted view of the complex relationships between evidence, policy and practice.

Trial proponents have argued, for example, that only an RCT can produce evidence that will both answer the scientific question *and* do so in a way credible to policy makers.^{10,11} They argue that equipoise exists and that a trial is feasible (or at least that its feasibility is an open question). Their defenses, however, tend to unproblematically frame RCTs as 'higher-quality' forms of evidence without sufficiently addressing the many serious methodological challenges this trial would face, challenges we have seen affect the ability of trials like VOICE and MIRA to confidently answer the question they set out to tackle. Proponents have also made compelling arguments about the moral and political urgency of conducting the trial and the need to avoid thousands of preventable HIV infections in women using DMPA. In doing so, however, they have tended to elide other health risks of not using DMPA.

Critics of the proposed trial offer contrasting arguments.^{12,13} They maintain that, given existing evidence, equipoise does not exist and the trial would be unethical. They argue that existing policy options and further modeling research could effectively mitigate the risk of DMPA use and that the opportunity costs of a trial—which will require tens of millions of dollars—are considerable. They argue about the likely health trade-offs for many women between effective HIV prevention and effective family planning. And they argue that hard-fought progress in increasing access to contraception, especially in sub-Saharan Africa, will be threatened if governments are too quickly scared off of support for DMPA. Critics, however, tend to gloss over problems with the existing evidence, assume too easily that resources are finite and opportunities for research funding are fungible, and do not always acknowledge the limits of modeling studies on their own to answer policy questions. Like proponents, they also often frame the question of DMPA use in terms of its impacts on women's lives and bodies, only here the emphasis is on maternal mortality and other risks of pregnancy.

We believe that rhetorical arguments about one's desire to protect the lives of women are not the best ways to address the question at stake here. Neither are abstract arguments about the relative value and hierarchies of different forms of evidence. One of the real contributions we believe made by Ralph and colleagues is their nuanced discussion of what their study adds and what is possible with existing and future forms of evidence. Their study evaluates the main findings and key strengths and weaknesses in the observational data. It also, however, identifies numerous ways in which further modeling research, epidemiological studies, behavioural and clinical research, and basic biological science could work synergistically to push our knowledge forward. And it addresses the complicated policy decision points and local contextual factors that are at work here, factors that guarantee that

the link between evidence—any evidence—and policy and practice is never a straight line. What they describe is an approach to evidence, policy and practice that sees an 'ecology of evidence'¹⁴ as the foundation for thinking through next steps. The current polarized climate of debate around the need for a trial makes this kind of more holistic approach all the more difficult, and necessary.

Acknowledgements

Time to work on this paper was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number R24HD077976. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. 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(2):233–239. [PubMed: 1988508]
2. 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(13):1771–1777. [PubMed: 17690576]
3. Morrison CS, Richardson BA, Mmiro F, et al. Hormonal contraception and the risk of HIV acquisition. *AIDS*. 2007; 21(1):85–95. [PubMed: 17148972]
4. Kleinschmidt I, Rees H, Delany S, et al. Injectable progestin contraceptive use and risk of HIV infection in a South African family planning cohort. *Contraception*. 2007; 75(6):461–467. [PubMed: 17519153]
5. Polis CB, Curtis KM. Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence. *Lancet Infect Dis*. 2013; 13(9):797–808. [PubMed: 23871397]
6. Polis CB, Phillips SJ, Curtis KM, et al. Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence. *Contraception*. 2014; 90(4):360–390. [PubMed: 25183264]
7. Westhoff CL, Winikoff B. DMPA and HIV: do we need a trial? *Contraception*. 2014; 90(4):353. [PubMed: 25183262]
8. Ralph LJ, McCoy SI, Shiu K, Padian NS. Does hormonal contraceptive use increase women's risk of HIV acquisition? A meta-analysis of observational studies. *Lancet Infectious Diseases*. 2014
9. McConnell J. Editor's note. *The Lancet Infectious Diseases*. 2014; 14(3):182. [PubMed: 24571968]
10. Rees H, Consortium E. DMPA and HIV: why we need a trial. *Contraception*. 2014; 90(4):354–356. [PubMed: 25183263]
11. Cates W. Evidence for Contraceptive O, Consortium HIVO. Research on hormonal contraception and HIV. *Lancet*. 2014; 383(9914):303–304. [PubMed: 24461116]
12. Jones HE. Time to focus on improving the contraceptive method mix in high HIV prevalence settings and let go of unanswerable questions. *Contraception*. 2014; 90(4):357–359. [PubMed: 24993486]
13. Gollub EL, Stein Z. Research on hormonal contraception and HIV. *Lancet*. 2014; 383(9914):304–305. [PubMed: 24461117]
14. Petticrew M. 'More research needed': plugging gaps in the evidence base on health inequalities. *European journal of public health*. 2007; 17(5):411–413. [PubMed: 17962338]