Hormonal Contraception and HIV-1 Infectivity: An Overview

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International Conference on Family Planning: Research and Best Practices
Kampala, Uganda, 15-18 November 2009
Hormonal contraception and HIV-1

• Critical public health issue
  – ~60% of HIV-infected people in sub-Saharan Africa are women\(^1\)
  – Hormonal methods of contraception are used by ~150 million women worldwide (~15 million in SS Africa) \(^2\)
  – High unmet need: average in Africa: ~25% (highest in Botswana with 45%) \(^2\)
  – Effective contraception
    • Reducing maternal and infant mortality
    • Allowing women to control when/how often to be pregnant

• Condom use remains low within marriage

• Use of hormonal contraception is associated with systemic and genital tract changes, and thus may potentially influence the infectivity in women infected with HIV-1

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\(^1\) UNAIDS, 2008
\(^2\) UN Population division, 2007
Hormonal contraception and HIV-1

Does use of hormonal contraception influence HIV-1 infectivity?
Hormonal contraception and HIV-1 infectivity

• In general, factors that increase HIV-1 susceptibility (e.g., STIs, genital tract inflammation) also increase HIV-1 infectiousness

• Very limited data examining infectiousness directly
  • No association between contraception and female-to-male HIV-1 transmission (Eur Study Group on Heterosex Transm of HIV, BMJ 1992)

• Genital HIV-1 shedding (or viral load) is a good proximate marker of infectiousness (Pedraza, JAIDS 1999; Baeten, Curr HIV Res 2003)

• Contraception may increase HIV-1 infectivity through at least 2 general mechanisms:
  • Direct effects on the genital mucosa or on local virus replication to increase genital viral shedding
  • Indirect effects, such as increased STD susceptibility, which in turn increase genital viral shedding
Sampling of the female genital tract for HIV

(1) Sno-strip® wick
(2) Cervicovaginal lavage
(3) Cytobrush or Sterile swab
Direct mechanisms by which hormonal contraceptive use might increase HIV infectivity.
Direct effects of hormonal contraception on genital HIV-1 shedding

Cross-sectional
1. Strong association in STD patients, Kenya
2. No association between HCC and shedding of HIV-1 RNA in HIV-1 infected women in US

Prospective

<table>
<thead>
<tr>
<th>Cervical HIV-1 DNA prevalence</th>
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<tr>
<td>Before HC</td>
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<td>42%</td>
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But no statistically significant effect of initiation of hormonal contraception on HIV-1 RNA quantity

- Genital shedding measured ~2 months before and after initiation of HCC

2. Kovacs, Lancet 2001

Wang, AIDS 2004
Indirect mechanisms by which hormonal contraceptive use might increase HIV infectivity
Hormonal contraception, STIs, and HIV-1 infectivity: Possible pathway

Use of hormonal contraception (OCP, injectables)

?  

Increased risk for vaginal/cervical STI

?  

Increased risk for genital tract shedding

?  

Increased infectivity
Hormonal contraception, STIs, and HIV-1 infectivity: Possible pathway

Use of hormonal contraception (OCP, injectables)

Increased risk for vaginal/cervical STI

Increased risk for genital tract shedding

Increased infectivity
Hormonal contraception and risk for STIs

• Possible association between hormonal contraception and STIs
  – Oral contraceptive pills have long been thought to increase risk of infection with *C. trachomatis* (Washington, JAMA 1985)
    • Meta-analysis OR 1.93 (95% CI 1.77-2.11) (Cottingham, Genitourin Med 1992)
  – Effect seems independent of differences in sexual behavior, although not accounted for in all studies

• More recent evidence:
  – From US: increased risk for cervical inflammation in women, both HIV-1 positive and negative, on progesterone-based contraception (Ghanem, JID 2005)
  – From Kenya: increased risk in HIV-1 positive women for cervical STIs *C. trachomatis* and cervicitis, but not for gonorrhea (Lavreys, AIDS 2004)
Hormonal contraception and cervical STIs among HIV-1 infected female commercial sex workers in Mombasa

<table>
<thead>
<tr>
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<th>No contraceptive method or tubal ligation</th>
<th>DMPA</th>
<th>Oral contraceptive pills</th>
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<tbody>
<tr>
<td></td>
<td>Incidence (no. cases)</td>
<td>Incidence (no. cases)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>4.1 (8)</td>
<td>14.4 (13)</td>
<td>3.1 (1.0-9.4)</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>14.2 (65)</td>
<td>17.7 (44)</td>
<td>1.0 (0.6-1.7)</td>
</tr>
<tr>
<td>Cervicitis#</td>
<td>16.6 (76)</td>
<td>29.8 (74)</td>
<td>1.6 (1.0-2.3)</td>
</tr>
</tbody>
</table>

Multivariate HRs adjusted for age, yrs of education, yrs of prostitution, parity, workplace, number of sexual partners per week, and condom use

# Thirty-two cases of cervicitis also had a laboratory diagnosis of *N. gonorrhoeae* or *C. trachomatis* infection

Lavreys, AIDS 2004
Hormonal contraception and HSV-1/2 reactivation

- In mice
  • HSV-1 reactivation associated with administration of estrogen and MPA

- In human
  • Cross-sectional studies: increased shedding of HSV-2 for both OCP and DMPA
    (Mostad, JID 2000; Cherpes, CID 2005)
  • Prospective study found no association in HIV-1 positive women in Kenya
    (McClelland, JID 2002)

→ Inconsistent results
Hormonal contraception, STIs, and HIV-1 infectivity: Possible pathway

Use of hormonal contraception (OCP, injectables)

For some STIs, not all

Increased risk for vaginal/cervical STI

Increased risk for genital tract shedding

Increased infectivity
Vaginal/cervical STI and risk for increased genital tract HIV-1 shedding

- Genital HIV-1 levels during early infection were increased by presence of a non-viral STIs in Zimbabwe/Uganda (Chlamydia, gonorrhea) (Morrison, in press, AIDS)

- Vaginal and cervical STIs (gonorrhea, Chlamydia, vaginal GUD) predict shedding of HIV-1 during chronic phase of HIV in Mombasa (Baeten, unpublished results)

- In US, plasma RNA was only predictor of shedding, but there were no gonorrhea or Chlamydia cases in that cross-sectional study (Kovacs, Lancet 2001)

- HSV-2 reactivation associated with increased genital HIV-1 shedding (Baeten, JID 2004)

- GUD (likely HSV-2) associated with HIV-1 transmission (Gray, JID 2001)
Hormonal contraception, STIs, and HIV-1 infectivity: Possible pathway

Use of hormonal contraception (OCP, injectables)

For some STIs, not all

Increased risk for vaginal/cervical STI

In some studies, not all

Increased risk for genital tract shedding

?  

Increased infectivity
Other indirect mechanisms by which hormonal contraception might increase HIV-1 infectivity

- **Ectopy**
  - Associated with HIV-1 DNA shedding in one study (Clemetson, JAMA 1993)

- **Plasma viral load**
  - Is a strong predictor of infectiousness (Quinn, NEJM 2000)
    - DMPA use at time of HIV-1 acquisition associated with higher set point plasma viral load in FSW cohort in Mombasa (Lavreys, JID 2004; Sagar, J Virol 2003)
    - However, this association was not found in the GS study in Uganda and Zimbabwe (Morrison, in press, AIDS)
HIV-1 genital shedding during early HIV-1 infection

• Early (acute) HIV-1 infection is characterized by high cervical HIV-1 RNA, independent of plasma VL (Lavreys, AIDS 2006)

• No association between DMPA or OC use and cervical HIV-1 VL early in infection (Morrison, in press, AIDS)
Hormonal contraception and HIV-1 infectivity
Summary of possible pathways

HIV seropositive
early infection

DMPA/OCP at time of
infection

↑ Plasma viral load

Genital infections

↑ Genital shedding of HIV

↑ Infectivity

HIV seropositive
chronic infection

DMPA/OCP during
chronic HIV disease

Genital infections

↑ Genital shedding of HIV

↑ Plasma viral load

↑ Infectivity

Important Note: Not all studies support the above links
HIV-1 genital shedding, hormonal contraception and antiretroviral treatment

• Limited information

• Mombasa sex workers cohort, 98 ARV-naïve women who began ARV treatment

• Overall mean drop of cervical HIV-1 RNA shedding was $2.32 \log_{10}$ copies/swab

• In first 3 months after ART initiation, in women using DMPA, decrease in cervical HIV-1 RNA achieved by ART was reduced by $0.28 \log_{10}$ copies/swab

• Thereafter adherence is the primary predictor of infectivity

$\rightarrow$ ART can overwhelm any small negative effect of contraception

Graham, CROI 2008
Hormonal contraception and HIV-1 infectivity
Key messages (1)

• Important public health question

• Current available information on possible association between hormonal contraception and HIV-1 infectivity is limited and inconsistent

• Current findings driven by indirect observations, mostly through co-infections with STIs (e.g. herpes)

• Still many unanswered scientific questions
Hormonal contraception and HIV-1 infectivity
Key messages (2)

• Current findings on the interaction between use of hormonal contraception and HIV-1 infectivity do not require any change in contraception policy

• Regardless of use/no use of hormonal contraception, HIV-1 infected women should use (male/female) condoms when having intercourse to protect themselves from super-infection, and to protect the partner of getting infected.
Research issues and priorities to study hormonal contraception and HIV infectivity

• Direct measure of the risk of transmission will require HIV-1 discordant couples, BUT
  – is challenging
  – might not show realities in populations at high risk (e.g. FSW)

• Therefore: indirect measure through long term studies of infectiousness using genital viral load

• Further studies required to look at effect of HCC on genital HIV-1 shedding in women on antiretroviral therapy

• Is there a role of herpes infection as mediating factor?
Acknowledgements

University of Washington, Seattle, WA, USA
University of Nairobi, Nairobi, Kenya
Kenya Medical Research Institute, Kilifi, Kenya
• Jared Baeten, MD, PhD
• R Scott McClelland, MD, MPH
• Susan Graham, MD, MPH

Fred Hutchinson Cancer Research Center, Seattle, WA, USA
• Julie Overbaugh, PhD

University of Witwatersrand, Johannesburg, South Africa
• Helen Rees, PhD

Family Health International, North Carolina, USA
• Charlie Morrison, PhD

All the women worldwide, infected with HIV-1, who participated in studies that looked at possible effects from hormonal contraception