The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study Questions and Answers, August 2019

ECHO Results

1. What is the ECHO Study?

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study was a randomised clinical trial that for the first time compared three highly effective, reversible methods of contraception to evaluate whether there was any difference in the risk of acquiring HIV among women using them. The study products were: a progestogen-only hormone called depot medroxyprogesterone acetate given through intramuscular injection (DMPA-IM); a non-hormonal copper intrauterine device (IUD); and a sub-dermal implant containing the progestogen levonorgestrel (LNG). The study also compared side effects, pregnancy rates and women's patterns of use for the three contraceptive methods. In total 7 829 participants took part in the study at 12 research sites in Eswatini, Kenya, South Africa and Zambia.

2. Why was the ECHO Study needed?

More than 150 million women worldwide use various hormonal contraceptives, including progestogen-only contraceptives such as injectables. In sub-Saharan Africa, progestogen-only injectable contraceptives are the most commonly used contraceptive method. Over the past 30 years, researchers have been trying to determine whether or not hormonal methods increase the risk of HIV. The cumulative evidence suggested a possible increased risk, particularly with DMPA-IM, but some studies showed no risk. Few studies had examined whether hormonal implants or intrauterine devices (IUDs) affected users' risk of HIV infection. All the data that were available on contraception and HIV risk came from observational studies — a type of study that is subject to bias and has other limitations — and most of the studies were not specifically designed to assess the relationship.

Filling these gaps in the research with high-quality evidence from a randomised clinical trial was critical, given the widespread use of DMPA-IM in areas with high rates of HIV. Women needed to know whether using DMPA-IM or other contraceptive methods affected their risk of HIV, so they could make informed choices about contraception and HIV prevention.

3. What were the ECHO Study's main findings?

The ECHO Study found no substantial difference in HIV risk among 7 829 African women who were randomly assigned to use DMPA-IM, a copper IUD or an LNG implant. The results are reassuring, indicating that none of the three contraceptive methods substantially increases the risk of HIV acquisition compared with the other two. However, the overall rate of new HIV infections was high among study participants, regardless of which contraceptive they used. All the contraceptive methods studied were safe, highly effective and well-accepted by the women who used them.

4. What was the rate of new HIV infections?

All ECHO Study participants were HIV-negative at the start of the study and received comprehensive counselling, condoms, STI screening and treatment, and pre-exposure prophylaxis (PrEP) as this option became available in the study countries. Even so, because rates of HIV are high in those countries, some women acquired HIV during the study period. A total of 397 HIV infections occurred, or 3.8 percent per year, highlighting the urgent need to strengthen HIV prevention efforts and integrate HIV prevention and contraceptive services.

5. What was the HIV incidence by study method?

Data on new HIV infections (incidence) by study group were as follows:

- 143 in the DMPA-IM group, representing an annual incidence of 4.19%.
- 138 in the copper IUD group, representing an annual incidence rate of 3.94%.
- 116 in the LNG implant group, representing an annual incidence 3.31%.

6. How did the risk of HIV acquisition compare among the study groups?

The ECHO trial was designed to detect a 50 percent increase in new HIV infections for each of the three contraceptive methods compared to each other method. This design was based on consultations held with stakeholders before the trial began to determine a difference in risk that would be likely to inform policy change (see question 24). The trial did not find a substantial difference in HIV risk among the methods evaluated: no method showed a 50 percent increase in HIV risk compared to the other two. Under this design, the trial could not detect differences smaller than 30 percent, at least not reliably. Even small effects, however, could be important considerations for individual women making decisions about contraception and HIV prevention.

7. Was HIV risk by method influenced by age or other factors, such as having an STI?

Participants who were younger than 25 years or who tested positive for herpes simplex virus 2 (HSV-2) at enrolment had an increased risk of acquiring HIV, but that risk was the same across the method groups. In other words, age or HSV-2 status did not influence the relationship between use of any of the methods and risk of HIV acquisition.

8. Did the study results differ by country?

Most of the participants (5 768) lived in South Africa, so we compared the results for South Africa with the overall results for all the women who participated in the trial. The South Africa results were the same as those for all participants, showing no substantial difference in the risk of HIV acquisition among users of any method compared to the other two methods.

9. What were the main findings about the safety and effectiveness of the contraceptive methods in the ECHO Study?

All three study methods proved safe and highly effective in preventing pregnancy. Only about 1 percent of participants became pregnant over the course of a year, considering only the time when women were using their randomly assigned methods. Of the 255 pregnancies that occurred, 61 were in the DMPA-IM group, 116 were in the copper IUD group and 78 were in the LNG implant group. However, most pregnancies (71 percent) occurred after women had stopped using their assigned contraceptive methods.

10. What else can we learn from the ECHO Study results?

Results from ongoing secondary analyses will provide additional information about ECHO participants' contraceptive preferences; their experiences with the assigned methods and pre-exposure prophylaxis (PrEP); sexually transmitted infections, including HSV-2; factors associated with contraceptive method continuation; and the influence of contraceptive methods on early HIV disease progression among women who acquired HIV. Several ancillary studies are underway that may shed additional light on the relationship between hormonal contraception and HIV risk.

11. How did the ECHO Study differ from previous studies of hormonal contraception and the risk of HIV acquisition?

The ECHO Study is the first large-scale randomised clinical trial to address this important public health question. Randomised trials are considered the best way to collect reliable scientific evidence about the effect of a medical intervention. In the ECHO trial, women were randomly allocated by computer to use one of three contraceptive methods. When women have an equal chance of using any of the contraceptive methods under study, sexual behaviours and other factors that might influence HIV risk are equally likely to occur across the three groups. As a result, with a randomised trial there is more certainty that a true difference in HIV acquisition is being measured and that any differences measured can be more certainly attributed to the contraceptive method used. As a well-executed randomised clinical trial that met rigorous standards, the ECHO Study provides high-quality evidence to inform contraceptive decision-making.

12. What standards did the ECHO Study meet?

Given concerns about women's willingness to use randomly assigned methods and other challenges in designing the ECHO Study, the study team and funders agreed on measures of

quality before the study began. If the study had been unable to meet the targets for those measures, the study would have been stopped. Instead, the ECHO Study met or exceeded all the targets built into the study design, achieving high standards of quality in clinical research. For example, almost 94 percent of participants stayed in the study through the final study visit. More than 99 percent of the women accepted a randomly assigned contraceptive method, and they used their assigned contraceptive methods for nearly 92 percent of their time in the study.

13. Are any changes in contraceptive policies or guidelines expected now that the results have been announced?

The ECHO Study provides evidence, not policy prescriptions. We have shared the results with the Guideline Development Group of the World Health Organization (WHO). WHO convened the group in late July 2019 to consider the most recent research, including the ECHO trial results, and determine whether any changes are needed in WHO's guidance on contraceptive use. The WHO's contraceptive guidance, or Medical Eligibility Criteria (MEC) for Contraceptive Use, is used worldwide by programme managers, policy-makers and clinicians. WHO plans to communicate the outcome of this process to these stakeholders and the public by the end of August 2019; the guideline review process is described at: https://www.who.int/publications/guidelines/guidelines_review_committee/en/.

14. What is the current WHO guidance on the use of hormonal contraception by women at high risk of HIV?

Based on a December 2016 expert consultation to review the latest evidence on hormonal contraception and HIV, in March 2017 the WHO changed its recommendation on progestogen-only injectables for women at high risk of HIV from 'can use without restriction' (MEC category 1) to 'can use because the advantages of these methods generally outweigh the possible increased risk of HIV acquisition' (MEC category 2).

The ECHO team then informed all study participants of this updated WHO guidance, which says that women at high risk of acquiring HIV can use progestogen-only injectables but should be advised about: 1) concerns that these methods may increase their risk of HIV acquisition; 2) continued uncertainty about that potential risk; and 3) how to minimise their risk of acquiring HIV.

15. How available are the LNG implant and copper IUD methods in eastern and southern Africa?

These products are not as available in the study countries and the region as the injectable method (DMPA-IM), although access to and use of implants has been increasing. The ECHO Study has shown that with adequate resources, provider training and support, and consistent supplies, it is possible to provide these methods safely and effectively in clinics in the region.

16. Did participants have the option to receive antiretroviral pre-exposure prophylaxis (PrEP)? If so, did their use of PrEP affect the study results?

Women interested in oral PrEP were referred to services providing PrEP as it became available in each study community. In response to the South African Medical Research Council's recommendation in November 2017 that participants in clinical trials be offered oral PrEP as an HIV prevention option, the ECHO Study incorporated the offering of PrEP at all the study sites in South Africa. Oral PrEP was also available through referral at all ECHO sites. Because PrEP became the national standard of care relatively late in the study, experience with PrEP was too limited to affect the study results. A total of 622 participants reported using PrEP while on the study, for a median duration of 85 days, or less than 2 percent of the total time all the women were in the trial.

17. Have the participants been informed of the ECHO Study results?

The ECHO team moved quickly to ensure that participants were among the first stakeholders who were informed about the results. In the weeks leading up to the 13 June 2019 presentation of the results at the 9th South African AIDS Conference in Durban and their simultaneous publication in *The Lancet,* each site invited participants to return to the sites to learn about the results and ask questions. Site staff also called participants who were unable to attend those meetings, asking them if they would like to be informed of the results by phone and thanking them for their invaluable contributions to the study. Additional outreach will be conducted in the weeks following the public announcement to communicate the study results to other members of the study communities and give them opportunities to ask questions.

About the Study

18. How many women enrolled in the ECHO Study? And who was eligible to join the study?

A total of 7 829 sexually active HIV-negative women ages 16 to 35 years were enrolled and followed up in the ECHO Study. Women were eligible to join the study if they were seeking effective contraception, were willing to be randomly assigned to any of three contraceptive methods and did not want to become pregnant for the duration of the study. Women who had recently given birth had to be at least six weeks postpartum to be eligible to enrol. Another eligibility requirement was that participants intended to stay in the area for the duration of their participation in the study.

19. Did women younger than 18 enrol in the study?

Young women ages 16 and 17 years were eligible to join the study based on local and national regulations and guidance from ethics committees. Many of the young women in this age group who enrolled in the study were in Kenya, where a previously pregnant 16- to 17- year-old is considered a legally 'emancipated minor' and can give informed consent on her own. In the other ECHO countries, the informed consent of a parent or

legal guardian was required in addition to that of the minor participant. Although they were eligible and willing to participate in the study, many young women in this age group in Eswatini, South Africa and Zambia were not willing to advise their parents that they were sexually active.

20. How were participants recruited for the study?

Recruitment teams partnered with local organisations and conducted community outreach to introduce the study to potential participants, encouraging women who were interested in the study to visit the sites for more information. At the sites, educational sessions were held, and women received additional information that they could take home to learn more about the study before deciding whether to participate.

After a woman had decided that she wanted to participate, she sat with a staff member, and together they went through the informed consent form, discussing the aims of the study, the study procedures, and the risks and benefits of participation. This discussion was part of an informed consent process that continued during the trial. After a potential participant understood and had signed the informed consent form, screening tests and counselling were carried out. If the tests confirmed that the woman was eligible and if she still wanted to participate in the study, only then could she be enrolled.

21. What was the informed consent process?

Women participating in the trial engaged in a comprehensive informed consent process, conducted in their respective local languages, which involved multiple counselling sessions, testing of their understanding of the study before enrolment, reinforcement of the informed consent at each study visit, and documentation of written informed consent. In addition, after the WHO MEC categorisation for injectable contraceptive was changed in March 2017 (see question 14), the ECHO Consortium revised its informational materials and informed consent forms and discussed this change with each participant in the trial. The ECHO trial investigators respect and greatly appreciate the decisions made by the 7 829 women who chose to participate in the trial.

22. How did the ECHO Study work?

Women interested in joining the study learned about the study procedures and the risks and benefits of participation through an informed consent process. Study staff carefully explained how the study randomly assigned participants to receive one of three contraceptives. They also counselled each woman about all three methods to ensure she would be happy with any one of them. Extensive contraceptive counselling was provided before and after each woman was randomly assigned to a method. Women were told that they could leave the study at any time, could change their method to one of the other study methods or to any other contraceptive of their choice, or could stop using contraception.

Screening and enrolment occurred during separate visits to ensure that women had time to consider options and did not feel pressured to take part in the study or to start a method they did not want. Women who enrolled in the study and were randomly

assigned to a method were asked to visit the study clinic every three months. During these regular visits, they received counselling on contraception and HIV risk reduction and were assessed for pregnancy, HIV and other sexually transmitted infections (STIs), and side effects from the contraception. They were also asked limited questions about sexual behaviour (for example, about condom use and number of partners) and their experiences with the contraceptive method they were using.

23. How were the results of the ECHO Study analysed?

To analyse the study results, the researchers compared the number of women in each group who acquired HIV, became pregnant or experienced side effects that led them to stop using the contraceptive method to which they were randomly assigned. Data from each study group were compared with data from the other two study groups: DMPA-IM vs. copper IUDs, DMPA-IM vs. LNG implants and copper IUDs vs. LNG implants.

24. The study was designed to detect a 50 percent difference in HIV risk in any of the three comparisons of the three methods. How was that threshold determined?

The research protocol for the ECHO Study was designed over several years (2012-15) through an extensive consultative process and was updated during the course of the study (2015-18). In 2012, as the ECHO trial was being proposed, formative research was conducted to assess the level of difference in HIV risk associated with a contraceptive that would be likely to prompt changes in policies or programmes. This question was also among those discussed in meetings and teleconferences that the ECHO investigators convened with a range of stakeholders before and during protocol development. During this time, the observational data in aggregate suggested a possible 50 percent increase in HIV risk with use of DMPA-IM compared to no method, and an observational study published in 2011 had associated DMPA-IM use with a doubling (a 100% increase) in the risk of HIV acquisition. However, these observational data were considered to be of low quality and subject to substantial biases.

The stakeholders consulted included researchers with expertise in HIV prevention and contraception, policy and programme officials in Africa and globally, ethicists, and HIV advocates and women's health advocates from the African region and from other global networks. The ECHO Consortium also asked the Research Protocol Review Panel of WHO's Special Program of Research, Development, and Research Training in Human Reproduction and the Prevention Science Research Committee of the US National Institute of Allergy and Infectious Diseases, US National Institutes of Health, to conduct an independent scientific and ethical review of the protocol. Through these consultations and reviews, a 50 percent increase in HIV risk, proposed as the design for the trial by the study team, was determined to be most appropriate.

25. Did the study participants benefit directly from the study?

Participants received contraceptives and ongoing health services and care throughout the study, including STI screening and management. They received high-quality contraceptive services, with counselling and support for method continuation and management of side

effects. They also received counselling on HIV prevention and care and were offered pre-exposure prophylaxis (PrEP) either at the study site or through referrals.

26. Were participants compensated for expenses related to study participation?

Yes. Remuneration of participants was done in accordance with the requirements of local ethics committees to provide fair compensation without inducement.

27. How were the rights of participants in the ECHO Study safeguarded?

The ECHO Study was planned and conducted with careful attention to the rights and interests of participants. The trial began only after extensive scientific, ethical and community consultation (see question 24). Nine independent ethics review committees reviewed and approved the ECHO Study protocol. They included ethics committees in each of the countries where the study was conducted — the Kenya Medical Research Institute Scientific and Ethics Review Unit, the Swaziland Scientific and Ethics Committee for Ministry of Health and Social Welfare Research, the University of Cape Town Human Research Ethics Committee, the University of Witwatersrand Human Research Ethics Committee, and the University of Zambia Biomedical Research Ethics Committee — as well as the ethics committees of the World Health Organization, FHI 360, Columbia University and the University of North Carolina at Chapel Hill.

The motivation and driving force behind ECHO was a commitment to the health and well-being of women. At each of the 12 study sites, the conduct of the ECHO Study was monitored through a site-specific Good Participatory Practice plan designed to operationalize the GPP principles of respect, transparency, accountability and community stakeholder autonomy. Every site team worked closely with local community advisory boards (CABs), providing updated information about the trial and receiving feedback from the community and its representatives. The study's Global Community Advisory Group (GCAG), which included advocates for women's health and rights from each of the countries where the study was conducted, advised the ECHO Consortium on the study's protocol and its conduct before, during and after the trial was completed.

28. How did the study monitor the safety and well-being of study participants?

The study had several mechanisms for monitoring the safety of participants and implementation of the study. An independent Data and Safety Monitoring Board (DSMB) was responsible for reviewing all safety study data at regular intervals to ensure that participants' well-being was protected. If the DSMB members had had any safety concerns, they could have recommended that the study be modified or stopped. The study site investigators were responsible for continuous safety monitoring of all study participants and for alerting the safety monitor and protocol management team if unexpected concerns arose. The safety oversight committee reviewed safety data from all sites monthly and was available 24 hours a day, seven days a week to the sites for clinical

advice. In addition, independent clinical monitors visited each study site at regular intervals to evaluate whether the protocol was being properly implemented, whether safety issues had been reported, and whether the participants had provided consent to taking part in the study.

29. What happened if a participant acquired HIV during the study?

The well-being of the women enrolled in the study was the ECHO Consortium's highest priority. Researchers strove to reduce each participant's risk by providing condoms, HIV prevention counselling, STI treatment and PrEP as it became available in the four countries. Even so, because the rates of HIV are high in their communities, some women did acquire HIV during the study period. Women who acquired HIV during the study received counselling and were referred to local care providers for ongoing care and treatment. They were asked to remain in the study until completion of the follow-up period, which gave participants the opportunity to continue receiving services at the sites and allowed researchers to continue collecting data on the other study questions.

30. What happened to participants who became pregnant during the study?

Study staff provided care or referred for further care women who became pregnant, according to their wishes. If a pregnancy continued, the woman discontinued her assigned method but remained in the study, which gave her the opportunity to continue receiving services at the clinical site. If a pregnancy ended prior to completion of study follow-up, the woman was encouraged to resume her allocated method of contraception but was offered a choice of any method available at the study site. If a pregnancy continued beyond the end of the study, the woman was referred for further care of her pregnancy.

31. What happened to participants who wanted to switch to a different contraceptive method during the study?

The study team paid close attention to the eligibility criteria and conducted thorough counselling before enrolling women in the study, to ensure that participants were comfortable with random assignment to a method and were willing to continue using that method throughout the study. If a woman experienced side effects or concerns regarding her assigned method, she was advised to come to the clinic to discuss her questions and experience. Trained clinicians worked closely with participants to resolve any challenges.

Some women wished to switch to another contraceptive method despite receiving counselling and treatment for any side effects. Participants were free to change methods at any time during the study. If a participant preferred a non-study contraceptive method, she received that method either on site or by referral. All women who switched methods were asked to remain in the study and be seen according to the same schedule as other participants. Women who chose not to use any contraceptive method also continued to be followed according to the same schedule as all other participants.

32. What happened to study participants' contraception after their final study visits?

When a participant exited the ECHO Study, she was given the option to remain on the same contraceptive to which she had been randomly assigned at the beginning of the study. Any woman who wished to switch methods could have her study-assigned method removed (if she was assigned to an IUD or implant) and have any new method provided by the site at no cost. Participants who had been assigned to an IUD or implant who wished to stop using contraception could also have their devices removed. Referral links were established with local clinics to which participants could go for further contraceptive services after leaving the study.

33. Where were the trial sites?

The 12 trial sites were in four countries: Eswatini (formerly Swaziland), Kenya, South Africa and Zambia (see question 34 for full list of sites). These countries were selected because women in southern and eastern Africa continue to be among the hardest hit by HIV and maternal mortality. DMPA-IM is also the most widely used modern method of contraception in the region. It was important to work with affected communities to ensure the study provided evidence based on the population most in need of guidance on hormonal contraceptive use and any possible link with HIV acquisition.

34. Who conducted the ECHO Study?

Leading global and national institutions collaborated on the ECHO Study. The study was jointly sponsored by FHI 360, the Wits Reproductive Health and HIV Institute (WRHI) and the University of Washington, who coordinated the implementation. The World Health Organization collaborated on study management and leads stakeholder engagement in reviewing the evidence on hormonal contraception and HIV acquisition. Other partners include investigators from the Kenya Coast Provincial Hospital/International Centre for Reproductive Health, the Kenya Medical Research Institute, the University of Fort Hare and the University of Zimbabwe.

The following collaborating study site partners conducted the study.

In South Africa:

- Aurum Institute in Klerksdorp
- Desmond Tutu Foundation Emavundleni Research Centre in Cape Town
- Effective Care Research Unit in East London
- Madibeng Centre for Research in Brits
- MRU (MatCH Research Unit) in Durban
- MRU (MatCH Research Unit) in Pietermaritzburg
- Qhakaza Mbokodo Research Clinic in Ladysmith
- Setshaba Research Centre in Shoshanguve
- WRHI/University of the Witwatersrand in Johannesburg

In Kenya:

- KEMRI-RCTP Study Centre, Lumumba Health Centre, in Kisumu

In Eswatini:

- Family Life Association of Swaziland and ICAP-Columbia in Manzini

In Zambia:

- UNC Global Projects Zambia/Kamwala Clinic in Lusaka

35. When did the study begin, and when did it end?

The study began in December 2015, when two sites in South Africa started screening and enrolling participants. Full enrolment was achieved on 12 September 2017, and participant follow-up was completed on 31 October 2018. Data verification was completed and data analysis began in early 2019, and the results were announced at the 9th South African AIDS Conference in Durban, South Africa, on 13 June 2019.

36. How was the study funded?

The trial was made possible by the combined generous support of the Bill & Melinda Gates Foundation, the American people through the United States Agency for International Development and the President's Emergency Plan for AIDS Relief, the Swedish International Development Cooperation Agency as part of the EDCTP2 programme supported by the European Union, the South African Medical Research Council and the United Nations Population Fund. Contraceptive supplies were donated by the Government of South Africa and United States Agency for International Development.

37. How do the study contraceptives work?

All the contraceptives that were assessed in the ECHO Study are highly effective, reversible, private methods that can be used without interrupting sex.

DMPA-IM is given by intramuscular injection every three months and is slowly absorbed into the blood stream to prevent pregnancy. DMPA-IM contains a synthetic progestogen that acts like the hormone progesterone, which occurs naturally in a woman's body. It works primarily by preventing the release of eggs from the ovaries (ovulation) and by thickening the cervical mucus, which prevents sperm from moving into the uterus (womb) and fallopian tubes and meeting an egg. Once a woman stops using DMPA-IM, there may be a six- to nine-month delay before she is able to conceive.

The copper IUD is a small, flexible, plastic frame with copper sleeves or wire around it. Once inserted in the uterus, it provides contraceptive protection for 10-12 years but can be removed at any time. The copper IUD prevents pregnancy mainly by preventing fertilisation. Once an IUD has been removed, fertility returns quickly.

A levonorgestrel (LNG) implant consists of two thin, flexible rods that are inserted just under the skin of a woman's upper arm, where they continuously release low doses of the synthetic progestogen levonorgestrel into the bloodstream. Once inserted, the LNG

implant protects against pregnancy for up to five years but can be removed at any time. Like DMPA-IM, it works primarily by preventing ovulation and thickening the cervical mucus. Implants do not delay the return of a woman's fertility after they are removed. Women who stop using implants can become pregnant as quickly as women who stop using non-hormonal methods. (See additional information in the table below.)

Contraceptives used in the ECHO Study

Family Planning	DMPA-IM 	Levonorgestrel (LNG) Implant 	Copper IUD 
What it is	DMPA-IM, or Depo Provera, is the most widely used progestogen-only injectable. It is injected deep into the muscle of the upper arm, buttocks or hip.	The LNG implant consists of 2 thin, flexible rods filled with a progestogen (levonorgestrel) that are inserted just under the skin of a woman's upper arm.	The copper-bearing intrauterine device is shaped like a 'T' and is the size of a matchstick. It is made of soft but strong plastic with copper bands and has a 'tail' made of 2 strings. A doctor or nurse places it in the womb.
Frequency	Given every 3 months	Once inserted, lasts up to 5 years; can have it removed at any time	Once inserted, lasts up to 10–12 years; can have it removed at any time
Benefits	• Long-acting and privacy of use • No interruption of sex • Often stops monthly periods • Can be used during breastfeeding • Protects against endometrial cancer (cancer of the lining of the uterus) and uterine fibroids • May protect against iron-deficiency anaemia	• Long-acting and privacy of use • No interruption of sex • May stop monthly periods while being used • Can be used during breastfeeding • Protects again symptomatic pelvic inflammatory disease • May protect against iron-deficiency anaemia	• Long-acting and privacy of use • No interruption of sex • Can be used during breastfeeding • May protect against endometrial and cervical cancer • Reduces risk of ectopic pregnancy
Side Effects	Most users report irregular or prolonged menstrual bleeding initially, followed by infrequent, irregular or no bleeding, Some users report: • Weight gain • Headaches • Dizziness • Abdominal bloating and discomfort • Mood changes • Reduced sex drive	Some users report: • Lighter, irregular, infrequent, prolonged or no menstrual bleeding initially, followed by infrequent, light, irregular or no bleeding • Headaches • Mood changes • Dizziness • Acne (can improve or worsen) • Breast tenderness • Nausea • Abdominal pain • Weight changes	Some users report: • Heavier and longer menstrual bleeding and more cramps and pain during monthly bleeding, especially in the first 3–6 months of use • Irregular bleeding during the first 1–2 months after insertion.
Return of Fertility	• Return of fertility is often delayed by 6–9 months after the last injection.	• Rapid return of fertility once removed	• Rapid return of fertility once removed

Source: World Health Organization (WHO) Department of Reproductive Health and Research and Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs (CCP). Family Planning: A Global Handbook for Providers (2018 update). Baltimore and Geneva: CCP and WHO; 2018. Available at: http://www.who.int/reproductivehealth/publications/fp-global-handbook/en.