Hormonal Contraception and the Risk of HIV Acquisition

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Member of the ECHO Consortium
Disclosures

- No known Conflicts of Interest
Objectives

■ To describe the epidemiology of HIV and its global interface with Progestin injectables

■ To outline the research on injectable progestin contraception and the possible increased risk of HIV acquisition

■ To outline the content of WHO discussions and recommendations from meetings of experts and of advocates and their consequences
“Love is the answer, but while you are waiting for the answer, sex raises some pretty good questions.” Woody Allen
Patterns of modern method use

In some regions high HIV prevalence coincides with high use of injectable hormonal contraceptives

HIV prevalence among 15-49 year-old women*

Injectable hormonal contraceptive use among 15-49 year-old women

Progestin contraceptives differ

- Chemical structure
- Pharmacokinetic and pharmacodynamic parameters
- Bioavailability
  - Oral and vaginal
- Progestational potency
- Mechanism of action via different steroid receptors
  - Impact on side-effects, safety, benefits
- Different impacts on immune system
The possible mechanisms for an interaction between hormonal contraception and HIV-1

- Vaginal and cervical epithelium
- Cervical mucus
- Menstrual patterns
- Vaginal and cervical immunology
  - HIV Receptor concentrations and types vary by cell and tissue type
- Impact on HIV replication
- Acquisition of other STIs

The impact of all these differences on clinical outcomes is unknown
When did the concern begin...?

1988 onwards: multiple secondary analysis

1987 Plummer IAS Washington DC

1996 NIH Review

1996 Preston Marx monkey study

2008 First WHO MEC review
Progesterone implants enhance SIV vaginal transmission and early virus load


Progestin-based contraceptive suppresses cellular immune responses in SHIV-infected rhesus macaques

Nataliya Trunova, Lily Tsai, Stephanie Tung, Eric Schneider, Janet Harouse, Agegnehu Gettie, Viviana Simon, James Blanchard, Cecilia Cheng-Mayer

Abrogation of Attenuated Lentivirus-Induced Protection in Rhesus Macaques by Administration of Depo-Provera before Intravaginal Challenge with Simian Immunodeficiency Virus mac239

Kristina Abel, Tracy Rourke, Ding Lu, Kristen Bost, Michael B. McChesney and Christopher J. Miller

DMPA Virology, 2006

- Pal et al., Virology 2009
- Turville et al., PLoS One 2008

DMPA J. Infect. Dis., 2004
Making sense of the data:

WHO’s Medical Eligibility Criteria for Contraceptive Use
Eligibility Criteria for Contraceptive use: WHO Classifications based on the GRADE approach to evidence and expert opinion

<table>
<thead>
<tr>
<th>Classification of 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>
Contraception and HIV: Considerations

Women at risk for HIV
- Prevention
- Acquisitio
- Infectiousness

Women infected with HIV
- Disease progression
- Drug interactions
2009 WHO Medical Eligibility Criteria
Guidance for women at high risk of HIV acquisition:

**Copper IUD**
- Limited data: Overall Category 2
- For women at high risk of chlamydia or gonorrhea Category 3

**Combined oral contraceptive pills**
- Category 1 – ‘No Restriction’
Injectable Progestins (DMPA and NET-EN)

- Category 1 – ‘No Restriction’

‘Balance of evidence suggests no association between progestin contraceptives, although studies of DMPA use conducted among higher risk populations have repeated inconsistent findings’
The trigger for a renewed debate:

■ Partners in Prevention Study: Analysis of HIV acquisition and Hormonal Contraception use presented at IAS Conference, Rome, July 2011

■ Prospective cohort study of 3790 HIV-1 discordant couples from East and Southern Africa

Heffron et al, IAS July 2011
## Contraception and HIV acquisition from men to women

<table>
<thead>
<tr>
<th></th>
<th>HIV incidence per 100 person years</th>
<th>Adjusted Cox PH Regression analysis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No hormonal contraception</strong></td>
<td>3.78</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td><strong>Any hormonal contraception</strong></td>
<td>6.61</td>
<td>1.98 (1.06 – 3.68)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Injectables</strong></td>
<td>6.85</td>
<td>2.05 (1.04 – 4.04)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Oral contraceptives</strong></td>
<td>5.94</td>
<td>1.80 (0.55 – 5.82)</td>
<td>0.33</td>
</tr>
</tbody>
</table>
Hormonal Contraception and the Risk of HIV Acquisition: An Individual Participant Meta-Analysis

10/6/2013—slide 18

Female hormonal contraception linked to higher risk of HIV acquisition.
WHO Expert Consultation on HC and HIV

- Jan 2012, Geneva, 75 participants from 18 countries
  - HIV Acquisition
  - HIV Transmission
  - HIV Progression
- GRADE rating of the evidence
- Discussion of MEC criteria
- Programmatic implications
- Research agenda
The WHO consultation focused on eight 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)
The Great Debate

Observational data

Unmeasured selection bias

Potential for Confounding

Not always primary study endpoint

HC use not always well documented

Self reported condom use unreliable

Condom use differed between non-HC arms and HC arms
After detailed, prolonged deliberation...

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

However, because of the inconclusive nature of the evidence, women using progestogen-only injectable contraception should be strongly advised to also always use condoms...

The group further wished to draw the attention of policy-makers and programme managers to the potential seriousness of the issue and the complex balance of risks and benefits.

Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential.
What then happened? .......

HIV warning to women using injectable contraception

World Health Organisation advises use of oral contraceptives to prevent HIV infection

Sarah Boseley, health editor
guardian.co.uk, Thursday 16 February 2012 14:00 EST

The New York Times
February 17, 2012

Switzerland: Agency Stands by

The Asian Age

‘Hormonal contraceptives safe for women’

TEENA THACKER
263 words
18 February 2012

Top News

Women Using Injectable Contraception Warned of HIV

The Herald

Zimbabwe: World Health Organisation Recommends Use of Hormonal Contraceptives

BY PAIDAMOYO CHIPUNZA, 22 FEBRUARY 2012

The Star

Kenya: Hormonal Contraception

BY JOHN MUCHANGI, 18 FEBRUARY 2012

Uganda Picks

World Health Organization Clarifies Guidance on Hormonal Contraception and HIV

Published: February 18, 2012
What then happened......

- Some activists, women's organisations and journalists said they did not understand the Category ‘1’ and the clarification

- Requested clarity on the messaging that should be given to women users

- Some researchers and donors considering an RCT as a definitive study

- Widespread calls for increasing the method mix in developing countries

- And the modellers are involved......
Public health implications of a hypothesised injectable hormonal contraception – HIV interaction

Excess HIV infections per year

- South Africa
- Kenya
- Malawi
- Tanzania
- Uganda
- Zimbabwe
- Nigeria
- Zambia
- Mozambique
- Lesotho
- Egypt
- Ethiopia

Extra maternal deaths per year

- South Africa
- Kenya
- Malawi
- Tanzania
- Uganda
- Zimbabwe
- Nigeria
- Zambia
- Mozambique
- Lesotho
- Egypt
- Ethiopia

Butler et al. AIDS 2012, 26:000–000
Use of injectable contraceptives and HIV acquisition (all studies, regardless of quality)

Figure 3: Use of injectable contraceptives and HIV acquisition (all 16 studies)
For studies in which both Cox proportional hazards (Cox) and marginal structural model (MSM) analyses were reported, both are shown. Error bars show 95% CIs. IRR = incidence risk ratio. OR = odds ratio. HR = hazard ratio. DMPA = depot-medroxyprogesterone acetate. * Analysis showed significant findings.

Polis CB, Curtis KM. *Lancet Infectious Diseases* 2013;13(9):797-808.
To unlock the uncertainty... An RCT?
Thank You

- Ward Cates
- Charlie Morrison
- Chelsea Polis
- Tim Hallett
- John Cleland
- Vivian Black
- Sharon Phillips
- Mary Lyn Gaffield
- Mitchell Warren
- Maggie Kilbourne-Brook
- Melanie Pleanar
Hormonal Contraception and the Risk of HIV Acquisition: An Individual Participant Meta-Analysis

Charles Morrison PhD and Pai Lien Chen PhD, FHI360
Disclosures

- No known conflicts of interest
Learning Objectives

- Describe the basic design of the new individual participant data (IPD) meta-analysis of hormonal contraception and HIV acquisition
- State the overall findings of the meta-analysis
- Describe the strengths and limitations of the IPD meta-analysis
Background

- Evidence on whether hormonal contraception (HC) alters a woman’s risk of HIV acquisition is mixed

- To date no randomized control trials of HC use and HIV acquisition have been completed

- Associations between HC use and HIV acquisition have been examined in prospective cohort studies
Objectives

- To determine whether use of different hormonal contraceptives (COCs, DMPA and Net-En, separately) increases the risk of HIV acquisition compared to women not using hormonal contraception (HC).
  - Among women 15 – 24 years of age
  - Among women 25 – 49 years of age
  - To evaluate whether HSV-2 infection status modifies the effect of HC on the risk of HIV acquisition
- To compare the risks of HIV acquisition among the three HC groups.
Inclusion Criteria

To be included in the meta-analysis, studies met the following criteria:

- Measured HIV prospectively and at multiple time points using a standardized testing algorithm;
- Measured hormonal contraception use prospectively and at multiple time points using a standardized questionnaire;
- Included women between 15 – 49 years of age;
- Included women who used injectable contraception;
- Included at least 15 incident infections in the dataset; and
- Measured important covariates (e.g. age, condom use, number of sex partners)
IPD Meta-analysis – Two-stage approach

■ First stage: Estimate adjusted HRs of HC on HIV for each individual study based on covariates from:
  ■ A common set of covariates across studies, or
  ■ Individual set of covariates (‘best fit’ for each study)

■ Second stage: Obtain weighted HR from estimated adjusted HRs using:
  ■ Random effects model (include each adjusted HR variability)
  ■ Fixed effect model

■ Primary results based on random effects model using adjusted HRs and common set of covariates
Stratified Sensitivity Analyses

Based on:

- Age groups (15-24 vs. > 25 years)
- HSV-2 exposure status
- HC exposure switching (censor before 1st switch)
- Person-time where no condoms use reported
- Study region
Intravaginal Practices, Bacterial Vaginosis, and HIV Infection in Women: Individual Participant Data Meta-analysis

Nicola Low1*, Matthew F. Chersich2,3, Kurt Schmidlin1, Matthias Egger1, Suzanna C. Francis4, Janneke H. M. van de Wijgert5, Richard J. Hayes4, Jared M. Baeten6, Joelle Brown4,7, Sinead Delany-Morely8, Rupert Kaul9, Nuala McGrath9,10, Charles Morrison11, Landon Myer12,13, Marleen Temmerman3, Ariane van der Straten14, Deborah Watson-Jones4, Marcel Zwahlen1, Adriane Martin Hilber1

1Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland, 2Centre for Health Policy, School of Public Health, University of Witwatersrand, Johannesburg, South Africa, 3International Centre for Reproductive Health, Department of Obstetrics and Gynaecology, Ghent University, Ghent, Belgium, 4Department of Infectious Disease Epidemiology and Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom, 5Academic Medical Center of the University of Amsterdam and Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands, 6Departments of Global Health, Medicine, and Epidemiology, University of Washington, Seattle, Washington, United States of America, 7Department of Epidemiology, University of California, Los Angeles, California, United States of America, 8Reproductive Health and HIV Research Unit, University of Witwatersrand, Hillbrow, South Africa, 9Department of Medicine, University of Toronto, Toronto, Canada, 10Africa Centre for Health and Population Studies, University of Kwa-Zulu Natal, Durban, South Africa, 11Clinical Sciences Department, HIV Research Triangle Park, North Carolina, United States of America, 12Centre for Infectious Diseases Epidemiology and Research, School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa, 13Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York, United States of America, 14Women’s Global Health Imperative, RTI International, San Francisco, California, United States of America

Abstract

Background: Identifying modifiable factors that increase women’s vulnerability to HIV is a critical step in developing effective female-initiated prevention interventions. The primary objective of this study was to pool individual participant data from prospective longitudinal studies to investigate the association between intravaginal practices and acquisition of HIV infection among women in sub-Saharan Africa. Secondary objectives were to investigate associations between intravaginal practices and disrupted vaginal flora; and between disrupted vaginal flora and HIV acquisition.
Flow Diagram of Included Studies

Identification

Vaginal Practices Research Partnership Studies (n = 10)

Additional Studies Identified (n = 14)

Eligibility

Studies assessed for eligibility (n = 24)

Studies Excluded (n = 6)
- No contact with investigator, n = 1
- No agreement or no dataset, n = 2
- Did not meet inclusion criteria, n = 3

Included

Studies included in quantitative synthesis (meta-analysis) (n = 18)
Studies Included in Meta-Analysis

- 18 studies
- 3 regions
  - Eastern Africa
  - Southern Africa
  - South Africa
- 38,591 participants
- 1,887 incident HIV infections
## Baseline Characteristics by Contraceptive Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-Hormonal (n=18216)</th>
<th>COC (n= 5835)</th>
<th>DMPA (n= 9722)</th>
<th>NETEN (n= 3200)</th>
<th>Total (n=36973)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>32 (24-40)18216</td>
<td>26 (23-31)5835</td>
<td>27 (22-33)9722</td>
<td>23 (20-29)3200</td>
<td>28 (23-36)36973</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - 24</td>
<td>5163 (28.3)</td>
<td>2251 (38.6)</td>
<td>3760 (38.7)</td>
<td>1851 (57.8)</td>
<td>13025 (35.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Married/Living with partner</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8867 (48.7)</td>
<td>3849 (66.0)</td>
<td>4787 (49.3)</td>
<td>628 (19.6)</td>
<td>18131 (49.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>9347 (51.3)</td>
<td>1985 (34.0)</td>
<td>4932 (50.8)</td>
<td>2572 (80.4)</td>
<td>18836 (51.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex Worker</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1949 (17.8)</td>
<td>498 (11.8)</td>
<td>744 (11.6)</td>
<td>15 (0.9)</td>
<td>3206 (13.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>8993 (82.2)</td>
<td>3720 (88.2)</td>
<td>5697 (88.45)</td>
<td>1710 (99.1)</td>
<td>20120 (86.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Any condom use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes</td>
<td>9352 (52.8)</td>
<td>2564 (44.2)</td>
<td>4230 (44.0)</td>
<td>1426 (45.4)</td>
<td>17572 (48.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>6495 (36.7)</td>
<td>3090 (53.3)</td>
<td>4924 (51.2)</td>
<td>1619 (51.6)</td>
<td>16128 (44.5)</td>
<td></td>
</tr>
<tr>
<td>No sex</td>
<td>1868 (10.5)</td>
<td>147 (2.5)</td>
<td>465 (4.8)</td>
<td>95 (3.0)</td>
<td>2575 (7.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Consistency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Consistent</td>
<td>5963 (39.1)</td>
<td>1280 (24.2)</td>
<td>2540 (32.0)</td>
<td>966 (52.4)</td>
<td>10749 (35.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inconsistent</td>
<td>2476 (16.2)</td>
<td>1181 (22.3)</td>
<td>1470 (18.5)</td>
<td>218 (11.8)</td>
<td>5345 (17.6)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4948 (32.4)</td>
<td>2692 (50.8)</td>
<td>3462 (43.6)</td>
<td>563 (30.6)</td>
<td>11665 (38.5)</td>
<td></td>
</tr>
<tr>
<td>No Sex</td>
<td>1868 (12.3)</td>
<td>147 (2.8)</td>
<td>465 (5.9)</td>
<td>95 (5.2)</td>
<td>2575 (8.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Coital frequency past month</strong></td>
<td>6 (3-12)16890</td>
<td>12 (6-16)5626</td>
<td>8 (4-12)9312</td>
<td>8 (4-12)3192</td>
<td>8 (4-12)35020</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HSV-2 positive</td>
<td>8039 (69.4)</td>
<td>2805 (58.3)</td>
<td>4053 (63.8)</td>
<td>609 (49.0)</td>
<td>15506 (64.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
## Time-varying Contraceptive Use by Region¹ (women-years)

<table>
<thead>
<tr>
<th>Region</th>
<th>Number²</th>
<th>Non-hormonal WY (%)</th>
<th>COC WY (%)</th>
<th>DMPA WY (%)</th>
<th>Net-En WY (%)</th>
<th>Total WY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Africa</td>
<td>9890</td>
<td>7059.9 (53.8)</td>
<td>2473.3 (18.9)</td>
<td>3539.2 (27.0)</td>
<td>0.5 (0.0)</td>
<td>13112.4</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>6667</td>
<td>2885.5 (33.9)</td>
<td>3354.2 (39.4)</td>
<td>2261.3 (26.5)</td>
<td>59.2 (0.7)</td>
<td>8523.9</td>
</tr>
<tr>
<td>South Africa</td>
<td>20567</td>
<td>9042.1 (41.1)</td>
<td>2351.2 (10.7)</td>
<td>6384.0 (29.0)</td>
<td>3379.4 (15.4)</td>
<td>21977.2</td>
</tr>
<tr>
<td>All Studies</td>
<td>37124</td>
<td><strong>18988 (43.5)</strong></td>
<td><strong>8178.7 (18.8)</strong></td>
<td><strong>12184 (27.9)</strong></td>
<td><strong>3439.1 (7.9)</strong></td>
<td><strong>43613.5</strong></td>
</tr>
</tbody>
</table>

¹ Participant was <50 years old at enrollment and had one follow-up before 30 months from enrollment
² Women dropped from study from time of taking POP or having implant If multiple use, all contraception methods use in a time period are assigned the full time period
Contraceptive Use Patterns Compared to Baseline by Contraceptive Group$^{1,2,3}$

<table>
<thead>
<tr>
<th>Contraceptive Use During Follow-up</th>
<th>No HC (N=16626)</th>
<th>COC$^4$ (N= 5753)</th>
<th>DMPA$^4$ (N= 9548)</th>
<th>Net-En (N= 3163)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>No switch from baseline</td>
<td>11983 (72.1)</td>
<td>3453 (60.0)</td>
<td>6220 (65.1)</td>
<td>1972 (62.4)</td>
</tr>
<tr>
<td>Switched to HC</td>
<td>2783 (16.7)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Switched to different HC</td>
<td>N/A</td>
<td>374 (6.5)</td>
<td>665 (7.0)</td>
<td>385 (12.2)</td>
</tr>
<tr>
<td>Switched to no HC</td>
<td>N/A</td>
<td>1055 (18.3)</td>
<td>1242 (13.0)</td>
<td>333 (10.5)</td>
</tr>
<tr>
<td>Multiple Switching</td>
<td>1860 (11.2)</td>
<td>871 (15.1)</td>
<td>1421 (14.9)</td>
<td>473 (15.0)</td>
</tr>
</tbody>
</table>

$^1$Participant was <50 years old and did not use POP or Implant at enrollment, and had one valid HIV test before 30 months from enrollment.

$^2$151 women were excluded from baseline tables: 94 due to multiple HC use, and 57 due to missing contraception; therefore the total number of women at baseline in the meta-analysis is 37124.

$^3$1883 women were dropped from table due to missing follow-up contraception which precluded their classification.

$^4$379 unspecified OC classified as COC, 1116 unspecified injectable classified as DMPA at baseline.
## Unadjusted Hazard Ratios for Time-varying Contraceptive Use by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Time-varying COC (^1)</th>
<th>p-value</th>
<th>Time-varying DMPA (^2)</th>
<th>p-value</th>
<th>Time-varying Net-EN</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted HR (95% CI)</td>
<td></td>
<td>Unadjusted HR (95% CI)</td>
<td></td>
<td>Unadjusted HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Eastern Africa</td>
<td>1.49 (1.14, 1.96)</td>
<td>0.004</td>
<td>2.05 (1.66, 2.54)</td>
<td>&lt;.001</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Southern Africa</td>
<td>0.77 (0.58, 1.00)</td>
<td>0.053</td>
<td>0.91 (0.68, 1.20)</td>
<td>0.493</td>
<td>1.06 (0.30, 3.74)</td>
<td>0.934</td>
</tr>
<tr>
<td>South Africa</td>
<td>0.89 (0.69, 1.16)</td>
<td>0.398</td>
<td>1.46 (1.25, 1.70)</td>
<td>&lt;.001</td>
<td>1.38 (1.11, 1.70)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>All Studies</strong></td>
<td><strong>1.01 (0.84, 1.21)</strong></td>
<td><strong>0.944</strong></td>
<td><strong>1.56 (1.31, 1.86)</strong></td>
<td><strong>&lt;.001</strong></td>
<td><strong>1.51 (1.21, 1.90)</strong></td>
<td><strong>&lt;.001</strong></td>
</tr>
</tbody>
</table>

\(^1\) Includes unspecified OC
\(^2\) Includes unspecified injectable
**Adjusted Hazard Ratios for HC on HIV for All Studies**

<table>
<thead>
<tr>
<th>All Studies</th>
<th>Time-varying COC$^2$</th>
<th>Time-varying DMPA$^3$</th>
<th>Time-varying Net-EN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Two-stage: Random Effect Model</td>
<td>1.03 (0.88, 1.20)</td>
<td>0.723</td>
<td>1.5 (1.24, 1.83)</td>
</tr>
<tr>
<td>$I^2$</td>
<td>N/A</td>
<td>47.33</td>
<td>41.52</td>
</tr>
</tbody>
</table>

1 Adjusted for region, age, married/living with partner, time-varying >1 sex partner, time-varying condom use.
2 Includes unspecified OC
3 Includes unspecified injectable
Adjusted HIV Hazard Ratio for DMPA Use

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>McClelland</td>
<td>2.09 (1.47, 2.96)</td>
<td>10%</td>
</tr>
<tr>
<td>Myer</td>
<td>1.71 (0.87, 3.34)</td>
<td>5%</td>
</tr>
<tr>
<td>Morrison</td>
<td>1.22 (0.86, 1.72)</td>
<td>11%</td>
</tr>
<tr>
<td>Kaul</td>
<td>1.03 (0.45, 2.37)</td>
<td>4%</td>
</tr>
<tr>
<td>Francis</td>
<td>4.52 (1.92, 10.65)</td>
<td>4%</td>
</tr>
<tr>
<td>Watson Jones</td>
<td>2.21 (1.06, 4.59)</td>
<td>5%</td>
</tr>
<tr>
<td>MIRA</td>
<td>1.09 (0.83, 1.43)</td>
<td>12%</td>
</tr>
<tr>
<td>Palesa</td>
<td>0.36 (0.05, 2.78)</td>
<td>1%</td>
</tr>
<tr>
<td>Delaney-Morettwe</td>
<td>1.10 (0.38, 3.15)</td>
<td>3%</td>
</tr>
<tr>
<td>McGrath</td>
<td>1.69 (0.70, 4.08)</td>
<td>4%</td>
</tr>
<tr>
<td>Brown</td>
<td>0.93 (0.44, 1.94)</td>
<td>5%</td>
</tr>
<tr>
<td>Carraguard</td>
<td>1.07 (0.79, 1.43)</td>
<td>12%</td>
</tr>
<tr>
<td>Hayes Uganda</td>
<td>0.97 (0.29, 3.21)</td>
<td>2%</td>
</tr>
<tr>
<td>Hayes Tanzania</td>
<td>2.45 (1.04, 5.82)</td>
<td>4%</td>
</tr>
<tr>
<td>Partners in Prevention</td>
<td>1.93 (0.97, 3.81)</td>
<td>5%</td>
</tr>
<tr>
<td>MDP301</td>
<td>1.82 (1.41, 2.35)</td>
<td>12%</td>
</tr>
<tr>
<td>CAPRISA</td>
<td>2.52 (0.34, 18.65)</td>
<td>1%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>3.86 (0.15, 101.3)</td>
<td>0%</td>
</tr>
<tr>
<td>Overall (I^2=47%, p&lt;.001)</td>
<td>1.50 (1.24, 1.83)</td>
<td>100%</td>
</tr>
</tbody>
</table>
Adjusted HIV Hazard Ratio for COC Use

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>McClelland</td>
<td>1.49</td>
<td>(0.94, 2.34)</td>
<td>12%</td>
</tr>
<tr>
<td>Myer</td>
<td>0.83</td>
<td>(0.41, 1.68)</td>
<td>1%</td>
</tr>
<tr>
<td>Morrison</td>
<td>1.03</td>
<td>(0.72, 1.48)</td>
<td>20%</td>
</tr>
<tr>
<td>Kaul</td>
<td>0.50</td>
<td>(0.11, 2.17)</td>
<td>1%</td>
</tr>
<tr>
<td>Francis</td>
<td>1.04</td>
<td>(0.14, 8.01)</td>
<td>1%</td>
</tr>
<tr>
<td>Watson Jones</td>
<td>2.00</td>
<td>(0.99, 4.01)</td>
<td>5%</td>
</tr>
<tr>
<td>MIRA</td>
<td>0.94</td>
<td>(0.63, 1.40)</td>
<td>16%</td>
</tr>
<tr>
<td>Palesa</td>
<td>0.72</td>
<td>(0.15, 3.35)</td>
<td>1%</td>
</tr>
<tr>
<td>Delaney-Moretlwe</td>
<td>0.89</td>
<td>(0.11, 6.97)</td>
<td>1%</td>
</tr>
<tr>
<td>McGrath</td>
<td>0.72</td>
<td>(0.30, 1.74)</td>
<td>3%</td>
</tr>
<tr>
<td>Brown</td>
<td>0.79</td>
<td>(0.49, 1.28)</td>
<td>11%</td>
</tr>
<tr>
<td>Carraguard</td>
<td>0.58</td>
<td>(0.07, 4.83)</td>
<td>1%</td>
</tr>
<tr>
<td>Hayes Uganda</td>
<td>1.61</td>
<td>(0.48, 5.47)</td>
<td>2%</td>
</tr>
<tr>
<td>Hayes Tanzania</td>
<td>1.26</td>
<td>(0.38, 4.18)</td>
<td>2%</td>
</tr>
<tr>
<td>Partners in Prevention</td>
<td>1.08</td>
<td>(0.78, 1.51)</td>
<td>24%</td>
</tr>
<tr>
<td>MDP701</td>
<td>0.74</td>
<td>(0.08, 7.24)</td>
<td>0%</td>
</tr>
<tr>
<td>CAPRISA</td>
<td>2.60</td>
<td>(0.28, 24.07)</td>
<td>1%</td>
</tr>
<tr>
<td>FEM-PrEP</td>
<td>1.07</td>
<td>(0.91, 1.25)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Decreased Risk of HIV

Increased Risk of HIV

10/6/2013—slide 46
Adjusted HIV Hazard Ratio for Net-En Use
### Adjusted Hazard Ratios for HC on HIV Stratified by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Time-varying COC&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Time-varying DMPA&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Time-varying Net-EN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>15 – 24</td>
<td>0.91 (0.72, 1.16)</td>
<td>0.450</td>
<td>1.25 (1.00, 1.58)</td>
</tr>
<tr>
<td>25+</td>
<td>1.17 (0.88, 1.56)</td>
<td>0.282</td>
<td>1.69 (1.25, 2.28)</td>
</tr>
<tr>
<td>Test for HC x Age Interaction</td>
<td>0.522</td>
<td></td>
<td>0.384</td>
</tr>
</tbody>
</table>

<sup>1</sup> COC: Combined Oral Contraceptives

<sup>2</sup> DMPA: Depo-Provera
### Adjusted Hazard Ratios for HC on HIV Stratified by Baseline HSV-2 Status

<table>
<thead>
<tr>
<th>HSV Status</th>
<th>Time-varying COC¹</th>
<th></th>
<th>Time-varying DMPA²</th>
<th></th>
<th>Time-varying NetEN</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>HSV Positive</td>
<td>1.1 (0.87, 1.39)</td>
<td>0.430</td>
<td>1.6 (1.18, 2.17)</td>
<td>&lt;.001</td>
<td>1.61 (1.09, 2.37)</td>
<td>0.017</td>
</tr>
<tr>
<td>HSV Negative</td>
<td>1.23 (0.69, 2.21)</td>
<td>0.486</td>
<td>1.61 (1.09, 2.36)</td>
<td>0.015</td>
<td>1.14 (0.69, 1.88)</td>
<td>0.614</td>
</tr>
<tr>
<td>Test for HSV x HC Interaction</td>
<td>0.598</td>
<td></td>
<td>0.697</td>
<td></td>
<td>0.310</td>
<td></td>
</tr>
</tbody>
</table>
## Adjusted Hazard Ratios for Direct HC Comparisons

<table>
<thead>
<tr>
<th></th>
<th>DMPA vs. COC</th>
<th>DMPA vs. NET-EN</th>
<th>Net-EN vs. COC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>1.43 (1.23, 1.67)</td>
<td>1.32 (1.08, 1.61)</td>
<td>1.30 (0.99, 1.71)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>&lt;.001</td>
<td>0.006</td>
<td>0.055</td>
</tr>
<tr>
<td><strong>I²</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
### Adjusted Hazard Ratios for HC on HIV Censored at Visit Prior to First Condom Use

<table>
<thead>
<tr>
<th></th>
<th>Time-varying COC¹</th>
<th></th>
<th>Time-varying DMPA²</th>
<th></th>
<th>Time-varying NETEN</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>All Studies</td>
<td>1.08 (0.71, 1.65)</td>
<td>0.720</td>
<td>1.6 (1.11, 2.31)</td>
<td>0.012</td>
<td>1.32 (0.65, 2.69)</td>
<td>0.446</td>
</tr>
<tr>
<td>$I^2$</td>
<td>N/A</td>
<td>23.35</td>
<td>46.93</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ COC: Combined Oral Contraceptives
² DMPA: Depo-Provera
## Adjusted Hazard Ratios for HC on HIV by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Time-varying COC(^1) HR (95% CI)</th>
<th>p-value</th>
<th>Time-varying DMPA(^2) HR (95% CI)</th>
<th>p-value</th>
<th>Time-varying NETEN HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Africa</td>
<td>1.58 (1.19, 2.09)</td>
<td>&lt;.001</td>
<td>2.09 (1.68, 2.60)</td>
<td>&lt;.001</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Southern Africa</td>
<td>0.81 (0.61, 1.06)</td>
<td>0.130</td>
<td>0.94 (0.70, 1.26)</td>
<td>0.676</td>
<td>1.18 (0.33, 4.25)</td>
<td>0.799</td>
</tr>
<tr>
<td>South Africa</td>
<td>0.83 (0.63, 1.08)</td>
<td>0.159</td>
<td>1.3 (1.11, 1.53)</td>
<td>&lt;.001</td>
<td>1.17 (0.81, 1.70)</td>
<td>0.399</td>
</tr>
</tbody>
</table>

Test for Region x HC Interaction

- Southern Africa and HC Interaction: 0.007 <.001 0.963
- South Africa and HC Interaction: 0.003 0.002 0.964

Reference: Eastern Africa and no HC use
Summary of Results

- This IPD meta-analysis was large: comprised 18 studies, >38,000 participants, ~1,900 incident HIV infections

- Primary analysis results: 2-stage random effects
  - HR for DMPA: 1.50 (95% CI 1.24-1.83)
  - HR for COCs: 1.03 (95% CI 0.88-1.20)
  - HR for Net-En: 1.24 (95% CI 0.84-1.82)

- Many sensitivity analyses supported these overall results
Summary of Results

- HR for DMPA > Net-En > COCs

- Modification of HC effect on HIV:
  - No effect based on age, HSV-2 status
  - Effect seen by region

- Generally low heterogeneity in effect of HC on HIV across studies
Limitations of IPD Meta-analysis

- Bias due to study design or conduct cannot be avoided (e.g., 3 vs. 6 month follow-up)

- Limited ability to control for:
  - Selection biases: systematic differences between participants’ characteristics in HC exposure groups
  - Heterogeneity: Imbalances in prognostic factors associated with HIV acquisition across studies
  - Residual confounding: Not all subgroups and potential confounding variables are available in all studies
Strengths of IPD Meta-analysis

- Use of same analysis method in all trials can reduce the heterogeneity due to use of different analytic approaches in original analyses.

- Use of subgroup analysis to explore variability among trial level, study site level, and patient level across studies (e.g., region, age).

- Adjustment for imbalances in baseline characteristics.
Conclusions

Use of DMPA but not COCs or Net-En significantly increased the risk of HIV acquisition in this large IPD meta-analysis.

Overall results were consistent across many sensitivity analyses.

While this meta-analysis has many strengths (size, consistent modeling strategy), it cannot correct for potential selection and confounding biases of component studies.

A well conducted RCT is needed to conclusively answer this question.
Acknowledgements

- We wish to thank the following Co-Investigators for their contributions to this project.
  - **Nicola Low**, Institute of Social and Preventive Medicine, University of Bern, Switzerland
  - **Matthias Egger**, Institute of Social and Preventive Medicine, University of Bern, Switzerland
  - **Suzanna C. Francis**, Department of Infectious Disease Epidemiology and Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom
  - **Janneke H.H.M. van de Wijgert**, Academic Medical Center of the University of Amsterdam and Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands
  - **Richard Hayes**, Department of Infectious Disease Epidemiology and Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom
  - **Jared Baeten**, Department of Global Health and Epidemiology, University of Washington, Seattle, Washington, United States of America
  - **Joelle Brown**, Department of Epidemiology, University of California, Los Angeles, California, United States of America
  - **Sinead Delany-Moretiwe**, Wits Reproductive Health & HIV Institute, Hillbrow, Johannesburg, South Africa
  - **Rupert Kaul**, Department of Medicine, University of Toronto, Toronto, Canada
  - **Nuala McGrath**, Department of Infectious Disease Epidemiology and Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom and Africa Centre for Health and Population Studies, University of Kwa-Zulu Natal, Somkhele, South Africa
  - **Landon Myer**, Centre for Infectious Disease Epidemiology and Research, School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa
  - **Ariane van der Straten**, Women’s Global Health Imperative, RTI International, San Francisco, California, United States of America
  - **Deborah Watson-Jones**, Department of Infectious Disease Epidemiology and Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom
  - **Scott McClelland**, Department of Global Health and Epidemiology, University of Washington, Seattle, Washington, United States of America
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  - **Shenna McCormack**, Medical Research Council, Clinical Trials Unit, London, United Kingdom
  - **Saidi Kapiga**, Department of Infectious Disease Epidemiology and Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom
  - **Barbara Friedland**, Population Council, New York, New York, United States of America
  - **Helen Rees**, Wits Reproductive Health & HIV Institute, Hillbrow, Johannesburg, South Africa
  - **Lut Van Damme**, Department of Global Health, Bill and Melinda Gates Foundation, Seattle, Washington, United States of America
  - **Quarraisha Karim**, Center for the AIDS Program and Research, University of Kwa-Zulu Natal, Somkhele, South Africa
A (Potential) Randomized Clinical Trial to Assess the Relative Benefits and Risks, Including HIV Acquisition, of Different Highly-Effective Contraceptive Methods

Jared Baeten MD PhD
Departments of Global Health, Medicine, and Epidemiology
University of Washington
I have received research funding to explore the interaction between hormonal contraception and risk of HIV acquisition, and related questions, from the US National Institutes of Health and the Bill & Melinda Gates Foundation.

I have no other financial conflicts of interest.
Learning Objectives

- Summarize the limitations of currently-available evidence evaluating a potential association between contraceptive method and risk of HIV acquisition

- Overview the rationale for conduct of randomized trials in general and specifically what could be learned with a trial of this question

- Review the design of a proposed randomized trial of contraceptive methods and HIV acquisition risk

- Consider three key potential challenges to the conduct of a randomized trial
Starting Point

- 25+ years of epidemiologic and biologic studies have attempted to determine whether there is truly increased risk of HIV acquisition associated with use of certain types of contraception.

- The fact that there remains uncertainty today suggests that better evidence is needed to provide clarity for this important issue.
Limitations of Currently-Available Data

- Multiple observational studies, of variable quality, have assessed the question of whether specific contraceptive types heighten HIV acquisition risk.

- These data suffer from important limitations:
  - Inconsistency of results across studies
  - The potential for unmeasured confounding, particularly with regard to sexual behavior
  - Often, poor measurement of hormonal contraceptive exposure and evaluation of HIV outcomes
A Randomized Trial?

- Because of uncertainty and disagreement in the observational data, a randomized trial of contraception and HIV risk has been considered for well over a decade.

- In principle, unlike observational studies, a randomized trial would be substantially protected from bias by randomization:
  - Balancing HIV risk, risk behaviors, risk factors across study groups by randomization.
Why consider a randomized trial?

- In general, the primary reason to consider a major endeavor like a randomized clinical trial is whether it will change public health practice.
- HIV and reproductive health are of global public health importance.
- Current global and national policies call for obtaining high-quality data and there is uncertainty (equipoise) about for the answer to this question.
What If No Trial?

- Evidence base is unlikely to improve
- Counseling messaging will be continue to be challenging for providers, policymakers, and patients
- If HIV risk exists, unnecessary infections will occur
- If HIV risk does not exist, policies in some settings or individual women’s choices may react, with potentially negative consequences for maternal morbidity/mortality
Generic Trial Design

- Primary answer from the trial:
  - Relative HIV risk of different contraceptive methods compared to each other (= the public health question)
- Secondary outcomes: pregnancy, safety, discontinuation
- What a trial would not answer: contraception vs. nothing, other methods
### Potential Design

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Multi-center, open-label randomized clinical trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study arms</strong></td>
<td>1) DMPA, 2) NET-EN, 3) progestin implant (Jadelle), 4) copper IUD</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Sexually active HIV uninfected women, 18-35 years, seeking highly effective contraception, willing to be randomized to any study arm</td>
</tr>
<tr>
<td><strong>Study Sites</strong></td>
<td>Up to 25 sites in Eastern and Southern Africa</td>
</tr>
<tr>
<td><strong>Study Power</strong></td>
<td>80% power to detect a 1.5-fold increased risk between arms</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>~11,500 women (2875 per arm) ~600 HIV infection endpoints</td>
</tr>
</tbody>
</table>
FAQs

- Why multiple arms:
  - Provides relative risks for HIV of different highly-effective, widely-used methods
  - Inform (& jump start) goal of wider use of highly-effective methods

- Who will this trial inform:
  - Policymakers: highest-quality evidence
  - Providers: clear evidence for counseling
  - Patients: informed choice

- Wow. Can it be done?
Trial Integrity

- In general, randomized clinical trials maintain their integrity only if they are done well:
  - High retention, protocol and product adherence
  - Post-randomization changes non-differential across study arms (usually protected by blinding)
  - Ethical conduct

- One reason no trial has been initialed to date has been questions about feasibility challenges to a potential trial.  (Ralph et al., Lancet 2013)
Key Challenges

- **Evidence** *(is the question already answered?)*
  - Global/national policies call for high-quality evidence

- **Ethics** *(is it ethical to randomize, and to randomize to different methods [DMPA]?)*
  - Trials require equipoise – this question is not yet answered and DMPA specifically remains a highly-used contraceptive method globally

- **Feasibility** *(will women agree to randomization and continuation?)*
  - Arguably, to be seen and only knowable in a trial. Counseling ahead of randomization for trial willingness and provision of highly-effective methods both key.
Additional Considerations

- Community and advocacy engagement throughout the planning and execution process
- Policy planning before and while the trial is ongoing
- Scale-up of contraceptive services generally and expanded method mix (particularly LARCs)
- Messaging at all levels and in different geographies/populations
- Many more…, including costs
Summary

- Randomization would bypass many limitations of observational studies and provide highest-quality evidence.

- The principal considerations for a trial are whether key public health questions can be answered ethically and successfully.

- Willingness to be randomized, likelihood of holding to randomization group (adherence), and ability to remain in follow-up (retention) will be primary drivers of trial integrity.
ECHOCongsortium

**ECHO: The Evidence for Contraceptive Options and HIV Outcomes Trial**

- *World Health Organization* (Geneva, Switzerland): Marleen Temmerman, Mario Merialdi, Sharon Philips
- *University of Washington* (Seattle, USA): Jared Baeten, Connie Celum
- *Fred Hutchinson Cancer Research Center* (Seattle, USA): Deborah Donnell
- *Wits RHI* (Johannesburg, South Africa): Helen Rees
- *Eastern Cape Department of Health* (East London, South Africa): G Justus Hofmeyr
- *University of Nairobi* (Nairobi, Kenya): Peter Gichangi
- *KEMRI* (Nairobi, Kenya): Nelly Mugo
- *University of Zimbabwe* (Harare, Zimbabwe): Tsungai Chipato
Feasibility of the proposed randomized trial

Justus Hofmeyr and Mandisa Singata,
Effective Care Research Unit,
University of the Witwatersrand/Fort Hare/
Eastern Cape Department of Health,
on behalf of the ECHO Study Consortium
Disclosures

- No known conflicts of interest
Learning Objectives

■ To describe one clinical context within which the proposed trial could take place

■ To review previous randomized trials of hormonal contraception versus IUD

■ To present new data from randomized trial of DMPA vs. IUD: effects on depression and sexual dysfunction

■ To evaluate the feasibility of the proposed trial in the light of clinical experience and evidence from previous trials
Mdantsane, Eastern Cape (near East London, South Africa)
Obstetric services in East London, Eastern Cape, SA

- One in four pregnant women in our services have pregnancy terminations

- A substantial proportion of preterm births are from self-induced late pregnancy termination

- Survey of postpartum women (Mshweshwe 2007):
  - Two-thirds of women giving birth had unintended pregnancy
  - Three quarters had used contraception (97% depot progestins)
  - Stopped for various reasons, mainly side-effects

- The great majority of maternal and perinatal deaths are the result of unintended pregnancy

- We need robust evidence to improve our contraception services: is a randomized trial feasible?
FHI Trial 2005

- Feasibility study of random allocation to T380A IUD or DMPA contraception conducted by Family Health International in Brazil, Egypt, Guatemala and Vietnam

- Of 555 women screened, 368 (66%) recruited

- Lost to follow up: 8%

- Concluded randomization is feasible

Zambia trial: Stringer et al 2007

6 weeks postpartum HIV infected women in Zambia recruited

Randomly assigned to IUD vs. their choice of hormonal contraception

Followed at week 4 then 6 month intervals for 2 years or more

Of 908 eligible women, 599 (66%) agreed and returned for enrolment. Withdrawals: 13%

Lost to follow-up: 15%

Method discontinuation <15% in the first year

Stringer EM et al, A randomized trial of the intrauterine contraceptive device vs. hormonal contraception in women who are infected with the human immunodeficiency virus. Am J Obstet Gynecol 2007; 197: 144
Expanding Contraceptive Health Options: RCT of injectable progestins vs IUD (East London, ongoing)

- Objective: to improve knowledge on relative benefits and risks for future counselling
- Recruited women post pregnancy termination April 2009 to October 2012
- Study very well received and supported by clients
RCT: Effects of DMPA vs. IUD on depression and sexual function: Singata M (2013, in progress)

- Setting: Frere and Cecilia Makiwane Hospitals, East London, SA
- Recruited 242 postnatal women 4 Dec 2012 to 20 March 2013
- Telephone follow up 1 month 234 (97%)
- Telephone follow up 3 months 230 (95%)
  - Beck Depression inventory
  - Edinburgh Postnatal Depression Scale
  - Arizona Sexual Experience Scale
Effects of DMPA vs. IUD on depression and sexual function:

- 3 months sexual dysfunction (Arizona Sexual Dysfunction Scale)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DMPA</th>
<th>IUD</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex Drive Dysfunction ≥5</td>
<td>43</td>
<td>113</td>
<td>31</td>
<td>117</td>
</tr>
<tr>
<td>Arousal Dysfunction 5+</td>
<td>44</td>
<td>113</td>
<td>33</td>
<td>117</td>
</tr>
<tr>
<td>Wetness Dysfunction ≥5</td>
<td>37</td>
<td>112</td>
<td>35</td>
<td>115</td>
</tr>
<tr>
<td>Orgasm Dysfunction ≥5</td>
<td>11</td>
<td>45</td>
<td>7</td>
<td>63</td>
</tr>
<tr>
<td>Satisfaction Dysfunc.t.≥5</td>
<td>7</td>
<td>45</td>
<td>3</td>
<td>63</td>
</tr>
<tr>
<td>Arizona Sex. Experien 19+</td>
<td>12</td>
<td>113</td>
<td>12</td>
<td>117</td>
</tr>
<tr>
<td>Not having intercourse</td>
<td>58</td>
<td>111</td>
<td>51</td>
<td>115</td>
</tr>
</tbody>
</table>
Effects of DMPA vs. IUD on depression and sexual function:

- 3 month depression scores (Edinburgh Postnatal Depression Scale and Beck’s Depression Inventory)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DMPA Events</th>
<th>DMPA Total</th>
<th>IUD Events</th>
<th>IUD Total</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPDS ≥ 9</td>
<td>20</td>
<td>113</td>
<td>17</td>
<td>117</td>
<td>1.22 [0.67, 2.20]</td>
</tr>
<tr>
<td>EPDS ≥ 12</td>
<td>9</td>
<td>113</td>
<td>10</td>
<td>117</td>
<td>0.93 [0.39, 2.21]</td>
</tr>
<tr>
<td>BDI ≥ 14</td>
<td>30</td>
<td>113</td>
<td>23</td>
<td>118</td>
<td>1.36 [0.84, 2.20]</td>
</tr>
<tr>
<td>BDI ≥ 20</td>
<td>20</td>
<td>113</td>
<td>12</td>
<td>118</td>
<td>1.74 [0.89, 3.39]</td>
</tr>
<tr>
<td>BDI ≥ 29</td>
<td>8</td>
<td>113</td>
<td>2</td>
<td>118</td>
<td>4.18 [0.91, 19.25]</td>
</tr>
</tbody>
</table>
Effects of DMPA vs. IUD on depression and sexual function:

Conclusions

- Results statistically inconclusive
- Trend to more depression and sexual dysfunction with DMPA vs. IUD
- Possible effects of contraception methods on sexual function have implications for HIV acquisition
- Further research justified
- High level of acceptance of randomization and interest in the trial
Feasibility of a large RCT: New Contraception clients per annum (approx.)

- Postpartum: 11,000 women
- Post-Pregnancy termination: 3,000 women
- HIV uninfected 70%: approx. 10,000 women
- DMPA (75%) and NET-En: (20%): 95%
- OC: 3% IUD: 2%
- Need 8% uptake to recruit 800 women in 1 year
- The majority of women recruited would be women who would otherwise have received DMPA
Conclusions

A randomized trial comparing various family planning options is feasible (four previous trials showed good uptake and interest)

Such a trial will have tangible benefits for participants and the broader settings in which it takes place (exposure to increased range of methods)

It will provide robust evidence on various benefits and risks (including HIV acquisition) to support contraceptive choice in the future