Hormonal contraceptive methods & HIV acquisition in women: updated systematic review of epidemiological evidence

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September 16, 2016
AVAC Webinar
Acknowledgements

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  – James N. Kiarie, WHO
  – Daniel J. Westreich, University of North Carolina
  – Petrus S. Steyn, WHO

• Study investigators who provided additional information about their analyses

• Women and men who participated in studies advancing our understanding on this complex topic
Introduction

• Empowering women and couples with the tools necessary to prevent unintended pregnancy and avoid STIs including HIV is critically important for individual and public health

• Hormonal contraceptive (HC) methods are highly effective for prevention of unintended pregnancy; contributing to prevention of outcomes including maternal mortality

• However, some studies suggest an association between specific HC methods (particularly injectable DMPA) and HIV acquisition in women
Objective

To update a previous systematic review on HC and HIV acquisition in women with new epidemiological evidence published between Jan 15, 2014 & Jan 15, 2016
## Included studies

<table>
<thead>
<tr>
<th></th>
<th>HC vs. no-HC</th>
<th>Head-to-head comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Women who were HIV-negative at baseline</td>
<td></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Use of a specific HC method (Method A)</td>
<td></td>
</tr>
<tr>
<td><strong>Comparison group</strong></td>
<td>Non-users of HC, including:</td>
<td>Use of a specific HC method (Method B)</td>
</tr>
<tr>
<td></td>
<td>• Women using a non-hormonal contraceptive method, or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Women using no contraceptive method</td>
<td></td>
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<tr>
<td><strong>Outcome</strong></td>
<td>Incident HIV acquisition</td>
<td></td>
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</tbody>
</table>
Quality assessment

Studies were “unlikely to inform the primary question” if they had:

- No adjustment for any measure of condom use, or
- Unclear measurement of exposure to HC, such as:
  - Failure to include time-varying analysis of HC exposure, if appropriate.
  - Failure to provide separate estimates for different types of HC methods.
  - Comparison group included a substantial or unclear number of users of another HC method (except in an intentional head-to-head comparison).
  - Intersurvey interval >6 months.

Studies were “informative but with important limitations” (IBWIL) if they had none of these flaws.
Studies identified for inclusion

- 22 studies included in our previous review were retained (except 1 superseded by a new analysis)

- Of 312 new references screened, 10 met inclusion criteria:
  - 8 HC vs. non-HC users
  - 1 head-to-head (DMPA vs. NET-EN)
  - 1 meta-analysis contained both HC vs. non-HC comparisons & head-to-head comparisons
## Study quality

### Included studies (n=31)
- 21 studies from past review + 10 new studies

### Studies by comparison type
- 29 HC vs. no HC
- 1 head-to-head
- 1 both types

### Informative but with important limitations (n=14, 5 new)
- 12 studies (3 new)
- 1 study (new)
- 1 study (new)
Implants & HIV acquisition: 2 IBWIL studies

Studies with statistically significant results have a red marker. Newly included studies are highlighted in yellow.

OCs & HIV acquisition: 11 IBWIL studies

Studies with statistically significant results have a red marker. Newly included studies are highlighted in yellow. Polis, Curtis, Hannaford, Phillips, Chipato, Kiarie, Westreich, Steyn. AIDS 2016 (in press).
**NET-EN & HIV acquisition: 6 IBWIL studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimated Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kleinschmidt et al (2007)</td>
<td>adjlRR: 1.76 (0.64-4.84)</td>
</tr>
<tr>
<td>Myer et al (2007)</td>
<td>adjlRR: 1.60 (0.63-4.09)</td>
</tr>
<tr>
<td>Morrison et al (2015) subanalysis</td>
<td>adjHR: 1.58 (0.66-3.79)^</td>
</tr>
<tr>
<td>McCoy et al (2013)</td>
<td>adjHR: 1.33 (0.76-2.33)^§</td>
</tr>
<tr>
<td>Crook et al (2014)</td>
<td>adjHR: 1.20 (0.84-1.69)</td>
</tr>
<tr>
<td>Morrison et al (2012)</td>
<td>adjHR: 0.87 (0.60-1.25)</td>
</tr>
</tbody>
</table>

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Head-to-head comparisons: 2 IBWIL studies

<table>
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<tr>
<th>Study</th>
<th>Estimated risk (95% CI)</th>
<th>AdjHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPA vs. NET-EN</td>
<td></td>
<td>adjHR: 1.41 (1.06-1.89)*</td>
</tr>
<tr>
<td>Noguchi 2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morrison 2015 meta-analysis</td>
<td></td>
<td>adjHR: 1.32 (1.08-1.61)*</td>
</tr>
<tr>
<td>DMPA vs. COC</td>
<td></td>
<td>adjHR: 1.43 (1.23-1.67)*</td>
</tr>
<tr>
<td>Morrison 2015 meta-analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NET-EN vs. COC</td>
<td></td>
<td>adjHR: 1.30 (0.99-1.71)</td>
</tr>
<tr>
<td>Morrison 2015 meta-analysis</td>
<td></td>
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Meta-analysis: DMPA vs. non-use of HC

Effect modification

- **Age**: of 10 studies, only 1 suggested a statistically significant interaction for age

- **HSV-2**: of 8 studies, 2 suggested a statistically significant interaction for HSV-2 status, in opposite directions
  - Morrison 2010: DMPA associated with increased HIV risk (adjHR 4.5, 95% CI 2.0–10.2) in HSV2-, not HSV2+ women (1.0; 0.7–1.6)
  - Noguchi 2015: DMPA associated with increased HIV risk (vs. Net-En users) (2.01; 1.12-3.63) in HSV2+, not HSV2- women.

- **Site**: of 4 studies, 2 reported significant interaction by study site
Summary of current HC-HIV data

- **Patches, rings, hormonal IUDs**: no data

- **Implants**: very limited data on LNG implants; does not suggest increased risk

- **OCPs**: substantial amount of data; does not suggest increased risk

- **NET-EN**: limited data; less concerning than in 2014, still worthy of investigation

- **DMPA**: substantial amount of data; newer data are increasingly concerning & converging around HR: 1.2-1.6
What does “a potential 40% increase in risk with use of DMPA” mean?

…for an average woman in a particular country?

…for a woman having vaginal sex with an HIV-infected male partner without using condoms?

…for a policy-maker considering next steps?
What does a potential 40% increase in risk mean for an average young women in South Africa?

- In South Africa in 2012, an average young woman aged 15-24 not using DMPA had an approximately **2.4%** chance of contracting HIV over one year (Shisana 2012).

- If using DMPA increases the risk of HIV acquisition by 40%, that young woman’s chances would increase to about **3.3%**. Of course, an individual woman’s risk depends on many factors, such as whether her sexual partner(s) is HIV+, circumcised, or on ART; whether she is using condoms or PrEP; how often she has sex; etc.


With gratitude to Professor Marie-Claude Boily and Dr. Jennifer Smith for their help in creating this slide.
What does a potential 40% increase in risk mean for a woman having sex with an HIV+ male partner without condoms?

Approximate % chance of a woman acquiring HIV from condomless, vaginal sex with an HIV+ male partner, by number of sex acts

Graphic uses data from Boily et al. *Lancet* 2009;9(2):118-29 and applies a Bernoulli equation to approximate a 40% increase in risk by coital frequency. Estimates with DMPA use are more reliable for reflecting a 40% increase in risk at lower coital frequencies (i.e., <50 per year).

With gratitude to Professor Marie-Claude Boily and Dr. Jennifer Smith for their help in creating this slide.
Balance of increasing maternal deaths and decreasing HIV-related deaths (%)

% change in net maternal and AIDS deaths on cessation of injectable HC use

Publication availability

*Manuscript is currently available to individuals with access to the journal *AIDS*.*

*It will be available Open Access (i.e., free of charge) soon.*

*See also a simultaneously published Opinion Piece in *AIDS*, entitled “Levonorgestrel in contraceptives and multipurpose prevention technologies: does this progestin increase HIV risk or interact with antiretrovirals?”*
Thank you!

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Update on the Evidence for Contraceptive Options and HIV Outcomes (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 (IUD)

Jared Baeten MD PhD, University of Washington
On behalf of the ECHO Consortium

AVAC-ICW EA webinar – September 2016
ECHO Team

ECHO is funded currently from the Bill & Melinda Gates Foundation, the Swedish International Development Cooperation Agency, the Medical Research Council of South Africa, and the United Nations Population Fund, with contraceptive supplies from the Government of South Africa and the United States Agency for International Development.
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; and
  - Permitting women to make fully informed choices.
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 Summary

### Design
Multi-center, open-label randomized trial

### Arms
Random allocation to: DMPA, levonorgestrel (LNG) implant, or copper IUD

### Population
Sexually active HIV-uninfected women, ages 16-35 years, living in areas of high HIV risk, seeking highly effective contraception, willing to be randomized to any study arm

### Sample size
7800 women (~2600 per study group)

### Outcomes
**Primary** = HIV (80% power to observe 50% increase across the 3 methods)
**Secondary** = pregnancy, SAEs, method continuation

### Duration
Quarterly visits for 18 months; study will last ~36 months

### Prevention
Risk-reduction counselling, condoms, offer of partner testing, STI screening, PrEP and microbicides as they become part of regular care, linkage to HIV and contraceptive care

### Sites
12 sites in Kenya, South Africa (9), Swaziland, Zambia
Key Metrics

- To do this study with high validity, it has to be done well. The study team has defined key metrics that will be monitored in real-time:
  - Accrual rate
  - Refusal of contraceptive method assigned at randomization
  - Retention
  - Rate of contraceptive discontinuation
  - HIV incidence
  - Quality of study performance (timeliness, data quality, etc.)
Approvals and Oversight

- Study protocol was reviewed and approved by the Institutional Review Boards (IRBs) of FHI360 and locally for each study site.

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

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

- A global CAB has been chartered as well as CABs at each site. Each site has an active GPP plan.

- The trial will meet all regulatory requirements (both US and each country), conduct ongoing quality control and assurance activities, and be reviewed by qualified independent clinical monitors.
Implications of some possible outcomes

• **No difference in HIV risk** (DMPA=implant=IUD): Reassurance to continue these methods in use.

• **Difference in HIV risk (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
Differing opinions

- **Evidence** → Is the question already answered?
  - While there are studies suggesting that some contraception, particularly DMPA, may be associated with HIV risk, the evidence has not been sufficiently definitive to change policy. Observational data may be limited by confounding. Importantly, it is not clear if alternatives would be better.

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

- **Feasibility** → Will women agree to randomization?
  - Assessable only in the trial itself.
ECHO current status

- **Started** December 2015.
- **Open** at 11 of 12 sites.
- **Enrollment** currently >2000 (>25%).
- **Few** method refusals.
- **High** retention so far.
- **DSMB** met in August – recommended study continue.
- **Ongoing review** of ICFs and participant / counseling materials as new information and recommendations emerge
ECHO in summary

- In the absence of a trial, the observational evidence base is unlikely to improve. Messaging will be continue to be challenging for providers, policymakers, and patients. Essentially:
  - If HIV risk exists in truth, unnecessary infections will continue to occur.
  - If HIV risk does not exist in truth, policies and/or individual women’s choices may alter, with potentially serious negative consequences for maternal morbidity/mortality

- Results from 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 programs