Hormonal Contraception and HIV Acquisition

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3rd International Workshop on HIV & Women
January 14, 2013
Hormonal Contraception and HIV: Presentation Outline

• Background
• Data from non-human primates
• Biologic rationale in humans
• Epidemiologic studies of hormonal contraception (HC) and HIV acquisition
• WHO Consultation
• Next steps
Hormonal Contraception and HIV

- 1.75 billion women of reproductive age
- 16 million women HIV-infected; 80% in SSA
- Hormonal contraception used >150 million women (COCs: >100 million; DMPA: ~50 million)
- Injectable progestin (DMPA and Net-En) use is high in Sub-Saharan Africa
- Condom use remains low with marriage
Hormonal Contraception and HIV Prevalence

Adult HIV Prevalence

- 20% — 28.0%
- 10% — <20.0%
- 5% — <10.0%
- 1% — <5.0%
- 0% — 0.9%

Hormonal Contraceptive Prevalence

- > 35%
- 20 — 35%
- 10 — 20%
- 10 — <10%
- <10%

Sources: UNAIDS, 2011; represents married or in union
HC-HIV Infection Research Timeline

• 1987   –  Plummer IAS presentation
• 1988-on – Multiple secondary analyses
• 1996    –  Marx monkey data/NIH review
• 2005   –  HC-HIV Study results reported
• 2007    –  1st WHO HC/HIV Consultation
• 2011    –  Partners in Prevention results
• 2012    –  2nd WHO HC/HIV Consultation
Female hormonal contraceptives linked to higher HIV risk

Women who use hormonal contraceptives are roughly twice as likely to become infected with HIV or pass on the virus to their partner, according to a large study published on Monday.

The study, conducted in Kenya, revealed that women who used hormonal contraceptives were 1.8 times more likely to become infected with HIV than those who did not use contraceptives. The researchers also found that the risk of transmission to partners was 2.4 times higher among women using hormonal contraceptives.

The findings suggest that hormonal contraceptives may not be as effective in preventing HIV transmission as previously thought. The researchers called for more research to understand the mechanisms behind this increased risk and to develop new strategies to prevent HIV transmission among women using hormonal contraceptives.

Researchers have long been aware of the potential risks of hormonal contraceptives in the context of HIV transmission, but this is the first large-scale study to quantify the extent of the risk. The study is published in the journal Lancet and was conducted by a team of researchers from the University of California, San Francisco, and the University of Washington.

The researchers studied a sample of 4,000 women in Kenya who were at risk of HIV infection. The women were monitored for an average of 18 months, during which time 99 HIV infections were confirmed. The study found that women using hormonal contraceptives were more likely to become infected with HIV than those who did not use contraceptives.

The researchers also found that the risk of transmission to partners was significantly higher among women using hormonal contraceptives. The study found that women who used hormonal contraceptives were 2.4 times more likely to transmit HIV to their partners than women who did not use contraceptives.

The findings are important because they suggest that hormonal contraceptives may not be as effective in preventing HIV transmission as previously thought. The researchers called for more research to understand the mechanisms behind this increased risk and to develop new strategies to prevent HIV transmission among women using hormonal contraceptives.

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Vaginal SHIV Exposure during Menstrual Cycles of Macaques

- 19 female macaques challenged during undisturbed menstrual cycles
- Repeated low-dose SHIV exposures
- 18 displayed viremia during follicular, 1 during luteal phase
- Due to viral eclipse phase, most frequent transmission between days 24-31 (late luteal phase)
- Supports higher HIV susceptibility during progesterone-dominated periods

Source: Vishwanathan 2011
Risk of SIV Acquisition of Female Monkeys with Progesterone Implants (200 mg)

<table>
<thead>
<tr>
<th>Exposure Status</th>
<th>Number Exposed</th>
<th>Number Infected</th>
<th>Rate</th>
<th>RR 95% (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone Implants</td>
<td>18</td>
<td>14</td>
<td>77.8</td>
<td>2.1 (0.9-4.9)</td>
</tr>
<tr>
<td>Placebo-Both Phases</td>
<td>11</td>
<td>4</td>
<td>36.4</td>
<td>7.8 (2.8-16.1)</td>
</tr>
<tr>
<td>Placebo-Follicular Phase</td>
<td>10</td>
<td>1</td>
<td>10.0</td>
<td></td>
</tr>
</tbody>
</table>

Source: Marx (1996); Duerr (1997)
DMPA and SHIV Transmission

- 9 macaques received single DMPA dose 5 weeks prior to challenge; compared to 7 DMPA-naïve controls.
- Challenged with varying dosages of mixed X4 and R5-SHIV.

Comparing DMPA-treated to DMPA-naïve animals:

- Acute viremia higher in DMPA-treated animals (regardless of inoculum dose).
- Greater genetic complexity and greater replication of X4 virus.
- DMPA treatment did not impact development of anti-SIV binding antibodies but slowed cellular immune response rates (in virus-specific IFN-gamma production to SIV-Gag).
- Immunosuppressive effects of DMPA on cellular immune response increased viral burden, diversity and predominance of X4 virus.

Source: Trunova (Virology, 2006)
DMPA Treated Immunized Macaques

- About 60% of macaques are protected from SIV with prior immunization with nonpathogenic SHIV

- 6 of 10 randomly selected treated SHIV immunized macaques given DMPA.
  - Lower rate of protection after intravaginal challenge with SIVmac
  - Higher acute postchallenge plasma viral RNA levels (p<.006)

- Treatment with DMPA before challenge with a pathogenic virus can ↓ efficacy of a model vaccine in primate model

- DMPA in macaques appears to:
  - ↑ initial susceptibility to infection
  - ↓ initial immune response in naive host

Source: Abel, 2004
Progesterone, Estrogen and SIV Transmission

- Ovariectomized macaques received progesterone, estrogen or no treatment followed by intravaginal SIV
- 6/6 untreated macaques and 5/6 progesterone treated animals became infected; no estrogen-treated macaques infected
- Estrogen deficient women at higher risk for HIV infection?
- Topical vaginal estrogen therapy may reduce HIV vaginal transmission?

Source: Smith, 2004
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What can we learn from menopause?

- Represents combined effects of aging & reduced hormones
- Various effects seen:
  - Loss of acidity, lactobacilli, TLR function (Shaw 2008)
  - Loss of E → thinning, less cervical mucus
  - More CCR5+ T cells/molecules in cervix (Meditz 2011)
  - ↑ HIV RNA transcription in ectocervical explants (Rollenhagen 2011)
  - Higher chronic serum levels of IL-6 and TNFα, and ↓ CD4+ cells, B lymphocytes, and NK activity (Gameiro 2010)
  - Reduced antimicrobial secretion (lower levels of SLPI), reversible with HRT (Shimoya 2005);
Effects of DMPA in humans

- High dose, high MPA levels (peak levels ~4 ng/ml)
- Leads to very low estradiol levels (15-50pg/ml) – lower than other progestins (NET, Lng, ENG)
- Often leads to amenorrhea
- Prolonged return to fertility (~8 months post-injection)
- MPA has high affinity for the GR; GR could be key to HIV’s pathogenic success (Hapgood 2010)
- Other progestins (NET, LNG) have lower affinity for the GR, and NET has antagonist effects; could make these progestins less immunosuppressive
MPA binds to most receptors with greater affinity than P.

Table 6
Relative binding affinities of progesterone and synthetic progestins to steroid receptors and serum binding proteins

<table>
<thead>
<tr>
<th>Progesterone</th>
<th>PR</th>
<th>AR</th>
<th>ER</th>
<th>GR</th>
<th>MR</th>
<th>SHBG</th>
<th>CBG</th>
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</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>100</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>100</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Chlormadinone acetate</td>
<td>67</td>
<td>5</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>90</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Medroxyprogesterone acetate</td>
<td>115</td>
<td>5</td>
<td>0</td>
<td>29</td>
<td>160</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Megestrol acetate</td>
<td>65</td>
<td>5</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nomegestrel</td>
<td>125</td>
<td>6</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pronegestone (R5020)</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>53</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drosperitone</td>
<td>35</td>
<td>65</td>
<td>0</td>
<td>6</td>
<td>230</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>75</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>150</td>
<td>45</td>
<td>0</td>
<td>1</td>
<td>75</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Norgestimate</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3-Keto-desogestrel</td>
<td>150</td>
<td>20</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Gestodene</td>
<td>90</td>
<td>85</td>
<td>0</td>
<td>27</td>
<td>290</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Dienogest</td>
<td>5</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The reference steroids are listed. Taken from reference [8,10,13,15]. PR: progesterone receptor (pronegestone = 100%). AR: androgen receptor (meibolone = 100%). ER: estrogen receptor (estradiol-17β = 100%). GR: glucocorticoid receptor (dexamethason = 100%). MR: mineralocorticoid receptor (aldosterone =100%). SHBG: sex hormone-binding globulin (dihydrotestosterone = 100%). CBG: corticosteroid-binding globulin (cortisol = 100%).

From Schindler 2003
Atrophic vaginal epithelium develops during the post-menopausal period; result of hypoestrogenic state.

Post-menopausal women appear to be at increased risk of HIV-1 acquisition.

European Study Group on Heterosexual Transmission, 1992

However, studies in women on effect of DMPA on vaginal structure have conflicting results.

Mauck, 1999; Bahamondes, 2000; Miller, 2000
Hormonal Contraception and Cervical Ectopy

- Highly prevalent among younger women
- More common among women using COCs but not among DMPA users
  
  Critchlow 1995; Baeten, 2001; Bright 2011

- Associated with HIV-1 acquisition in some but not all studies
  
  Plourde 1994; Morrison, personal communication
Non-ulcerative genital tract infections increase HIV susceptibility.

An association between HC use and STD risk could mediate a link between hormonal contraception and HIV.
Hormonal Contraception and Cervical STIs among HIV-1 Negative Women in Mombasa

<table>
<thead>
<tr>
<th></th>
<th>Oral contraceptive pills</th>
<th>DMPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>1.8 (1.1-2.9)</td>
<td>.03</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>1.4 (0.9-2.1)</td>
<td>.1</td>
</tr>
<tr>
<td>Cervicitis</td>
<td>1.8 (1.5-2.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

- Women using OCs or DMPA compared with those using no contraceptive method or with tubal ligation.
- Multivariate HRs adjusted for age, education, yrs of prostitution, parity, workplace, number of sexual partners, number of sexual acts, condom use.
HC and Alterations in Vaginal Flora

- COC users have increased incidence of yeast vaginitis (direct effect of estrogen?); vaginal yeast colonization shown to increase HIV risk
  
  Baeten 2001; van de Wijgert 2008; Martin 1998

- Studies show DMPA decreases vaginal colonization with H$_2$O$_2$-producing Lactobacilli and H$_2$O$_2$-producing Lactobacilli protective against HIV
  
  Miller 2000; Martin 1999

- Studies consistently suggest that BV is associated with increased HIV acquisition
  
  van de Wijgert 2008

- However, DMPA and COCs were negatively associated with BV in both HC-HIV and Mombasa studies
  
  Baeten 2001; van de Wijgert 2008
Compared cervical samples from 832 women from UG and ZM: 199 becoming HIV-pos at next visit with matched samples from 633 remaining HIV-neg

- HIV seroconversion: Increase in RANTES and decrease in SLPI
- DMPA use: Increased RANTES and ICAM-1; reduced BD-2 levels
- COC use: Increase in pro-inflammatory mediators (IL1β, IL6, IL8, MIP3α, and SLPI); decrease in protective anti-inflammatory markers (IL1RA:IL1 ratio and BD-2). Similar for pregnant women
- HC use and pregnancy may affect the immuno-inflammatory environment in the female genital tract; should be considered when evaluating HIV infection risk

(Source: Morrison 2012)
Genital tract immunology and DMPA

• 15 woman provided vaginal biopsies during the follicular and the luteal phases of the cycle and 12 weeks following DMPA injection
• No significant differences in epithelial thickness and density of epithelial tight junction proteins among the follicular, luteal and post-DMPA vaginal mucosal tissues
• However, DMPA caused changes in immune cell populations (compared to either follicular and/or luteal phases) known to be involved in early HIV infection:
  • ↑ CD45+ leukocytes and CD3+ T lymphocytes (& CD8+ subsets) in tissue
  • ↑ in HLA-DR+ and CCR5 bearing immune cells

(Source: Chandra 2012)
Direct Viral Effects of Contraception on HIV-1

- Steroid hormones may bind the hormone-responsive element in the HIV-1 LTR and upregulate viral expression
  *Furth 1990*

- MPA resulted in increased proliferation of CCR5 and CXCR4-tropic viruses in activated PBMC cultures
  *Hel 2012*

- Studies from macaques demonstrate increased early viral replication in animals treated with progesterone
  *Abel 2004*

- Studies from Mombasa found HC use to predict early viral genetic diversity; genetic diversity associated with ↑ viral load and faster CD4 decline
  *Sagar 2004; Sagar 2003*
Summary: Possible Mechanisms in Humans

- Menopause: reduction in hormones
- Changes in vaginal and cervical structure (vaginal thinning, cervical ectopy)
- Changes in vaginal flora
- Genital tract infections
- Changes in genital tract immunity
- Direct effect (viral replication)
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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
### Adjusted Hazard Ratios for HIV Acquisition by Contraceptive Group: Original and MS Modeling Reanalysis

<table>
<thead>
<tr>
<th>Contraceptive Group</th>
<th>Original Analysis(^1) HR (95% CI)</th>
<th>All data without weight</th>
<th>MSM Reanalysis HR(^2) (95%CI)</th>
<th>All data with weight</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HC</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>P</td>
</tr>
<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>
<td>1.19 (0.80, 1.76)</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>
<td>1.48 (1.02, 2.15)</td>
</tr>
</tbody>
</table>

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.
### HIV Incidence Rates and Multivariate Hazard Ratios for Incident HIV by Age and Contraceptive Exposure: MS Modeling 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>Age group: &lt; 24</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<tr>
<td><strong>Age group: &gt; 24</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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
Partners/HSV Study: HC/HIV Analysis

- Secondary analysis of HSV acyclovir suppression trial
- 7 African countries, 14 sites
- 3790 discordant couples
  - Followed for 1-2 years
  - 2/3 couples – woman HIV-positive
- Linked HIV incidence
  - Male → Female – 4.1/100 p-y
  - Female → Male – 1.7/100 p-y

Source: Heffron (2011)
Partners/HSV Study: HC/HIV Acquisition – HIV-negative Women

- 1314 HIV- women – 7% OCs, 16% injectables (11% of follow-up time)
  - 73 women acquired HIV: 3 OC users and 10 injectable users
- HIV+ male: transmission to HIV- female
  - Adjusted HR for OCs: 1.8 (0.6-5.8)
  - Adjusted HR for injectables: 2.1 (1.0-4.0)

Source: Heffron (2011)
Prospective, observational studies of OCs & HIV acquisition, regardless of study quality
Adjusted OR, IRR, or HR (log scale) and 95% CI

Plummer 1991†
Sinei 1996
Kilmarx 1998
Heffron 2012*
Feldblum 2010
Baeten 2007†
Morrison 2007/2010*
Kiddugavu 2003
Kapiga 1998
Saracco 1993
Wand 2012
Reid 2010
Laga 1993
McCoy 2013
Morrison 2012*
Myer 2007
Ungchusak 1996

OCs DECREASE HIV risk

OCs INCREASE HIV risk
Prospective, observational studies of injectables & HIV acquisition, regardless of study quality
Adjusted OR, IRR, or HR (log scale) and 95% CI

Ungchusak 1996 †
Kumwenda 2008 †
Wand 2012 †
Feldblum 2010
Heffron 2012 †,*
Bulterys 1994
Kleinschmidt 2007
Baeten 2007 †
Watson-Jones 2009
Kilmarx 1998
Morrison 2007/2010 *, δ
McCoy 2013
Morrison 2012 *
Myer 2007
Reid 2010
Kiddugavu 2003
Kapiga 1998

LEGEND
- DMPA alone
- Net-En alone
- Any injectable
- Mostly injectable, some OC

0.1 Injectables DECREASE HIV risk
1 10 Injectables INCREASE HIV risk
Prospective, observational studies of OCs and HIV
STUDIES MEETING MINIMUM QUALITY CRITERIA

Heffron 2012

Baeten 2007

Morrison 2007/2010

Kiddugavu 2003

Reid 2010

Morrison 2012

Myer 2007

OCs DECREASE HIV risk

OCs INCREASE HIV risk

MSM \downarrow \downarrow \text{Cox}

\text{Cox} \downarrow \downarrow \text{MSM}

\text{MSM} \downarrow \downarrow \text{Cox}
Prospective, observational studies of injectables and HIV acquisition
STUDIES MEETING MINIMUM QUALITY CRITERIA
De picting estimates that combine DMPA and Net-En, if provided
Summary: HC and HIV Acquisition

• OCs - 2/17 prospective studies found significantly increased HIV risk
• DMPA – 6/17 prospective studies found significantly increased HIV risk
• Only 3 studies designed to test HC-HIV hypothesis
• All studies were observational
• Better evidence urgently needed
Cohort studies: Strengths & Weaknesses

- **Strengths**
  - Provide incidence data and establish time sequence for causality
  - Have accurate measurement of HC exposure, HIV outcome
  - Have sufficient HC users and non-users
  - Have high retention rates and low switching

- **Weaknesses**
  - Selection bias: reduced but not eliminated by analyses
  - Unmeasured confounding: Condom use, HIV status of partners, differences in sexual practices
  - Self-reported information on sensitive sexual behaviors
Potential Spurious Associations

• Self-selection into HC use can affect risk of HIV exposure (selection bias)
  – HC users may have higher coital frequency, lower condom use; could be at greater risk of exposure to HIV due to behavioral differences

• HC users often compared to “non-users”
  – Definition of “non-users” varies, often includes condom-contraceptors
  – Self-reported condom use unreliable; dual use of HC, condoms is rare

- Study 1: No condoms or DMPA
- Study 2: largely condom users

Exposure to HIV
Exposure to HIV?
Evidence in Context

• Possible increased risk of HC on HIV acquisition must be balanced against:
  – Risks of unintended pregnancy (maternal death, maternal morbidity, unsafe abortion, infant mortality)
  – Any increased risk of HIV acquisition associated with pregnancy
Does Pregnancy Affect HIV Risk?
HIV-negative Women

- Partners HSV/HIV Trial - same database
- 3321 Discordant Couples
- Linked HIV Incidence: Male → Female – 3.6/100 p-y
- 320 pregnancies in HIV- women – 29%
- HIV+ male: transmission to HIV- pregnant female
  - HIV Incidence: 7.4/100 p-y
  - Crude HR: 2.3 (1.3 – 4.1), p = 0.003
  - Adjusted HR: 1.7 (0.9 – 3.1), p = 0.08

Source: Mugo (2011)
So...What’s An Uninfected Woman To Do?

• If she uses DMPA,
  — Less risk of pregnancy
  — More risk of HIV acquisition?
• If she becomes pregnant,
  — More risk of HIV acquisition?
  — More risk of pregnancy M&M
• Tradeoffs
“C’mon, c’mon – it’s either one or the other.”
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WHO Consultation – The Agenda

• Jan 31 – Feb 2, 2012 in Geneva
• Synthesis of published literature on hormonal contraception/HIV
  – Acquisition
  – Transmission
  – Progression
• GRADE rating of the evidence
• Discussion of MEC criteria
WHO Consultation – GRADE Process

• Goal - To achieve transparency, standardization and rigor in summarizing evidence
• Adapted by many groups – WHO, CDC, et.al.
• Starting points
  – RCTs = “high quality”
  – Observational = “low quality”
• HC/HIV acquisition evidence
  – 8 cohort studies met minimum quality criteria
  – Serious limitations; rated “low overall quality”
### WHO Medical Eligibility Criteria for Contraceptive Use

<table>
<thead>
<tr>
<th>Classification of Known Conditions</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No restriction on use</td>
</tr>
<tr>
<td>2</td>
<td>Benefits generally outweigh risks</td>
</tr>
<tr>
<td>3</td>
<td>Risks generally outweigh benefits</td>
</tr>
<tr>
<td>4</td>
<td>Unacceptable health risk</td>
</tr>
</tbody>
</table>
Hormonal contraception and HIV
Technical statement

Executive summary
Following new findings from recently published epidemiological studies, the World Health Organization (WHO) convened a technical consultation regarding hormonal contraception and HIV acquisition, progression and transmission. It was recognized that this issue was likely to be of particular concern in countries where women have a high lifetime risk of acquiring HIV, where hormonal contraceptives (especially progestogen-only injectable methods) constitute a large proportion of all modern methods used and where maternal mortality rates remain high. The meeting was held in Geneva between 31 January and 1 February 2012, and involved 75 individuals representing a wide range of stakeholders. Specifically, the group considered whether the guideline Medical eligibility criteria for contraceptive use, Fourth edition 2009 (MEC) should be changed in light of the accumulating evidence.

After detailed, prolonged deliberation, informed by systematic reviews of the available evidence and presentations on biological and animal data, GRADE profile summaries on the strength of the epidemiological evidence, and analysis of risks and benefits to country programmes, the group concluded that the World Health Organization should continue to recommend that there are no restrictions (MEC Category 1) on the use of any hormonal contraceptive method for women living with HIV or at high risk of HIV. However, the group recommended that a new clarification (under Category 1) be added to the MEC for women using progestogen-only injectable contraception at high risk of HIV as follows:

Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition, other studies do not show this association. A WHO expert group reviewed all the available evidence and agreed that the data were not sufficiently conclusive to change current guidance. However, because of the inconclusive nature of the body of evidence on possible increased risk of HIV acquisi-
WHO Consultation – The Outcome

- Recommendation – MEC Category 1 (no restrictions)
- 1* Clarification – “women using progestogen-only injectables strongly advised to also always use condoms”
WHO Consultation – Programmatic Recommendations

• Withdrawal of injectable progestins (DMPA-Net-EN) from FP programs is not warranted
• Contraceptive method mix needs to be expanded (adding long-acting methods – e.g. IUDs, implants) especially for women at risk of HIV
• Condoms must be strongly emphasized
• FP and HIV programs should be integrated
WHO Consultation – Research Recommendations

• Higher quality clinical studies are needed to improve the HC/HIV acquisition evidence
• Developing new multipurpose technologies to prevent both HIV and unintended pregnancy – a high level priority
• Understanding the biology of HC/HIV interactions essential
Hormonal Contraception and HIV: Presentation Outline

- Background
- Data from non-human primates
- Biologic rationale in humans
- Epidemiologic studies of hormonal contraception (HC) and HIV acquisition
- WHO Consultation
- Next steps
Why an RCT Now?

- Macaque studies continue to find increased SIV transmission with DMPA
- HIV prevention trials have high HIV rates among young women; most using DMPA
- Programs promote CBD of DMPA in rural Africa
- Recent HC/HIV findings have raised visibility/concern
- We need to resolve this important global health issue once and for all
RCT Strengths/Limitations

• **Strengths**
  – Gold standard; Avoids selection and confounding biases associated with most cohort studies

• **Limitations**
  – Comparatively expensive
  – Need high product continuation and low loss to follow up
  – May be less generalizable
  – If unblinded - behaviors not guaranteed to remain comparable during follow-up
Design Issues for an HC-HIV RCT

- How many arms should the study have; what should those arms be?
- What should the target population be?
- Will women accept random assignment to dissimilar contraceptive methods?
- What age groups should we focus on?
- What level of effect is it important to detect?
- How do we maximize retention and adherence?
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  – USAID
  – WHO
  – CONRAD
  – Study Participants from African sites