Hormonal Contraception and the Risk of HIV Acquisition

Charles Morrison, PhD
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Hormonal Contraception and HIV

- About 16 million women HIV-infected, most heterosexually and 80% are in Sub-Saharan Africa
- Hormonal contraception used > 150 million women (COCs: >100 million; DMPA injections: > 50 million)
- Injectable progestin use (DMPA and Net-En) increasing rapidly especially among young and in Southern Africa
- Effective contraceptive use decreases maternal and infant mortality
- Condom use remains low within marriage and among women using highly effective contraception
HIV and Contraceptive Prevalence

Adult HIV Prevalence:
- 20.0-28.0%
- 10% - <20.0%
- 5% - <10.0%
- 1% - <5.0%
- 0% - 0.9%

Modern Contraceptive Prevalence:
- 60-75%
- 40% - 60%
- 20-40%
- <20%

UNAIDS, 2008; UNFPA 2007
Why Have Hormones Caused Concern?

Biologic mechanisms by which hormonal contraception might increase HIV acquisition risk:

- Changes in vaginal and cervical structure
- Genital tract infections/Inflammation
- Cellular level
- Direct effect (viral replication)
Changes in Vaginal and Cervical Structure

• In macaques, progesterone treatment leads to thinned vaginal epithelium and increase in SIV acquisition

• Atrophic vaginal epithelium develops post-menopause as a result of hypoestrogenic state; post-menopausal women may be at higher HIV risk.

• Women using DMPA also become hypoestrogenic; but studies on the effect of DMPA on vaginal wall thickness in women suggest no clinically important thinning

• Cervical ectopy more prevalent among young women and women using COCs. Ectopy associated with HIV acquisition in some studies but not in others.
Genital Tract Infections and Hormonal Contraception

• Non-ulcerative genital tract infections (e.g. chlamydia, gonorrhea) increase HIV-1 susceptibility

• An association between hormonal contraceptive use and STIs could mediate a hormonal contraception and HIV-1 association (recruitment of HIV susceptible cells to genital tract).

• Studies suggest an association between hormonal contraceptive use and increased risk of chlamydia.

• Progesterone use may also be associated with increased inflammatory cells in cervicovaginal fluid.
Genital Tract and Systemic Immunity and Hormones: Laboratory Studies

- Oral contraceptive pills and pregnancy associated with up-regulation of CCR5 co-receptor expression on CD4+ cells in the cervical epithelium.
- Progesterone incubation *in vitro* stimulates CCR5 co-receptor expression
- Estrogen and progesterone may also limit systemic immune responses
Direct Effects of Hormonal Contraception on HIV-1

- Steroid hormones may upregulate viral expression (through binding of the hormone-responsive element in the HIV-1 LTR)
- Studies from macaques demonstrate increased early viral replication in animals treated with progesterone
- Studies from Mombasa have found hormonal contraceptive use predicts early viral genetic diversity; associated with higher plasma viral load and faster CD4 decline
Possible Behavioral Differences between Contraceptive Groups

- Women on HC less likely to use condoms
- Women choosing DMPA or COCs could have riskier sexual practices than non-hormonal users
- Risky behavior + less condom use among HC users → higher HIV incidence
- OR risky behavior + less condom use among HC users → more STIs → higher HIV incidence
Prospective Studies of OC Use & HIV Acquisition
Prospective Studies of OC Use & HIV Acquisition: High vs. Low-Risk Populations

Relative Risk (Log Scale) & 95% CI

- Lavreys 2004
- Kilmarx 1998
- Ungchusak 1996
- De Vincenzi 1994
- Plourde 1994
- Saracco 1993
- Laga 1993
- Plummer 1991
- Morrison 2007
- Myer 2007
- Kiddugavu 2003
- Kapiga 1998
- Sinei 1996
Prospective Studies of DMPA Use & HIV Acquisition

Relative Risk (Log Scale) & 95% CI

Harmful

Protective

Watson-Jones 2009#
Kumwenda 2008
Morrison 2007
Myer 2006†
Kleinschmidt 2005*
Lavreys 2004
Kiddugavu 2003
Kilmarx 1998
Kapiga 1998
Ungchusak 1996
Bulterys 1994

# About two-thirds DMPA, one-third OC users
† About two-thirds DMPA, one-quarter Net-EN users
* About two-thirds Net-EN, one-third DMPA users
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Harmful

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Net-En and HIV Acquisition

- Injectable progestin given every 2 months
- Used widely in Southern Africa, especially among young women
- Only two published prospective studies:
  - Women 35-49 years in Capetown undergoing cervical cancer screening: RR=0.79 (95% CI 0.31-2.02)
  - Family planning clients in Johannesburg: HR=1.76 (95% CI 0.64-4.84)
Hormonal Contraception and the Risk of HIV Acquisition (HC-HIV) Study

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

**Sites:**
- Family Planning Clinic
  - 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 conducted from 1999-2004
HC-HIV Study Results

- Analysis limited to 4,439 women in Uganda and Zimbabwe
- 213 incident HIV infections
- High levels of retention (92%); mean follow-up of 21.5 months.
- Half of participants (52%) were HSV-2 positive at baseline
- About half of participants were below 25 years at baseline

<table>
<thead>
<tr>
<th>Contraceptive</th>
<th>Adjusted HR* (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condom use/None</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>DMPA</td>
<td>1.25 (0.89-1.78)</td>
<td>0.20</td>
</tr>
<tr>
<td>COC</td>
<td>0.99 (0.69-1.42)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

* Cox proportional hazards models, adjusted for: site, age, living with partner, participant behavioral risk, primary partner risk, condom use (consistent vs. inconsistent)
Mombasa Sex Worker Study

- Sexual activity relatively low: Median 1 sex partner, 2 sexual encounters/week
- Most women (81%) were HSV-2 seropositive at enrollment

<table>
<thead>
<tr>
<th>Contraceptive</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None/tubal ligation</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>DMPA</td>
<td>1.7 (1.3 - 2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COC</td>
<td>1.5 (1.0 - 2.1)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Cox proportional hazards models, adjusted for: age, duration of sex work, parity, work place, vaginal washing practices, number of sexual partners per week, condom use, and genital tract infections.
HC-HIV Study: Effect Modification of HC-HIV Relationship

- Examined whether the relationship between HC use and HIV acquisition was modified by STI (vaginal, cervical infection, HSV-2) or age
- Neither vaginal nor cervical infections modified the HC-HIV relationship
- HSV-2 infection status at enrollment significantly modified effect of HC on HIV acquisition
- Age at enrollment (18-24 vs. > 25 years) also significantly modified effect of HC on HIV acquisition
HSV-2 Status and HC-HIV Relationship

- HIV acquisition was higher among HSV-2 positive women than HSV-2 negative women (IR=3.87 vs 1.62 per 100 wy). Corroborates results of other studies.

- Among HSV-2 positive women hormonal contraceptive use was not associated with HIV acquisition.

- However, among HSV-2 negative women, both DMPA (HR=3.97, 95% CI 1.98-8.00) and COC users (HR=2.85, 95% CI 1.39-5.82) were at increased HIV risk.
Mombasa Cohort: HC and HIV-1 Acquisition
Stratified by HSV-2 Status

<table>
<thead>
<tr>
<th>HSV-2 positive</th>
<th># HIV-1 cases / py follow-up</th>
<th>HIV-1 incidence</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>116 / 1647</td>
<td>7.0</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COC</td>
<td>37 / 255</td>
<td>14.5</td>
<td>1.51</td>
<td>1.03-2.21</td>
<td>0.04</td>
</tr>
<tr>
<td>DMPA</td>
<td>73 / 511</td>
<td>14.3</td>
<td>1.68</td>
<td>1.23-2.29</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HSV-2 negative</th>
<th># HIV-1 cases / py follow-up</th>
<th>HIV-1 incidence</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2 / 171</td>
<td>1.2</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COC</td>
<td>1 / 65</td>
<td>1.5</td>
<td>0.77</td>
<td>0.05-11.40</td>
<td>0.9</td>
</tr>
<tr>
<td>DMPA</td>
<td>6 / 48</td>
<td>12.5</td>
<td>32.50</td>
<td>1.19- 885</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Interaction terms assessing differences by HSV-2 status: for OCPs p=0.7, for DMPA p=0.2
Source: Baeten AIDS 2007; 21:1771
HC-HIV Study: Effect Modification by Age

• Among younger women (18-24 years) both DMPA (HR = 2.36; 1.50-3.69) and COC use (HR = 1.59; 1.00-2.55) was associated with increased risk of HIV infection

• Among older women (≥ 25 years) neither DMPA nor COCs were associated with an increased HIV risk
## Mombasa Cohort

### HC and HIV-1 Acquisition, Stratified by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age 18-24 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCP</td>
<td>1.57</td>
<td>0.81-3.05</td>
<td>0.19</td>
</tr>
<tr>
<td>DMPA</td>
<td>1.51</td>
<td>0.77-2.95</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Age 25+ years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCP</td>
<td>1.55</td>
<td>1.01-2.37</td>
<td>0.04</td>
</tr>
<tr>
<td>DMPA</td>
<td>2.01</td>
<td>1.43-2.82</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

No difference in contraception/HIV-1 relationship by age. Relatively limited statistical power for those aged <25 years. Multivariate analysis, as previously defined, including adjustment for HSV-2. Age analyzed as time-dependent variable.

## Palesa Study (South Africa)

### Unadjusted Rate Ratios by Age

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Rate Ratio Injectable Versus Non Use (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>1.1 (0.5-2.8)</td>
</tr>
<tr>
<td>15-19</td>
<td>3.0 (0.3-36)</td>
</tr>
<tr>
<td>20-24</td>
<td>1.9 (0.4-12)</td>
</tr>
<tr>
<td>25-29</td>
<td>0.7 (0.1-9)</td>
</tr>
<tr>
<td>30-40</td>
<td>0.0 (0.0-1.4)</td>
</tr>
</tbody>
</table>
Biologic/Physiologic Explanation of HSV-2 and Age Effects

• No clear explanation for HC-HIV association in HSV-2 negative and young women.

• HSV-2: Possible that HSV-2 infection may overshadow or mask impact of HC use on risk of HIV acquisition Example: Disruption of genital epithelium or recruitment of target cells greater for HSV-2 than for HC (COCs); thus HC effect only seen in women without HSV-2.

• Age: Physiologic differences between young and older women. Example: Cervical ectopy more prevalent and larger in younger women and in COC users. Synergy of effects?

• Possible there are unmeasured confounders that are more prevalent in either of the different subgroups (HSV-2 positive/negative or younger/older women).
Summary: Hormonal Contraception and HIV Acquisition

- In populations at low risk behaviorally, there appears to be little increase in HIV acquisition risk among DMPA or COC users.

- Some high-risk groups of women (e.g. sex workers) who use DMPA or COCs may be at increased HIV risk (1.5-2x).

- Possible effect modification in particular subgroups so that some women using HC could be at increased HIV risk:
  - HSV-2 negative women
  - Young women (< 25 years)

- Little information on HIV risk associated with use of other HC methods including NET-EN and implants (Jadelle, Implanon)

- Clearly need more high quality studies of HC use and HIV.
Recommendations

Dual Protection Can Be Achieved in Two Ways

Dual Method Use

- pregnancy prevention
- STI prevention

Condom Only

- pregnancy and STI prevention

Figure: Family Health International
Acknowledgments

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HC-HIV Study participants in Uganda, Zimbabwe and Thailand

FHI                  U. of Washington/Tibotec
A. Rinaldi           L. Lavreys
P. Chen              J. Baeten
C. Kwok
K. Nanda