Next Up in Series on Px Research & Reality:
Hormonal contraception and HIV

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Executive Director, Wits Reproductive Health & HIV Institute
10 March 2014
“Love is the answer, but while you are waiting for the answer, sex raises some pretty good questions.”

Woody Allen
Contraception and HIV: Considerations

- Women at risk for HIV
  - Prevention
  - Acquisition

- Women infected with HIV
  - Infectiousness
  - Disease progression
  - Drug interactions
Progestin contraceptives differ

What differs?

- Chemical structures
# Progestin Types, By Structure

## Related to Progesterone
- **Pure progestational**
  - *Nestorone*
  - *Nomegestrol acetate (NOMAc)*
- **Anti-androgenic**
  - *Cyproterone acetate*
  - *Drospirenone, NOMAc*
- **Partly androgenic**
  - *Medroxyprogesterone acetate*
- **Partly glucocorticoid**
  - *Medroxyprogesterone acetate*
- **Anti-mineralocorticoid**
  - *Drospirenone*

## Related to Testosterone
- **Partly estrogenic and androgenic**
  - *Norethindrone*
  - *Net Acetate*
  - *Ethinodiol diacetate*
- **Partly androgenic**
  - *Norgestrel/Levonorgestrel*
  - *Desogestrel/etonogestrel*
  - *Gestodene*
- **Anti-androgenic**
  - *Norgestimate/norelgestromin*
  - *Dienogest*

*Source: Adapted from Sitruk-Ware, 2010*
Progestin contraceptives differ

What differs?

■ Chemical structures

■ Pharmacokinetic parameters

■ Bioavailability
  ▪ Oral and vaginal

■ Progestational potency

■ Work via different steroid receptors
  ▪ Impact side-effects, safety, benefits
  ▪ Binding does not equal activity

The Possible Impact of contraceptive progestins

■ Vaginal and cervical epithelium

■ Cervical mucus

■ Menstrual patterns

■ Vaginal and cervical immunology

■ Receptor concentrations and types vary by cell and tissue type

■ Steroid-induced modulation of receptor concentration
  ▪ Viral/HIV replication
  ▪ Acquisition of other STIs
Serum progestin levels in different hormonal contraceptives
Epidemiology: Distribution of injectable progestin contraceptive use

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

From: AR Butler, JA Smith, D Stanton, TB Hallett. The global impact of an interaction between injectable hormonal contraception and HIV risk
Method mix: among currently married (CM) & sexually active not married (NM) women, % using specific method

Source: Demographic and Health Surveys 2006-1010
Adult female HIV prevalence

UNAIDS 2011
Where does high HIV prevalence coincide with high use of injectable hormonal contraceptives?

*HIV prevalence among 15-49 year-old women*

*Adult HIV prevalence given for China.*

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

HIV: ‘high’ = > 1%; IHC: ‘high’ = upper quartile.
HC/HIV Acquisition Research Timeline

- 1987 - Plummer presentation - IAS Meeting, Wash DC
- 1988-on - Multiple secondary analyses
- 1996 - NIH/OPA review
- 1996 - Preston Marx: Monkey study
Progesterone implants enhance SIV vaginal transmission and early virus load

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

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

- DMPA Virology, 2006
- DMPA J. Infect. Dis., 2004
- Pal et al., Virology 2009
- Turville et al., PLoS One 2008
## Reported effects of progesterone and its derivatives on immune system & HIV-1 infection.

<table>
<thead>
<tr>
<th>Reported effect of progesterone or its derivatives</th>
<th>References</th>
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<tbody>
<tr>
<td>Inhibition of IgG and IgA production and trans-epithelial transport</td>
<td>(78;87-96;129-134)</td>
</tr>
<tr>
<td>Decreased frequency of antibody-secreting cells in women and female macaques</td>
<td>(90;96)</td>
</tr>
<tr>
<td>Decreased specific IgG and IgA responses following mucosal immunization with attenuated HSV-2; induction of permissive conditions for intravaginal infection of mice with HSV-2 and <em>Chlamydia trachomatis</em></td>
<td>(132-134)</td>
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<tr>
<td>Inhibition of T cell responses and cytotoxic activity</td>
<td>(139-143;147)</td>
</tr>
<tr>
<td>Inhibition of perforin expression in T cells</td>
<td>(140-142;144-146)</td>
</tr>
<tr>
<td>Decreased proliferation and Th1-type cytokine production by VZV-specific CD4* T cells in HIV-1 patients</td>
<td>(148)</td>
</tr>
<tr>
<td>Altered migration and decreased activity of NK cells</td>
<td>(105;106;106;135;159;251;252)</td>
</tr>
<tr>
<td>PIBF-mediated shift towards Th2 cytokine expression profile</td>
<td>(133;149-154)</td>
</tr>
<tr>
<td>Altered migration and infiltration of lymphocytes, macrophages, and NK cells into the female genital tract tissues</td>
<td>(117;118;157;158;183;191;253)</td>
</tr>
<tr>
<td>Increased expression of CCR5 on cervical CD4* lymphocytes</td>
<td>(81;82)</td>
</tr>
<tr>
<td>Thinning of cervico-vaginal epithelium in rhesus macaques</td>
<td>(42;66)</td>
</tr>
<tr>
<td>Increased frequency of Langerhans cells in vaginal epithelium</td>
<td>(76;77)</td>
</tr>
<tr>
<td>Regulation of HIV replication and LTR activity</td>
<td>(254)</td>
</tr>
<tr>
<td>Suppression of IL-1, IL-2, and IL-6 release by human lymphocytes</td>
<td>(148;177)</td>
</tr>
<tr>
<td>Inhibition of TLR-9-induced IFN-α production by human and mouse pDCs</td>
<td>(162)</td>
</tr>
<tr>
<td>Increased shedding of HIV-1 in the genital tract</td>
<td>(35-37)</td>
</tr>
<tr>
<td>Decreased FcyR expression on monocytes</td>
<td>(159;160)</td>
</tr>
<tr>
<td>Decreased vaginal colonization with H₂O₂-producing <em>Lactobacillus</em></td>
<td>(70)</td>
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</tbody>
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*Hel Z. et al., Endocrine Rev., 2010, 79-97*
WHO’s Medical Eligibility Criteria for Contraceptive Use
Eligibility Criteria for Contraceptive use: WHO Classifications based on the GRADE approach to evidence

<table>
<thead>
<tr>
<th>Classification of Conditions</th>
<th>Definition</th>
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<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>
2008, 1st WHO HC/HIV Consultation: MEC 2009

Hormonal contraceptive use for women at high risk of HIV-1 infection (HIV acquisition)

- DMPA – 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

Source: WHO Medical Eligibility Criteria fourth edition 2009
HC/HIV Acquisition Research Timeline

- July 2011 – University of Washington HC/HIV study presented at IAS, Rome

- 1st Week Oct 2011
  - University of Washington HC/HIV study published in *Lancet Infectious Diseases*
  - *New York Times* front page
  - Global media reaction
Prospective cohort study of 3790 HIV--1 discordant couples from East and southern Africa

Renee Heffron, Deborah Donnell, Helen Rees, Connie Celum, Edwin Were, Nelly Mugo, Guy de Bruyn, Edith Nakku---Joloba, Kenneth Ngure, James Kiarie and Jared Baeten

July 2011 – Partners in Prevention Study on HIV acquisition and HC presented at IAS Conference, Rome
## Contraception and HV 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>
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<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>No hormonal contraception</td>
<td>3.78</td>
<td>1.00</td>
</tr>
<tr>
<td>Any hormonal contraception</td>
<td>6.61</td>
<td>1.98 (1.06 – 3.68)</td>
</tr>
<tr>
<td>Injectables</td>
<td>6.85</td>
<td>2.05 (1.04 – 4.04)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>5.94</td>
<td>1.80 (0.55 – 5.82)</td>
</tr>
</tbody>
</table>

21.2% of women used HC at least once during study
The most popular contraceptive in Kenya doubles the risk of HIV, a new study shows.

Use of the injectable contraceptive also increases the risk of HIV among women using their male partners.

The results, published in the respected Lancet Infectious Diseases journal, underscore the critical need for safe and effective contraceptive methods that prevent HIV and other types of sexually transmitted infections.

Researchers at the University of Washington and Kenya’s National Hospital have conducted the study, which found that women using the injectable contraceptive were twice as likely to become infected with HIV compared to those not using it.

The study was conducted in partnership with the World Health Organization and involved a large-scale randomized trial of more than 3,000 women in Kenya, Uganda, Tanzania, Botswana, South Africa, and Zambia.

It was led by researchers from the University of Washington and Kenya’s National Hospital, with support from the World Health Organization and other international partners.

The findings highlight the need for improved contraceptive technologies and the development of safer, more effective methods that can prevent HIV transmission and other sexually transmitted infections.

The study was published in the Lancet Infectious Diseases journal, providing critical insights into the risks associated with contraceptive use and the need for safer, more effective methods to prevent HIV and other sexually transmitted infections.
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
- Research agenda
- Programmatic implications
The Epidemiologists
Studies Meeting Minimal Criteria

Heffron 2011
Baeten 2007
Morrison 2012
Morrison 2010
McCoy 2013
Myer 2007
Reid 2010
Kiddugavu 2003
Kleinschmidt 2007
Use of progestin injectables and HIV acquisition

**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.

www.thelancet.com/infection  Vol 13  September 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?.......

The Guardian
HIV warning to women using injectable contraception
World Health Organisation advises users against infection

Sarah Boseley, health editor

February 21, 2012

The New York Times

February 17, 2012

Switzerland: AIDS Cases Soar by

POZ
Health, Life & HIV

February 21, 2012

Women on Hormonal

The Asian Age
‘Hormonal contraceptives safe for women with HIV,’

Teena Thacker
263 words

Women Using Injectable Contraception Warned of HIV

The Herald
Zimbabwe: World Health Organisation wire

Uganda Picks
World Health Organization Clarifies Guidance on Hormonal Contraception and HIV

Published: February 18, 2012

Kenya: Hormonal Contraceptives Safe, WHO Assures

BY JOHN MUCHangi, 18 FEBRUARY 2012

The STAR

Forum
Family Planning
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......
The Modelers

- 3 models
  - Jain, 2012 – *Contraception*
  - Rodriguez/Reeves, 2012 – *Br J ObGyn*
  - Butler, et al., 2012 - AIDS

- Different assumptions, analytic algorithms and levels of rigor

- Similar conclusions
  - Conclusions differ according to HIV incidence and DMPA usage in countries
  - DMPA withdrawal has pregnancy consequences
  - Switching to implants/IUDs better than DMPA
  - Switching to orals/condoms worse than DMPA
An RCT?