Contraception and Risk of HIV Transmission: Evidence, Unknowns, Implications

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Starting point: Contraception

- Safe and effective contraception is essential to the health and development of women, children, and families worldwide.
- In many settings, the unmet need for contraception is large.
Starting point: HIV

- 1.75 billion women are of reproductive age
- 16 million women are infected with HIV, one-half of those with the virus; 80% are in Africa
Starting point:
Contraception for women with HIV

- For women with HIV, safe and effective contraception an imperative
- Moreover, an added benefit of effective contraception for women with HIV is the prevention of infant HIV infection
Starting point: Contraception and HIV risk

- Contraceptives have important and potentially serious “non-contraceptive” effects, including on cancer, thromboembolism, and bone density.

- An adverse relationship between contraception and HIV risk would be of individual and public health importance.
The question

- Does using hormonal contraceptives increase a woman’s risk of acquiring HIV?
The question(S)

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• For a woman who is HIV+, does using hormonal contraceptive increase her risk of transmitting HIV?
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• Does using hormonal contraceptives increase a woman’s risk of acquiring HIV?
• For a woman who is HIV+, does using hormonal contraceptive increase her risk of transmitting HIV?

• For both of these questions,
  • Is increase risk driven by a biologic effect, changes in sexual behavior, some of both?
  • Is it for all contraceptives or just some?
  • How to weigh HIV risk against contraception’s benefits and other strategies for HIV prevention?
Contraceptive use as a risk factor for HIV transmission from women to men

Nearly all attention (and most research) related to the effect of contraception on HIV risk has been aimed at understanding whether contraception increases the risk of HIV acquisition (susceptibility) in women.

→ HIV acquisition (susceptibility)
Contraceptive use as a risk factor for HIV transmission from women to men

However, the question of whether contraceptive use might increase HIV transmission risk (i.e., infectiousness of transmission from women to men) is also of individual and public health importance.

\[
HIV\text{ transmission} \rightarrow \text{(infectiousness)}
\]
Contraceptive use as a risk factor for HIV transmission from women to men

Of course, many of the same factors appear to be related to both HIV susceptibility and infectiousness.

HIV transmission $\rightarrow$ (infectiousness) $\rightarrow$ HIV acquisition (susceptibility)

Behavior
STIs
Viral load

Behavior
STIs
Male circumcision
Outline

EVIDENCE

• Epidemiologic and biologic data relating use of contraceptive methods, specifically hormonal methods, to risk of HIV transmission from women to men

UNKNOWNWS

• Limitations in the data, challenges with better defining this potential risk

IMPLICATIONS

• What are the ways forward? Both research and policy
Evidence
Direct Evidence

- Direct evidence relating contraceptive use to HIV transmission risk from women to men is extremely limited.
Prospective studies of injectable contraceptive use and HIV acquisition

- Ungchusak 1996
- Kumwenda 2008
- Feldblum 2010
- Heffron 2012
- Wand 2012
- Baeten 2007
- Kilmarx 1998
- Morrison 2012
- McCoy 2012
- Morrison 2007/2010
- Myer 2007
- Reid 2010
- Kiddugavu 2003
- Kleinschmidt 2007
- Kapiga 1998

0,01 0,10 1,00 10,00

Decreases HIV-1 risk Increases HIV-1 risk
Prospective studies of injectable contraceptive use and HIV transmission

Heffron 2012

Decreases HIV-1 risk

Increases HIV-1 risk
Direct Evidence

• Direct evidence relating contraceptive use to HIV transmission risk from women to men is extremely limited.
  • Studies directly exploring HIV transmission require studying both HIV-infected persons and their sexual partners
  • Thus, only prospective studies, enrolling HIV-infected women and their initially-HIV-uninfected partners, can determine whether contraceptive use is a risk factor for incident transmission of HIV
Exploring the data we have

Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study

Renee Heffron, Deborah Donnell, Helen Rees, Connie Celum, Nelly Muga, Edwin Ware, Guy de Bruyn, Edith Nakku-Joloba, Kenneth Ngure, James Kilie, Robert W Coombs, Jared M Bater, 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.

Heffron et al., Lancet Infect Dis 2012
Population

- Prospective cohort study of 3790 HIV-1 discordant couples from East and southern Africa
- Couples recruited as part of 2 studies conducted between 2004 and 2010
  - **Partners in Prevention HSV/HIV Transmission Study**
    Randomized trial of acyclovir herpes suppression to reduce HIV-1 transmission (n=3321)
  - **Couples Observational Study**
    Prospective cohort study of immune correlates of HIV-1 protection (n=469)
Study sites

South Africa
- Cape Town
- Orange Farm
- Soweto

Botswana
- Gaborone

Zambia
- Kitwe
- Ndola
- Lusaka

Rwanda
- Kigali

Kenya
- Eldoret
- Kisumu
- Nairobi
- Thika

Uganda
- Kampala

Tanzania
- Moshi
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

• Participants ≥18 years old and sexually active

• HIV-1 infected partners not eligible, at enrollment, for ART, under national guidelines

• For HIV-1 negative partners, HIV-1 testing done quarterly; for HIV-1 positive partners, CD4 counts measured every 6 months and plasma and genital viral load measured at enrollment and 6 months later

• Contraceptive use and sexual behavior measured quarterly with standardized questionnaires
  – No data on adherence or brand of contraception used
Statistical methods

Primary analysis: multivariate Cox proportional hazards model
Adjusted for
- Age
- Plasma viral load
- Sex without a condom (time dependent)
- Pregnancy (time dependent)

Secondary analysis: marginal structural model
Weights balance the distribution of time varying covariates (unprotected sex and pregnancy) within hormonal contraceptive use groups

- For all analyses, periods with hormonal contraceptive use were compared to periods without hormonal contraceptive use
- Because of small numbers, time periods with IUD and implant usage were censored
- All time periods after ART initiation were also censored
Analyses

1. HIV-1 acquisition by women
   - Association between contraceptive use and HIV-1 seroconversion among initially-HIV-1 seronegative women

2. HIV-1 transmission from women to men
   - Association between female partner’s contraceptive use and HIV-1 seroconversion among initially-HIV-1 seronegative men
   - Analysis limited to infections determined – by viral genetic sequencing – to have been acquired from the study partner
## Couple characteristics

<table>
<thead>
<tr>
<th></th>
<th>HIV-1 acquisition among women</th>
<th>HIV-1 transmission from women to men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) or median (IQR)</td>
<td>N (%) or median (IQR)</td>
</tr>
<tr>
<td></td>
<td>N=1314</td>
<td>N=2476</td>
</tr>
<tr>
<td>Married</td>
<td>1081 (82.3)</td>
<td>1846 (74.6)</td>
</tr>
<tr>
<td>Partnership duration, years</td>
<td>6.5 (2.7-13.4)</td>
<td>4.9 (2.1-9.4)</td>
</tr>
<tr>
<td>Number of children together</td>
<td>2.0 (0.0-3.0)</td>
<td>1.0 (0.0-2.0)</td>
</tr>
<tr>
<td>Number of sex acts together, past month</td>
<td>3.0 (2.0-6.0)</td>
<td>4.0 (2.0-8.0)</td>
</tr>
<tr>
<td>Any unprotected sex together, past month</td>
<td>312 (23.7)</td>
<td>727 (29.4)</td>
</tr>
<tr>
<td>Couple experienced a pregnancy during study</td>
<td>390 (29.7)</td>
<td>571 (23.1)</td>
</tr>
<tr>
<td>Enrollment plasma viral load (log10 copies/mL)</td>
<td>4.4 (3.7-4.9)</td>
<td>4.0 (3.2-4.6)</td>
</tr>
</tbody>
</table>
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></th>
<th>Incidence*</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>1.51 (n=40)</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>2.61 (n=19)</td>
<td>1.97 (1.12-3.45)</td>
<td>0.02</td>
<td>2.05 (1.12-3.74)</td>
<td>0.02</td>
</tr>
<tr>
<td>Injectable</td>
<td>2.64 (n=15)</td>
<td>1.95 (1.06-3.58)</td>
<td>0.03</td>
<td>3.01 (1.47-6.16)</td>
<td>0.003</td>
</tr>
<tr>
<td>Oral</td>
<td>2.50 (n=4)</td>
<td>2.09 (0.75-5.84)</td>
<td>0.16</td>
<td>2.35 (0.79-6.95)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*per 100 person years

**Adjusted for age, enrollment plasma viral load level of the HIV-1 infected partner and time dependent unprotected sex and pregnancy.
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

• **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
Prospective studies of injectable contraceptive use and HIV transmission

Heffron 2012
Possible biologic mechanisms

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

- Direct evidence of increased female-to-male HIV infectiousness related to hormonal contraceptive use is limited.

- As a result, the remainder of the evidence we have for a contraception/HIV transmission relationship is indirect evidence – i.e., of factors that suggest HIV infectiousness.
HIV levels predict HIV transmission risk

- The quantity of HIV in plasma & genital secretions is the prime determinant of HIV transmission risk

Quinn et al. NEJM 2000
Baeten et al. Science Transl Med 2011
HIV levels predict HIV transmission risk

• The quantity of HIV in plasma & genital secretions is the prime determinant of HIV transmission risk

• Thus, more studies of the relationship between contraception and HIV levels have been done

## Contraceptive use and genital HIV: Partners in Prevention study

### Any genital HIV-1 RNA detected

<table>
<thead>
<tr>
<th></th>
<th>Adjusted odds ratio* (95% CI)</th>
<th>p-value</th>
<th>Adjusted regression coefficient* (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hormonal contraception</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>1.51 (1.13-2.01)</td>
<td>0.01</td>
<td>+0.14 (+0.04, +0.23)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Injectable</td>
<td>1.67 (1.21-2.31)</td>
<td>0.02</td>
<td>+0.19 (+0.08, +0.30)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Oral</td>
<td>1.06 (0.62-1.84)</td>
<td>0.49</td>
<td>-0.05 (-0.24, +0.14)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

*Adjusted for plasma viral load and CD4 count
Other studies

- Early cross-sectional study of endocervical HIV DNA detection (yes/no) among 318 HIV-infected sex workers in Mombasa, Kenya (Mostad et al., Lancet 1997)
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• Several additional studies (with variable methods and of inconsistent quality) have had inconsistent findings
Other studies

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• Several additional studies (with variable methods and of inconsistent quality) have had inconsistent findings

• Notably, modest increases in genital HIV RNA (or DNA) alone are not necessarily sufficient to fully account for up to a doubling in HIV transmission risk
  • A $1.0 \log_{10}$ increase in genital HIV RNA needed to result in a 1.7-2.2-fold increase in HIV transmission risk (Baeten et al., Sci Transl Med 2011)
Additional hypotheses

- Limited evidence (not necessarily supported by confirmatory studies or consistent across studies) suggests that contraceptives could have additional effects that might increase HIV infectiousness:
  - Direct effects on plasma HIV levels
  - Effects on acquisition of STIs that increase HIV infectiousness

![Diagram showing the relationship between DMPA/OCP during chronic HIV disease and various outcomes such as genital infections, genital shedding of HIV, plasma viral load, and infectivity.](image)
Evidence

• Direct evidence of increased female-to-male HIV infectiousness related to hormonal contraceptive use is limited to a single study.

• Indirect evidence is mixed, with some studies finding increased genital HIV in women using hormonal contraceptive methods, but others not. These studies are of variable quality and design.
Unknowns
The challenge of confounding by condom use
The challenge of confounding by condom use

Disentangling a direct contraception → HIV relationship is very difficult.
Challenges of studies of this question

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

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

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HIV exposure

↓↓

↓

↓↓↓

↓

HIV infection, then seropositivity

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Time →
Challenges of studies of this question

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

![Diagram showing the timeline of HIV exposure and infection]
Challenges of studies of this question

- Exposures measurement needs precision
  - Large studies essential, with accuracy of reporting and precision of timing (=perfect capture of contraceptive use is the ideal).
  - Notably, there are essentially no studies of implants, hormone-containing IUDs, and other (relatively) newer methods

- Outcome measurement challenging also
  - HIV seroconversion is objective, but its temporal relationship to exposures and confounders is not trivial. Perfect control of behavioral confounding is particularly challenging to envision.
HIV-1 transmission from women to men

• All the challenges for studies of HIV acquisition in women apply similarly to studies of HIV transmission from women to men
  • With the added caveat that there are very, very few opportunities to directly study female-to-male transmission risk for HIV
Many unknowns:

- Limited data
- Potentially confounded by behavior (although a result confounded by behavior is still increased risk)
- Prospects for additional data limited
Implications
What do we do?

Possible HIV-1 risk with some hormonal contraceptives

Uncertainty in data, more data difficult to gather

Tremendous benefit of hormonal contraceptives, ethics/human rights

Public health conundrum
Intersection of injectable hormonal contraceptive use and HIV prevalence

Most concern

...the group agreed that the data were not sufficiently conclusive to change current guidance.

- Women living with HIV can continue to use all existing hormonal contraceptive methods without restriction.
- Consistent and correct use of condoms, male or female, is critical for prevention of HIV transmission to non-infected sexual partners.
- Voluntary use of contraception by HIV-positive women who wish to prevent pregnancy continues to be an important strategy for the reduction of mother-to-child HIV transmission.
National programmes are encouraged to systematically introduce, adapt or adopt evidence-based family planning guidelines according to local contexts…

A commitment by programmes to respecting reproductive and human rights, integrating family planning and HIV prevention…

Ensure the availability of a wider variety of highly effective contraceptive methods…

Provide easy-to-understand and comprehensive information to women and their partners about the benefits of contraceptive options available to them as well as any associated risks…
“The Ministry has not changed its policy on use of hormonal contraception. Users and providers of hormonal contraception are encouraged to continue using these methods, although, as always, we recommend that women wanting no more children use available long-acting or permanent methods. It is important to remember that other than the male or female condom, none of the other contraceptive methods provide any protection against HIV and other STIs. This requires that we provide condoms to couples who are at risk of HIV infection, in addition to another contraceptive method for dual protection.”

Republic of Kenya Ministry of Public Health and Sanitation, 9 October 2011
Antiretroviral therapy to mitigate transmission risk

“Treatment as prevention is a one-two knockout punch. It saves the life of the person already affected and has a 96 percent chance of preventing transmission to another person.”

-Tony Fauci, Director of NIAID, speaking at Stanford University, April 2012

**RECOMMENDATIONS**

4. People living with HIV who are in serodiscordant couples and who are started on ART for their own health should be advised that ART is also recommended to reduce HIV transmission to their uninfected partner. *Strong recommendation, high-quality evidence.*

5. Antiretroviral therapy for HIV-positive partners with >350 CD4 cells/μL in serodiscordant couples should be offered to reduce HIV transmission to uninfected partners. *Strong recommendation, high-quality evidence.*
Conclusions
Next steps

• The key question here is how to weigh the individual and public health risks and benefits for different contraceptive options:
  – HIV (with uncertainty), unintended pregnancy, important side effects, related morbidity and mortality

• More clinical, behavioral, and biologic research could help clarify HIV risk

• Most importantly, implement other strategies – particularly ART – that can arguably bypass risk, with substantial additional benefits
Concluding Point

• The benefits of contraception are unequivocal

• For areas of highest HIV risk, having as many safe and effective contraceptive options available is utmost importance.
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• For areas of highest HIV risk, having as many safe and effective contraceptive options available is utmost importance.

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

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• Partners in Prevention HSV/HIV Transmission Study Team
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