

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

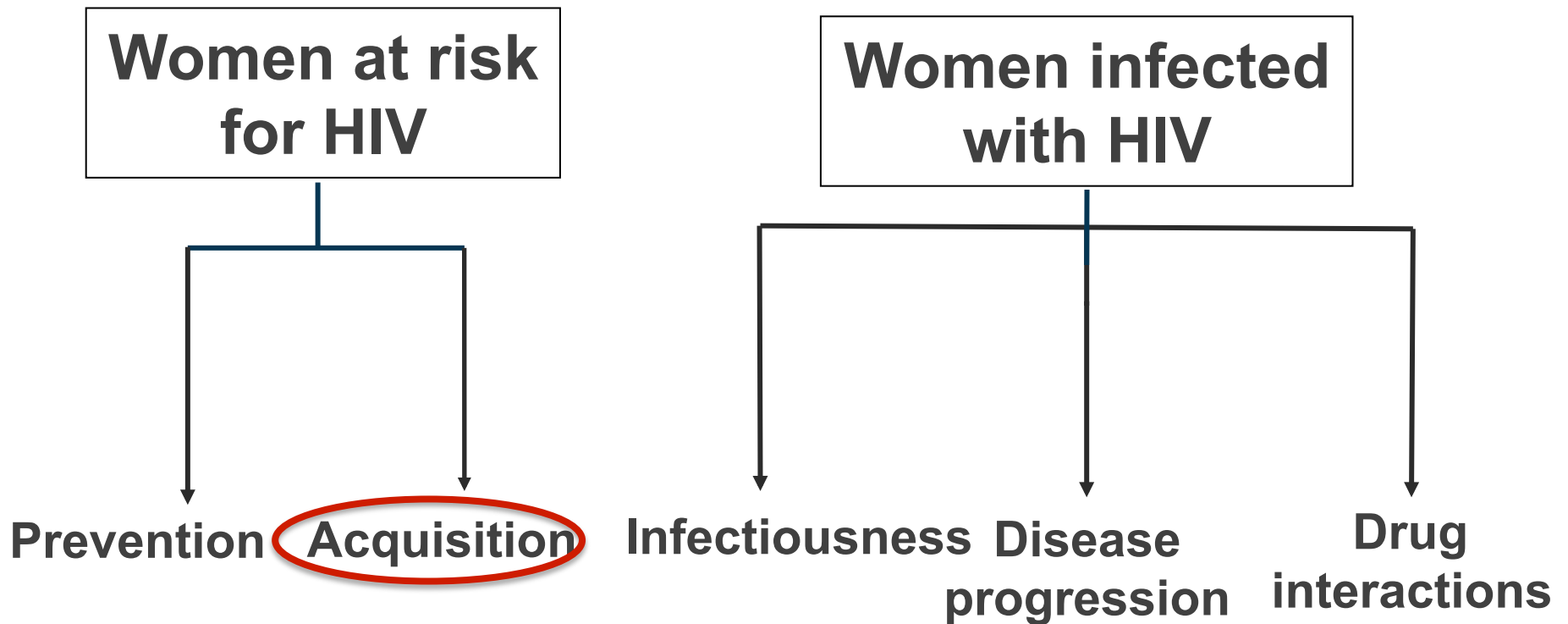
Prof. Helen Rees
Executive Director, Wits Reproductive Health & HIV Institute
10 March 2014



“Love is the answer, but while you are waiting for the answer, sex raises some pretty good questions.”

Woody Allen

Contraception and HIV: Considerations



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*

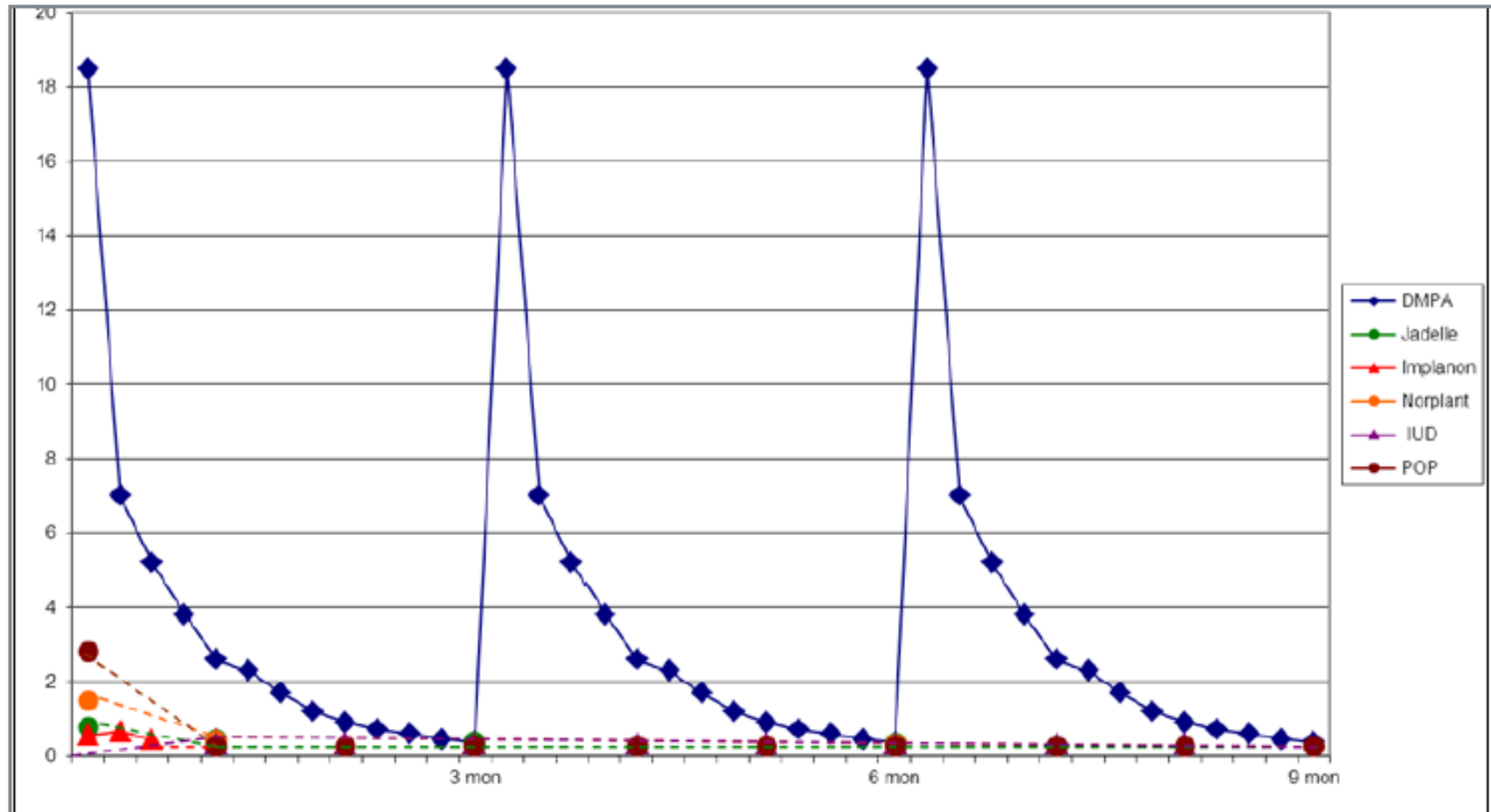
Source: Adapted from Sitruk-Ware, 2010

Progestin contraceptives differ

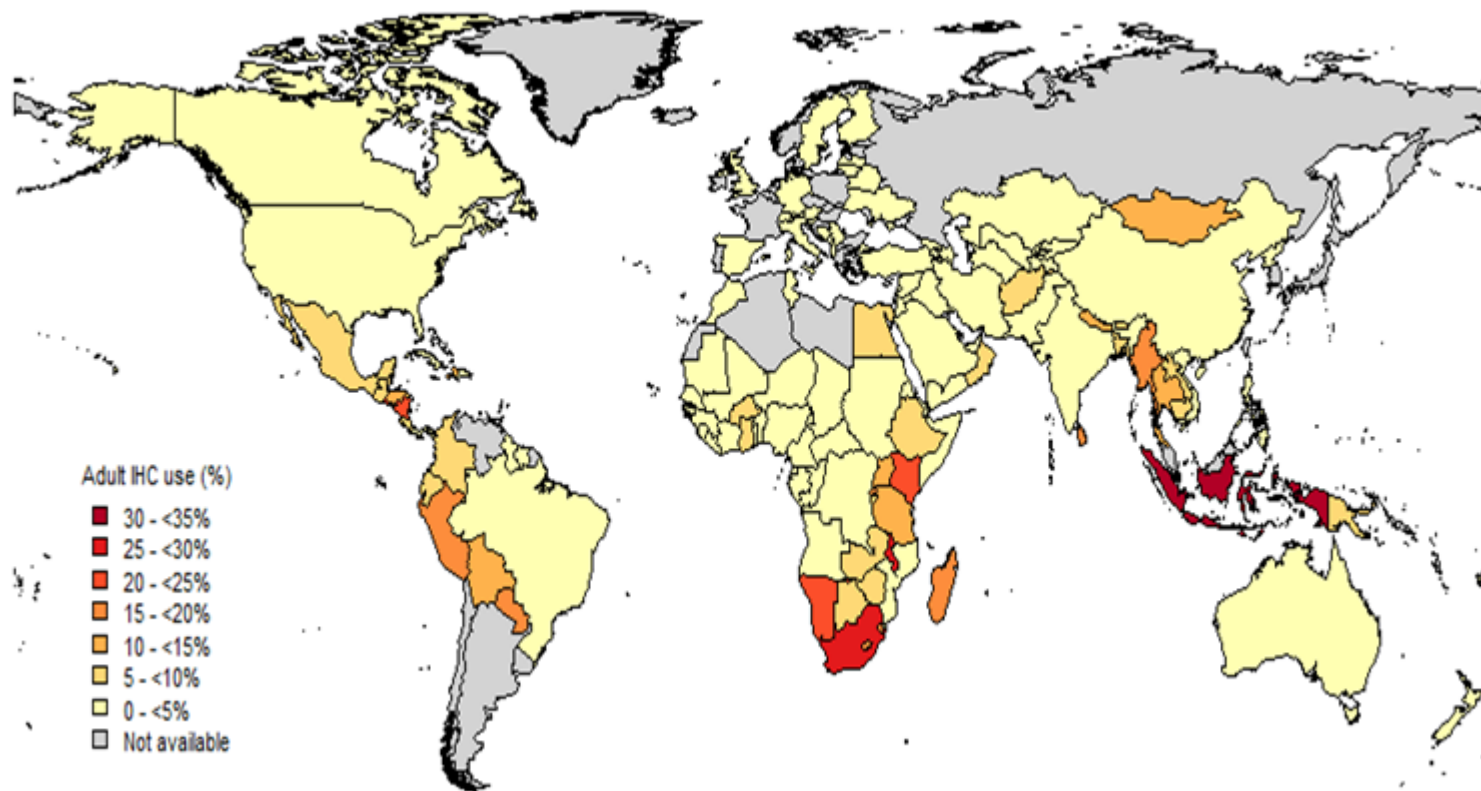
What differs?

- 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 progesterin levels in different hormonal contraceptives



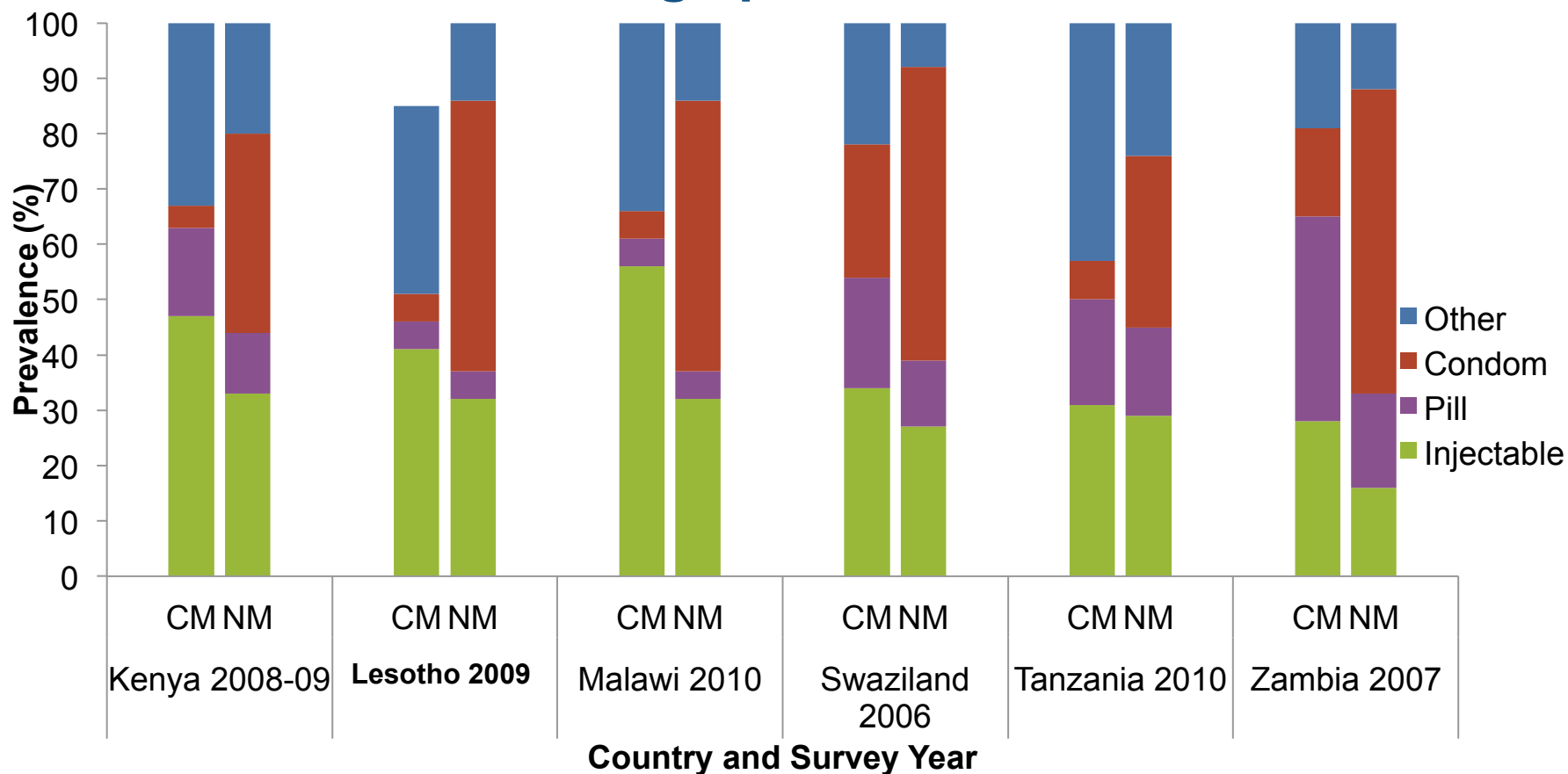
Epidemiology: Distribution of injectable progestin contraceptive use



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

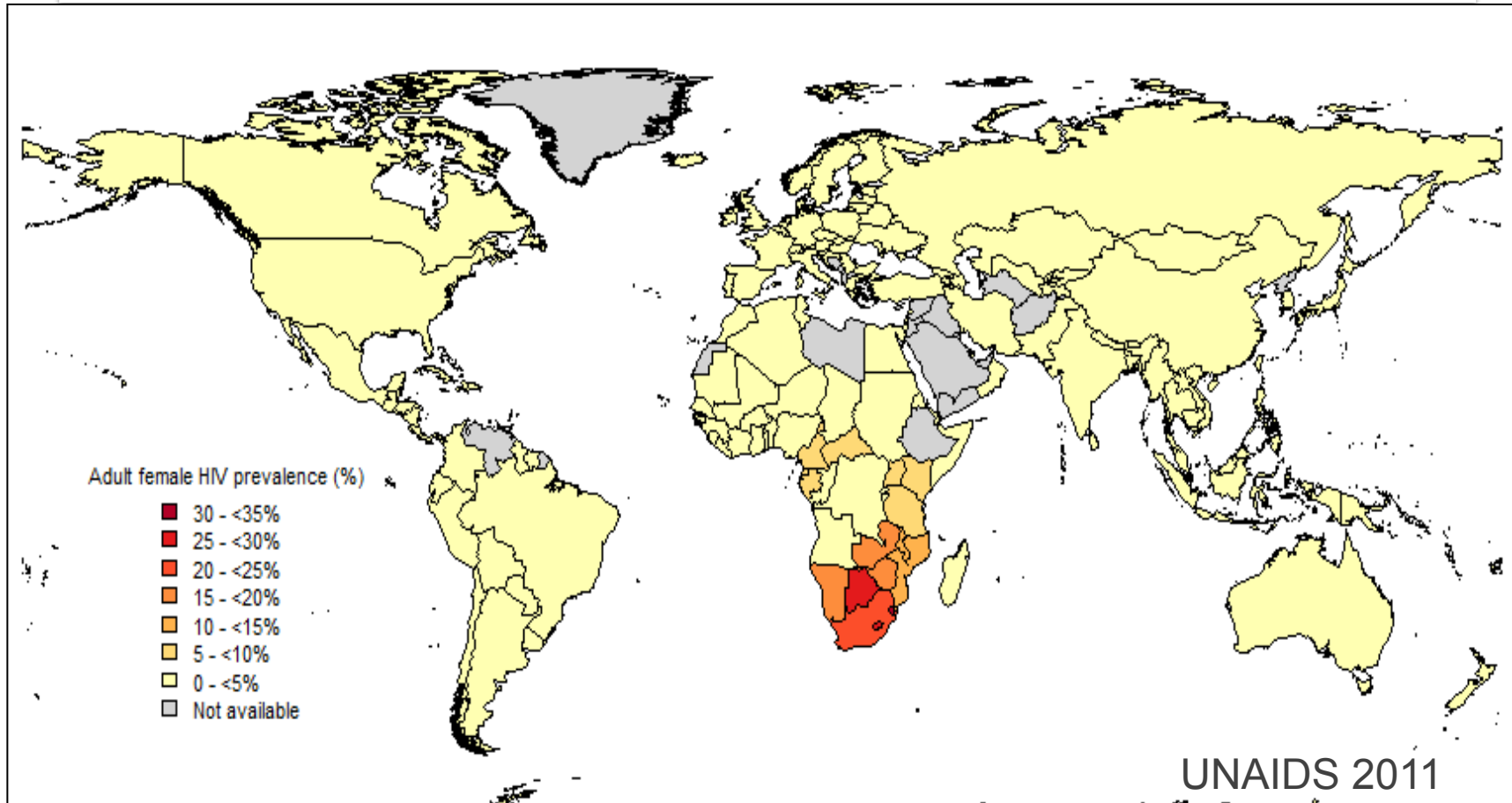
From: AR Butler, JA Smith, D Stanton, TB Hallett. *The global impact of an interaction between injectable hormonal contraception and HIV risk*

Method mix: among currently married (CM) & sexually active not married (NM) women , % using specific method



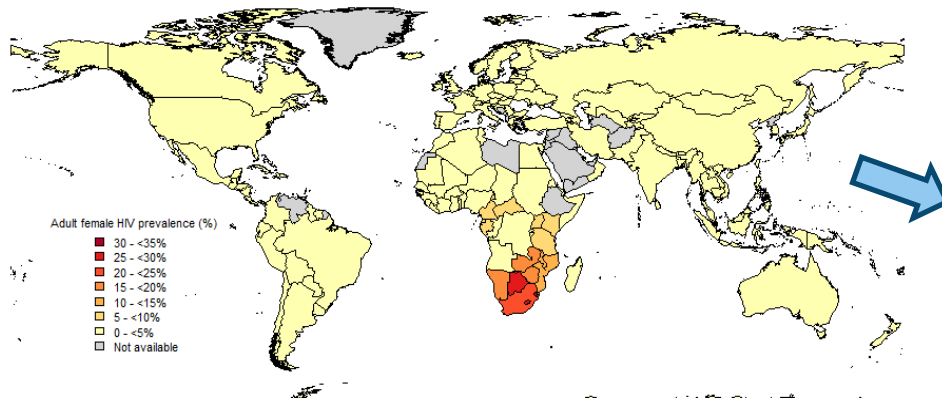
Source: Demographic and Health Surveys 2006-1010

Adult female HIV prevalence



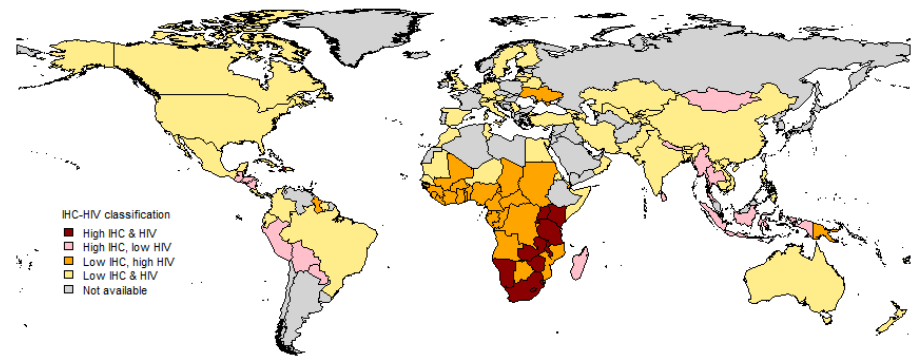
Where does high HIV prevalence coincide with high use of injectable hormonal contraceptives?

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



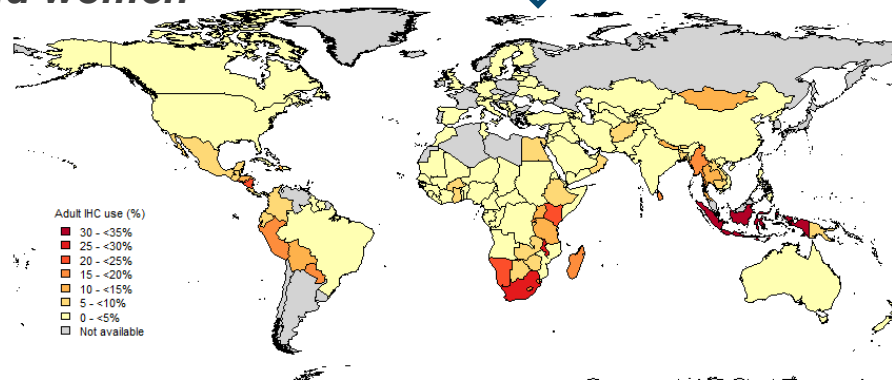
*Adult HIV prevalence given for China.

The overlap between use of injectables and HIV prevalence



HIV: 'high' = > 1%; IHC: 'high' = upper quartile.

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



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

PRESTON A. MARX^{1,2}, ALEXANDER I. SPIRA^{1,2}, AGEGNEHU GETTIE¹, PETER J. DAILEY³, RONALD S. VEAZEY⁴, ANDREW A. LACKNER⁴, C. JAMES MAHONEY⁵, CHRISTOPHER J. MILLER⁶, LEE E. CLAYPOOL⁷, DAVID D. HO¹ & NANCY J. ALEXANDER⁸

- Progesterone
Nature Med.,
1996

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

Nataliya Trunova^a, Lily Tsai^a, Stephanie Tung^a, Eric Schneider^a, Janet Harouse^a, Agegnehu Gettie^a, Viviana Simon^a, James Blanchard^b, Cecilia Cheng-Mayer^{a,*}

- DMPA
Virology, 2006

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

Kristina Abel,¹² Tracy Rourke,¹² Ding Lu,¹² Kristen Bost,¹² Michael B. McChesney,¹⁵ and Christopher J. Miller^{1,2,3,4}

- DMPA
J. Infect. Dis.,
2004

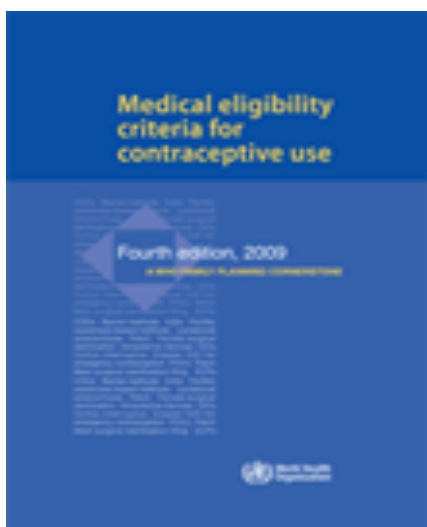
- - Genescà et al., J. Med. Primatol. , 2007
- - Mascola et al., Nature Med. 2000
- - Veazey et al., Proc. Natl. Acad. Sci. USA 2008
- - Pal et al., Virology 2009
- - Turville et al., PLoS One 2008

Reported effects of progesterone and its derivatives on immune system & HIV-1 infection.

Reported effect of progesterone or its derivatives	References
Inhibition of IgG and IgA production and trans-epithelial transport	(78;87-96;129-134)
Decreased frequency of antibody-secreting cells in women and female macaques	(90;96)
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 <i>Chlamydia trachomatis</i>	(132-134)
Inhibition of T cell responses and cytotoxic activity	(139-143;147)
Inhibition of perforin expression in T cells	(140-142;144-146)
Decreased proliferation and Th1-type cytokine production by VZV-specific CD4 ⁺ T cells in HIV-1 patients	(148)
Altered migration and decreased activity of NK cells	(105;106;106;135;159;251;252)
PIBF-mediated shift towards Th2 cytokine expression profile	(133;149-154)
Altered migration and infiltration of lymphocytes, macrophages, and NK cells into the female genital tract tissues	(117;118;157;158;183;191;253)
Increased expression of CCR5 on cervical CD4 ⁺ lymphocytes	(81;82)
Thinning of cervico-vaginal epithelium in rhesus macaques	(42;66)
Increased frequency of Langerhans cells in vaginal epithelium	(76;77)
Regulation of HIV replication and LTR activity	(254)
Suppression of IL-1, IL-2, and IL-6 release by human lymphocytes	(148;177)
Inhibition of TLR-9-induced IFN- α production by human and mouse pDCs	(162)
Increased shedding of HIV-1 in the genital tract	(35-37)
Decreased Fc γ R expression on monocytes	(159;160)
Decreased vaginal colonization with H ₂ O ₂ -producing <i>Lactobacillus</i>	(70)

Hel Z. et al., *Endocrine Rev.*, 2010, 79-97

WHO's Medical Eligibility Criteria for Contraceptive Use



World Health Organization

Eligibility Criteria for Contraceptive use: WHO Classifications based on the GRADE approach to evidence

Classification of Conditions	Definition
1	No restriction on use
2	Benefits generally outweigh risks
3	Risks generally outweigh benefits
4	Unacceptable health risk

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



UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER
PARTNERS IN PREVENTION

NORTH AMERICAN
FORUM
ON
FAMILY PLANNING

Contraception and HIV acquisition from men to women

		Adjusted Cox PH Regression analysis	
	HIV incidence per 100 person years	HR (95% CI)	P-value
No hormonal contraception	3.78	1.00	
Any hormonal contraception	6.61	1.98 (1.06 – 3.68)	0.03
Injectables	6.85	2.05 (1.04 – 4.04)	0.04
Oral contraceptives	5.94	1.80 (0.55 – 5.82)	0.33

21.2% of women used HC at least once during study

Los Angeles Times BOOSTER SHOTS

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Africa study suggests hormonal contraceptive tie to HIV infection

FRANCE 24 INTERNATIONAL NEWS 24H/7

NEWS WIRES

FR - EN - AR

04 October 2011 12:20 PM GMT

13 hours 44 min ago - health

Female hormonal contraceptive linked to HIV risk

Mobile Site | Nation Media Group | Nation Careers | Africa Review | The EastAfrican | Business Daily | NTV | NTV Uganda

DAILY NATION

Wednesday, October 5, 2011

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ONLINE RATE FAIR Exhibitors: DAYKIO Housing Finance

Control method blamed for HIV

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The New York Times

WORLD U.S. N.Y. / REGIONAL

Contraceptive U

By PAM BELLUCK
Published: October 3, 2011

The most popular contraceptive in Africa, a hormone shot, has been shown to double the risk the women who use it will have a large study published in the journal. The women, their male partners, had a 100 percent increase in the risk of HIV if the women had used

Miguna Miguna
Uhuru won propaganda war but lost legal battle
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Building online
Nairobi Council starts e-Construction permits
Property: Page 38

FRESH, INDEPENDENT, DIFFERENT

the STAR

NO. 1287
WEDNESDAY, OCTOBER 5, 2011
www.the-star.co.ke
Ksh40/00

CONTRACEPTIVES DOUBLE HIV RISK

BY JOHN MUCHANGI

THE most popular contraceptive in Kenya doubles the risk of women becoming infected with HIV, a new study shows. Use of the injectable contraceptive also increases the risk of HIV-positive women infecting their male partners. The results present a predicament for women because injectables and the pill are Kenya's most popular contraceptives, in part because women can keep them secret. The study was published in the respected Lancet Infectious Diseases journal on Monday and involved 3,800 couples from Kenya, Uganda, Tanzania, Botswana, Rwanda, South Africa and Zambia. It was led by University of Washington but also included researchers from Kenyatta National Hospital, University of Nairobi and Moi University. The study has prompted the World Health Organisation to convene a meeting next January to consider if evidence is now strong enough to advise women against injectable contraceptives. Two past studies showed similar results but researchers yesterday said the current study is the strongest. "We want to make sure that we warn when there is a real need to warn, but at the same time we don't want to come up with a hasty judgement that would have far-reaching severe consequences for the

Continued on page 6

the guardian

Updated 13.23

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could spread if birth control
ons increase, warn
ts
rs call for new guidelines for
ng family planning services in
as

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



World Health Organization

The Epidemiologists

Studies Meeting Minimal Criteria

Heffron 2011

Baeten 2007

Morrison 2012

Morrison 2010

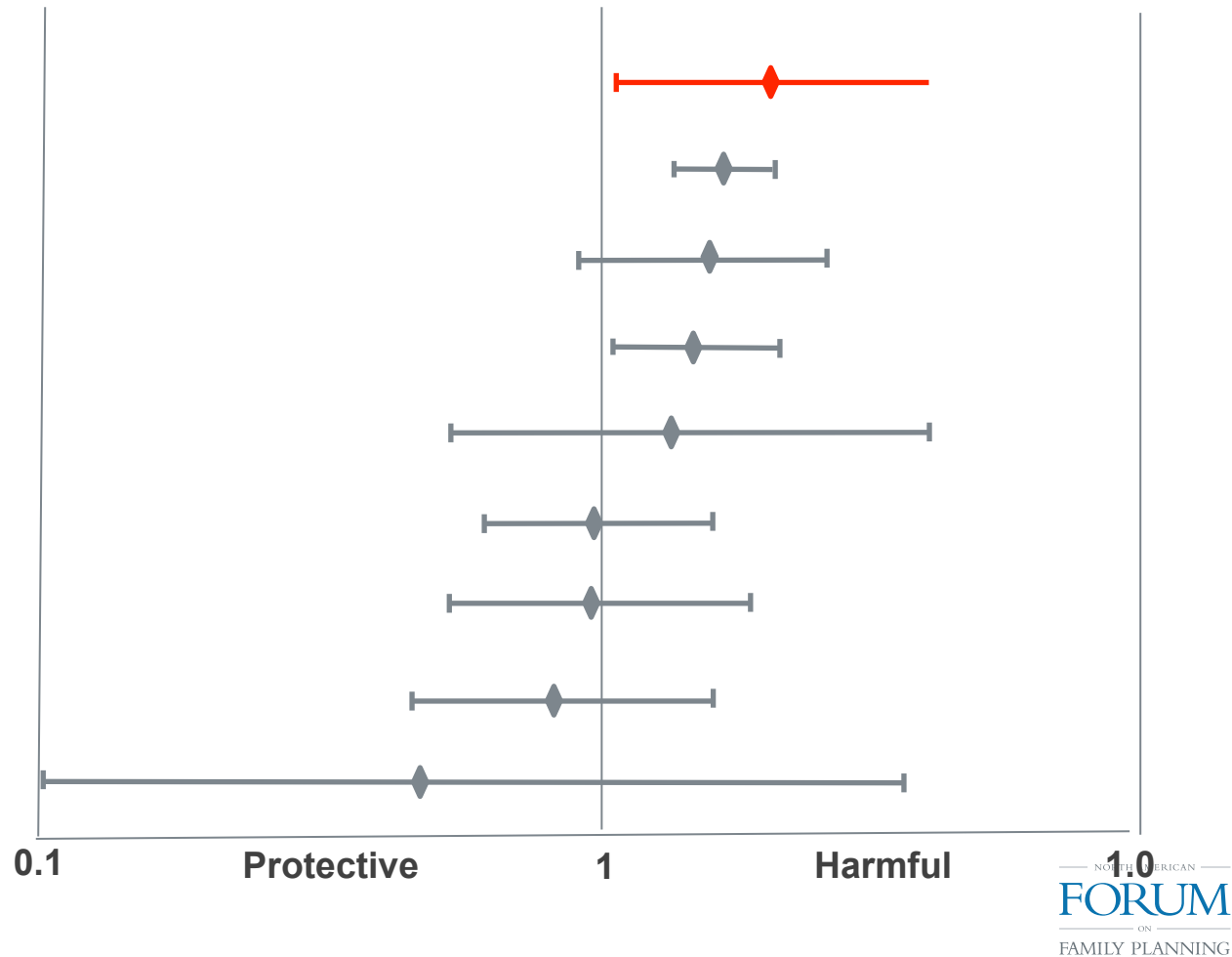
McCoy 2013

Myer 2007

Reid 2010

Kiddugavu 2003

Kleinschmidt 2007



Use of progestin injectables and HIV acquisition

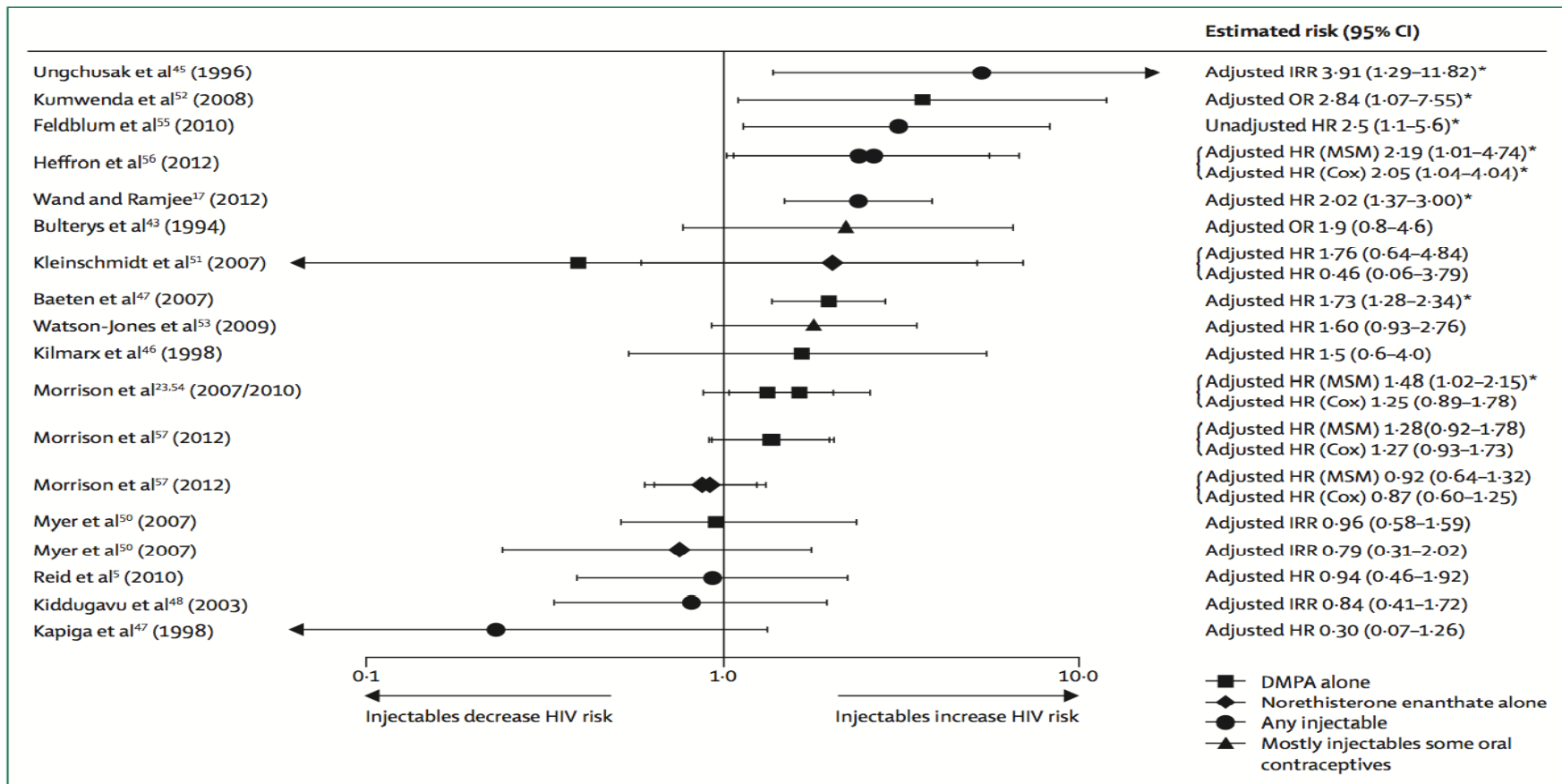


Figure 3: Use of injectable contraceptives and HIV acquisition (all 16 studies)

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.

The Great Debate

Observational data

Unmeasured selection bias

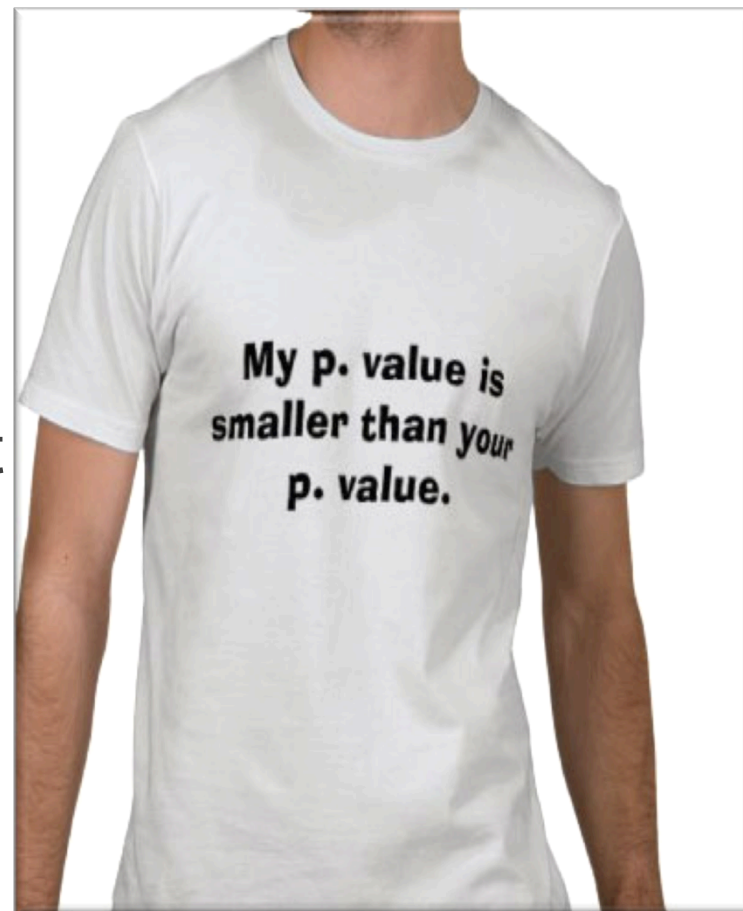
Potential for Confounding

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



WHO statement February 2012

Hormonal contraception and HIV Technical statement

After detailed, prolonged deliberation...

Executive summary

...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?.....

theguardian

HIV warning to women using injectable contraception

World Health Organisation advises us against infection

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

The New York Times

February 17, 2012

... by

POZ

HEALTH, LIFE & HIV

February 21, 2012

Women on Hormonal

THE ASIAN AGE

'Hormonal contraceptives safe for women with

TEENA THACKER
263 words

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Women Using Injectable Contraception Warned of HIV

THE HERALD

Zimbabwe: World Health Organisation F Contraceptives

Uganda Picks

World Health Organization Clarifies Guidance on Hormonal Contraception and HIV

Published: February 18, 2012

theSTAR

Kenya: Hormonal Contraceptives Safe, WHO Assures

BY JOHN MUCHANGI, 18 FEBRUARY 2012

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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?



?