Fertility Intentions, Hormonal Contraception and HIV: Damned if You Do…

Ward Cates
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Scientific Acknowledgments

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  - WRHI/UWits
  - University of Washington
  - USAID
  - CDC
  - And many more…
Today’s Talk

- The History of a Hypothesis
- The Current Evidence
- The 2nd WHO Consultation
- “So What” for Future Research?
Woman’s Fertility Intentions

- **Woman**
  - **Desires Pregnancy**
  - **Does not Desire Pregnancy**

**Pre-Conception Counseling**

**Contraception**
- **Hormonal**
- **Other**
Hormones and HIV Possible Mechanisms

- Vaginal and cervical epithelium (ectopy)
- Cervical mucus
- Menstrual patterns
- Vaginal and cervical immunology
- Viral (HIV) replication
- Acquisition of other STI
The History of the HC/HIV Hypothesis
HC/HIV Acquisition Research Timeline

- 1987 – Plummer presentation - IAS Meeting, Wash DC
- 1988-on – Multiple secondary analyses
- 1996 – NIH/OPA review of HC/HIV
- 2008 – 1st WHO HC/HIV Consultation
HC/HIV Acquisition Research Timeline

• July 2011 – University of Washington HC/HIV study presented at IAS, Rome

• 1st Week Oct 2011 – The Week That Was:
  – University of Washington HC/HIV study published in *Lancet Infectious Diseases*
  – *New York Times* front page
  – Global “viral” media reaction
Female hormonal contraceptives linked to higher HIV risk

Women who use hormonal contraceptives are roughly twice as likely to become infected with HIV or pass on the virus to their partner, according to a study published Tuesday.

The study was carried out among women in Africa and found that those using hormonal contraceptives were twice as likely to become infected with HIV compared to those who were not using hormonal contraceptives.

Health

Contraceptive Used in Africa May Double Risk of H.I.V.

By MARLOUCK
Published: October 2, 2011

The most popular contraceptive for women in eastern and southern Africa, a hormone shot given every three months, appears to double the risk the women will become infected with H.I.V., according to a large study published Monday. And when it is used by H.I.V.-positive women, their male partners are twice as likely to become infected than if the women had used no contraception.
Contraceptives double HIV risk

FROM PAGE 1

tual and reproductive health of women,” said Mary Lysi Golli, an epidemiologist in the World Health Organisation’s department of reproductive health and research posted in the New York Times. Kenya’s Ministry of Public Health says they are waiting for direction from the WHO. They may however be a policy change to promote alternative family planning solutions for women.

Injectables have been the most popular form of contraception in Kenya and are used by 48 percent of married women, according to the 2009 Kenya Demographic and Health Survey. About 40 percent of total users prefer the pill while women using implants account for about 14 percent of total users.

The Lancet study says that women using hormonal contraception through injectables became infected at a rate of 6.61 per 100 person-years, compared with 3.78 for those not using them.

Transmission of HIV to men occurred at a rate of 2.61 per 100 person-years for women using hormonal contraception compared with 1.31 for those who did not.

Researchers have been trying to explain the link between contraceptive use and HIV infection.

They said it is possible hormonal contraception causes biological changes, such as changes to the cells that line the vagina or cervix, and that influence susceptibility to HIV.

Karen Hafford, an epidemiologist and co-author of the study, however said research examining whether the hormonal changes genital or vaginal mucosa had been inconclusive.

“It could be that progestins in injectable hormones arrested acute changes in the vagina and cervix or could increase the HIV’s ability to replicate,” Charles Morrison, senior director of clinical sciences of PHI 367, an NGO whose work includes researching the introduction of family planning and HIV told the Star.

Researchers also found that there was more HIV in the genital fluid of those using hormonal contraception than those who were not, which could explain why menstrual might have increased risk of infection from women using injectables.

The researchers also found that oral contraceptives significantly increased risk of HIV infection and transmission, but the number of pill users in the study was too small.

Others suggested that women on birth control other antiretroviral use condoms for protection.

The study however revealed condom use, thus excluding the possibility that increased infection occurred because couples using contraceptives were less likely to use condoms.

Injectable contraceptives in Kenya include Depo-Provera. Nairobi-based manufacturer of the branded version of Depo-Provera, declared to continue to the New York Times in the study, saying officials had not yet read it.

The study’s authors however said the injectables used by the African women were probably generic versions.

Depo-Provera has never been approved for use as a contraceptive in the US. It is controversial because it reportedly cause heavy bleeding, weight gain, headaches, nervousness and depression.
Partners/HSV Study: HC/HIV Acquisition – HIV-negative Women

- 1314 HIV-neg women – 7% COCs, 16% DMPA
- HIV+ male: transmission to HIV-negative female
  - HIV Incidence: 4.1/100 p-y
  - Adjusted HR for COCs: 1.8 (0.6-5.8)
  - Adjusted HR for DMPA: 2.1 (1.0-4.0)

Source: Heffron (2011)
Partners/HSV Study: HC/HIV Transmission – HIV-positive Women

- 2476 HIV-pos women – 9% COCs, 27% DMPA
- HIV+ woman: transmission to HIV- male
  - HIV Incidence: 1.7/100 p-y
  - Adjusted HR for COCs: 2.1 (0.8-5.8)
  - Adjusted HR for DMPA: 1.9 (1.1-3.6)

Source: Heffron (2011)
Studies of Injectables & HIV Acquisition

Kumwenda 2008
Ungchusak 1996
Feldblum 2010
Heffron 2011
Bultery's 1994
Baeten 2007
Watson-Jones 2009
Kilmarx 1998
Morrison 2010
Myer 2007
Reid 2010
Kiddugavu 2003
Kleinschmidt 2007
Kapiga 1998

Source: Adapted from Polis (2011)
Limitations of HC/HIV Observational Studies

• Potential for unmeasured selection bias
• Potential for confounding
• Hormonal contraceptive use not adequately documented
• Non-hormonal comparison group with greater condom use
But Wait, There’s More
Hormonal Contraception in Context

- Woman
  - Desires Pregnancy
  - Does not Desire Pregnancy

Pre-Conception Counseling

Pregnancy

Contraception

Failure

Hormonal

Other
Pregnancy/HIV Acquisition – HIV-negative Women

- 320 pregnancies in HIV- women – 29%
- HIV+ male: transmission to HIV-pregnant female
  - HIV Incidence: 7.4/100 p-y
  - Crude HR: 2.3 (1.2 – 3.7), p = 0.003
  - Adjusted HR: 1.5 (0.9 – 3.1), p = 0.08

Source: Mugo (2011)
Pregnancy/HIV Transmission – HIV-positive Women

- 503 Pregnancies in HIV+ women — 22%
- HIV+ pregnant female: transmission to HIV– male
  - Incidence: 3.5/100 p-y
  - Crude HR: 2.3 (1.2 – 4.4), p = 0.01
  - Adjusted HR: 2.5 (1.3-4.9), p = 0.01

Source: Mugo (2011)
So... What’s An Uninfected Woman To Do?

- If she uses DMPA,
  - Less risk of pregnancy
  - ?More risk of HIV acquisition

- If she becomes pregnant,
  - ?More risk of HIV acquisition
  - More risk of pregnancy complications

- Tradeoffs
So… What’s An Infected Woman To Do?

• If she uses DMPA,
  – Less risk of pregnancy
  – ?More risk of HIV transmission to partner

• If she becomes pregnant
  – ?More risk of HIV transmission to partner
  – Potential for transmission to infant
  – More risk of pregnancy M&M to self

• Tradeoffs
"C'mon, c'mon — it's either one or the other."
The WHO 2\textsuperscript{nd} Consultation
Geneva
Jan 31-Feb 2, 2012
## Eligibility Criteria: WHO Classifications

<table>
<thead>
<tr>
<th>Classification of Known Conditions</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No restriction on use</td>
</tr>
<tr>
<td>2</td>
<td>Benefits generally outweigh risks</td>
</tr>
<tr>
<td>3</td>
<td>Risks generally outweigh benefits</td>
</tr>
<tr>
<td>4</td>
<td>Unacceptable health risk</td>
</tr>
</tbody>
</table>
The WHO Consultation – The Setting

• 75 participants from 18 countries

• Days 1 & 2 review evidence
  – GRADE rating of the evidence
  – Discussion of MEC criteria

• Day 3 identify programmatic and research implications
WHO Consultation – GRADE Process

- **Goal** – To achieve standardization and rigor in summarizing evidence

- Adopted by many groups – e.g. WHO, CDC, ACP, USPSTF

- Independent reviewers from other fields evaluated the published HC/HIV studies
WHO Consultation – GRADE Criteria

• Overall study quality based on:
  – Limitations of individual studies
  – Precision
  – Directness

• Starting points
  – RCTs = “high quality”
  – Observational = “low quality”
WHO Consultation – GRADE Rating

• HC/HIV acquisition evidence
  – 8 cohort studies met minimum quality criteria
  – Serious limitations
  – Rated “low overall quality”

• HC/HIV transmission evidence
  – Rated “low overall quality”

• HC/HIV progression evidence
  – 1 RCT, 6 cohort studies
  – Rated “low overall quality”
WHO Consultation – The Dilemma

• Discussion focused on
  – DMPA and HIV acquisition
  – The Medical Eligibility Criteria category
  – “Women at high risk of HIV”

• Did the new evidence justify a change?
  – If left a Category 1 – no change implies DMPA has a clean bill of health
  – If moved to Category 2 – a change implies the evidence is strong enough to taint DMPA

• Bell-shaped curve of opinion
The World Health Organization (WHO) has concluded that women living with HIV or at high risk of HIV can safely continue to use hormonal contraceptives to prevent pregnancy. The recommendation follows a thorough review of evidence about links between hormonal contraceptive use and HIV acquisition.
The WHO Consultation – The Solution

• Recommendation – MEC Category 1 (no restrictions)

• 1* Clarification – “women choosing progestogen-only injectable strongly advised to always use condoms”
WHO Consultation – Programmatic Recommendations

• Withdrawal of hormonal contraception from FP programs is not warranted

• Contraceptive method mix needs to be expanded, especially for women at risk of HIV

• Condoms must be strongly emphasized

• FP and HIV programs should be integrated
What Does this Mean for Future Research?
WHO Consultation – Research Recommendations

• Conduct higher quality clinical studies to improve the HC/HIV acquisition evidence

• Develop new multipurpose technologies to prevent both HIV and unintended pregnancy – a high priority

• Investigate the biology of HC/HIV interactions
RCT Strengths

• Gold standard for research design

• Eliminates most cohort study limitations
  – Avoids selection bias
  – Reduces confounding, whether known or not

• GRADE rating – “high quality”
RCT Limitations

• Comparatively expensive
• Need high product continuation and low loss to follow up
• May be less generalizable
• If unmasked – behaviors not guaranteed to remain comparable during follow-up
## Elements of Open-Label RCT Design

<table>
<thead>
<tr>
<th>Design element</th>
<th>Most likely choice</th>
<th>Remaining open questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contraceptive arms</td>
<td>DMPA, risk reference, Net-En/implant/both</td>
<td>▪ Feasibility of including a 4th arm to study both implant and Net-En</td>
</tr>
<tr>
<td>Risk reference</td>
<td>Copper IUD</td>
<td>▪ Assumption that true HR is 1 or &gt;= 1.4</td>
</tr>
<tr>
<td>Study size</td>
<td>80% power to measure or exclude HR = 1.4 with 95% statistical significance</td>
<td>▪ Should age range be extended from 30 years old to 40 years old?</td>
</tr>
<tr>
<td>Target population</td>
<td>18 – 30 year old women, postpartum or post-abortion</td>
<td>▪ For which HIV risk factors should data be collected? What are best ways to do so?</td>
</tr>
<tr>
<td>Effect to be measured</td>
<td>Combined effect with ability to separate out biological effect for subsequent analyses</td>
<td>▪ What intensity of follow-up is required to maintain discon. below acceptable levels?</td>
</tr>
<tr>
<td>Follow-up protocol</td>
<td>Quarterly follow-up visits for 12–18 months; intensive HIV risk factor data collection</td>
<td>▪ How correlated is discon. to HIV risk factors?</td>
</tr>
<tr>
<td>Planning for discontinuation</td>
<td>Set threshold for acceptable level of discontinuation</td>
<td>▪ How much discontinuation can be tolerated?</td>
</tr>
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</table>

*Source: BMGF/BCG (2012)*
Summary – Why an RCT Now?

- Recent HC/HIV findings have raised visibility
- All previous studies observational – selection/confounding biases likely
- HIV prevention trials have high HIV rates among young women; most using DMPA
- We need “high quality” evidence to resolve this important global health issue
Thank You