Hormonal contraception and HIV risk

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On behalf of the ECHO Consortium

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ECHO Team
Starting Point

Safe and effective contraception is essential to health and development of women, children, and families worldwide.
Outline

• Contraception and HIV risk: the evidence and the challenge
• Rationale for a randomized trial
• Design and oversight of ECHO
• ECHO status
• Potential outcomes and challenges
Evidence

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

• Evidence has included:

**Laboratory and non-human primate studies**

Progesterone implants enhance SIV vaginal transmission and early virus load

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Preston A. Marx¹², Alexander I. Spira¹², Agegnehu Gettie¹, Peter J. Dailey³, Ronald S. Veazey⁴, Andrew A. Lackner⁴, C. James Mahoney⁴, Christopher J. Miller⁴, Lee E. Claypool⁵, David D. Ho¹ & Nancy J. Alexander⁴

Evidence

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• Evidence has included:

Epidemiologic studies, particularly prospective cohort analyses

Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

Renee Heffron, Deborah Donnell, Helen Rees, Connie Celum, Nelly Mugo, Edwin Were, Guy de Bruyn, Edith Nakku-Joloba, Kenneth Njure, James Kiarie, Robert W Coombs, Jared M Baeten, for the Partners in Prevention HSV/HIV Transmission Study Team*

Heffron et al. Lancet ID 2012
Evidence

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- Evidence has included:

**Meta-analyses**

An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women

Chelsea B. Polis\textsuperscript{a,b}, Kathryn M. Curtis\textsuperscript{c}, Philip C. Hannaford\textsuperscript{d}, Sharon J. Phillips\textsuperscript{e}, Tsungai Chipato\textsuperscript{f}, James N. Kiarie\textsuperscript{g}, Daniel J. Westreich\textsuperscript{h} and Petrus S. Steyn\textsuperscript{g}

Polis et al. AIDS 2016
Evidence

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

• Evidence has included:

  Policy statements

“Women at high risk of acquiring HIV should be informed that progestin-only injectables may or may not increase their risk of HIV acquisition”
Evidence

Summary:

- The greatest potential concern has centered on the use of the injectable progestin depot medroxyprogesterone acetate (DMPA) – in a recent meta-analysis, the magnitude of effect was 1.40 (95% CI 1.23-1.59)

- Oral contraceptive pills appear not to increase HIV risk

- Norethisterone enanthate (NET-EN), another injectable may have less HIV risk than DMPA but data are somewhat limited

- Limited data are available for hormonal implants and hormonal and non-hormonal IUDs with respect to HIV risk

Polis et al. AIDS 2016
Limitations of Observational Data

- Disagreement across studies
- Potential risk for bias and confounding by factors that are difficult to measure
- Imperfect data: marginal contraceptive measurement, modest/high loss to follow-up or missing visits, sometimes long intervals between visits
- Contraceptive use often self-reported or otherwise unverified
- Laboratory studies in disagreement about mechanisms, or unclear what the key mechanisms even are
Additional Evidence

- In Africa, there is significant unmet need for contraception and injectables are the most used method.

![Graph showing contraceptive use in different regions](from data in the UN World Contraceptive Use 2011 Wall)
Additional Evidence

- Unintended pregnancy rates are high, and high in areas where HIV is prevalent

FIGURE 1  Unintended pregnancies per 1,000 women aged 15–44, by subregion, 2012

Sedgh, Singh, Hussain. Studies in Family Planning 2014
The Challenge

Possible HIV acquisition risk with some hormonal contraceptives

Uncertainty in the data

Life-saving benefits of hormonal contraceptives

Public health conundrum
Female hormonal contraception linked to higher HIV risk

Women who use hormonal birth control are roughly twice as likely to become infected with HIV as those who do not use any form of contraception, according to a study published on Tuesday.

The research was carried out among 3,750 heterosexual couples in Africa, where one partner of each had the human immunodeficiency virus (HIV) and the other was uninfected.

The findings, if confirmed, would suggest that the benefits from using contraceptives to prevent pregnancy are offset by the risk of catching HIV from male partners who are HIV-positive.

The study was conducted in Kenya, Malawi and South Africa and was published in the journal Epidemiology and Infection.

The researchers said their findings were consistent with other studies suggesting a link between female hormonal contraception and the transmission of HIV.

They said the results were important because they highlighted the need for more research into the potential risks and benefits of different contraceptive methods.

The study is one of several recent studies that have suggested a link between female hormonal contraception and the risk of HIV infection.

AIDS and Contraceptives: Bad choices in Africa

Researchers call for new guidelines (Source: UNFPA, 2016)

The risk of HIV infection increases with the use of hormonal contraceptives, according to a study published Monday. The risk is particularly high for women who use hormonal contraceptives in combination with male partners who are HIV-positive.

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Rationale for a Randomized Trial

A randomized trial, if done well, provides the highest-quality evidence:

- Providing clear guidance for policymakers and programs
- Helping to formulate clear counselling messages for clinicians
- Permitting women to make fully informed choices
The ECHO Trial

A Multi Center, Open-Label, Randomised Clinical Trial Comparing HIV Incidence and Contraceptive Benefits in Women using Depot Medroxyprogesterone Acetate (DMPA), Levonorgestrel (LNG) Implant, and Copper Intrauterine Devices (IUDs)

The Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial
ECHO: Overarching Goal

To answer the pressing public health question of the relative risks (HIV acquisition) and benefits (pregnancy prevention) of three commonly-used, effective contraceptive methods among women who desire contraception.
ECHO Trial Design

7,800 women ages 16-35 wanting to prevent pregnancy and willing to be randomized

Randomize (1:1:1 ratio)

- DMPA (2,600 women)
- LNG implant (2,600 women)
- Copper IUD (2,600 women)
# ECHO Overview

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Multi-center, open-label randomized trial</th>
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<tr>
<td><strong>Arms</strong></td>
<td>Random allocation to: DMPA, levonorgestrel (LNG) implant, <em>or</em> copper IUD</td>
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<tr>
<td><strong>Population</strong></td>
<td>Sexually active HIV-uninfected women, ages 16-35 years seeking highly effective contraception, willing to be randomized to any study arm</td>
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<tr>
<td><strong>Sample size</strong></td>
<td>7,800 women (~2,600 per study group)</td>
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| **Outcomes**       | Primary = HIV *(80% power to rule out 50% increases across the 3 methods)*  
|                    | Secondary = pregnancy, SAEs, method continuation |
| **Duration**       | Up to 18 months per woman; study will last ~36 months |
| **Sites**          | 12 sites in Kenya, South Africa (9), Swaziland, Zambia |
**ECHO Contraceptive Methods**

**DMPA**
- Most commonly used reversible contraception in sub-Saharan Africa
- Highly effective when used consistently (0.2% failure rate)
- Easy to administer (IM injection), can be used covertly

**Jadelle (LNG) implant**
- Highly effective and user-independent
- Failure rates of <1% for both perfect and typical use

**Copper IUD**
- Extremely safe, non-hormonal, highly effective, and reversible
- Approved for 10 years of use
- Failure rates of <1% in both perfect and typical use if inserted properly
Study Visits

Study visits are quarterly for up to 18 months and include:
- HIV testing and contraceptive counseling
- Brief questionnaires on contraceptive use, behaviors, symptoms, and related factors

All participants are provided a comprehensive contraceptive, HIV prevention, and HIV care package:
- Risk-reduction counselling, condoms, offer of partner testing
- STI screening and treatment
- Other prevention options (like PrEP and microbicides), as they become part of regular care
- HIV care plans for seroconverters
- Linkage to contraceptive services at the end of follow-up
Oversight

- An **independent DSMB** reviews data on participant safety, study conduct, and scientific validity and integrity of the trial approximately every 6 months.

- **Ethical review** of protocol conducted prior to study start and annually by IRBs/ECs at FHI 360, WHO, and each study site.

- A **safety oversight committee** reviews safety data from all sites monthly and has 24/7 availability for clinical advice.

- A **Global Community Advisory Group** and **CABs** at each site meet regularly. Each site has an active **Good Participatory Practice** plan.

- To assure the trial meets all **regulatory requirements** (both US and each country), the study is conducting quality control and assurance activities, and being reviewed by qualified independent clinical monitors.
Evidence, Ethics, and Feasibility of ECHO

Prior to ECHO’s initiation, many people (including members of the ECHO consortium) questioned whether the trial needed to be done and could be done well. Key questions included:

• **Evidence** → Is the question already answered?
  • While studies suggest some contraception, particularly DMPA, may be associated with enhancing HIV risk, the evidence has not shifted policy and data from a trial may be clarifying. Importantly, it is not clear if alternatives to DMPA would be better.

• **Ethics** → Is it ethical to randomize?
  • Randomization can be done ethically, with informed consent.

• **Feasibility** → Will women agree to randomization, method continuation, etc.?
  • Assessable only by doing the trial itself.
ECHO Performance Standards

To do the ECHO trial well, the team, funders, and DSMB agreed prior to initiation that a key operational metrics would be reviewed continually during the study and if not met would trigger careful reevaluation of whether to stop the trial:

<table>
<thead>
<tr>
<th>ECHO Performance Standard</th>
<th>Target (*=overall and at each site)</th>
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<tbody>
<tr>
<td>#1 Accrual</td>
<td>Achieve target sample within ~18 months</td>
</tr>
<tr>
<td>#2 Method refusal</td>
<td>&lt;5% of subjects*</td>
</tr>
<tr>
<td>#3 Retention</td>
<td>Per-visit completion of ≥90% and ≤10% of expected person-years lost*</td>
</tr>
<tr>
<td>#4 Method discontinuation</td>
<td>≤10% of all person-time off assigned method*</td>
</tr>
<tr>
<td>#5 HIV incidence</td>
<td>sufficient to meet the study objectives (≥3.5%/year)</td>
</tr>
<tr>
<td>#6 Ineligible enrollments</td>
<td>&lt;1-2% of total*</td>
</tr>
<tr>
<td>#7 HIV endpoint adjudication</td>
<td>up-to-date for each DSMB review*</td>
</tr>
<tr>
<td>#8 Data quality</td>
<td>current for each DSMB, QC ≤5/100 CRFs, fax time ≤7d*</td>
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Implications of some possible outcomes

- **No difference in HIV risk** (DMPA=implant=IUD): Evidence that all methods can be continued in use.

- **Difference in HIV risk** (example possible scenarios):
  - Implant lowest risk: Strengthen access to implant
  - IUD lowest risk: Strengthen access to IUD
  - DMPA highest risk: Help women/programs shift to less use of DMPA and greater use of alternative highly-effective methods, including messaging, delivery, alternatives
ECHO Current Status

- Started December 2015
- Open at 12 of 12 sites
- DSMB met on 5 August 2016 & 2 March 2017 and strongly endorsed continuation of the study
- Enrollment currently 5,390 (69%) (as of 3 Apr 2017)
- Expect enrollment to be completed in ~Q3 2017 and study visits to be completed in ~Q3 2018
- Performance standards are excellent (no add’l info available while trial ongoing)
New WHO Guidance

On 2 Mar 2017, WHO released new guidance regarding injectable progestin contraceptives. The guidance derived from an expert consultation in December 2016 (which members of the ECHO Team did not attend, to avoid conflict of interest) and changed the Medical Eligibility for Contraception (MEC) categorization for injectable progestins from a “1” (“no restriction”) to a “2” (“advantages outweigh theoretical or proven risks”).
WHO recommends women considering DMPA/NET-EN be advised:

- There are concerns about a possible increased risk of HIV.
- There is uncertainty about whether injectable contraceptive methods actually cause increased risk.
- There are ways to minimize the risk of becoming infected, such as use of male and female condoms and PrEP, where available.

The WHO guidance also called for data from randomized trials.
### Steps Following WHO Announcement

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<td>ECHO statement and updated Q&amp;A posted to ECHO website.</td>
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<td>DSMB met the day WHO released its guidance – endorsed continuing the trial as designed.</td>
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<td>Calls with ECHO Team and CABs were used to discuss the WHO guidance changes and train on the updated counselling guidance.</td>
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<td>Informed consent updated and an information sheet was created in line with WHO recommended counselling.</td>
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<td>ECHO team members participated in participant and stakeholder engagement activities (e.g., AVAC webinar).</td>
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ECHO Summary

- The ECHO Study is enrolling in 12 sites in Kenya, South Africa, Swaziland and Zambia
- Accrual is on schedule, performance metrics are excellent, counseling is directly responsive to current WHO guidance, and the DSMB has active oversight
- Results from the trial will be highest quality evidence, and as a result:
  - Women will have highest quality information to make informed choices
  - Providers will have highest quality information for contraceptive counseling
  - Policymakers will have highest quality information about contraceptive risks and benefits for family planning programs
ECHO Team
ECHO Funders

Bill & Melinda Gates Foundation
USAID
Sida
saMRC
UNFPA
Republic of South Africa

Contraceptive supplies donated by USAID and the Republic of South Africa