FP2020 & AVAC
A Roadmap for Results: Understanding the ECHO Trial Findings
WEBINAR OUTLINE

- Opening
  - HIV Perspective
  - Family Planning Perspective
- Overview of ECHO Trial and Results
- Civil Society Response and Planning
- Q&A
- Final Remarks
The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial: Primary Results

The ECHO Trial Consortium

9th SA AIDS Conference, Durban, South Africa

13 June 2019
ECHO Trial Consortium
Starting point

Safe and effective contraception is essential to the health and development of women, children and communities worldwide
Women represent over half of the 37 million persons currently living with HIV; nearly 600,000 new HIV infections occur yearly among adolescent girls and women in Africa.

Modern contraceptive methods are used by >700 million women worldwide, including >58 million African women.

Use of these methods substantially improves the health of women and children by averting unintended pregnancy and sequelae and contributes to women’s empowerment and to economic and social development.
Injectable contraceptive use and HIV

• In many settings in Africa where HIV incidence is high, the intramuscular injectable progestin depot medroxyprogesterone acetate (DMPA-IM) is the predominant contraceptive used.

Source: Butler et al., AIDS 2013
Prior evidence

• 30 years of epidemiologic and laboratory studies have tried to determine whether there is truly increased risk of HIV acquisition associated with use of hormonal contraception.

• Some studies showed that progestin-only injectables, particularly the intramuscular injectable depot medroxyprogesterone acetate (DMPA-IM), were linked to increased HIV risk, but other studies did not show this result.
  – In meta-analyses, the magnitude of increased HIV risk was approximately 40-50% (i.e., hazard ratios of 1.4-1.5)

• Very few research studies have looked at HIV risk for other highly effective contraceptives, such as intrauterine devices (IUDs) and hormonal implants, including levonogestrel (LNG) implants.

Source: Polis et al., AIDS 2016
WHO guidance

• Over the past decade, WHO has repeatedly reviewed the evidence relating hormonal contraceptive use to HIV risk.

• In 2017, WHO guidance summarized that women at risk for HIV can use progestin-only injectables but should be advised about:
  – Concerns about possible ↑ risk of HIV
  – Uncertainty about causal relationship
  – How to minimize their risk
Women’s right to know

- Women need to know whether certain contraceptives increase their chances of getting HIV. This information will help them make informed choices about which contraceptive they want to use and which HIV prevention methods they need.

A randomised trial provides the highest quality evidence to enable women to make fully informed choices, inform clear counselling messages for clinicians, and offer guidance for policymakers and programs.
ECHO

- ECHO was a multicentre, open-label, randomised clinical trial comparing HIV incidence and contraceptive benefits in women living in areas of high HIV incidence and using one of three highly-effective, licensed contraceptive methods:
  - intramuscularly-delivered depot medroxyprogesterone acetate (DMPA-IM)
  - a copper intrauterine device (IUD)
  - and a levonorgestrel (LNG) implant

- The primary objective was to compare HIV incidence among women randomised to DMPA-IM, a copper IUD, or an LNG implant.

- Secondary objectives included comparison by randomised method of rates of pregnancy, contraceptive method continuation, and serious adverse events and adverse events leading to method discontinuation.

- The trial began in December 2015 and concluded in October 2018.
Contraceptive methods rationale

- **DMPA-IM** was included in the trial because it is the contraceptive that observational data suggested could increase HIV susceptibility and is commonly used in many African settings that have high HIV prevalence.

- We included the **copper IUD** to have a highly-effective non-hormonal comparator.

- The **LNG implant** was included to represent another progestin-based contraceptive and because use of long-acting reversible methods like implants is rapidly increasing in Africa. LNG is also a part of many oral contraceptive pills and multipurpose prevention technologies in development.
The trial was undertaken in 12 sites in 4 countries: Eswatini (1), Kenya (1), South Africa (9), and Zambia (1)
Eligibility criteria:
- desired effective contraception,
- not pregnant,
- HIV seronegative,
- aged 16-35 years,
- agreed to use the assigned method for 18 months,
- reported not using injectable, intrauterine, or implantable contraception for the prior six months, and
- able to provide written, informed consent.

Women were recruited for this trial based on residing in geographies that had high risk of HIV but not individual characteristics of HIV risk, such as transactional sex, history of STIs, or self-reported high-risk behaviours.
Follow-up

- Study follow-up occurred at one month to address contraceptive side effects, then quarterly for up to 18 months, including HIV testing, contraceptive counselling, and safety monitoring.
  - Women were counselled that they could at any time choose to discontinue their randomised method, choosing another trial method, a different contraceptive method, or no method.
    - Women discontinuing their randomised method were retained in the trial.
  - In 2017, all women were provided updated information based on WHO guidance.
HIV prevention

- At every visit, participants received a comprehensive package of HIV prevention services, including HIV risk reduction counselling, partner and participant HIV and STI testing and management, condoms, and, as it became a part of national standard of prevention, pre-exposure prophylaxis (PrEP).
The ECHO Trial
is dedicated to the memory of

Dr. Ward Cates
1942 - 2016
President – Research
FHI 360
ECHO results
Statistical design

- The trial was designed with 80% power to detect a 50% increase in the hazard of HIV for each contraceptive method compared to each of the others

DMPA-IM vs copper IUD | DMPA-IM vs LNG implant | copper IUD vs LNG implant

- We chose a 50% increase in HIV risk based on formative work with stakeholders to determine a meaningful difference that would inform policy change.
7829 women ages 16-35 desiring contraception and willing to be randomised

Randomise (1:1:1 ratio)

- DMPA–IM (2609 women)
- Copper IUD (2607 women)
- LNG implant (2613 women)

<table>
<thead>
<tr>
<th>Country</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eswatini</td>
<td>502</td>
</tr>
<tr>
<td>Kenya</td>
<td>901</td>
</tr>
<tr>
<td>South Africa</td>
<td>5768</td>
</tr>
<tr>
<td>Zambia</td>
<td>658</td>
</tr>
</tbody>
</table>
Participant characteristics

Average age 23 (range 16-35), 63% <25 years of age

Most (81%) were not married & most (81%) had previously been pregnant at least once

Half did not use a condom with their last sex act, but only 7% reported >1 partner in the prior 3 months

STIs were common: 18% had *C. trachomatis*, 5% *N. gonorrhoeae*, and 38% HSV-2

MPA levels in blood samples were tested in a subset of participants from the enrolment visit – 13% had levels suggesting potential use in the prior 6 months
Follow-up

- 99% completed at least one post-randomization HIV test, and retention was 93.6% at the final study visit

- 7785 / 7829 women (99.4%) accepted their randomised method at enrolment.
  - Of the 44 who initially declined, 0 were assigned DMPA-IM, 36 (1.4%) copper IUD, 8 (0.3%) LNG implant

- Participants used their methods for 92% of the time they were in the study
In total, **397 of the 7829** women acquired HIV during the study.

The overall rate of new HIV infections was **3.81% per year** (95% CI 3.45-4.21).
HIV incidence

**Intention-to-treat analysis**

<table>
<thead>
<tr>
<th></th>
<th>DMPA-IM</th>
<th>Copper IUD</th>
<th>LNG Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># HIV infections</strong></td>
<td>143</td>
<td>138</td>
<td>116</td>
</tr>
<tr>
<td><strong>HIV incidence, per 100 woman-years (95% CI)</strong></td>
<td>4.19 (3.54-4.94)</td>
<td>3.94 (3.31-4.66)</td>
<td>3.31 (2.74-3.98)</td>
</tr>
</tbody>
</table>

Cumulative probability of HIV acquisition over months since enrolment.
# HIV Incidence – Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th>Intention-to-treat analysis</th>
<th>DMPA-IM</th>
<th>Copper IUD</th>
<th>LNG Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong># HIV infections</strong></td>
<td>143</td>
<td>138</td>
<td>116</td>
</tr>
<tr>
<td><strong>HIV incidence, per 100 woman-years (95% CI)</strong></td>
<td>4.19 (3.54-4.94)</td>
<td>3.94 (3.31-4.66)</td>
<td>3.31 (2.74-3.98)</td>
</tr>
</tbody>
</table>

**DMPA-IM vs. Copper IUD**

| HR = 1.04 | 96% CI = 0.82-1.33 | p = 0.72 |
HIV incidence – intention-to-treat analysis

<table>
<thead>
<tr>
<th>Intention-to-treat analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td># HIV infections</td>
</tr>
<tr>
<td>DMPA-IM</td>
</tr>
<tr>
<td>143</td>
</tr>
</tbody>
</table>

HIV incidence, per 100 woman-years (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>DMPA-IM</th>
<th>Copper IUD</th>
<th>LNG Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV incidence</td>
<td>4.19</td>
<td>3.94</td>
<td>3.31</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(3.54-4.94)</td>
<td>(3.31-4.66)</td>
<td>(2.74-3.98)</td>
</tr>
</tbody>
</table>

DMPA-IM vs. Copper IUD

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HR = 1.04</td>
</tr>
<tr>
<td>96% CI = 0.82-1.33</td>
</tr>
<tr>
<td>p = 0.72</td>
</tr>
</tbody>
</table>

DMPA-IM vs. LNG Implant

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HR = 1.23</td>
</tr>
<tr>
<td>96% CI = 0.95-1.59</td>
</tr>
<tr>
<td>p = 0.097</td>
</tr>
</tbody>
</table>
HIV incidence – intention-to-treat analysis

<table>
<thead>
<tr>
<th>Intention-to-treat analysis</th>
<th>DMPA-IM</th>
<th>Copper IUD</th>
<th>LNG Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td># HIV infections</td>
<td>143</td>
<td>138</td>
<td>116</td>
</tr>
<tr>
<td>HIV incidence, per 100 woman-years (95% CI)</td>
<td>4.19 (3.54-4.94)</td>
<td>3.94 (3.31-4.66)</td>
<td>3.31 (2.74-3.98)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DMPA-IM vs. Copper IUD</th>
<th>DMPA-IM vs. LNG Implant</th>
<th>Copper IUD vs. LNG Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR = 1.04</td>
<td>HR = 1.23</td>
<td>HR = 1.18</td>
</tr>
<tr>
<td>96% CI = 0.82-1.33</td>
<td>96% CI = 0.95-1.59</td>
<td>96% CI = 0.91-1.53</td>
</tr>
<tr>
<td>p = 0.72</td>
<td>p = 0.097</td>
<td>p = 0.19</td>
</tr>
</tbody>
</table>
Pregnancy

<table>
<thead>
<tr>
<th>Primary intention-to-treat analysis</th>
<th>DMPA-IM</th>
<th>Copper IUD</th>
<th>LNG Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td># Pregnancies</td>
<td>61</td>
<td>116</td>
<td>78</td>
</tr>
<tr>
<td>Pregnancy incidence, per 100 woman-years</td>
<td>1.75</td>
<td>3.27</td>
<td>2.19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuous use analysis</th>
<th>DMPA-IM</th>
<th>Copper IUD</th>
<th>LNG Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td># Pregnancies</td>
<td>18</td>
<td>35</td>
<td>21</td>
</tr>
<tr>
<td>Pregnancy incidence, per 100 woman-years</td>
<td>0.61</td>
<td>1.11</td>
<td>0.63</td>
</tr>
</tbody>
</table>

- Pregnancy rates were low, in all three groups, and most pregnancies (71%) occurred among women who had previously discontinued their randomised method.

- All methods had high contraceptive effectiveness – the two hormonal methods had statistically lower pregnancy rates than the IUD.
Safety

- Serious adverse events were rare across all groups

- Adverse events that resulted in method discontinuation were relatively uncommon (7% of women overall) and more common among women randomised to the copper IUD or LNG implant compared to DMPA-IM

<table>
<thead>
<tr>
<th></th>
<th>DMPA-IM</th>
<th>Copper IUD</th>
<th>LNG Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>49 (1.88%)</td>
<td>92 (3.53%)</td>
<td>78 (2.99%)</td>
</tr>
<tr>
<td>AE resulting in method discontinuation</td>
<td>109 (4.18%)</td>
<td>218 (8.36%)</td>
<td>226 (8.65%)</td>
</tr>
</tbody>
</table>
ECHO Summary

- This multi-country randomised trial measured HIV incidence among African women assigned to one of three highly-effective contraceptive methods.

- Acceptance of randomised method, contraceptive continuation, and retention were very high across all methods.

- All three methods were effective at preventing pregnancy and were well tolerated.

- HIV incidence was high for all three groups.
Discussion – HIV risk

- We designed this trial to detect a 50% increase in HIV incidence for each of the contraceptive methods compared to each of the others. None of the comparisons showed a 50% increase in HIV incidence.
Discussion – HIV risk

- We designed this trial to detect a 50% increase in HIV incidence for each of the contraceptive methods compared to each of the others. None of the comparisons showed a 50% increase in HIV incidence.

- Under the design of this study an observed approximately 30% increase in HIV incidence would have been found to be statistically significant, and hazard ratios less than approximately 1.17 would have excluded a 50% increase in risk from the confidence interval.
Discussion — HIV risk

- We designed this trial to detect a 50% increase in HIV incidence for each of the contraceptive methods compared to each of the others. None of the comparisons showed a 50% increase in HIV incidence.

- DMPA-IM and copper IUD had comparable HIV risk.

<table>
<thead>
<tr>
<th>DMPA-IM vs. Copper IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR = 1.04</td>
</tr>
<tr>
<td>96% CI = 0.82-1.33</td>
</tr>
<tr>
<td>p = 0.72</td>
</tr>
</tbody>
</table>
Discussion – HIV risk

We designed this trial to detect a 50% increase in HIV incidence for each of the contraceptive methods compared to each of the others. None of the comparisons showed a 50% increase in HIV incidence.

DMPA-IM and copper IUD had point estimates >1.17 & <1.30 compared to LNG implant, with CIs that included both no difference and a 50% increase.

<table>
<thead>
<tr>
<th></th>
<th>DMPA-IM vs. LNG Implant</th>
<th>Copper IUD vs. LNG Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>1.23</td>
<td>1.18</td>
</tr>
<tr>
<td>96% CI</td>
<td>0.95-1.59</td>
<td>0.91-1.53</td>
</tr>
<tr>
<td>p</td>
<td>0.097</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Discussion – other methods

- For logistical and financial feasibility, we chose to include three highly-effective contraceptive methods available in the African region, including one non-hormonal and two different progestin-only methods.

- Our results cannot be generalized to other contraceptive methods not included in the study (e.g., NET-En, DMPA-SC, hormone-containing IUDs, etc.)

- We enrolled women who desired effective contraception and did not include a placebo or no contraceptive group in this trial. The salient question is weighing the relative risks and benefits of different methods, not no method.
Discussion – HIV incidence

- In spite of an individualized HIV prevention package provided to all participants throughout follow-up and country-wide HIV treatment and prevention programmes, HIV incidence was alarmingly high in this population throughout the course of the trial and STI prevalence at baseline was also very high.

- Our results strongly emphasize the need for more aggressive HIV and STI prevention and management efforts for African women, including PrEP and HIV prevention integrated with contraceptive services.
Conclusions

- Many women in Africa are at high risk for HIV infection and for morbidity and mortality from unintended pregnancy.

- This well-executed randomised trial did not find a substantial difference in HIV risk among the methods evaluated, and all methods were safe and highly effective.

- These results underscore the importance of continued and increased access to these three contraceptive methods, as well as expanded contraceptive choices, complemented by high-quality HIV and STI prevention services.
Acknowledgements

- We thank the women who participated in this study for their motivation and dedication and the communities that supported this work. We are grateful to the members of the trial’s Data and Safety Monitoring Board, Global Community Advisory Group and local community advisory boards at each trial site, and overseeing ethics review committees for their expertise and guidance.
We thank the funders of the ECHO Trial who had the confidence to invest in this globally-important study.

Contraceptive supplies donated by USAID and the Republic of South Africa
Website - www.echo-consortium.com

Results published *The Lancet* Online First today:
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31288-7/fulltext
How Will WHO Addresses New Evidence Presented by ECHO

Evidence Synthesis
- Values and Preferences
- Additional studies after 2016 review
- What does ECHO study add to the current evidence

Guideline development
- Guideline development Group advertised
- GDG meeting 29-30 July 2019
- Revised recommendations anticipated August 2019

Technical support
- Communicating results and immediate policy responses
- Strengthening HIV/SRH integration
- Continuing access to method options and choice