

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

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About the ECHO Study

1. What is the ECHO Study?

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Study is an open-label randomised clinical trial comparing three highly effective, reversible methods of contraception—the progestogen-only injectable depot medroxyprogesterone acetate (DMPA), a progestogen implant called Jadelle and the copper IUD—to evaluate whether there is any difference in the risk of HIV acquisition among women using these methods. The study will also compare side effects, pregnancy rates and women’s patterns of use for the three contraceptive methods.

2. Why is the ECHO Study needed?

More than 150 million women worldwide use various hormonal contraceptives, including progestogen-only contraceptives such as injectables, for family planning. In sub-Saharan Africa, progestogen-only injectable contraceptives are the most commonly used method. Over the past 25 years, as the HIV epidemic took hold in many countries, a number of observational studies explored whether or not hormonal methods increase the risk of HIV acquisition. No association between combined hormonal contraceptive methods—which include the use of two hormones (estrogen and progestogen) to prevent pregnancy from occurring—and HIV acquisition has been shown. For women using progestogen-only injectables, the cumulative evidence from observational studies indicates a possible increased risk of HIV acquisition (particularly with DMPA), but it is uncertain whether there is a causal relationship, as opposed to just an observed association, due to the methodological limitations of these studies. Few studies have examined whether hormonal implants or intrauterine devices (IUDs) affect users’ risk of HIV acquisition. (See [Background](#) for additional information.)

Given the widespread use of DMPA in areas of high HIV incidence, the question of whether DMPA increases women's risk of HIV is a critical public health issue requiring the strongest evidence possible. Women need to know whether the use of DMPA or highly effective alternatives to DMPA affects their risk of acquiring HIV so they can make informed choices about contraception. ECHO will provide high-quality information about contraceptive risks and benefits that women can use in making contraceptive decisions, that healthcare providers will use for contraceptive counselling, and to inform policy-makers' decisions for programmes.

3. What is the status of the ECHO Study?

The ECHO Study began enrolling participants in December 2015, with a plan to enrol 7 800 women. The study reached this target on 29 August 2017 and officially closed enrolment on 12 September 2017 with a total of 7 830 participants at 12 sites in South Africa, Kenya, Swaziland and Zambia. Results are expected in 2019.

The trial's independent Data and Safety Monitoring Board (DSMB) has met five times, most recently in March 2017, to conduct planned periodic reviews of data from the study and performance metrics such as enrolment, retention and method refusal rates. After each review, the DSMB reaffirmed the continued need for ECHO and its ongoing equipoise and recommended that the study continue. (See question #11 for further details.)

4. How do the latest changes to the WHO guidelines on the use of hormonal contraception for women at high HIV risk affect the ECHO Study?

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 for progestogen-only injectables for women at high risk of HIV from 'can use without restriction' (Medical Eligibility Criteria 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 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 over whether the use of these methods *causes* increased risk; and 3) how to minimise their risk of acquiring HIV.

5. What does the WHO guidance say about the ECHO Study?

The WHO recommendations reaffirm the need for randomised clinical trials, such as ECHO, to determine whether there is a causal relationship between hormonal contraceptive use and the risk of HIV acquisition.

6. How was the change in the WHO guidance communicated to ECHO Study participants?

The ECHO team is fully committed to ensuring all study participants are kept informed about any updates in the science and guidelines. All study materials, including outreach and recruitment materials and the informed consent form, were updated to reflect the change in the WHO guidelines on DMPA. These revisions were reviewed by local ethics committees (institutional review boards). All women interested in joining ECHO were informed about the new WHO guidance by trained staff as part of the recruitment and informed consent process. Women already enrolled in the ECHO Study were also informed about the new guidance, and counsellors were equipped to answer any questions they had. (See [How the Study Works](#), questions #14–15)

7. What data will the ECHO Study produce, and how will the data be used?

The primary findings will be the comparative risk of HIV acquisition among the three contraceptive methods studied. This information will be published and submitted to WHO for review of its contraceptive guidance. WHO's contraceptive guidance is used worldwide by programme managers, policy-makers and clinicians. The study team is committed to ensuring that study participants and other women at high risk of HIV, as well as other stakeholders, have timely access to the information provided by the study. Results will also be presented to national and international policy-makers, scientists and advocates.

Background of the ECHO Study and Implications for the Field

8. What are the origins of the ECHO Study?

In February 2012, a World Health Organization expert group met to review all the available data on hormonal contraception and HIV risk. The group found that the information on combined oral contraceptive pills was reassuring, but the data on the safety of progestogen-only injectables were inconclusive, with some but not all studies showing an increased risk of HIV acquisition. These data came from observational studies and secondary analyses that are subject to bias and other limitations, making it difficult to interpret the data. The group concluded that there was an urgent need for further research carefully designed to show whether or not use of progestogen-only injectables increases the risk of HIV acquisition—a conclusion that was reaffirmed in 2014 and 2017.

9. What are the current data available? What does the evidence say?

Research on hormonal contraceptive (HC) use and risk of HIV acquisition has yielded mixed results. The most recent data are from a systematic review¹ commissioned by the World Health Organization to analyse studies published from 15 January 2014 to 15 January 2016 and to synthesise the results with those from a previous systematic review.²

The updated systematic review found that most of the data for oral contraceptive pills, injectable norethisterone enanthate (NET-EN) and levonorgestrel implants do not suggest an association with HIV acquisition, though data for NET-EN and especially implants are very limited. Data are also very limited on the copper intrauterine device (IUD), and no data are available on whether contraceptive rings or patches, combined injectables or levonorgestrel IUDs affect the risk of HIV acquisition.

Some studies suggest increased risk of HIV acquisition among users of DMPA. Data from recent studies included in the latest systematic review strengthen concerns about a possible increased risk of HIV acquisition associated with DMPA use.¹ After reviewing the evidence, a WHO technical consultation concluded that the available evidence continues to indicate an association between use of progestogen injectables and an increased risk of acquiring HIV; however, it is unknown whether the associations seen in these observational studies were due to a true biological effect or the limitations of such studies.

10. What are the limitations of the studies on the potential link between DMPA use and HIV risk?

All the studies have been observational studies, in which women choose which contraceptive methods they use. Women who choose to use DMPA may be different from women who do not use DMPA—particularly those who do not use contraception at all—in important ways that affect their risk of HIV and are difficult to measure. (See #12.) The WHO statement notes that ‘data from observational studies come with a high level of uncertainty’ and calls for randomised clinical trials to provide better information about possible causality.

11. What are the implications of these findings for the ECHO Study?

ECHO is a randomised controlled trial (RCT) designed to address the long-standing concern in the public health community of a possible association between hormonal contraception (especially

¹ Polis CB, Curtis KM, Hannaford PC, et al. An updated systematic review of the epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. *AIDS* 2016; **30**(17): 2665-83.

² 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**: 360-90; Polis CB, Curtis KM. Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence. *Lancet Inf Dis* 2013; **13**: 797-808.

DMPA) and the risk of HIV acquisition. On 2 March 2017, the ECHO Study's DSMB met and agreed that the results of the updated systematic review and the new WHO guidance underscore the need for an RCT that will yield higher-quality evidence than the available data from observational studies. The DSMB members also weighed the data and potential risk with the benefits of injectable contraception, along with the ease and acceptability of use, and concluded that the ECHO trial is in equipoise. This means there is scientific uncertainty about methods. Importantly, ECHO is designed to assess the relative risks and benefits of alternative contraceptive methods—the levonorgestrel implant and the copper IUD—compared to DMPA and to each other. The recent systematic review includes very little data to weigh whether implants and IUDs are better alternatives to DMPA with respect to HIV or other risks and benefits.

12. Why is a randomised study needed?

Randomised clinical trials are considered the gold standard in producing reliable scientific evidence about the effect of a medical intervention. 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 groups of women who are randomly allocated by computer to use one of the study methods. 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.

How the Study Works

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

A total of 7 830 sexually active HIV-negative women ages 16 to 35 years enrolled 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 the study groups and did not want to become pregnant for the duration of the study. Women who had recently given birth also 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.

Young women ages 16 and 17 years were eligible to join the study upon approval based on local and national regulations and the relevant ethics committee's guidance. Where required, as in South Africa, the study sought the informed consent of a parent or legal guardian in addition to that of the minor participant. In other countries, such as Kenya, a previously pregnant 16- to 17- year-old is considered a legally 'emancipated minor'; in these instances, informed consent was sought directly from the young woman.

14. How were participants recruited for the study?

Recruitment teams partnered with local organisations and conducted community outreach events to introduce the study to potential participants. They handed out flyers, gave health talks and encouraged women who were interested in the study to visit the local study site for further 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 decided that she wanted to participate, she engaged in an informed consent process. Each potential participant sat with a counsellor, and together they went through the informed consent form, discussing why the study was being conducted, the aims of the study, the study procedures, and the risks and benefits of participating. After the 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.

15. How does 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. Counsellors carefully explained how the study randomly assigned participants to receive one of three contraceptives: DMPA, a hormonal implant containing levonorgestrel or the copper IUD. They counselled each woman to ensure she would be happy with any of the three study methods. Screening and enrolment occurred during separate visits to ensure that each woman had time to consider her options and did not feel pressured to take part in the study or to start a method she did not want.

Women who enrolled in the study and were randomly assigned to a method are asked to visit the study clinic every three months. During these regular visits, they receive counselling on contraception and HIV risk reduction and are assessed for pregnancy, HIV and other sexually transmitted infections (STIs), and side effects from the contraception. They are also asked limited questions about sexual behaviour (for example, about condom use and number of partners) and their experiences with the contraceptive method they are using. Women assigned to receive injectable contraception are given injections according to the product's dosing schedule.

To analyse the study results, the researchers will compare 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.

16. Do the study participants benefit directly from the study?

All participants receive contraceptives and ongoing health services and care throughout the study. All participants also receive counselling on HIV prevention and care, as well as screening and treatment for sexually transmitted infections, and are offered pre-exposure prophylaxis (PrEP) either at the study site or through referrals.

17. Do participants have the option to receive antiretroviral pre-exposure prophylaxis (PrEP)?

The ECHO Study is committed to providing the highest standards of HIV prevention services to participants as recommended by Good Participatory Practice guidelines. Participants interested in antiretroviral pre-exposure prophylaxis (PrEP) have been referred to services as programmes 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 PrEP, the ECHO Study moved quickly to incorporate the offering of PrEP at the study sites in South Africa. PrEP continues to be available through referral at all ECHO sites; in addition, all South Africa ECHO sites offer PrEP on site.

18. Where is the study being conducted?

The ECHO Study is being conducted at 12 trial sites in four countries: Kenya, South Africa, Swaziland and Zambia (see next question for full list of sites). These countries were selected because women in southern and East Africa continue to be among the hardest hit by HIV and maternity mortality. DMPA is also the most widely used modern method of contraception in the region. It is important to work with affected communities to ensure the study provides evidence based on the population most in need of guidance on hormonal contraceptive use and any possible link with HIV acquisition.

19. Who is conducting the ECHO Study?

Leading global and national institutions are collaborating on the ECHO trial. The study is jointly sponsored by FHI 360, the Wits Reproductive Health and HIV Institute (WRHI) and the University of Washington, who are coordinating to implement the trial. The World Health Organization collaborates in 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.

Collaborating study site partners include: in South Africa, the Aurum Institute in Klerksdorp, the Desmond Tutu Foundation Emavundleni Research Centre in Cape Town, the Effective Care Research Unit in East London, the Madibeng Centre for Research in Brits, Maternal, Adolescent and Child Health (MatCH) Research in Durban and Pietermaritzburg, the Qhakaza Mbokodo Research Clinic in Ladysmith, the Setshaba Research Centre in Shoshanguve and WRHI/University

of the Witwatersrand in Johannesburg; in Kenya, the KEMRI-RCTP Study Centre, Lumumba Health Centre, in Kisumu; in Swaziland, the Family Life Association of Swaziland and ICAP-Columbia in Manzini; and in Zambia, the UNC Global Projects Zambia/Kamwala Clinic in Lusaka.

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

The study began in December 2015, when two sites in South Africa started screening and enrolling participants. Enrolment was completed on 12 September 2017, and the total duration of the study in the field will be approximately 36 months from first enrolment. Data analysis will begin in early 2019, and results are expected in 2019.

21. How is the study funded?

A consortium of donors is funding the study. They include the Bill & Melinda Gates Foundation, the US Agency for International Development (USAID), the Swedish International Development Cooperation Agency (SIDA), the United Nations Population Fund (UNFPA) and the Medical Research Council of South Africa. In addition, USAID and the South African government are donating the contraceptives used in the study.

22. What approvals were required for this study?

The ECHO Study was reviewed and approved by the institutional review board (IRB) of FHI 360 and by local research ethics committees in the countries where it is being conducted. In addition, national regulatory authorities, including the South African Health Products Regulatory Authority (formerly the Medicines Control Council) and Kenya's Pharmacy and Poisons Board, were notified of the study.

23. Who oversees the study?

Several groups together oversee the ECHO Study. A stewardship committee composed of the funders oversees the ECHO Consortium, and their main role is to assure the financial resources and operational milestones of the trial. A management committee provides overall accountability of the ECHO Study, including meeting the timelines and major trial milestones; the management committee includes representatives from the three organisations sponsoring the study (FHI 360, WRHI and the University of Washington). Finally, the implementation team is responsible for overseeing the implementation of the protocol and has final responsibility for trial conduct, including Good Clinical Practice (GCP), quality assurance and regulatory oversight.

In addition, an independent Data and Safety Monitoring Board (DSMB), comprised of global experts in reproductive health, HIV and biostatistics, oversees the well-being of participants. The DSMB reviewed the protocol before the study began and conducts regular reviews of the study data. The DSMB can recommend modifying or stopping the study if there is a safety concern, or if a reliable result is unlikely by the end of the study. This could happen in the event of low

enrolment, low contraceptive continuation, poor retention or other potential operational challenges.

24. How does the study monitor participants' safety and well-being?

The study has several mechanisms for monitoring the safety of participants and implementation of the study. An independent Data and Safety Monitoring Board (see #23) is responsible for reviewing all safety study data and ensuring that participants' well-being is protected. If the DSMB members have safety concerns, they can recommend that the study be modified or stopped.

The study site investigators are responsible for continuous safety monitoring of all study participants and for alerting the safety monitor and protocol management team if unexpected concerns arise. The safety oversight committee reviews safety data from all sites monthly and is available 24-7 to the sites for clinical advice.

25. What happens if a participant acquires HIV during the study?

The well-being of the women enrolled in the study is the ECHO Consortium's highest priority. ECHO researchers do their best to reduce each participant's risk by providing condoms and HIV prevention counselling. Even so, because the rates of HIV are high in their communities, some women are likely to acquire HIV during the study period.

Women who seroconvert during the study receive counselling and are referred to local HIV care providers for on-going care, including assessment of CD4 cell counts and antiretroviral treatment according to local guidelines. They are asked to remain in the study until completion of the follow-up period. This gives participants the opportunity to continue receiving services at the clinical site and allows researchers to continue collecting data relevant to the additional study questions.

26. What happens to participants who become pregnant during the study?

Study staff provide care or refer for further care women who become pregnant, according to their wishes. If a pregnancy continues, the woman discontinues her assigned method but remains in the study to the end of the follow-up period, which gives her the opportunity to continue receiving services at the clinical site. Should a pregnancy end prior to completion of study follow-up, the woman will be encouraged to resume her allocated method of contraception but will be offered a choice of any method available at the study site. If a pregnancy continues beyond the end of the study, the woman will be referred for further care of her pregnancy.

27. What happens to participants who want to switch to a different contraceptive method during the study?

The study team pays close attention to the eligibility criteria and conducts thorough counselling before enrolling women in the study, to ensure that participants are comfortable with random assignment to a method and are willing to continue using that method throughout the study. If a woman experiences side effects or concerns regarding her assigned method, she will be advised to come to the clinic to discuss her questions and experience with the method. Trained clinicians work closely with participants to resolve any challenges faced.

Some women may wish to switch to another contraceptive method despite receiving counselling and treatment for any side effects. Participants are free to change methods at any time during the study. If a participant prefers a non-study contraceptive method, she will receive that method either on site or by referral. All women who switch methods remain in the study and are seen according to the same schedule as other participants. Women who choose not to use any contraceptive method also continue to be followed according to the same schedule as all other participants.

28. What will happen to study participants' contraception when the trial is over?

When a participant exits the ECHO Study, she is given the option to remain on the same contraceptive to which she was randomly assigned at the beginning of the study. Any woman who wishes to switch methods can 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 wish to stop using contraception can also have the device removed.

29. How is the operational feasibility of the study being monitored?

As with all clinical trials, the ECHO Study has a set of challenges which are being monitored closely. One anticipated challenge was whether women would accept randomisation. Several studies had successfully randomised women to use either an IUD or an injectable contraceptive.³ The ECHO Study team took great care to ensure women were properly selected and counselled appropriately, which has resulted in very few participants refusing to start the method to which they were assigned.

³Hubacher D, Raymond ER, Beksinka M, et al. Hormonal contraception and the risks of STI acquisition: results of a feasibility study to plan a future randomized trial. *Contraception* 2008; **77**: 366–70; Feldblum PJ, Caraway J, Bahamondes L, et al. Randomized assignment to copper IUD or depot-medroxyprogesterone acetate: feasibility of enrollment, continuation, and disease ascertainment. *Contraception* 2005; **72**: 187–91; Hofmeyr J. A randomized trial of DMPA and the Cu-IUD. Presented at the WHO Expert Group to Examine Hormonal Contraception and HIV. Geneva: January 31, 2012.

Method continuation is also critical to the success of the trial, because a high percentage of women must continue their assigned methods to ensure sufficient statistical power to detect any differences in HIV acquisition among the groups. To promote and support method continuation, study staff received intensive training in contraceptive method delivery and management, and women were carefully screened prior to study entry. The study sites are closely monitored to ensure that the study team responds quickly if retention is low or contraceptive discontinuation rates are higher than anticipated. This monitoring will allow the study leadership to intervene with sites that have difficulty in the conduct of the study, and to modify or discontinue the study if required.

About the Products

30. How do the contraceptives being tested work?




DMPA is given by injection every three months and is slowly absorbed into the blood stream to prevent pregnancy. DMPA 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 penetrating into the uterus (womb) and fallopian tubes and meeting an egg. Once a woman stops using DMPA, there may be a six- to nine-month delay before she is able to conceive.

Levonorgestrel implant (Jadelle) 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, Jadelle protects against pregnancy for up to five years but can be removed at any time. Like DMPA, 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 non-hormonal methods.

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 the IUD is removed, fertility returns quickly.

All the contraceptives being tested in the ECHO Study are highly effective, long-acting, reversible, private methods that do not interfere with sex.

Contraceptives used in the ECHO Study

Family Planning	DMPA 	Levonorgestrel Implant (Jadelle) 	Copper IUD 
What it is	Depot medroxyprogesterone acetate, also known as DMPA 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.	This 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	<ul style="list-style-type: none"> • Long-acting and privacy of use • No interference with 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 	<ul style="list-style-type: none"> • Long-acting and privacy of use • No interference with sex • May stop monthly periods while being used • Can be used during breastfeeding • Protects against symptomatic pelvic inflammatory disease • May protect against iron-deficiency anaemia 	<ul style="list-style-type: none"> • Long-acting and privacy of use • No interference with 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: <ul style="list-style-type: none"> • Weight gain • Headaches • Dizziness • Abdominal bloating and discomfort • Mood changes • Reduced sex drive 	Some users report: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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 to Fertility	<ul style="list-style-type: none"> • Return of fertility is often delayed by 6–9 months after the last injection. 	<ul style="list-style-type: none"> • Rapid return to fertility once removed 	<ul style="list-style-type: none"> • Rapid return to 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>.