Contraception and HIV Risk: Evidence and Unknowns

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Contraception

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

• Contraceptives have known “non-contraceptive” side effects (cancer, BMD, thromboembolism)
The question

- Does using hormonal contraceptives change a woman’s risk of acquiring (or, if she is HIV+, transmitting) HIV?
The question(s)

• Does using hormonal contraceptives change a woman’s risk of acquiring (or, if she is HIV+, transmitting) HIV?
  • Is that driven by a biologic effect, or it is mediated through changes in sexual behavior? Some of both?
  • If there is increased HIV risk, is it for all contraceptives or just some?
  • If there is increased HIV risk, how to weigh that within a context of other risks incurred by changing contraceptive options/choices?
Non-human primate studies

Progesterone implants enhance SIV vaginal transmission and early virus load

Preston A. Marx¹,², Alexander I. Spira¹,², Agegnehu Gettie¹, Peter J. Dailey³, Ronald S. Veazey⁴, Andrew A. Lackner⁴, C. James Mahoney⁵, Christopher J. Miller⁶, Lee E. Claypool⁷, David D. Ho³ & Nancy J. Alexander⁸

• Summary
  • High-dose progestosterone
  • Increased SIV transmission risk >7-fold
  • Thinned vaginal epithelium (mechanism?)
  • Also resulted in higher viral load in plasma
  • For many subsequent evaluation studies of vaccines and microbicides, pre-treatment with progestin is used to enhance transmission risk.

Marx Nature Medicine 1996
Possible biologic mechanisms

- Vaginal and cervical epithelium (mucosal thickness, cervical ectopy, etc.)
- Changes in cervical mucus
- Menstrual patterns
- Vaginal and cervical immunology
- Viral (HIV) replication
- Acquisition of other STI that may serve as mediators

However, data are often sparse or potentially could point in different directions, and, most importantly, no laboratory study would be sufficient for this question....
Epidemiologic studies

• Some epidemiologic studies have suggested that hormonal contraceptives may alter HIV-1 susceptibility in women
  • Evidence seems strongest for injectable progestin contraception
  • Results are inconsistent and study quality varies tremendously
Prospective, observational studies of injectables & HIV acquisition
Adjusted OR, IIR, or HR (log scale) and 95% CI

- Ungchusak 1996
- Kumwenda 2008
- Wand 2012
- Feldblum 2010
- Heffron 2011*
- Bulterys 1994
- Kleinschmidt 2007
- Baeten 2007
- Watson-Jones 2009
- Kilmarx 1998
- Morrison 2007/2010*
- Morrison 2012*
- Myer 2007
- Reid 2010
- Kiddugavu 2003
- Kapiga 1998

* includes MSM and Cox estimates

Legend:
- DMPA alone
- Net-En alone
- Any injectable
- Mostly injectable, some OC

NO EFFECT
Limitations

- Small sample size
- Long follow-up time between study visits
- Poor follow-up rates
- Inability to distinguish between types of hormonal contraceptives (oral v. injectable, etc.), or lack of a comparison group
- No or limited adjustment for confounding factors; insufficient adjustment
- Self-report of contraceptive use and sexual behavior
Looking at just 3 of the observational studies…

<table>
<thead>
<tr>
<th>Population</th>
<th>Results</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mombasa</strong> Lavreys 2004 Baeten 2007</td>
<td>Sex workers Kenya</td>
<td>Increased risk OCPs (HR 1.46, p=0.05) DMPA (HR 1.73, p&lt;0.001)</td>
</tr>
<tr>
<td><strong>Rakai</strong> Kiddugavu 2003</td>
<td>Community cohort Uganda</td>
<td>No increased risk OCP aIRR 1.12 injectable aIRR 0.84</td>
</tr>
<tr>
<td><strong>HC-HIV</strong> Morrison 2007 Morrison 2010</td>
<td>FP clinic attendees Uganda, Zimbabwe</td>
<td>Overall increased HIV for DMPA (HR 1.48, p=0.04) **Marked subgroup differences - - among age &lt;25: OCP HR 2.02, DMPA HR 2.76 among those HSV-2 neg: DMPA HR 4.49</td>
</tr>
</tbody>
</table>
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 Ngure, James Kiarie, Robert W Coombs, Jared M Baeten, for the Partners in Prevention HSV/HIV Transmission Study Team*

Summary

Background Hormonal contraceptives are used widely but their effects on HIV-1 risk are unclear. We aimed to assess the association between hormonal contraceptive use and risk of HIV-1 acquisition by women and HIV-1 transmission from HIV-1-infected women to their male partners.

Methods In this prospective study, we followed up 3790 heterosexual HIV-1-serodiscordant couples participating in two longitudinal studies of HIV-1 incidence in seven African countries. Among injectable and oral hormonal contraceptive users and non-users, we compared rates of HIV-1 acquisition by women and HIV-1 transmission from women to men. The primary outcome measure was HIV-1 seroconversion. We used Cox proportional hazards regression and marginal structural modelling to assess the effect of contraceptive use on HIV-1 risk.
Objective

- Compare HIV-1 incidence rates among women using and not using hormonal contraceptives
  - HIV-1 acquisition among women
  - HIV-1 transmission from women to men
Methods

• Prospective cohort study of 3790 HIV-1 discordant couples from 7 countries in East and southern Africa (Partners in Prevention HSV/HIV Transmission Study)

• Quarterly HIV-1 testing, contraceptive measurement, sexual behavior questionnaire

• Adjusted analyses (age, unprotected sex, HIV+ plasma VL, pregnancy)
  – Cox proportional hazards and marginal structural models
HIV-1 acquisition

• Overall, 21.2% of HIV-1 seronegative women used hormonal contraception at least once during follow up
  – Injectable contraception used at least once by 16.0% of women
  – Oral contraception used at least once by 6.7% of women

• There were a total of 73 incident HIV-1 infections
  – HIV-1 incidence rate: 4.09 per 100 person years
## HIV-1 acquisition

<table>
<thead>
<tr>
<th>Incidence rate*</th>
<th>HR (95% CI)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hormonal contraception</td>
<td>3.78</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>6.61</td>
<td>1.98 (1.06-3.68)</td>
<td>0.03</td>
<td>1.84 (0.98-3.47)</td>
</tr>
<tr>
<td>Injectable</td>
<td>6.85</td>
<td>2.05 (1.04-4.04)</td>
<td>0.04</td>
<td>2.19 (1.01-4.74)</td>
</tr>
<tr>
<td>Oral</td>
<td>5.94</td>
<td>1.80 (0.55-5.82)</td>
<td>0.33</td>
<td>1.63 (0.47-5.66)</td>
</tr>
</tbody>
</table>

*per 100 person years
HIV-1 transmission

- Overall, 33.3% of HIV-1 seropositive female partners used hormonal contraception at least once during follow up
  - Injectable contraception used at least once by 26.8% of women
  - Oral contraception used at least once by 8.9% of women

- There were 59 HIV-1 seroconversions in initially-HIV-1 seronegative men that were genetically linked to their female study partner
  - HIV-1 incidence rate: 1.75 per 100 person years
# HIV-1 transmission

<table>
<thead>
<tr>
<th>Incidence rate*</th>
<th>Adjusted Cox PH regression analysis</th>
<th>Adjusted marginal structural model analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>No hormonal contraception</td>
<td>1.51</td>
<td>1.00</td>
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<td>Any hormonal contraception</td>
<td>2.61</td>
<td>1.97 (1.12-3.45)</td>
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*per 100 person years

Injectable users also had small increase HIV-1 RNA in cervical swabs: +0.19 log copies/swab
Strengths and limitations

• **Strengths**
  – Large cohort
  – Frequent measurement of HIV, contraceptive use and sexual behavior
  – Very high rates of follow up (>90% retention)
  – HIV negative partners knew they were being exposed to HIV & all were exposed
  – Attention to confounding factors using multiple statistical techniques (multiple additional analyses demonstrate consistent findings)
  – First report of female to male transmission and partial biological explanation from increased genital viral loads

• **Limitations**
  – Observational data
  – Inability to distinguish between types of injectables used
  – Limited data on oral contraceptive risk
  – Limited number of infections among those using contraception
Why is this topic so difficult?
Principles of observational epidemiology

- Observational epidemiology is completely about:
  - Exposure (*contraception*)
  - Outcomes (*HIV acquisition*)
  - Confounders (*sexual behavior, etc.*)
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Time → HIV exposure

| HIV exposure | ↓ | ↓↓ | ↓ | ↓↓↓ | ↓ |  ↓ | ↓ | Time → |
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- Exposures measurement needs precision
  - Poor measurement of contraceptive exposure (both accuracy of reporting and precision of timing) risks bias towards the null
Principles of observational epidemiology

- Observational epidemiology is completely about:
  - Exposure (*contraception*)
  - Outcomes (*HIV acquisition*)
  - Confounders (*sexual behavior, etc.*)

- Outcome measurement is potentially easier
  - HIV seroconversion is objective, but its temporal relationship to exposures and confounders is not trivial
Principles of observational epidemiology

- Observational epidemiology is completely about:
  - Exposure (*contraception*)
  - Outcomes (*HIV acquisition*)
  - Confounders (*sexual behavior, etc.*)

- Confounders are tough to measure
  - Particularly self-reported sexual behaviors
Principles of observational epidemiology

- Observational epidemiology is completely about:
  - Exposure (*contraception*)
  - Outcomes (*HIV acquisition*)
  - Confounders (*sexual behavior, etc.*)

- Relative risk estimates <2 are extremely difficult to measure
  - Lots of opportunity for both imprecision and bias to result in spurious findings
Strengths of available observational data

• Large studies, low loss to follow-up
• Multinational populations
• Multiple risk groups
• Frequent measurement of contraceptive exposure and HIV outcome
• Measurement of confounding factors
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- Large studies, low loss to follow-up
- Multinational populations
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- Frequent measurement of contraceptive exposure and HIV outcome
- Measurement of confounding factors

Thus, available data have many of the design characteristics we’d like
What else would be the ideal?

- Perfect capture of contraceptive use
- Fully accurate characterization of confounding factors, particularly sexual behavior
- Capture of all potential confounding factors
- Large number of HIV seroconversions, including by different contraceptive types and within subgroups, so that study power is not limiting
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*These may be difficult to achieve*
New sources of data…

• Large randomized trials of novel HIV prevention strategies (PrEP, microbicides) could be analyzed for this question:
  • *Large sample sizes, geographic diversity*
  • *Very complete and careful collection of HIV outcomes*
  • *Prospective (but not necessarily good) measures of sexual behavior*
Limitations of prevention RCT datasets

- Careful measurement of contraceptive method was not a primary goal of these studies

- Many women in microbicide trials are unexposed to HIV and hard to know if that is related to contraceptive choice (in which case would be a huge confounder)

- Contraception often required for study entry
  - Possibility of limited/no “control” group
  - Accuracy of exposure is a potential concern – women may inaccurately self-report use in order to stay in the trial
And what about an RCT?
Challenges of an RCT (1)

• RCTs answer 1 question
  – *It is not clear whether the field has a single question here (beyond the too-vague “is DMPA bad?”)*
    • DMPA vs. IUD
    • DMPA vs. IUD vs. implant
    • Etc.
Challenges of an RCT (2)

• RCTs maintain their integrity when they are well-conducted:
  – High retention
  – High protocol and product adherence (no switching!)
  – Non-differential confounding (which is only likely protected by full blinding)

• Or might just end up analyzing as an observational study
Concluding Point

• 25 years of epidemiologic and biologic studies have attempted to assess the relationship between contraceptive use and HIV-1 acquisition (and transmission)

• The fact that there remains uncertainty today suggests that this is a question for which it is tough provide absolute clarity

Can we continue to make important public health decisions realizing that we may have to operate without certainty?
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