

Depo-Provera and HIV transmission: WHO to trust?

C. Sathyamala

Editor's note: Concerns about Depo-Provera and increased rates of HIV transmission are of vital importance to women's health, especially to those at high risk of HIV acquisition. Despite compelling evidence of a Depo-Provera-HIV link and regulatory bodies' unclear guidance around the method's use,¹ distribution of the injectable contraceptive has been on the rise. For instance, in 2017 the Indian government began offering free Depo injections through its public health system, despite opposition from women's and health groups in India.² Since 2008, a public-private partnership has tested and distributed the Sayana Press, which delivers a lower dosage formulation of Depo-Provera, in countries including Uganda, Senegal and Niger.³

In this *DifferenTakes*, scholar C. Sathyamala critically examines the ECHO trial, which aimed to conclusively answer the Depo-Provera-HIV question. It ended in spring 2019. The author argues that the trial results add to the existing evidence that Depo-Provera increases the risk of HIV transmission. She challenges the World Health Organization's June 13 statement reporting "no link." This stance, she argues, dangerously misrepresents the study's findings and, further, disregards key critical challenges, including those from AIDS and reproductive justice activists. As the author argues, the World Health Organization guidance fails to appropriately warn users of the potential risk associated with Depo-Provera use and wrongly concludes that it is "safe."

— Anne Hendrixson

DifferenTakes is a publication of the
Population and Development Program

Hampshire College | Amherst, Massachusetts
413.559.5506

<http://popdev.hampshire.edu>

Opinions expressed in this publication are those of the
individual authors unless otherwise specified.



On June 13, 2019, the medical journal *The Lancet* published the preliminary results of the ECHO trial, named after the *Evidence for Contraceptive Options and HIV Outcomes* Consortium that designed and oversaw its implementation in four African countries.⁴ The main purpose of this trial was to "settle" a two decades-long controversy of whether the three-monthly injectable contraceptive Depo-Provera (depot medroxyprogesterone acetate or DMPA) increased the chances

of transmission of HIV in users. The “no link” results wrongly suggest Depo-Provera has been proven “safe.” Further, the interpretation of the results seems to sweep aside the serious ethical issues in the ECHO trial itself. Among other concerns, approximately four percent of trial participants contracted HIV.

This article examines the problems of the ECHO trial and the interpretation of its results against the troubling history of inadequate Depo-Provera regulation.

This article examines the problems of the ECHO trial and the interpretation of its results against the troubling history of inadequate Depo-Provera regulation. Regulatory guidance has been ambiguous and sometimes conflicting, and seems to prioritize fertility control over the risk of HIV acquisition and transmission, leaving women who are at high risk of HIV with unhelpful, mixed messages.

Depo-Provera and Risk of HIV

In 1992, when Depo-Provera was approved for contraceptive use by the United States Food and Drug Administration (USFDA), its association with HIV transmission was yet to be documented in medical literature. However, this effect came to light in the immediate period following the licensing. The first published studies in the late 1990s showed that women users who were at high risk of contracting HIV, such as sex workers, were at an increased risk with Depo-Provera use. Until 2009, though evidence began to suggest that Depo-Provera could be an important risk factor for HIV transmission, the World Health Organization under its Medical Eligibility Criteria (MEC) graded the contraceptive as 1 (unrestricted use) even among those at high risk of HIV. Providers were therefore not mandated to counsel users about Depo-Provera’s potential adverse effect.⁵

In October 2011, a well-designed study by Heffron et al. concluded that use of Depo-Provera doubled the risks of acquiring *and* transmitting HIV.⁶ It took the WHO some months to set up an expert committee to reassess the HIV risk in light of this study. In their meeting of February 2012, the WHO first placed a gag order on the members attending it.⁷ The committee then, citing the “inconclusive nature” of the evidence, abstained from changing the category of Depo-Provera from MEC 1. Instead, in order to accommodate the disturbing conclusion of the study by Heffron et al., a concession was made by adding a caveat that the user “should be strongly advised to *also always use condom*” (emphasis as in original).⁸

It was in this context that the ECHO Consortium was formed in 2012 by the coming together of the US-based FHI 360, the University of Washington, the University of the Witwatersrand Reproductive Health and HIV Institute (Wits RHI) and the Bill & Melinda Gates Foundation, with the WHO joining one year later.⁹ Its mandate was to design a trial. The ECHO trial was founded on the critique that previous studies suggesting an association were observational and therefore subject to bias. For example, the Depo-Provera users might be less likely to use condoms or might have more frequent sexual intercourse.¹⁰

In contrast, the randomized design adopted in the ECHO trial was meant to provide “robust evidence” by overcoming these infirmities. However, considering that there was already a body of evidence to show that Depo-Provera could increase HIV transmission, the advisability of randomization was questioned by scholars.¹¹ The central ethical issue was the concern regarding lack of equipoise because the chances of being disadvantaged were not equal for all the participants. In other words, for the trial participants who would be assigned to the Depo-Provera arm not by choice but through random allocation, their participation would potentially put them at a higher risk of acquiring HIV.

Do the advantages outweigh the risks?

In March 2014, before participant recruitment began, the WHO's Guideline Development Group once again placed Depo-Provera in the category of MEC 1, i.e. "unrestricted use," but added an ambiguous qualification that "women at high risk of HIV infection should be informed that progestogen-only injectables may or may not increase their risk of HIV acquisition."¹² However, inexplicably, on October 21, 2015, two months before the screening of participants in the ECHO trial was to begin, the WHO issued another statement that, "[t]here [was] no evidence of a causal association between DMPA use and women's risk of HIV acquisition."¹³ This was immediately met with a protest. On behalf of 24 organizations and several individuals, mostly working on HIV/AIDS, an open letter was sent to the WHO remonstrating that its statement of "no causal association" was "demonstrably false" and contradicted the Guideline Development Group's 2014 guideline.¹⁴ The open letter demanded that the WHO should either furnish evidence to support its unsubstantiated claim or remove the statement from its website. The statement was removed. It is to be noted that the WHO's statement clearing Depo-Provera was released one month after the ECHO Consortium had registered its trial with the US National Institute of Health's clinical trial database.¹⁵

A year later, in November 2016, when recruitment for the ECHO trial was underway, a meta-analysis by Polis et al. estimated that the risk of HIV infection among Depo-Provera users could be 50 percent or less.¹⁶ The WHO's Guideline Development Group met the next month and upgraded the risk of Depo-Provera from MEC 1 (totally safe) to grade MEC 2: "can use because the advantages of this method generally outweigh the possible increased risk of HIV acquisition."¹⁷ This new advisory made the issue of equipoise mentioned earlier even more troubling. How ethical was it to randomly assign women to the Depo-Provera arm of the study, given the increased risk of acquisition? However, recruitment and randomization continued and was completed on September 12, 2017.

How ethical was it to randomly assign women to the Depo-Provera arm of the study, given the increased risk of acquisition?

The ECHO trial randomly assigned sexually active, non-pregnant, HIV negative girls/women aged 16-35 years to one of the three contraceptive methods: Depo-Provera, a levonorgestrel sub-dermal implant (Jadelle), and the intra-uterine copper IUD, and compared their HIV results at the end of 18 months follow-up.¹⁸ The trial recruited a total of 7,829 participants from four countries (South Africa—9 sites; eSwatini (Swaziland), Kenya and Zambia—one each).¹⁹ Follow-up was concluded on October 31, 2018. But before the results could be published, they were "inadvertently and temporarily released by the scientific journal,"²⁰ *The Lancet*, which was surprising considering the journal's high repute. Because of this leak, the preliminary results were published in June 2019, earlier than was planned.

Perfectly safe, as long as you take PrEP

Before the ink had dried, so to speak, the WHO released a statement with a heading "New study finds no link between HIV infection and contraceptive methods."²¹ However, the first sentence following this contained the key phrase, "no significant difference in risk of HIV infection." In epidemiological parlance, what it meant was that while a difference was observed among the methods, this was not *statistically* significant. This refers to what is termed the power of a study. When the sample size was decided by the ECHO Consortium, a deliberate decision was made to design the study to have power to detect an association only if Depo-Provera increased transmission of HIV by 50 percent or more.²² Therefore, the sample size (the number of girls/

... the study design made it difficult to find a statistically significant risk if it was less than 50 percent. Yet, even with this reduced possibility, the ECHO results showed that, compared to the sub-dermal implant, Depo-Provera users had 23-29% increased chances of getting HIV.

women participants recruited) in the trial was not large enough to find out the rates of transmission, statistically speaking, in case Depo-Provera increased the possibility of acquiring HIV by less than 50 percent when compared with the other methods.

The ECHO trial results showed that the overall HIV incidence rate in the trial was 3.81/100 woman-years (years of observation time per person or, in this study, per woman).²³ In one of its centers it was even higher at 6.5/100 woman-years.²⁴ The HIV incidence was high irrespective of the method tested: it was 4.19/100 woman-years in the DMPA-IM group, 3.94/100 woman-years in the copper IUD group, and 3.31/100 woman-years in the sub-dermal implant group. However, these results

were declared unimportant (“no link”) because the differences between the three methods were considered statistically invalid, and it could not be validated statistically because the sample size was not sufficient to validate it. In other words, the study design made it difficult to find a statistically significant risk if it was less than 50 percent. Yet, even with this reduced possibility, the ECHO results showed that, compared to the sub-dermal implant, Depo-Provera users had 23-29% increased chances of getting HIV. Further, the “no link” conclusion was based on the misuse and misinterpretation of statistical tests.²⁵

Given that the ECHO results were not definite in their support for Depo-Provera, the Guidance Development Group of the WHO that was to meet soon after the release of the ECHO results was urged not to make a decision in haste.^{26, 27, 28} Despite this, on August 29, the WHO declared that Depo-Provera was safe for use even in populations with high rates of HIV and assigned it back to category MEC 1.²⁹ Moreover, the WHO’s current guidance dilutes its previous advice to also always use condoms and instead recommends offering pre-exposure prophylaxis (PrEP) while using Depo-Provera.³⁰ In effect, what is being conveyed is that Depo-Provera is perfectly safe as long as PrEP is also taken to protect from acquiring HIV.

The ECHO trial and the WHO guidance raise two critical issues. One is the gross ethical violations of the rights and well-being of the girls/women who participated in the trial.³¹ Girls and women participating in this trial, particularly those who were allocated Depo-Provera, were not sufficiently informed about the potential for increased risk of HIV. And two, the results add to the evidence that Depo-Provera increases HIV transmission and should, in fact, be placed in category MEC-3—proven risks outweigh the advantages of using this method—as argued in the past by Gollub et al.³²

From the time evidence began to accumulate on the HIV risk associated with Depo-Provera, the WHO has thwarted every move to declare it unsafe for use in high HIV prevalence populations, citing flaws in study design. This time, the WHO has based its guidance on a trial that is flawed from the point of view of its design and analysis. Looking at the long convoluted history of Depo-Provera and HIV transmission regulation, it becomes necessary to ask: WHO (then) to trust?

C. Sathyamala is a public health physician and epidemiologist with a PhD in Development Studies. She is part of the health and women's movement in India. She has written extensively on and advocated against the use of injectable contraceptives in the family planning program in India. She helped draft the petition filed by women's groups in the Supreme Court of India in the 1980s against the injectable contraceptive NET-EN. Her 2000 book, *An Epidemiological Review of the Injectable Contraceptive, Depo-Provera*, (Pune: Medico Friend Circle; Mumbai: Forum for Women's Health) is available for download at http://www.mfcindia.org/main/Publications/Sathyamala_Epidemiological_review_depo_provera.pdf. She is currently a researcher with the International Institute of Social Studies (ISS), Erasmus University of Rotterdam, The Netherlands.

Endnotes

1. See for instance Marion Stevens, "Elevated Risk: Injectable Contraceptives and HIV—a Reproductive Justice Perspective from the Global South," *DifferenTakes*, no. 90, Summer 2017, <https://sites.hampshire.edu/popdev/elevated-risk-injectable-contraceptives-and-hiv-a-reproductive-justice-perspective-from-south-africa/>;
2. Shaifali Agrawal, "Risking Health Of Its Women, India Uses Controversial Contraceptive In Family Planning Programme," *IndiaSpend*, October 18, 2017, <https://archive.indiaspend.com/cover-story/risking-health-of-its-women-india-uses-controversial-contraceptive-in-family-planning-programme-36857>
3. See Daniel Bendix, Ellen E. Foley, Anne Hendrixson and Susanne Schultz, "Targets and Technologies: Sayana Press and Jadelle in Contemporary Population Policies," *Gender, Place & Culture*, <https://doi.org/10.1080/0966369X.2018.1555145>
4. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium, "HIV Incidence Among Women Using Intramuscular Depotmedroxyprogesterone Acetate, a Copper Intrauterine Device or a Levonorgestrel Implant for Contraception: A Randomised, Multicentre, Open-label Trial," *The Lancet*, (June 13, 2019) [http://dx.doi.org/10.1016/S0140-6736\(19\)31288-7](http://dx.doi.org/10.1016/S0140-6736(19)31288-7)
5. See for instance, World Health Organization, "Hormonal Contraceptive and HIV: Science and Policy," Geneva: World Health Organization, 2005, (https://www.who.int/reproductivehealth/topics/family_planning/nairobi_statement.pdf)
6. Renee Heffron, Deborah Donnell, Helen Rees, et al., "Use of Hormonal Contraceptives and Risk of HIV-1 Transmission: A Prospective Cohort Study" *Lancet Infectious Diseases*, vol. 12, (February 2012): 19–26.
7. Paula Donovan, "The UN's Gag Order on Reproductive Health," *AIDS-Free World*, February 13, 2012, <http://pharmpdf.com/a/aids-freeworld.org1.html>
8. World Health Organization, "Hormonal Contraception and HIV: Technical Statement. WHO/RHR/12.08." Geneva: WHO, 2012, https://www.who.int/reproductivehealth/topics/family_planning/Hormonal_contraception_and_HIV.pdf
9. G. Justus Hofmeyr, Charles S. Morrison, Jared Baeten, et al., "Rationale and Design of a Multi-center, Open-label, Randomised Clinical Trial Comparing HIV Incidence and Contraceptive Benefits in Women Using Three Commonly-used Contraceptive Methods (the ECHO study), [version 2; referees 2 approved]," *Gates Open Research* (2018), 1, 17. <https://doi.org/10.12688/gatesopenres.12775.2>
10. Gianni Di Perri, "How Does Contraceptive Use Increase the Risk of HIV Acquisition?" 15th European AIDS conference, October 21-24, 2015, https://www.eacsociety.org/files/giovanni_di_perri.pdf
11. Lauren J. Ralph, Sandra I. McCoy, Timothy Hallet and Nancy Padian, "Next Steps for Research on Hormonal Contraception and HIV," *The Lancet*, vol. 382, no.9903 (June 28, 2013): 1467–1469. [https://doi.org/10.1016/S0140-6736\(13\)61420-8](https://doi.org/10.1016/S0140-6736(13)61420-8)
12. World Health Organization. "Hormonal Contraceptive Methods for Women at High Risk of HIV and Living with HIV, 2014 Guidance statement," (2014), http://apps.who.int/iris/bitstream/10665/128537/1/WHO_RHR_14.24_eng.pdf?ua=1
13. Lillian Mworeko and Mitchell Warren, "Women's Response to new WHO statement on DMPA," Letter to Dr. Margaret Chan, Director General of the World Health Organization and Dr. James Kiari, Coordinator, Human Reproduction Team, World Health Organization. Undated. <https://www.avac.org/sites/default/files/u3/CivilSocietyWHOresponse.pdf>
14. Ibid.

15. ClinicalTrials.gov. "The Evidence for Contraceptive Options and HIV Outcomes Trial (ECHO)," Bethesda, MD: US National Library of Medicine. Identifier: NCT02550067, August 20, 2019, <https://clinicaltrials.gov/ct2/show/NCT02550067>
16. Chelsea Polis, Kathryn Curtis, Philip Hannaford, et al., "An Updated Systematic Review of Epidemiological Evidence on Hormonal Contraceptive Methods and HIV Acquisition in Women," *Aids*, vol. 30 no. 17 (November 1, 2016): 2665–2683. doi:10.1097/QAD.0000000000001228
17. World Health Organization, "Hormonal Contraceptive Eligibility for Women at High Risk of HIV: Guidance Statement" (2017), Geneva: Author. <http://echo-consortium.com/wp-content/uploads/2017/03/WHO-RHR-17.04-eng-1.pdf> (accessed November 27, 2019). Note that the WHO has removed this statement from its website and appears to selectively archive its official guidance on Depo-Provera.
18. Hofmeyr et al. (2018)
19. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium (2019)
20. Results 4 Informed Choice, "WHO Statement on the Early Release of ECHO Trial Results," (2019)
<https://resultsforinformedchoice.org/material/who-statement-on-the-early-release-of-echo-trial-results/>
21. World Health Organization, "New Study Finds No Link Between HIV Infection and Contraceptive Methods," June 13, 2019, <https://www.who.int/reproductivehealth/hc-hiv/en/>
22. Hofmeyr et al. (2018)
23. Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium, (2019)
24. Thesla Palanee-Phillips, Jared Baeten, Kate Heller, et al., "High HIV Incidence Among Young Women in South Africa: Data from the ECHO Trial," International AIDS Society, 2019 Mexico City, July 21-24, 2019, http://www.natap.org/2019/IAS/IAS_107.htm
25. C. Sathyamala, "Depot Contraception and HIV: An Exercise in Obfuscation," *British Medical Journal*, (October 7, 2019) 367:l5768, <https://www.bmj.com/content/367/bmj.l5768>
26. C. Sathyamala, "The Jury's Still Out," *BLISS* [blog], July 23, 2019, <https://issblog.nl/2019/07/23/depo-provera-and-hiv-transmission-the-jurys-still-out-by-c-sathyamala/>
27. Yvette Raphael et al., "Open letter to World Health Organization from Africa," (July 22, 2019). <https://www.sexrightsafrika.net/wp-content/uploads/2019/10/OPEN-LETTER-TO-WORLD-HEALTH-ORGANISATION.pdf>
28. Judy Norsigian and Norma Swenson, Re: Letter addressed to Dr. Petrus Steyn and Dr. James Kiarie, World Health Organization, (July 29, 2019).
29. World Health Organization, "Contraceptive Eligibility for Women at High Risk of HIV," 2019, <https://www.who.int/reproductivehealth/publications/contraceptive-eligibility-women-at-high-risk-of-HIV/en/>
30. World Health Organization, "WHO Revises Recommendations on Hormonal Contraceptive Use for Women at High HIV Risk," Press release, (August 29, 2019), <https://www.who.int/news-room/detail/29-08-2019-who-revises-recommendations-on-hormonal-contraceptive-use-for-women-at-high-hiv-risk>
31. C. Sathyamala, "In the Name of Science: Ethical Violations in the ECHO Randomised Trial," *Global Public Health*. (2019) <https://doi.org/10.1080/17441692.2019.1634118>
32. Erica L. Gollub, Heidi E. Jones, Lauren J. Ralph, et al. "The Need for Policy Change Regarding Progestin-Only Injectable Contraceptives," *Journal of Women's Health*, vol. 28, no. 9 (2019): 1180-4. <https://www.liebertpub.com/doi/pdf/10.1089/jwh.2018.7284>