TOPLINE STUDY RESULTS

• The overall rate of new HIV infections per year was high: 3.8 percent.
• The ECHO study found no substantial difference in the risk of getting HIV among 7,829 women randomly assigned to use one of three reversible, highly effective contraceptives: DMPA-IM, copper IUD and LNG implant.
• All three methods were safe and highly effective at preventing pregnancy. When women were using their contraceptive method, only about one percent of participants became pregnant over the course of one year.

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) study assessed the impact of three different contraceptive options on women’s HIV risk. The results, released on June 13, 2019, are of major significance to women and girls—especially in East and Southern Africa—providers, policy makers, funders and advocates.

This document is designed to help advocates understand some of the key issues related to the ECHO study, the questions it was designed to answer, its findings and next steps.

As we discuss below, the ECHO trial did not find substantial differences in HIV risk among women using three different contraceptive methods. For some readers, this might seem like good news. But as we and the advocates who have led this work in Africa have said in the months and years prior to the result: ECHO must prompt action. Overall, HIV infection rates among the study population were almost 4 percent. Now is the time for investment in woman-centered programs that offer a full range of contraceptive choices and HIV prevention strategies at the same site, and through an approach that is centered on women’s informed choice. The women who made the trial possible deserve nothing less.

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Understanding the Results of the ECHO Study

What are the topline findings?

The ECHO study did not find any substantial difference in HIV risk among women using the three methods studied: DMPA-IM, the copper IUD and LNG implant. Not very many women used oral pre-exposure prophylaxis, or PrEP, for HIV prevention during the trial. Women who used DMPA-IM reported more condom use and fewer partners. These choices don’t seem to have made a difference in HIV risk.

All of the contraceptive methods tested were safe, effective and acceptable. The majority of women stayed on the method that they were assigned to use. Very few became pregnant while they were using their method.

There were high HIV incidence rates in all three arms of the trial. This does not mean that the methods increased women’s risk. These incidence rates are comparable to those seen in young women in these countries in many

What is the ECHO trial?

The Evidence for Contraceptive Options and HIV Outcomes Study, or ECHO, was designed to evaluate the risk of acquiring HIV in HIV-negative women who used depot medroxyprogesterone acetate-intramuscular (DMPA-IM), also known as Depo-Provera, the copper intrauterine device (Cu-IUD) or a levonorgestrel (LNG) implant, also known as Jadelle. The trial also compared pregnancy rates among women using these methods, documented rates of method discontinuation and switching, and thus provides a valuable body of evidence about the acceptability of these methods among African women.

Why did the study happen?

Many women at risk for HIV are also concerned about avoiding or postponing pregnancy.

Some research has suggested that specific injectable contraceptives (e.g., progestogen-only DMPA-IM, also known as Depo-Provera) might increase women’s risk of acquiring HIV, while other studies have not suggested this link between DMPA-IM and HIV risk. Very little is known about other methods and their relationship to HIV risk. This study was designed to gather high quality information about how different methods affected risk, whether increasing or possibly decreasing it. The trial also sought to learn more about effective counseling messages and the acceptability of methods not widely used in trial countries.

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1 Throughout this document, “women and girls” refers specifically and exclusively to cisgender women and girls in all their diversities. Data on transgender women, hormonal contraception and HIV risk are not available.

2 The World Health Organization (WHO) identifies this “theoretical or possible risk” in its current classification of three products: DMPA-IM, NET-EN (another injectable that uses a different hormone from DMPA) and DMPA-subcutaneous, also known as DPMA-SC or Sayana Press, which contains the same hormone as DMPA-IM but uses a different, simpler injectable delivery method.
II ECHO Results: In-depth

How did the trial work?

The trial enrolled 7,829 HIV-negative women in eSwatini (previously Swaziland), Kenya, South Africa and Zambia who were sexually active, HIV-negative, ages 16-35, seeking highly effective contraception and willing to be randomly assigned to use one of three contraceptive methods. The study had three “arms”, each testing a different method. All of the women who enrolled in ECHO went through an informed-consent process at the start of the trial and agreed to be randomly assigned to use one of three contraceptive methods: DMPA-IM, the copper IUD or the LNG implant. Participants had HIV tests every three months at study visits and were referred to HIV treatment facilities if they were found to be HIV-positive. All of the women received counseling about HIV risk reduction and the risks and benefits of the study contraceptive method they were assigned to and, where available, were offered oral pre-exposure prophylaxis (PrEP) for HIV prevention either at a study site or through a referral. But oral PrEP was only introduced into the trial late in the process, depending on when countries approved PrEP for use. When taken correctly and consistently, daily oral PrEP—a single pill containing a tenofovir-based drug—dramatically reduces the risk of HIV acquisition in women and men.

What do the results mean?

The level of HIV risk among eSwatini, Kenyan, South African and Zambian women in the trial was notably high. The majority of the participants were under 25 years old and were not identified as at high risk for HIV—but were simply sexually active and seeking contraception. The results are a clear call for contraceptive programs that offer additional method choices, including DMPA-IM for women who want to start or continue it, along with comprehensive HIV prevention interventions. In the trial, acceptance of contraceptive methods not widely available in some trial countries was high, bolstering arguments for method mix. The new information from ECHO should be used to improve counseling, expand method choices and rapidly and urgently integrate HIV prevention and treatment with contraceptive programs.

Who should act?

The World Health Organization (WHO), in its capacity as a normative agency, can take steps to communicate the implications of this trial for both contraceptive programming and, importantly, for every stakeholder concerned about the health and well-being of women in sub-Saharan Africa.

Governments, providers, women and communities must use the ECHO study results to update policies and improve programming and messages about contraceptive choices and any associated risks.

ECHO shows that HIV prevention and treatment must be located with contraceptive services because expanding contraceptive access with integrated HIV prevention will reach women—especially young women—who are at high risk of HIV.
the option to leave the study or to discontinue the method at any time). The trial site staff also didn’t get to choose which women used which method, since there can be bias among providers as well. The assignment was by chance and truly random.

**Is incidence (the number of new infections in a year) among women using method X higher, lower or the same as women using methods Y or Z?**

The rate of new cases of HIV, also called the incidence rate, was calculated by looking at the percentage of women who acquired HIV during the study period. Incidence is the percentage of women in the study arm who contracted HIV during the course of the trial. The trial compared incidence across the three arms to answer the question.

**Does one (or more) of the methods evaluated increase women’s risk of HIV compared to the other methods in the trial?**

In order to answer this question, the ECHO study team used statistical tools and calculations to determine whether the differences, if any, were significant.

**What were the results?**

397 HIV infections occurred (3.81 per 100 woman-years) overall in the study:

- 143 in the DMPA-IM arm, for an incidence of 4.19 per 100 woman-years
- 138 in the copper IUD arm, for an incidence of 3.94 per 100 woman-years
- 116 in the LNG implant arm, for an incidence of 3.31 per 100 woman-years

ECHO used statistical analysis to compare the incidence rates among women in the different arms. They did this to see if the small differences in numbers of HIV infections translated into a real difference in HIV risk related to the contraceptive method women were using. They concluded there were no real differences.

**What primary questions did the trial answer?**

**What are the relative rates of new cases of HIV among HIV-negative women randomly assigned to either DMPA-IM, the copper IUD or the LNG implant?**

“Relative” here means “compared to”. “Randomly assigned” or “randomized” means that women did not get to choose their methods (though they could decide not to participate in the study if they didn’t like the method to which they were assigned, and they did have
This conclusion was based on the calculation of a hazard ratio (HR). A ratio is a comparison of two values. A hazard ratio compares the risk (or chance) of a certain event happening in two groups of people.

In ECHO, the “event” is HIV infection, and the primary difference between the groups of women was which contraceptive method they were using. These are the ECHO trial hazard ratios:

<table>
<thead>
<tr>
<th>Method Comparison</th>
<th>HR</th>
<th>96% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPA-IM vs. Copper IUD</td>
<td>1.04</td>
<td>0.82-1.33</td>
</tr>
<tr>
<td>DMPA-IM vs. LNG Implant</td>
<td>1.23</td>
<td>0.95-1.59</td>
</tr>
<tr>
<td>Copper IUD vs. LNG Implant</td>
<td>1.18</td>
<td>0.91-1.53</td>
</tr>
</tbody>
</table>

A hazard ratio of 1.0 means that there is no difference between two groups. (For a primer on statistical terms that are used in research findings, check out AVAC’s Advocates’ Guide to Statistical Terms.)

The ECHO study was designed to look for a 50 percent increase in HIV risk (a hazard ratio of 1.5) between any pair of study arms. A smaller increased risk, of less than 30 percent (a hazard ratio of less than 1.5) would not have been seen with statistical precision. This “precision” is quantified as the level of statistical significance, which measures the confidence that the result is a real finding and not a coincidence.

None of the differences between the trial arms, as indicated by the hazard ratios above, are statistically significant. Significance is always given with a confidence interval (CI). A 96 percent confidence interval—seen in the parentheses after the results above—includes a numerical range. There is at most a 4 percent likelihood that the true result falls outside of the range. The narrower the confidence interval, the stronger the chance that a result is real. In ECHO, the confidence intervals around the hazard ratio calculations are wide.

When the confidence interval of a hazard ratio crosses 1.0, as it did for each of the ratios above, this means that there is no difference between two groups. In other words, there is no evidence of a real difference in risk of HIV between women in the different ECHO study arms.

Bottom line: Every part of a trial result matters—and ECHO is no exception. Advocates will need to work together to ensure that all parts of the finding are understood and prompt action.

There was no substantial difference in the risk of HIV across the study arms. So why is this result still so important?

The ECHO trial is among the most closely watched trials in recent memory. It sits at the intersection of HIV, contraception, sexual and reproductive health and human rights. These are politicized fields with complex histories. History—personal history in terms of side effects, rumors and research, as well as political history in terms of the ways that governments have sought to control women’s bodies over the years—is the backdrop for any trial result. The ECHO study tells us that women who have no other risk factor for HIV other than being sexually active and wanting contraception have high rates of HIV. These women may not be attending or seeking HIV prevention services. HIV prevention has to come to them. The trial tells us that women in these four countries want and will use different contraceptive methods. These methods need to end up on the shelves of clinics in East and Southern Africa. The trial tells us that DMPA-IM does not increase women’s risk. But it should not be women’s sole option for a long-acting, discrete option. Women want choices, including short-acting contraception and HIV prevention.

What can we learn from ECHO?

Some of the methods tested in ECHO aren’t widely used in the trial countries, so this trial provides information about women’s response to different methods, and the side effects and safety. The trial also provides information on how many women stopped using their assigned method during or at the end of the study, and a comparison of how many women became pregnant in each study arm. Biological (e.g., blood and tissue) samples gathered from women were also used to understand how these contraceptive methods affected their bodies and whether any changes affected HIV risk.
**Bottom line:** This information contributes to understanding patterns of method use and will support expanded method choice in contraceptive programs. No matter what, expanding the range of methods available and ensuring informed decision-making must be a priority.

**What questions does ECHO not answer?**

ECHO does not answer questions about methods that were not evaluated in the trial, such as the Implanon and Nexplanon implants, hormonal IUDs, contraceptive vaginal rings, etc.

ECHO did not evaluate other progestogen-only injectables, notably DMPA-subcutaneous (also known as DMPA-SC or Sayana Press) or NET-EN. However, these methods are currently grouped together with DMPA-IM in the WHO classification system. WHO will be reviewing these classifications. Information gathered from the ECHO trial and previous research on possible biological mechanisms related to risk could be used by WHO during the review process. Now that the ECHO results are published, WHO will convene a Guideline Development Group to review the evidence and determine whether to publish separate recommendations for DMPA-IM, DMPA-SC and NET-EN.

ECHO did not answer how any of the three study methods affect HIV risk compared to no method. There was no “control” arm in the trial. A control arm in a trial might be an effective standard method or could be an inert substance that looks identical to the thing being tested. To be eligible to participate in ECHO, women had to be seeking effective contraception. It would not have been ethical to randomly assign women seeking effective contraception to no method at all, and information about HIV risk among women in a control group wouldn’t have added clarity to counseling messages for existing effective methods. Instead, ECHO compared three highly effective contraceptive methods. All contraceptives impact the vaginal environment and genital tract. This includes long- and short-acting methods and condoms. There isn’t a contraceptive method that can be considered “inert”. All of the women in ECHO received a contraceptive method that had some impact on their bodies.

**Bottom line:** ECHO results do not provide an answer about what countries, programs or individuals should do. It provides information that should prompt, inform and guide action by all stakeholders.

### III Next Steps

**Now that the results are out, what can we expect from WHO—and what can we hold it accountable for?**

WHO released a statement immediately after the results were released. This is not a policy or guidance document; it can be used to provide context for countries and other stakeholders regarding the next steps, including its convening of a panel of experts to review existing guidelines and propose any updates based on the ECHO results.

WHO should urge countries to continue with key activities that had already started, in anticipation of the trial, to explore how to integrate HIV prevention and contraceptive services. These services must be woman-centered, grounded in informed choice and youth-friendly.

**What should countries do—and be held accountable for?**

Many countries in the regions where these data are most relevant base their national guidelines and programs on WHO guidance, so they may wait for this process to be complete before updating national documents on the use of contraceptive methods. However, there are steps that can and should be taken before WHO guidance is updated:

- ECHO provides valuable information about the safety and acceptability of methods that are not widely used in many trial countries. This information should be used to push for policies, investment and programs
that expand method mix (the number of contraceptive methods available to a woman at her program or provider) and to improve provider training and messaging.

- ECHO provides information about HIV risk among women of different ages and backgrounds in the region. This information should be used to inform and expand integrated services providing contraception, PrEP, HIV prevention counseling, HIV treatment and more.

- The results should start conversations among stakeholders who often work in siloes—e.g., in HIV prevention or treatment versus programs focused on sexual and reproductive health. ECHO should be a catalyst to create new multidisciplinary forums or expand existing ones so that the many choices facing women are better understood and addressed.

What should happen after WHO guidance is released?

Updated WHO guidance should prompt swift review at the national level of relevant policies, programs and procurement strategies. International donors, funders and implementers—including FP2020, PEPFAR, Global Fund, UNFPA and the She Decides initiative—must work with countries to align investments and approaches with WHO guidance and the country context.
What are the best- and worst-case scenarios for what happens after the trial result?

The best-case scenario is that the ECHO result increases women’s access to different contraceptive methods and to HIV prevention and treatment, and that it does so via programs and policies that have women at the center, providing full information about risks and benefits and supporting informed choice.

The worst-case scenario is that the ECHO result is understood as “good news” that supports countries and funders continuing with the way they historically have approached contraceptive programs and HIV.

The incidence in this trial must be a call to action.

What can you do to get involved?

• **Stay informed by gathering information on existing contraceptive, HIV and integrated programs.** Many countries say “we have choices for women” or “we have integrated HIV prevention and family planning programs.” But this doesn’t mean that the stocks are on the shelves or that providers are giving full information. Develop a checklist (ICWEA, APHA and AVAC can help!), visit sites and ask your relatives, friends and service providers. Having a baseline for what is available already will help women say what needs to change.

• **Help your community get up to speed.** We need to be in control of messages, which means we need to understand, share, listen and discuss. There are a range of resources on basic topics and more complex issues, as well as meeting reports from civil society dialogues in ECHO countries.

• **Track the results and the immediate reactions.**

• **Track the decision-makers and engage with them.** Find out what governments are doing at the country level and demand that women are at the table. Reach out to your Ministry of Health Officials and WHO country offices and ask if they are planning to put together a Task Team and what other plans they have in relation to ECHO trial results. Demand to have women representatives on the Task Team if they aren’t there already, and if they are, demand to know who your representatives are.

• **Demand real change—now.** Women and their allies must demand investments, procurement, provider training and program designs that reflect a woman-centered, informed-choice approach. Now is the time for activists, advocates and allies to increase budget lines, insist on and monitor for integration so that program funding is tied to provision of method mix, integration of HIV and contraceptive services and stigma- and discrimination-free counseling for women.