Hormonal Contraception and HIV: What A Difference A Year Makes!

Ward Cates
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Acknowledgments

Colleagues from:

- FHI 360
- University of Washington
- WRHI
- Gates Foundation
- USAID
- And many more…
Today’s Talk

• Where We Were Last Year
• Major Intervening Events
• RCT or No RCT: That is the Question
Where We Were at HPTN Last Year
Studies of Injectables & HIV Acquisition

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

Source: Adapted from Polis 2012
Limitations of HC/HIV Observational Studies

- Potential for unmeasured selection bias
- Potential for confounding
- Hormonal contraceptive use not adequately documented
- Non-hormonal comparison group with greater condom use
HC/HIV Results – What Do They Mean?

- **Non-Hormonal Group**
  - Greater condom use
  - Higher partner risk score

- **DMPA Group**
  - Less condom use
  - Lower partner risk score
  - Biologic effect hypothetical
WHO Consultation – GRADE Rating

- **HC/HIV acquisition evidence**
  - 8 cohort studies met minimum quality criteria
  - Serious limitations
  - Rated “low overall quality”

- **HC/HIV transmission evidence**
  - Rated “low overall quality”

- **HC/HIV progression evidence**
  - 1 RCT, 6 cohort studies
  - Rated “low overall quality”
WHO Consultation – Recommendations

- Withdrawal of hormonal contraception from FP programs is not warranted
- Contraceptive method mix needs to be expanded, especially for women at risk of HIV
- Condoms must be strongly emphasized
- Conduct higher quality clinical studies to improve the HC/HIV acquisition evidence
Major Intervening Events
Unless FP is Increased in Africa, Eliminating MTCT Goal Will Not Be Met

• CROI 2013 – N’Galy-Mann Lecture

• Even with 90% ART coverage, unintended pregnancies lead to >40,000 HIV+ infants

• Contraceptive Prevalence

  ➢ Africa – 22%
  ➢ US – 73%

Source: Mofenson, CROI 2013
The London FP Summit – July 2012

Sponsors:

• Bill & Melinda Gates Foundation
• UK Government

Outcomes:

• Raised $4.2B
• Established FP 2020 goals
Injectable Contraception & HIV Acquisition Studies Meeting Minimal Criteria

Heffron 2011
Baeten 2007
Morrison 2012
Morrison 2010
McCoy 2013
Myer 2007
Reid 2010
Kiddugavu 2003
Kleinschmidt 2007

Source: Adapted from Polis (2013)
Effectiveness of Long-Acting Reversible Contraception

Brooke Winner, M.D., Jeffrey F. Peipert, M.D., Ph.D., Qiuhong Zhao, M.S., Christina Buckel, M.S.W., Tessa Madden, M.D., M.P.H., Jenifer E. Allsworth, Ph.D., and Gina M. Secura, Ph.D., M.P.H.

BACKGROUND
The rate of unintended pregnancy in the United States is much higher than in other developed nations. Approximately half of unintended pregnancies are due to contraceptive failure, largely owing to inconsistent or incorrect use.

METHODS
We designed a large prospective cohort study to promote the use of long-acting reversible contraceptive methods as a means of reducing unintended pregnancies in our region. Participants were provided with reversible contraception of their choice.
CHOICE – Main Findings

- >75% chose IUDs/Implants
- IUD/Implants associated with higher continuation & satisfaction than DMPA and OCs
- IUDs/Implants associated with 20-fold lower rates of unintended pregnancy
- Increasing IUDs/Implant use decreased unintended pregnancy and abortion at the population level
Method Mix Advocacy

- WHO Meeting on DMPA Counseling, May 2012
- AIDS 2012 – Community Forum on HC/HIV
- MTN’s Contraceptive Action Team Initiative
- CROI 2013 – Sessions on Contraceptive Trends in PEPFAR programs
RCT or No RCT –
That is the question
What If No RCT?

- "Etiologic purgatory" – "Low-quality" evidence will remain inconclusive
- WHO recommendations will not change
- Counseling messages will be awkward
- HIV prevention trials using DMPA will be vulnerable to ethical criticism if high HIV rates continue to occur
- Media/advocates will continue to stress worst case HC/HIV acquisition findings
## DMPA Use in Recent Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>DMPA Use as Percentage of Contraceptive Users</th>
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</thead>
<tbody>
<tr>
<td>PARTNERS/HSV</td>
<td>73%</td>
</tr>
<tr>
<td>CAPRISA 004</td>
<td>93%</td>
</tr>
<tr>
<td>MDP 301</td>
<td>71%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>69%</td>
</tr>
<tr>
<td>VOICE</td>
<td>75%</td>
</tr>
<tr>
<td>PARTNERS/PrEP</td>
<td>78%</td>
</tr>
</tbody>
</table>
What a Well-Done RCT Will Provide

- Results will have high internal/external validity
- Women will have accurate information to make individual decisions about use of long-acting contraceptive methods
- Providers will be better informed as to which contraceptive methods to offer
- Contraceptive method mix will be enhanced
HC/HIV RCT - Design

10,600 Women Wanting Not to Conceive Willing to be randomized

Randomize

DMPA  NET-EN  Jadelle  Cu IUD

3 Month Visits

1º Endpoint: HIV Infection

Other Endpoints: Method Continuation, Pregnancy
Framing the HC/HIV Trial

Eligible Women

- DMPA
- NET-EN
- Jadelle
- Cu IUD

- IUD as the Index Comparator

OR

- DMPA as the Index Comparator
Comparing Results – How to Frame?

• If IUD arm is the index
  – Hormonal methods assessed for relative harm

• If DMPA is the index
  – Alternatives are assessed for relative safety and convenience
HC/HIV Trial: Hypothetical Incidence

Eligible Women

- DMPA: 7.0
- NET-EN: 5.0
- Jadelle: 4.8
- Cu IUD: 4.9

Hypothetical Incidence Per 100 women-years
Hypothetical Outcome with IUD as Index

Eligible Women

- **DMPA**
  - Hazard Ratio: 1.6
- **NET-EN**
  - Hazard Ratio: 1.2
- **Jadelle**
  - Hazard Ratio: 1.0
- **Cu IUD**
  - Hazard Ratio: 1.0

**ASSUMPTIONS**

- DMPA significantly increases HIV risk compared to IUD
- NET-EN associated with slight, non-significant risk
- Jadelle has no difference
Hypothetical Outcome with DMPA as Index

ASSUMPTIONS
- Copper IUD and Jadelle significantly safer than DMPA
- NET-EN non-significantly safer than DMPA
Anticipated Feasibility Milestones

• Willingness of women to be randomized:
  – Feasibility established (Hofmeyer, Feldblum, Hubacher)

• Differential method continuation – would undermine the randomized design
  – Method continuation improved with careful planning and counseling (CHOICE study)
2012 → 2013 - What a Year for FP!

- Eliminating MTCT includes FP
- London Summit and FP 2020
- Additional observational evidence
- Contraceptive CHOICE findings – IUDs, Implants
- Growing Advocacy for Increasing Contraceptive Method Mix
Thank You