Hormonal Contraception and the Risk of HIV Acquisition: Reanalysis using Marginal Structural Modeling

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Hormonal Contraception and HIV

- 1.75 billion women of reproductive age
- 16 million women HIV-infected; 80% in Sub-Saharan Africa
- Hormonal contraception used >150 million women (COCs: >100 million; DMPA: >50 million)
- Injectable progestin (DMPA, Net-En) use is common; especially in young and in South Africa
- Effective contraception decreases maternal and infant mortality
- Condom use remains low within marriage and among women using highly effective contraception
Why Hormones Have Caused Concern?

Biologic mechanisms by which hormonal contraception may increase HIV acquisition:

• Changes in vaginal and cervical structure (vaginal thinning, cervical ectopy)
• Genital tract infections
• Cellular level
• Local and systemic immunity
• Direct effect on virus
Limitations of Previous HC-HIV Studies

- Number of HC users low
- Comparability of groups not assessed
- Crude measurement of exposure
- Timing of HC use and HIV unclear
- Poor follow-up
- Limited generalizability
Hormonal Contraception and the Risk of HIV Acquisition (HC-HIV) Study

Sponsor: National Institute of Child Health and Human Development (NICHD)

Sites: Family Planning Clinics
- Uganda: Kampala
- Zimbabwe: Harare, Chitungwiza
- Thailand: Chiang Mai, Khon Kaen, Hat Yai, Bangkok

Study Population: 6,109 HIV-uninfected women ages 18-35 years

Study Design: Multi-center prospective cohort

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Inclusion/Exclusion Criteria

Inclusion

• 18 to 35 years of age
• HIV seronegative
• Low dose COCs for ≥ 3 months
  • or DMPA for ≥ 3 months
  • or non-hormonal method or no method

Exclusion

• Pregnant (intending to become pregnant)
• Used an IUD in last month
• Used any HC besides COC or DMPA within 3 months
Study Procedures

Screening
- Info: Risks and benefits
- Info: Study requirements
- Pre-test HIV counseling
- HIV, syphilis and HSV-2 testing
- Assessed for study eligibility
- Return within 15 days (test results, enrollment?)

Enrollment
- Study Procedures
- Informed consent
- ID number
- Baseline interview
- Counseling
- Physical (speculum) exam
- Specimens collected
- Vaginal infections treated
- Recalled for treatment (Ct, Gc or syphilis)

Follow-up Visits
- Every 12 weeks for 15–24 months
- Similar to enrollment procedures
- HIV testing
- Pap smears (annual or exit-visit)
Study Retention

- 24-month retention rates were high:
  - 92% African participants (96% UG; 88% ZM)
  - Contraceptive groups (91% COC; 93% DMPA; 91% NH)
- Mean follow-up: 21.9 months
- Median time between visits: 11.5 weeks

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### Incident HIV Infections by Country and Contraceptive Group

<table>
<thead>
<tr>
<th>Country</th>
<th>COC N/wy (incidence rate per 100 wy)</th>
<th>DMPA N/wy (incidence rate per 100 wy)</th>
<th>NH N/wy (incidence rate per 100 wy)</th>
<th>Total N/wy (incidence rate per 100 wy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>20/1271 (1.57)</td>
<td>26/1384 (1.88)</td>
<td>17/1433 (1.19)</td>
<td>63/4075* (1.55)</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>51/1475 (3.46)</td>
<td>61/1413 (4.32)</td>
<td>41/841 (4.87)</td>
<td>150#/3683* (4.07)</td>
</tr>
<tr>
<td>Thailand</td>
<td>0/878 (0)</td>
<td>3/992 (0.30)</td>
<td>1/883 (0.11)</td>
<td>4/2732* (0.15)</td>
</tr>
<tr>
<td>Total</td>
<td>71/3625 (1.96)</td>
<td>90/3789 (2.38)</td>
<td>59/3157 (1.87)</td>
<td>217#/10490* (2.07)</td>
</tr>
<tr>
<td>Total Africa only</td>
<td>71/2747 (2.59)</td>
<td>87/2797 (3.11)</td>
<td>58/2274 (2.55)</td>
<td>213#/7758* (2.75)</td>
</tr>
</tbody>
</table>

* Total woman-years is less than sum of contraceptive method woman-years because some women used multiple methods within same segment

# 3 women used multiple methods in segment where seroconversion occurred
Why Marginal Structural Modeling (MSM)?

Several features in the HC-HIV study

• HC exposure and HIV risk factors (e.g., condom use) change over time;
• HC exposure and HIV risk factors are associated with and influenced by each other throughout the study

The effect of HC exposure on HIV acquisition may be confounded by HIV risk factors
Example: Condom use

- Condom use is associated with HIV infection;
- Women who use condoms might be less likely to use HC in future to prevent pregnancy (or vice versa);
- Women who used HC in previous month might subsequently use condoms less often (or vice versa).

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Why Marginal Structural Modeling (MSM)?

- Time-dependent confounders not sufficiently controlled for in standard analysis models (e.g. Cox Proportional Hazards); can lead to a biased estimation effect (Mark and Robins 1993; Hernan 2001)

- Marginal structural models (MSMs) allow proper adjustment for time-dependent confounding and reduce selection bias (Robins 1998)
HC-HIV Reanalysis Using MSM

• Reanalysis aims to replicate the original HC-HIV Study analysis; variable definitions and statistical model as close to original analysis as possible
• Used monthly HC exposure instead of exposure during visit segments
• Identified three time-dependent confounders: participant behavioral risk, primary partner risk, and any condom use
• Used a more appropriate statistical analysis method (Marginal Structural Modeling)
Results
## Adjusted Hazard Ratios for HIV Acquisition by Contraceptive Group: Original and MSM Reanalysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Original Analysis(^1)</th>
<th>P</th>
<th>MSM Reanalysis HR(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td></td>
<td>All data without weight</td>
<td></td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>All data with weight</td>
<td></td>
<td>P</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contraceptive Group</th>
<th>Non-HC</th>
<th>1.00</th>
<th>1.00</th>
<th>1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>COC</td>
<td>0.99 (0.69, 1.42)</td>
<td>0.94</td>
<td>1.05 (0.73, 1.52)</td>
<td>0.78</td>
</tr>
<tr>
<td>DMPA</td>
<td>1.25 (0.89, 1.78)</td>
<td>0.20</td>
<td>1.25 (0.89, 1.77)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

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1 Adjusted for time-varying contraceptive group, site, living with partner, age, time-varying participant behavioral risk, time-varying primary partner risk, time-varying coital frequency and time-varying consistent condom use.

2 Adjusted for time-varying contraceptive group, site, living with partner, age, baseline participant behavioral risk, baseline primary partner risk, baseline coital frequency and baseline any condom use.

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Investigated whether HC-HIV relationship was modified by age (18-24 vs. ≥25 years) and baseline HSV-2 status.

Age: DMPA $p<0.01$; COC $p=0.03$

HSV-2 Status: DMPA $p=0.02$; COC $p=0.54$
HIV Incidence Rates and Multivariate Hazard Ratios for Incident HIV Infection by Age and Contraceptive Exposure: MSM Reanalysis

<table>
<thead>
<tr>
<th>Age group: &lt; 24</th>
<th>N/wy (incidence rate/100wy)</th>
<th>Multivariate Hazard Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COC</td>
<td>38/1035 (3.7)</td>
<td>2.02 (1.15, 3.55)</td>
<td>0.014</td>
</tr>
<tr>
<td>DMPA</td>
<td>47/1079 (4.4)</td>
<td>2.76 (1.62, 4.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No HC use</td>
<td>33/1475 (2.2)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>118/3588 (3.3)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group: &gt; 24</th>
<th>N/wy (incidence rate/100wy)</th>
<th>Multivariate Hazard Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COC</td>
<td>25/1367 (1.8)</td>
<td>0.73 (0.42, 1.26)</td>
<td>0.258</td>
</tr>
<tr>
<td>DMPA</td>
<td>29/1489 (1.9)</td>
<td>0.81 (0.48, 1.39)</td>
<td>0.448</td>
</tr>
<tr>
<td>No HC use</td>
<td>41/1332 (3.1)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>95/4187 (2.3)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

1 Contraceptive exposure based on 42959 months and 116 infections
2 Contraceptive exposure based on 50192 months and 95 infections

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### Adjusted Hazard Ratios for Incident HIV Infection by Age (3-groups) and Contraceptive Exposure: MSM Reanalysis

<table>
<thead>
<tr>
<th>Contraceptive Group</th>
<th>Adjusted hazard (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 18-20 with weight</td>
</tr>
<tr>
<td>Non-HC</td>
<td>1.00</td>
</tr>
<tr>
<td>COC</td>
<td>3.68 (0.88, 15.31)</td>
</tr>
<tr>
<td>DMPA</td>
<td>9.29 (2.72, 31.69)</td>
</tr>
</tbody>
</table>

1 Adjusted for time-varying contraceptive group, site, living with partner, age, baseline participant behavioral risk, baseline primary partner risk, baseline coital frequency and baseline any condom use.

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HIV Incidence Rates and Multivariate Hazard Ratios for Incident HIV Infection by HSV-2 Infection Status and Contraceptive Exposure: MSM Reanalysis

<table>
<thead>
<tr>
<th></th>
<th>N/wy (incidence rate/100wy)</th>
<th>Multivariate Hazard Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HSV-2 positive at enrollment</strong>¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COC</td>
<td>42/1233 (3.4)</td>
<td>1.07 (0.69, 1.65)</td>
<td>0.772</td>
</tr>
<tr>
<td>DMPA</td>
<td>51/1371 (3.7)</td>
<td>1.03 (0.67, 1.59)</td>
<td>0.887</td>
</tr>
<tr>
<td>No HC use</td>
<td>59/1309 (4.5)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>152/3912 (3.9)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>HSV-2 negative at enrollment</strong>²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COC</td>
<td>21/1136 (1.8)</td>
<td>2.06 (0.87, 4.92)</td>
<td>0.102</td>
</tr>
<tr>
<td>DMPA</td>
<td>24/1143 (2.1)</td>
<td>4.49 (1.98, 10.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No HC use</td>
<td>15/1454 (1.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>60/3732 (1.6)</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

¹ Contraceptive exposure based on 46863 months and 152 infections
² Contraceptive exposure based on 44711 months and 58 infections

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Summary

• Use of MSM results in revised estimates of effects for the HC-HIV Study that should be less biased than the original study results

• Overall, DMPA but not COC use, was significantly associated with HIV acquisition

• Young women and HSV-2 negative women who used hormonal contraceptives were at increased risk of HIV acquisition; older women and HSV-2 positive women using HC were not
Strengths-Limitations of Reanalysis

- MSM controls for time-dependent confounding and should result in a less biased effect estimate than traditional analysis methods.
- Subgroup analyses (age, HSV-2) were specified prior to the MSM reanalysis being conducted.
- Not possible to measure all potential time-dependent confounders; cannot rule out residual confounding.
- All methods of handling pregnancy (censoring, adjustment) have inherent limitations.
Conclusions

• In areas of high HIV incidence, young women (< 25 years) who use DMPA and COCs may be at increased risk of HIV acquisition.

• If results are confirmed, young women in high HIV incidence areas may need other highly effective contraceptive options (besides DMPA and COCs).

• Need additional high-quality evidence to answer this crucial public health question.
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