

HIV and Hormonal Contraception



Southern African Clinicians Society 2012

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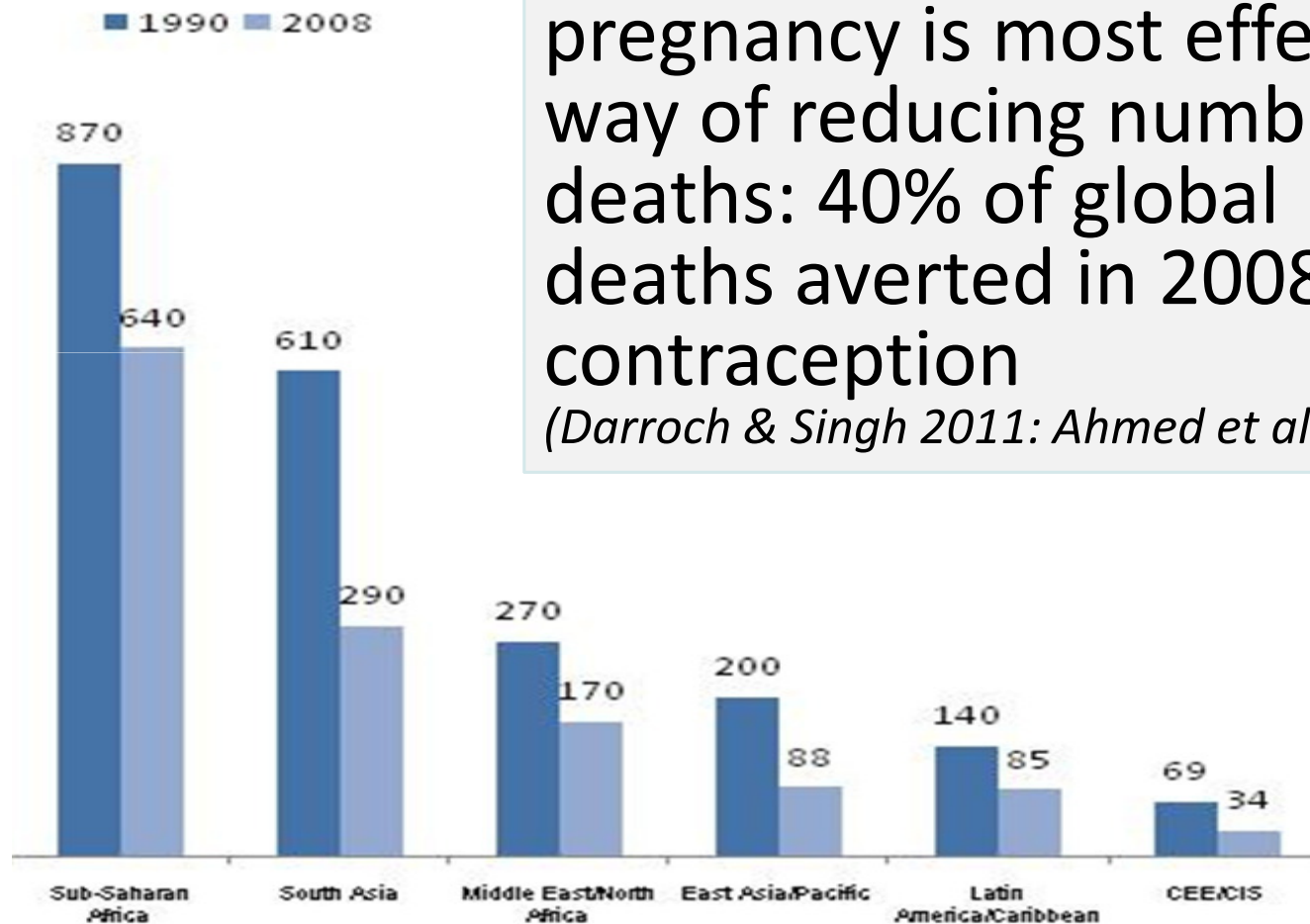
“Love is the answer, but while you are waiting for the answer, sex raises some pretty good questions.” Woody Allen

What do we know about contraception?

Women have a right to decide whether they want to become pregnant and bear children irrespective of their HIV status. Women must be enabled to make informed, voluntary decisions about contraception and then receive a safe, effective method of her choice.



Contraception and Maternal Mortality



Avoidance of unintended pregnancy is most effective way of reducing number of deaths: 40% of global deaths averted in 2008 by contraception

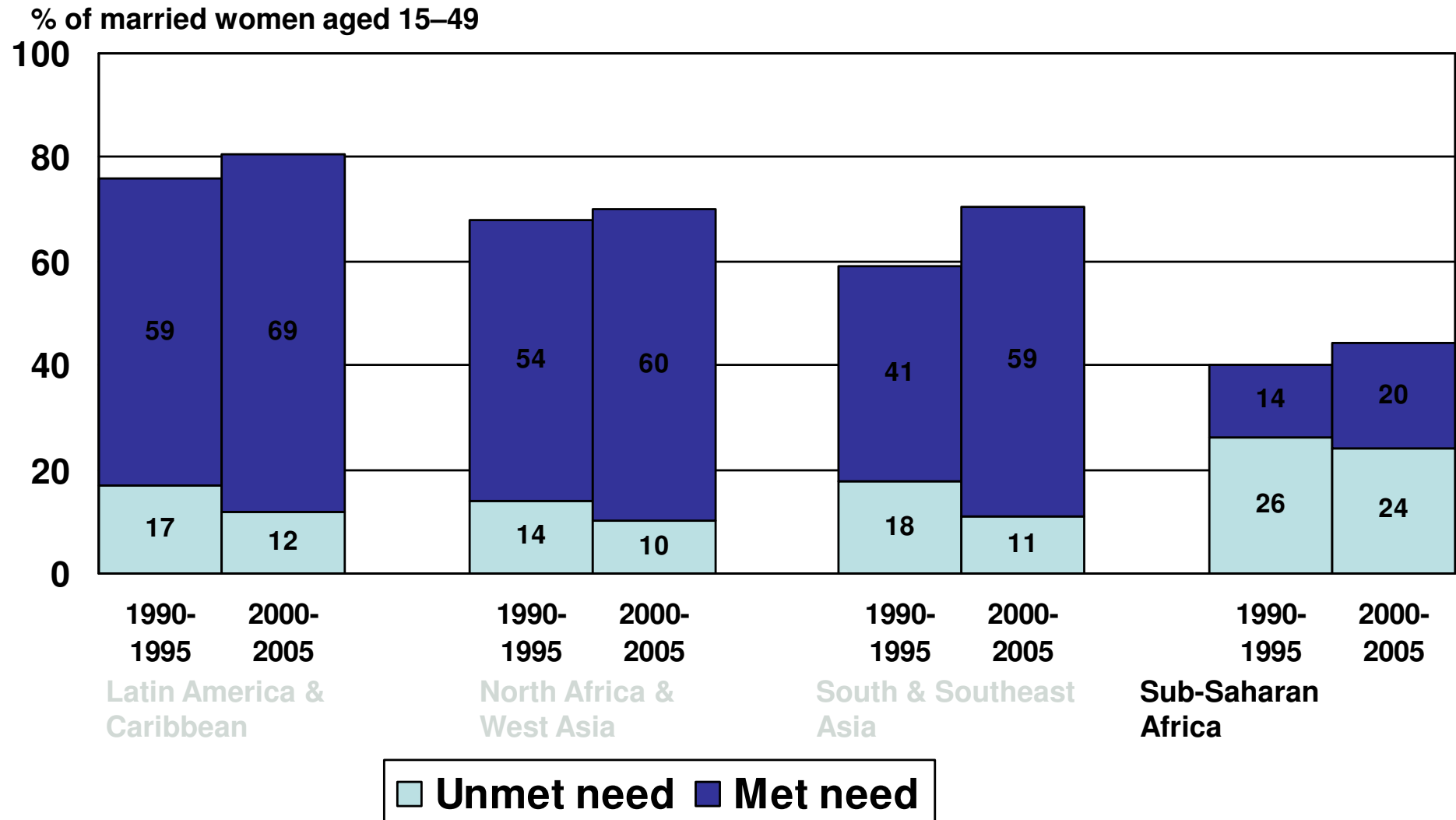
(Darroch & Singh 2011; Ahmed et al 2011)

Many women use hormonal methods



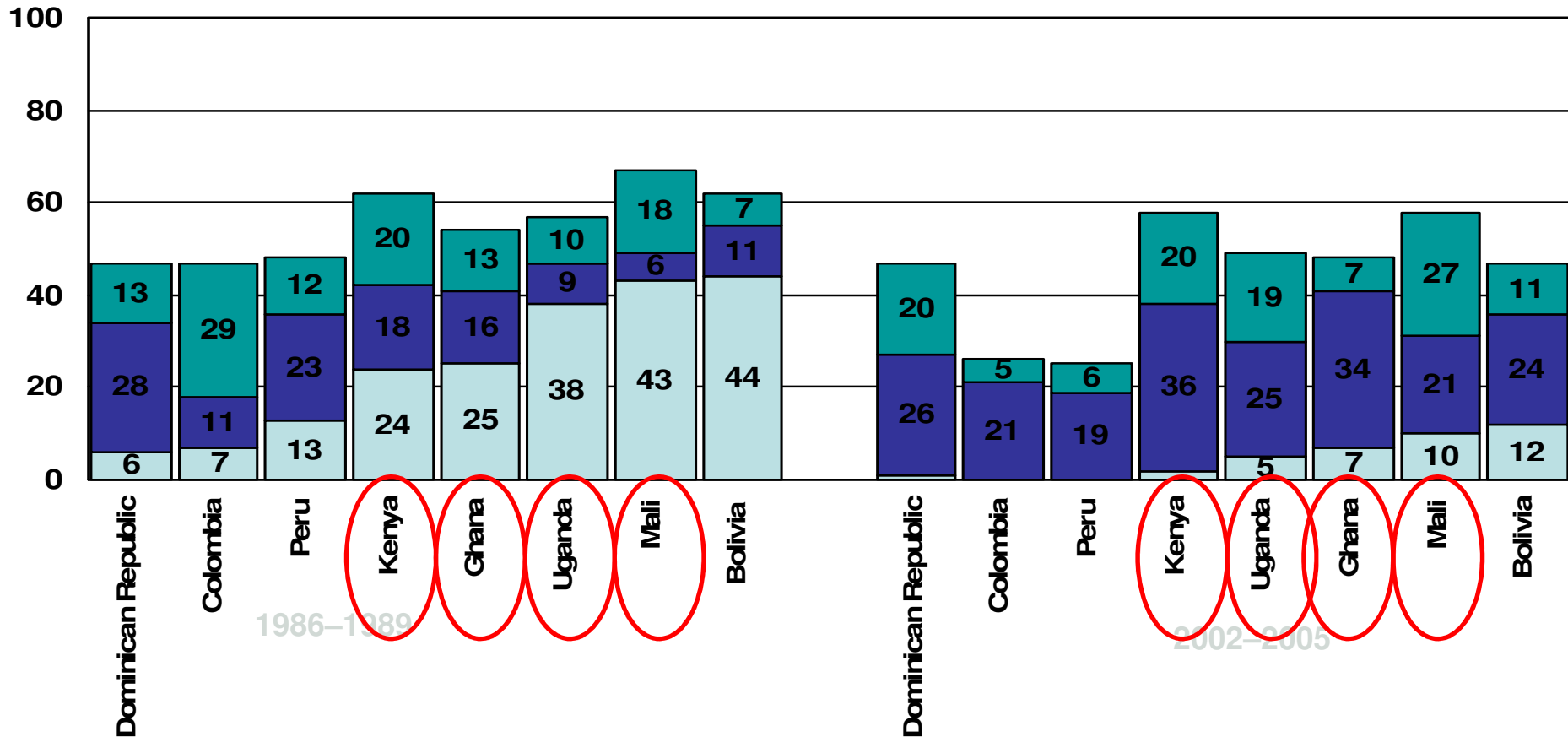
Over 150 million women use hormonal contraception worldwide, primarily oral contraceptives (OCs) and injectable depot-medroxyprogesterone acetate (DMPA).

The overall demand for contraception is increasing



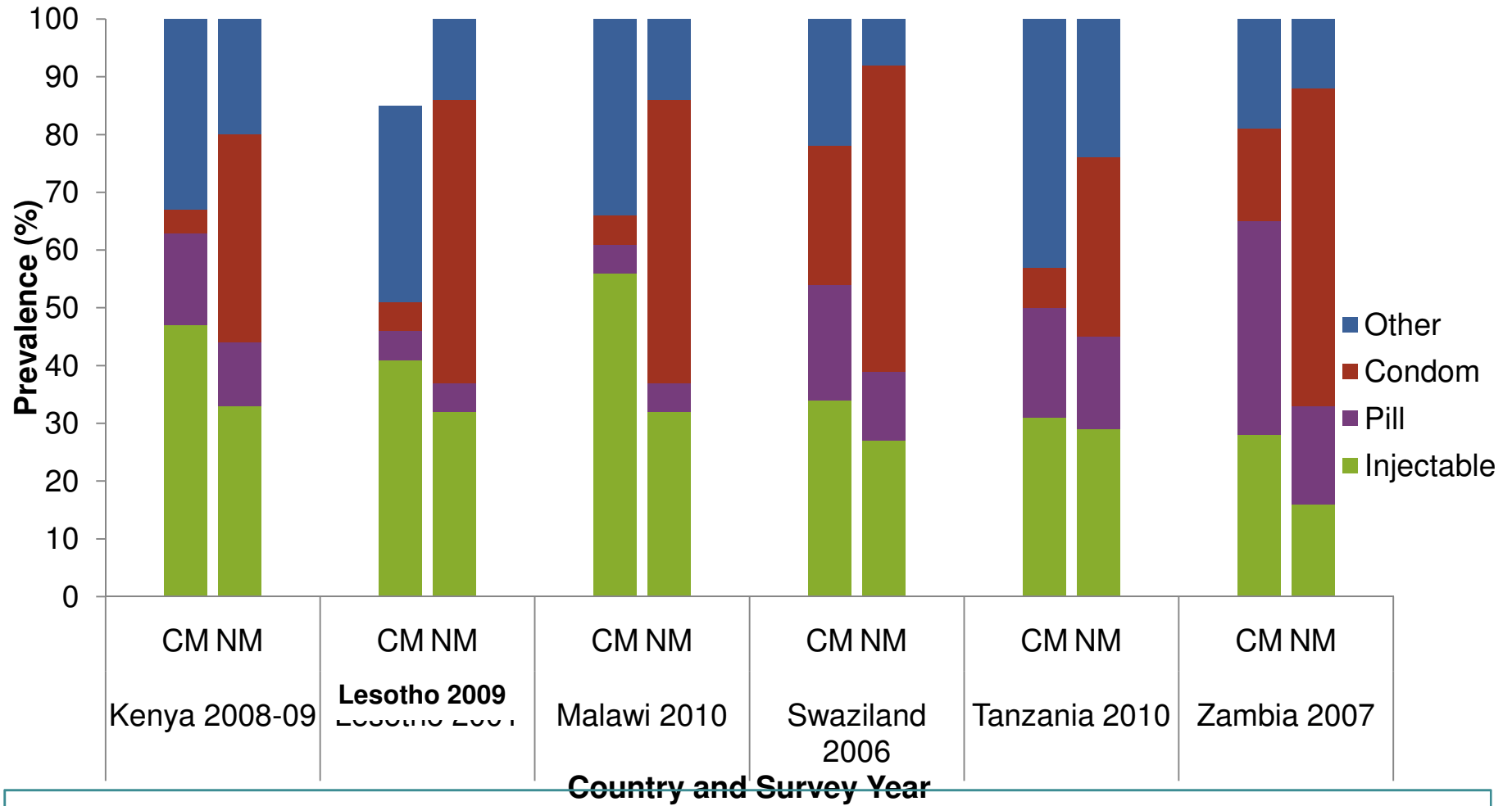
The importance of some reasons for non-use has changed over time

% of married women aged 15–49 with unmet need



Lack of knowledge
 Health/side effects
 Opposition

Women's choice of method is influenced by age, relationship status and health services



Currently married (CM) & sexually active not married (NM) women, % using specific method
 Source: DHS 2006-2010

Contraception is the neglected second element of PMTCT

Prevention of HIV in women, especially young women

Element 1

Prevention of unintended pregnancies in HIV-infected women

Element 2

Prevention of transmission from an HIV-infected woman to her infant

Element 3

Support for mother and family

Element 4

We are not very good at offering HIV positive women modern contraceptive methods

851 non-pregnant women on different ARV regimens recruited from 4 WRHI-supported sites between August 2009 – January 2010

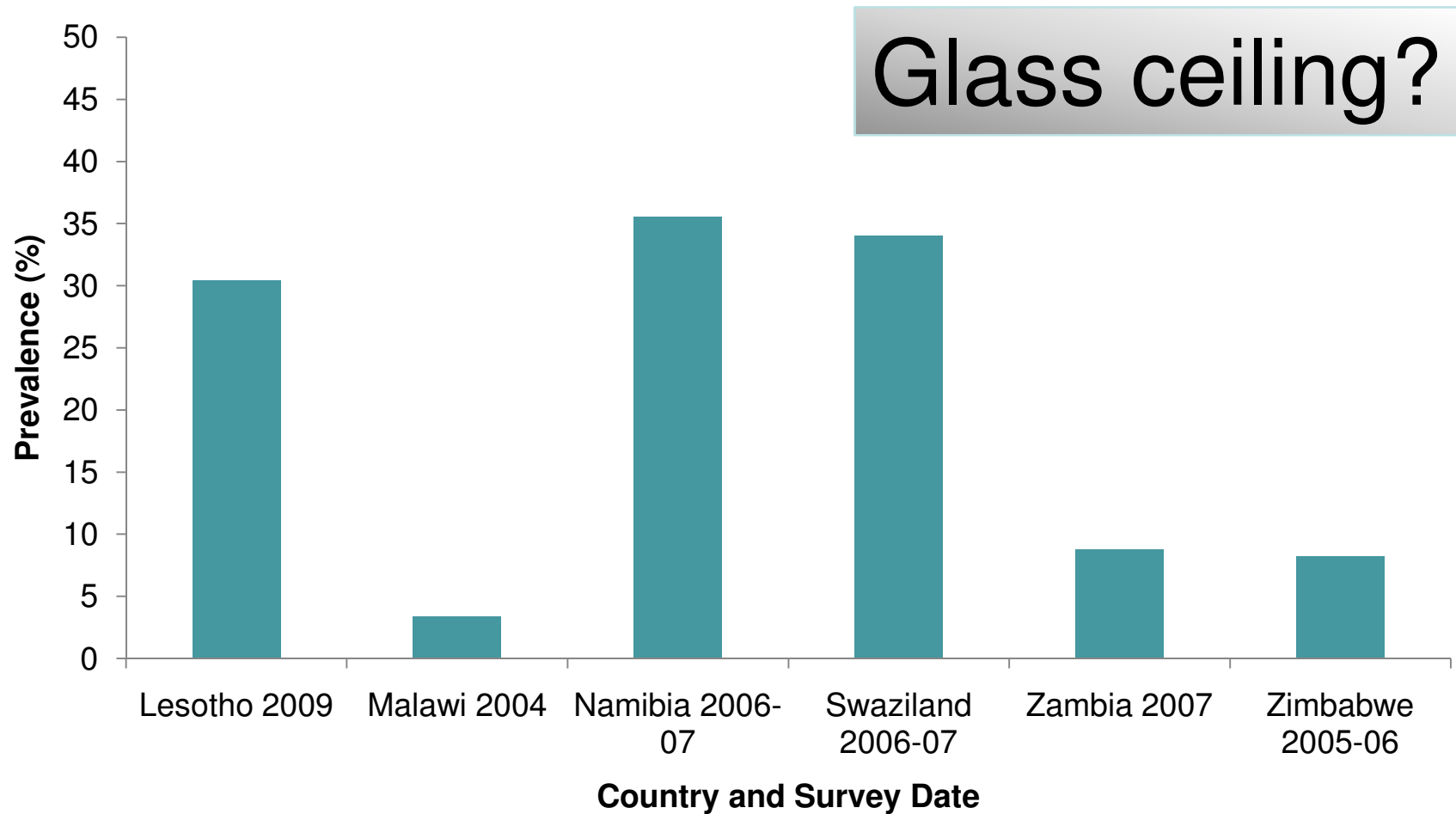
Schwartz, Black, Rees et al 2011

Contraceptive Use	n (%)
Consistent condom use	540 (63.5%)
Injectables	175 (20.6%)
Oral contraceptives	45 (5.3%)
Implants	4 (0.5%)
IUDs	1 (0.1%)
Dual (Condoms+HC)	131 (15.4%)
Overall	631 (74.1%)



How far can we push Dual Method use?

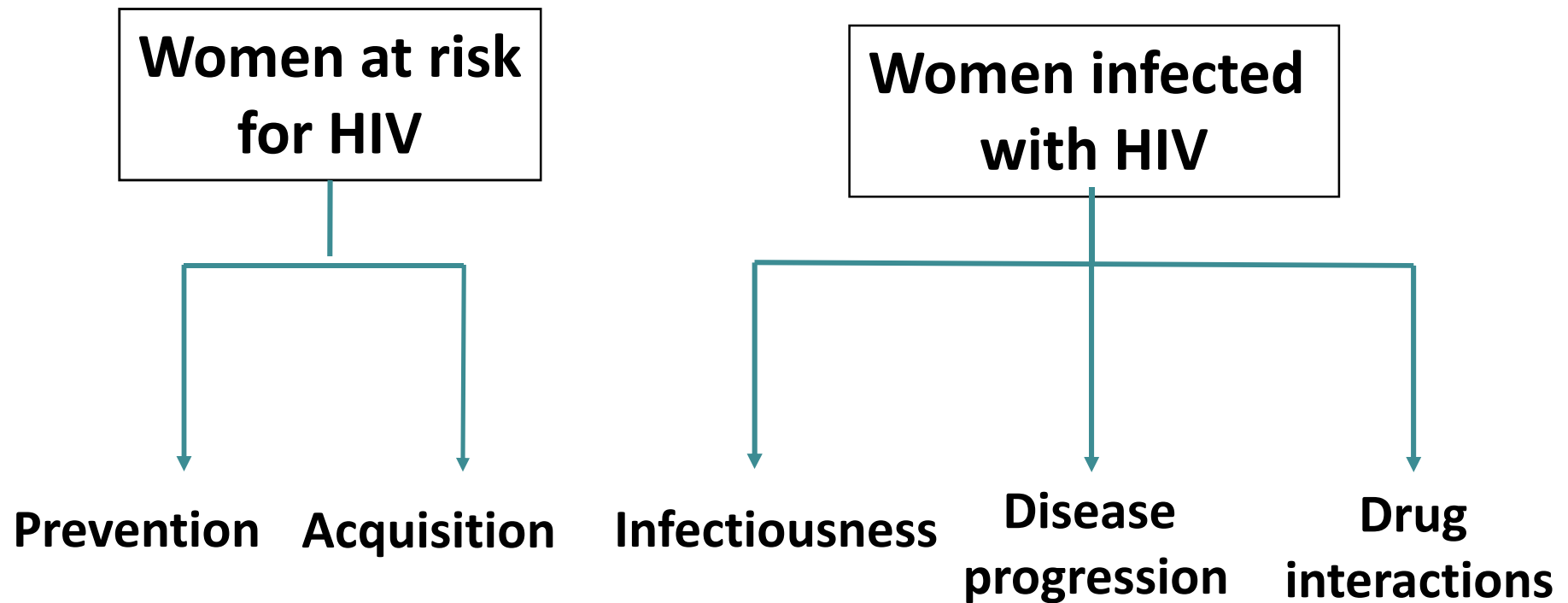
Condom use at last sexual intercourse, amongst
injectable contraception users



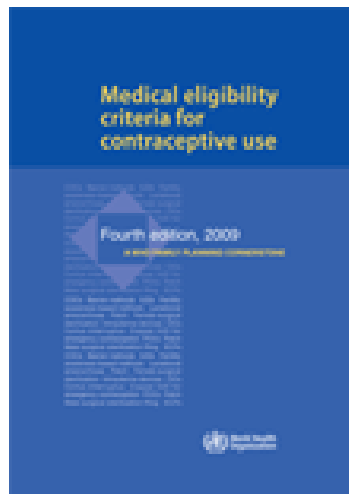
Source: Demographic and Health Surveys 2004-1010

Hormonal Contraception and HIV: Considerations

Hormonal Contraception and HIV: Considerations



WHO's Medical Eligibility Criteria for Contraceptive Use



Research



**WHO consultants & committee:
Systematic review, Grading of scientific evidence**



**The evidence is used to develop international recommendations
and includes expert opinion where evidence is not available**



**International recommendations are adapted for national
guidelines**



Job aids (tools) are developed



Eligibility Criteria for Contraceptive use: WHO Classifications

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

What triggered the concerns
about hormonal contraception
and HIV?

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,^{1,2} Tracy Rourke,^{1,2} Ding Lu,^{1,2} Kristen Bost,^{1,2} Michael B. McChesney,^{1,5} and Christopher J. Miller^{1,2,3,4}

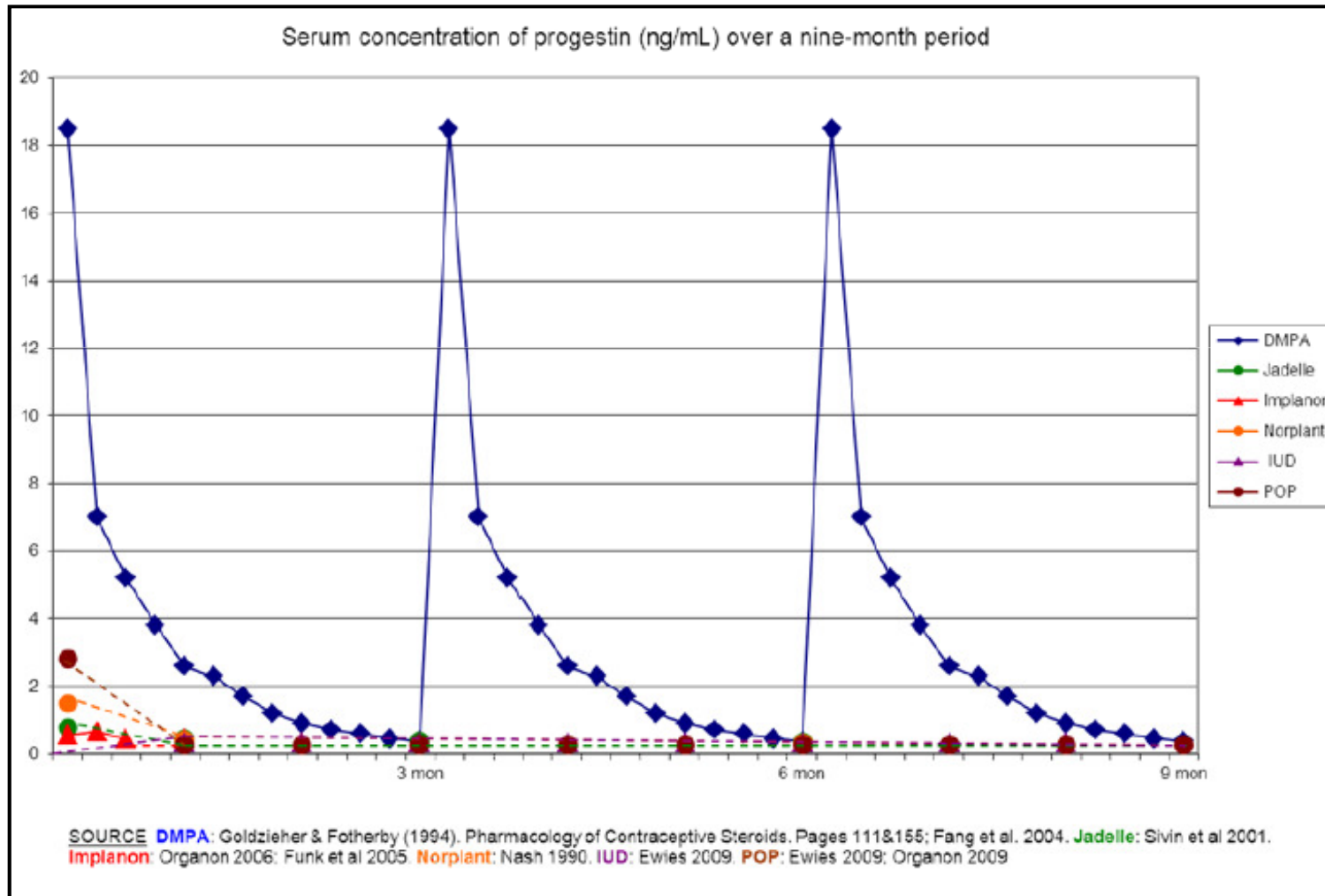
- **DMPA**
J. Infect. Dis., 2004

- - **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)

Serum progesterin levels in different hormonal contraceptives



Biology?

- Vaginal and cervical epithelium (mucosal thickness, cervical ectopy, etc.)
- Changes in cervical mucus
- Menstrual patterns
- Vaginal and cervical immunology
- Viral (HIV) replication
- Acquisition of other STI that may serve as mediators
- *However, data are often sparse or potentially could point in different directions, and, most importantly, no laboratory study would be sufficient for this question....*

WHO Medical Eligibility Criteria 2009

- Combined hormonal contraception use for women at high risk of HIV, HIV infected or AIDS
- “Intermediate” level of evidence
- Category 1 - “No Restriction” apart from women taking ARVs

WHO Medical Eligibility Criteria 2009

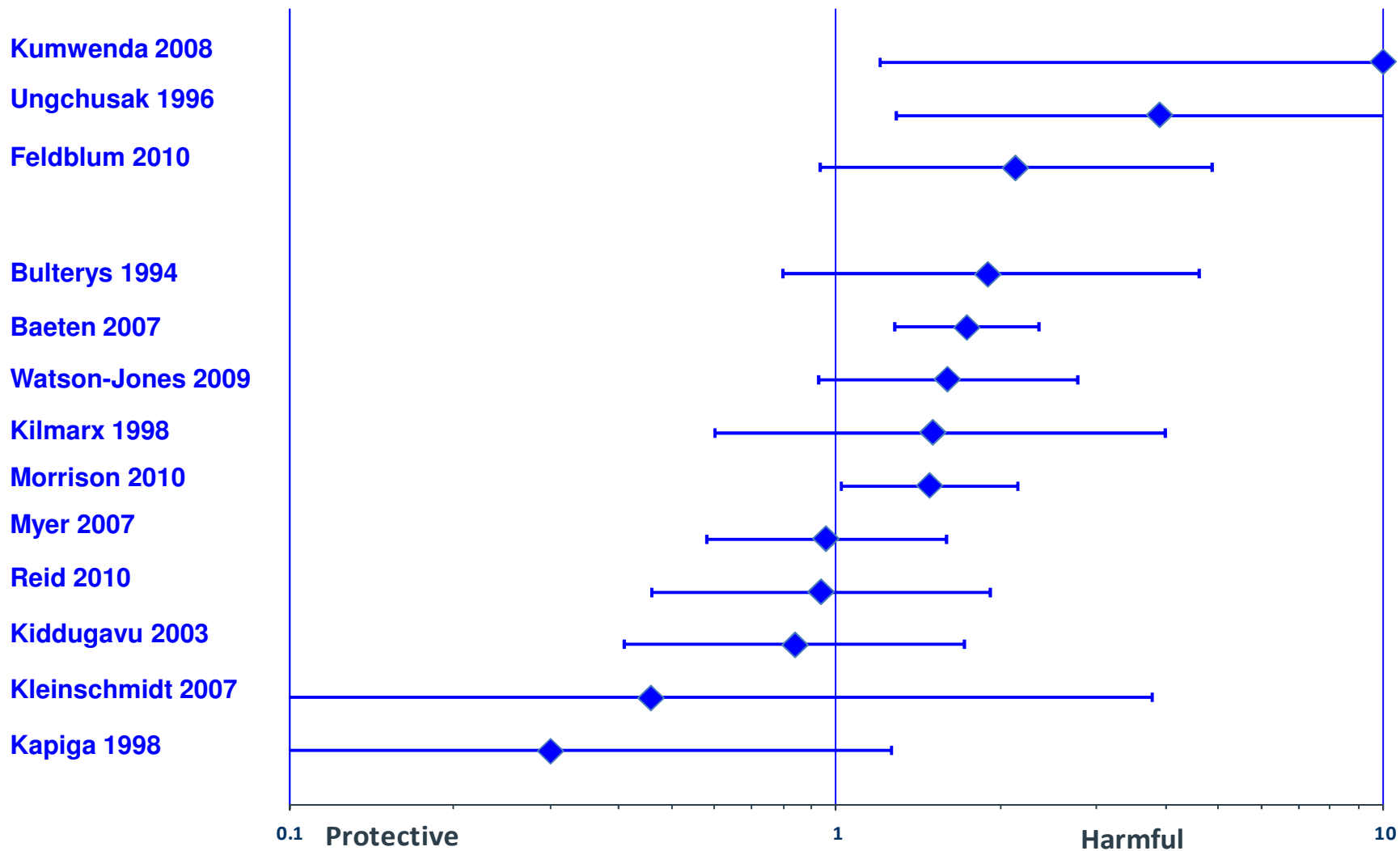
ARV	COC/P/R	CIC	POP	DMPA/ NET-EN	LNG/ETG Implants	CU IUD		LNG IUD	
NRTIs	1	1	1	1 1	1	I 2/3	C 2	I 2/3	C 2
NNRTIs	2	2	2	1 2	2	I 2/3	C 2	I 2/3	C 2
Ritonavir boosted protease inhibitors	3	3	3	1 2	2	I 2/3	C 2	I 2/3	C 2

WHO Medical Eligibility Criteria 2009

- Injectable progestins for women at high risk of HIV, HIV infected or AIDS
- “Intermediate” level of evidence
- Category 1 - “No Restriction” apart from women taking ARVs

“Balance of evidence suggests no association between progestin contraceptives, although studies of DMPA use conducted among higher risk populations have repeated inconsistent findings”

Studies of Progestin Injectables & HIV Acquisition



Source: Adapted from Polis (2011)

Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study



Renee Heffron, Deborah Donnell, Helen Rees, Connie Celum, Nelly Mugo, Edwin Were, Guy de Bruyn, Edith Nakku-Joloba, Kenneth Ngiire, James Kiarie, Robert W Coombs, Jared M Baeten, for the Partners in Prevention HSV/HIV Transmission Study Team*

Summary

Background Hormonal contraceptives are used widely but their effects on HIV-1 risk are unclear. We aimed to assess the association between hormonal contraceptive use and risk of HIV-1 acquisition by women and HIV-1 transmission from HIV-1-infected women to their male partners.

Methods In this prospective study, we followed up 3790 heterosexual HIV-1-serodiscordant couples participating in two longitudinal studies of HIV-1 incidence in seven African countries. Among injectable and oral hormonal contraceptive users and non-users, we compared rates of HIV-1 acquisition by women and HIV-1 transmission from women to men. The primary outcome measure was HIV-1 seroconversion. We used Cox proportional hazards regression and marginal structural modelling to assess the effect of contraceptive use on HIV-1 risk.

Published Online

October 4, 2011

DOI:10.1016/S1473-3099(11)70247-X

See Online/Comment

DOI:10.1016/S1473-3099(11)70254-7

*Members listed at end of paper

Department of Epidemiology
(R Heffron MPH, Prof C Celum MD,
J M Baeten MD). Global Health



UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER
PARTNERS IN PREVENTION

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

Contraception and HIV acquisition from women to men

		Adjusted Cox PH Regression analysis	
	HIV incidence per 100 person years	HR (95% CI)	P-value
No hormonal contraception	1.51	1.00	
Any hormonal contraception	2.61	1.97 (1.12 – 3.45)	0.02
Injectables	2.64	1.95 (1.06 – 3.55)	0.03
Oral contraceptives	2.50	2.09 (0.75 – 5.84)	0.16

Strengths and limitations

- **Strengths**

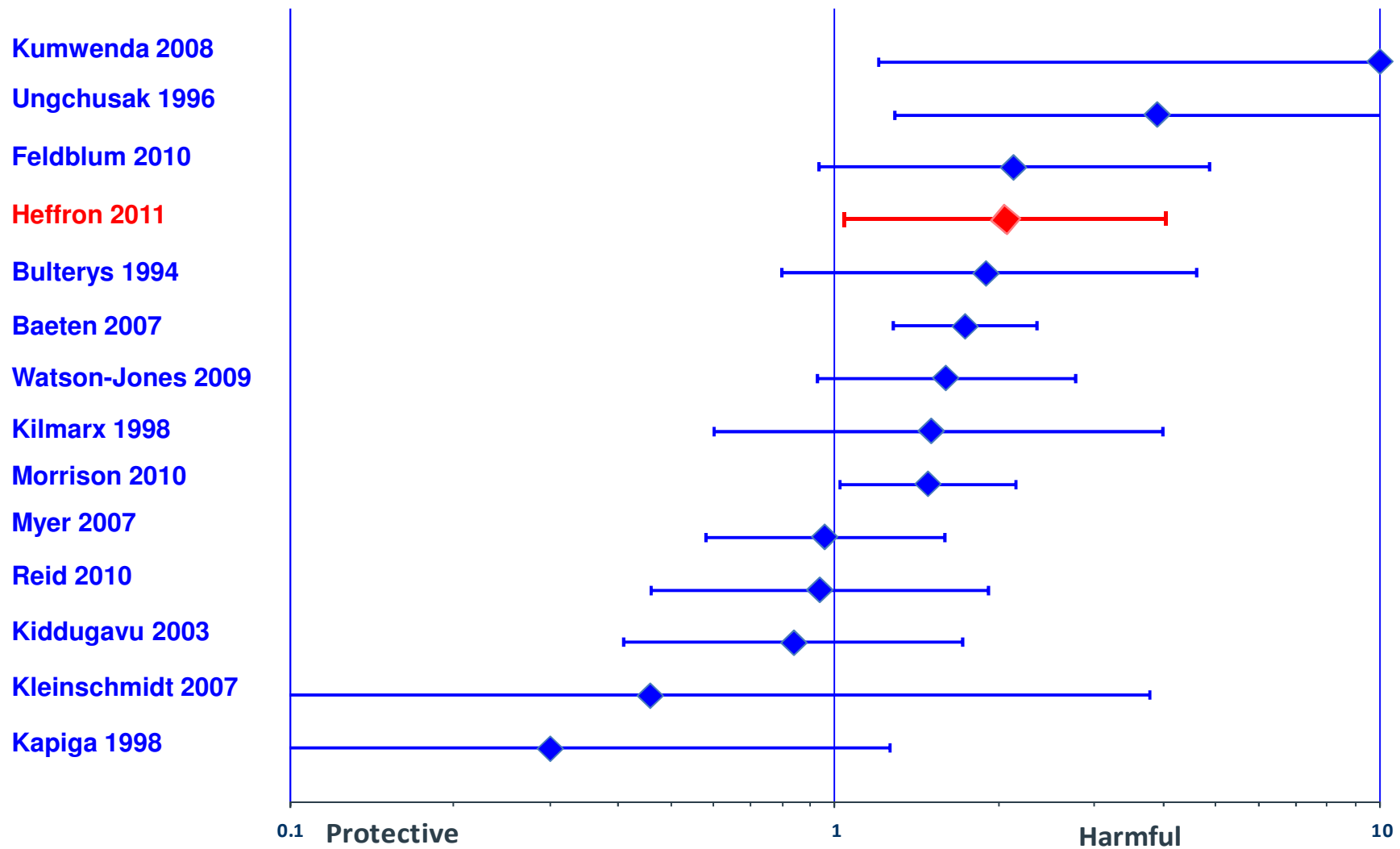
- Large cohort
- Frequent measurement of HIV, contraceptive use and sexual behavior
- Very high rates of follow up (>90% retention)
- HIV negative partners knew they were being exposed to HIV & all were exposed
- Attention to confounding factors using multiple statistical techniques (multiple additional analyses demonstrate consistent findings)
- First report of female to male transmission and partial biological explanation from increased genital viral loads

- **Limitations**

- Observational data
- Inability to distinguish between types of injectables used
- Limited data on oral contraceptive risk
- Limited number of infections among those using contraception



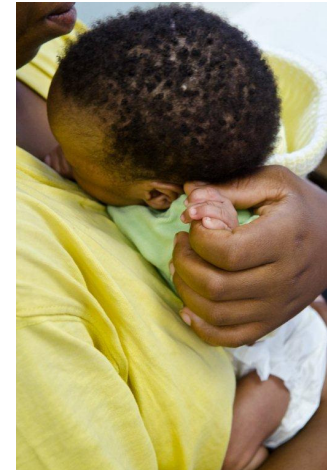
Studies of Progestin Injectables & HIV Acquisition, 2011



Source: Adapted from Polis (2011)

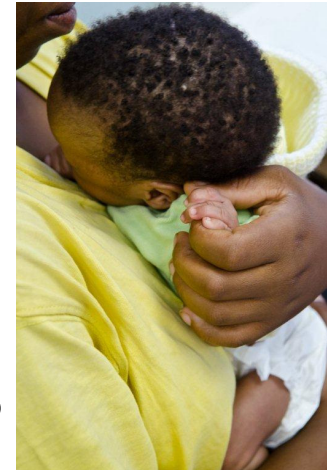
If the data is real then the choice for an HIV Uninfected Woman

- If she uses injectable progestins
 - Less risk of pregnancy
 - More risk of HIV acquisition
- If she stops injectable progestins
 - Does she have other contraceptive options?
 - If not, she may become pregnant
 - More risk of HIV acquisition
 - More risk of pregnancy morbidity & mortality
 - Unwanted pregnancy may have worse infant outcomes



If the data is real then the choice for an HIV Infected Woman

- If she uses injectable progestins
 - Less risk of pregnancy
 - More risk of HIV transmission to partner
- If she stops injectable progestins
 - Does she have other contraceptive options?
 - If not she may become pregnant
 - More risk of HIV transmission to partner
 - More risk of pregnancy Morbidity & Mortality
 - Potential for transmission to infant
 - Unwanted HIV infected babies have higher morbidity and mortality than wanted infants



Los Angeles Times BOOSTER SHOTS

LOCAL U.S. WORLD BUSINESS SPORTS ENTERTAINMENT HEALTH LIVING TRAVEL

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HEALTH TOPICS: TAINTED CANTALOUPE | COLON CANCER | CAFFEINE & WOMEN'S DEPRESSION

BOOSTER SHOTS: ODDITIES, MUSINGS AND NEWS FROM THE HEALTH WORLD

Africa study suggests hormonal contraceptive tie to HIV infection

FRANCE 24 INTERNATIONAL NEWS 24/7

FR - EN

04 October 2011 12:20 PM

NEWS WIRES

13 hours 44 min ago - health

Female hormonal contraceptive linked to higher HIV risk

DAILY NATION

Monday 04 October 2011 12:20 PM

Exhibitors: DAYKIO Housing Finance

method blamed for HIV

04.10.11 Updated 13.23

Miguna Miguna
Uhuru won propaganda war but lost legal battle
Comment: Page 24

Building online
Nairobi Council starts e-Construction permits
Property: Page 38

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the STAR

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 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 control of HIV/AIDS," researchers call for new guidelines for women using family planning services in Aids-hit areas

Continued on page 6

HOME PAGE TODAY'S PAPER VIDEO

The New York Times

WORLD U.S. N.Y. / REGION

Contraceptive U

By PAM BELLUCK
Published: October 3, 2011

The most popular contraceptive in Africa, a hormone shot, doubles the risk the women will become infected with HIV, a new study published. The results present a predicament for women, their male partners are twice as likely to become infected than if the women had used no contraception.

SIGN UP FOR OUR NEWSLETTER

EMAIL: [input] SIGN UP

PRIVATE [input]

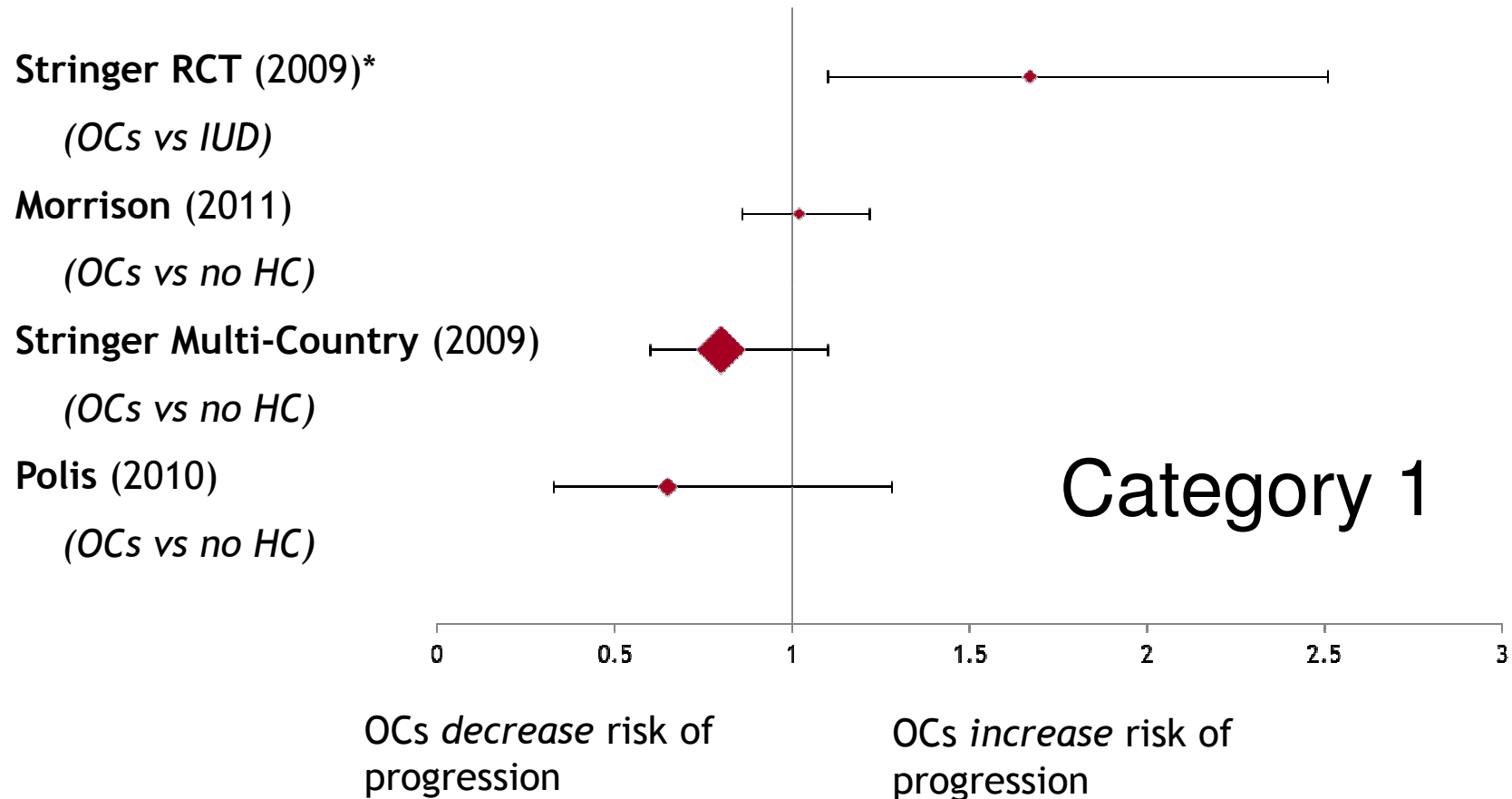
WHO Expert Consultation on HC and HIV

- Jan 2012, Geneva, 75 participants from 18 countries
 - HIV Acquisition
 - HIV Transmission
 - HIV Progression
- GRADE rating of the evidence
- Programmatic and research implications



World Health Organization

Studies assessing COCs and progression to AIDS OR mortality (Adjusted hazard ratio)



*Actual use analysis

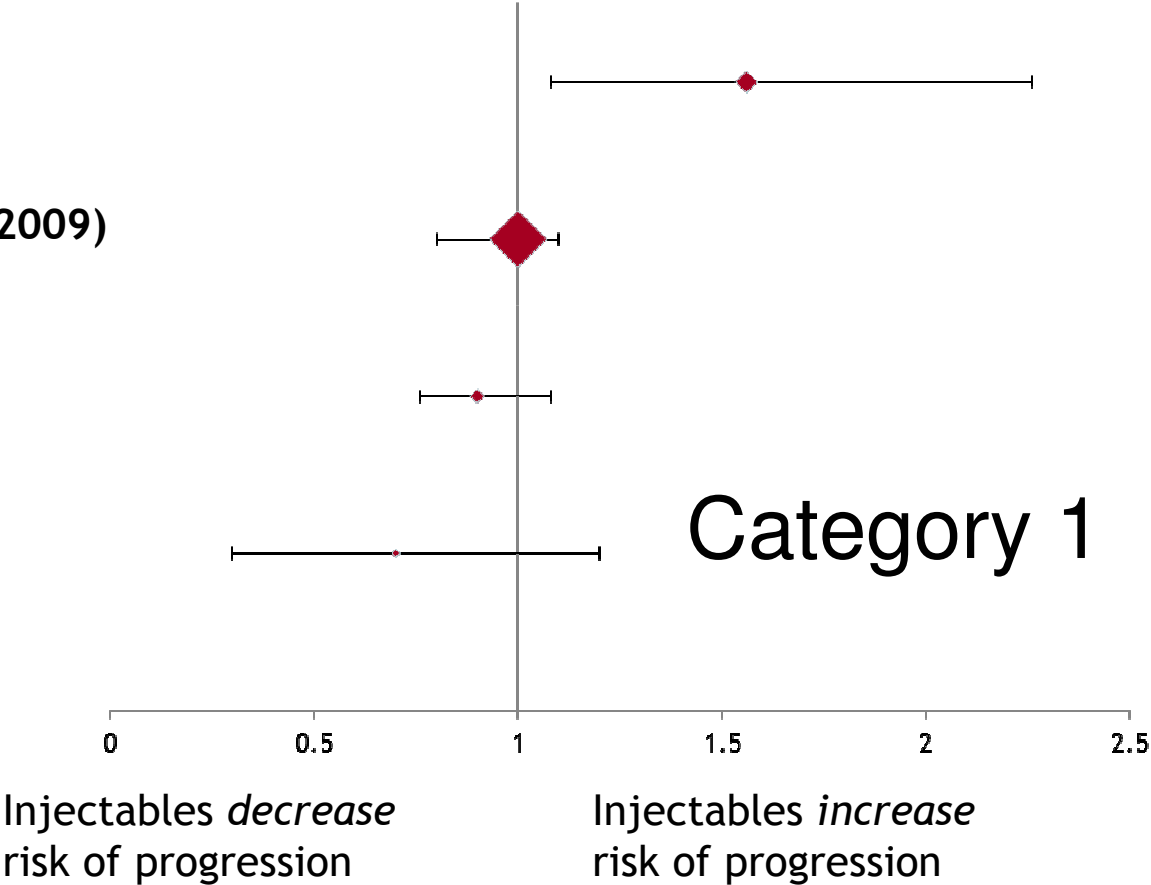
Studies assessing progestin injectables and progression to AIDS (Adjusted hazard ratio)

Stringer RCT (2009)*
(DMPA vs IUD)

Stringer Multi-Country (2009)
(Inj/imp vs no HC+)

Morrison (2011)
(DMPA vs no HC)

Kilmarx (2000)
(DMPA vs non-DMPA**)



Category 1

*Actual use analysis +DMPA, NET-EN or implant **Mostly OCs

WHO Expert Consultation on HC and HIV

- HC/HIV transmission evidence
 - Rated “low overall quality”
 - Category 1

The Elephant in the Room

A photograph of an elephant's head in a room, with a framed picture on the wall behind it. The elephant is looking towards the left. The background is a light-colored wall with a framed picture.

WHO Expert Consultation on HC and HIV

- Injectable progestins and HIV acquisition evidence
 - 8 cohort studies met minimum quality criteria
 - Rated “low overall quality” but better studies tended towards harm
 - Major focus of meeting

The Elephant in the Room



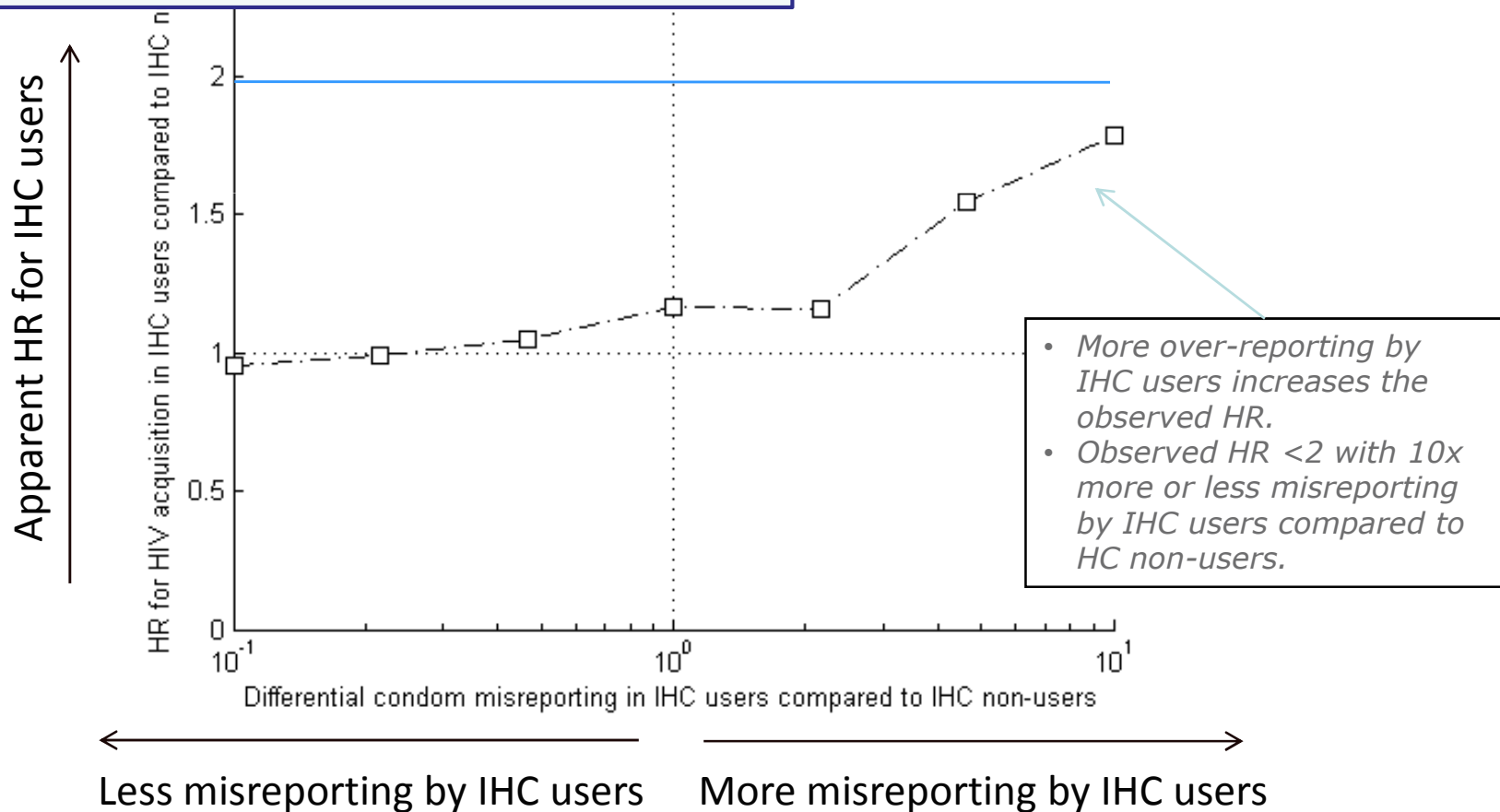
The Critique of the studies on Injectable progestins and HIV acquisition

- Observational data
- Possible 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

Differential condom misreporting

- Different levels of misreporting between reported IHC users and non-IHC users can generate a spurious association between HIV and HC use
- Large difference in misreporting required for observed HR to approach 2x risk
- Sensitive to reported level of condom use in the population

Adjusted Cox PH



Progestin injectables and HIV acquisition: The Great Debate

1. If left an MEC 1 – no change implies that the data are not convincing enough to support even theoretical concerns about injectable progestins and HIV acquisition
2. If moved to MEC 2 – a change implies that there are theoretical concerns which still allows use but if misunderstood might scare women and jeopardize global use without many alternatives being available
3. *The meeting was divided between 1 & 2*





Hormonal contraception and HIV Technical statement

WHO statement February 2012

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?.....

theguardian
HIV warning to women using injectable contraception
World Health Organisation advises use of condoms against infection
Sarah Roseley, health editor
guardian.co.uk, Thursday 16 February 2012 14:00 EST

The New York Times
February 17, 2012
Switzerland: Agency Stands by

POZ
HEALTH, LIFE & HIV

THE ASIAN AGE
'Hormonal contraceptives safe for women'
TEENA THACKER
263 words
18 February 2012

TOPNEWS
NEWS YOU CAN USE.....
Contraception Warned of HIV

THE HERALD
Zimbabwe: World Health Organisation Recommends Use of Hormonal Contraceptives
BY PAIDAMOYO CHIPUNZA, 22 FEBRUARY 2012

theSTAR
Kenya: Hormonal Contraception
BY JOHN MUCHANGI, 18 FEBRUARY 2012

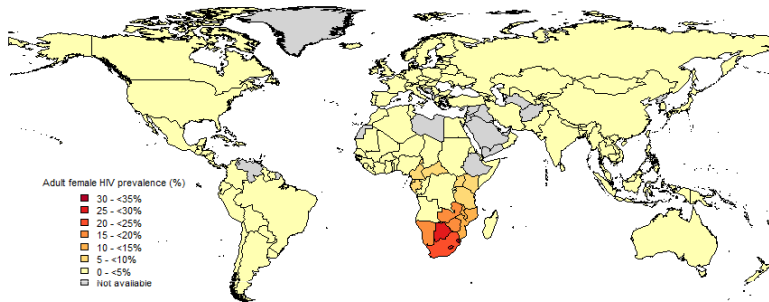
Uganda Picks
World Health Organization Clarifies Guidance on Hormonal Contraception and HIV
Published: February 18, 2012

What then happened.....

- Women's health 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
- Widespread calls for increasing the method mix in developing countries and less dependency on injectables
- Researchers and donors considering an RCT of progestins versus IUD as a definitive study
- And the modellers are involved.....

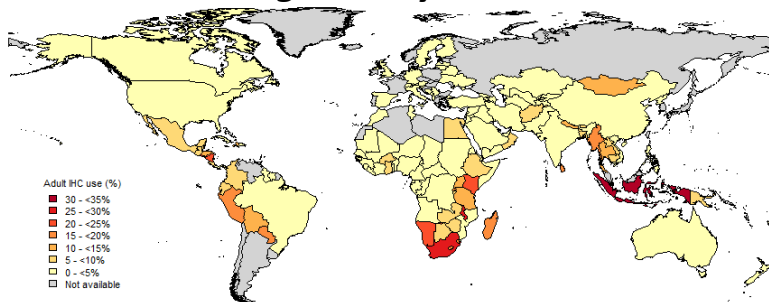
Where does high HIV prevalence coincide with high use of injectable hormonal contraceptives?

HIV prevalence among 15-49 year-old women*

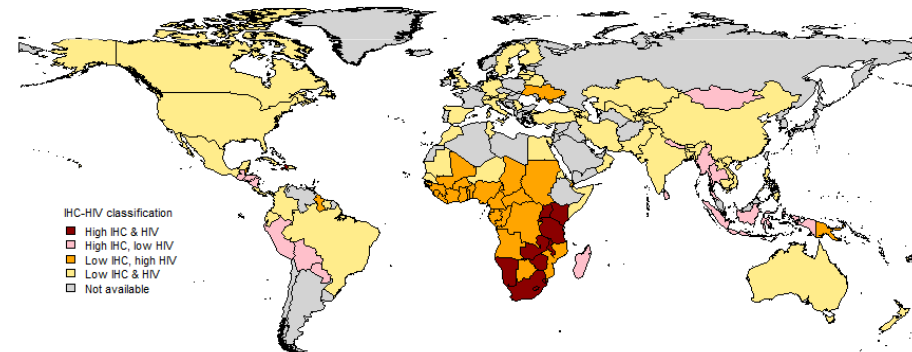


*Adult HIV prevalence given for China.

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



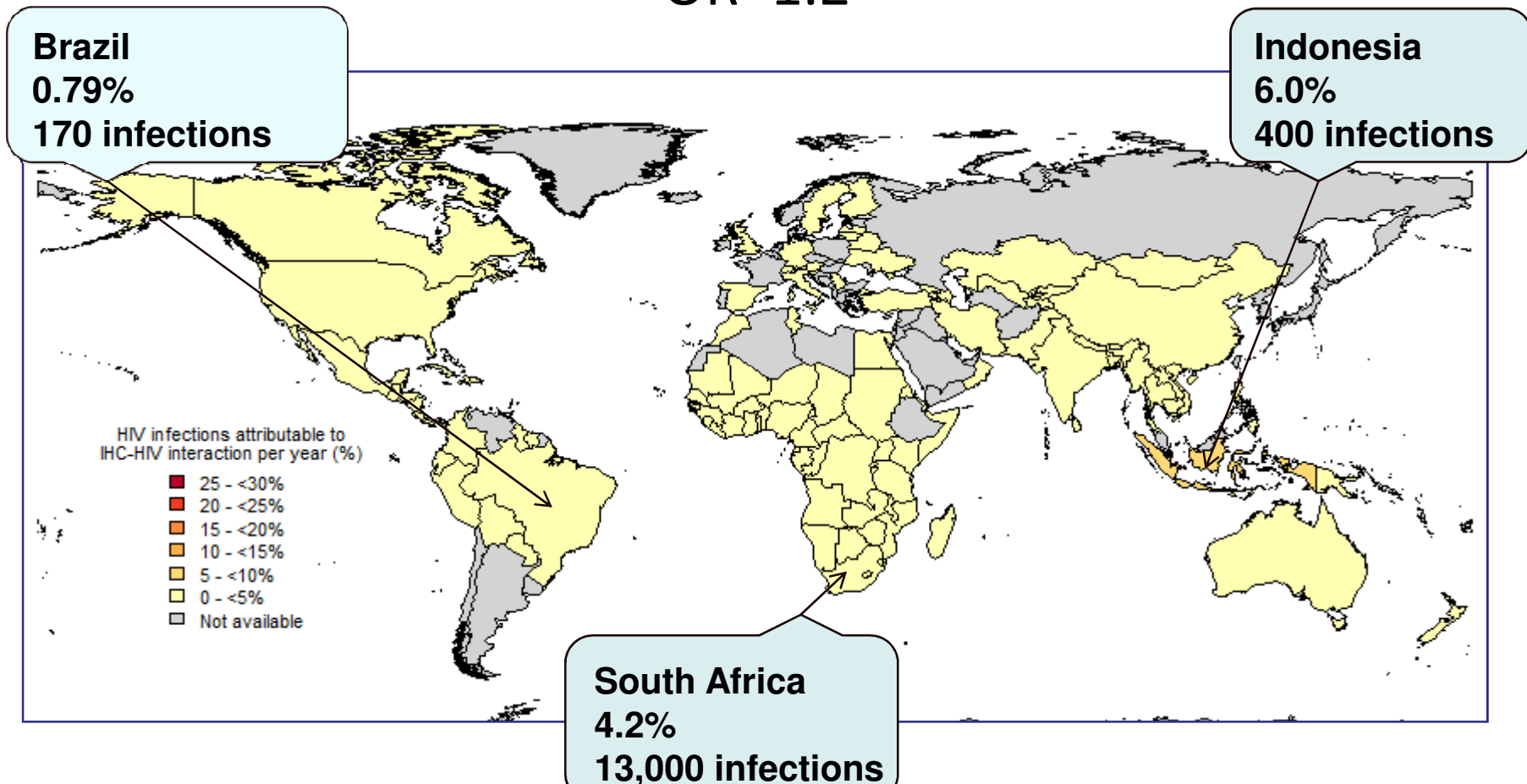
The overlap between use of injectables and HIV prevalence



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

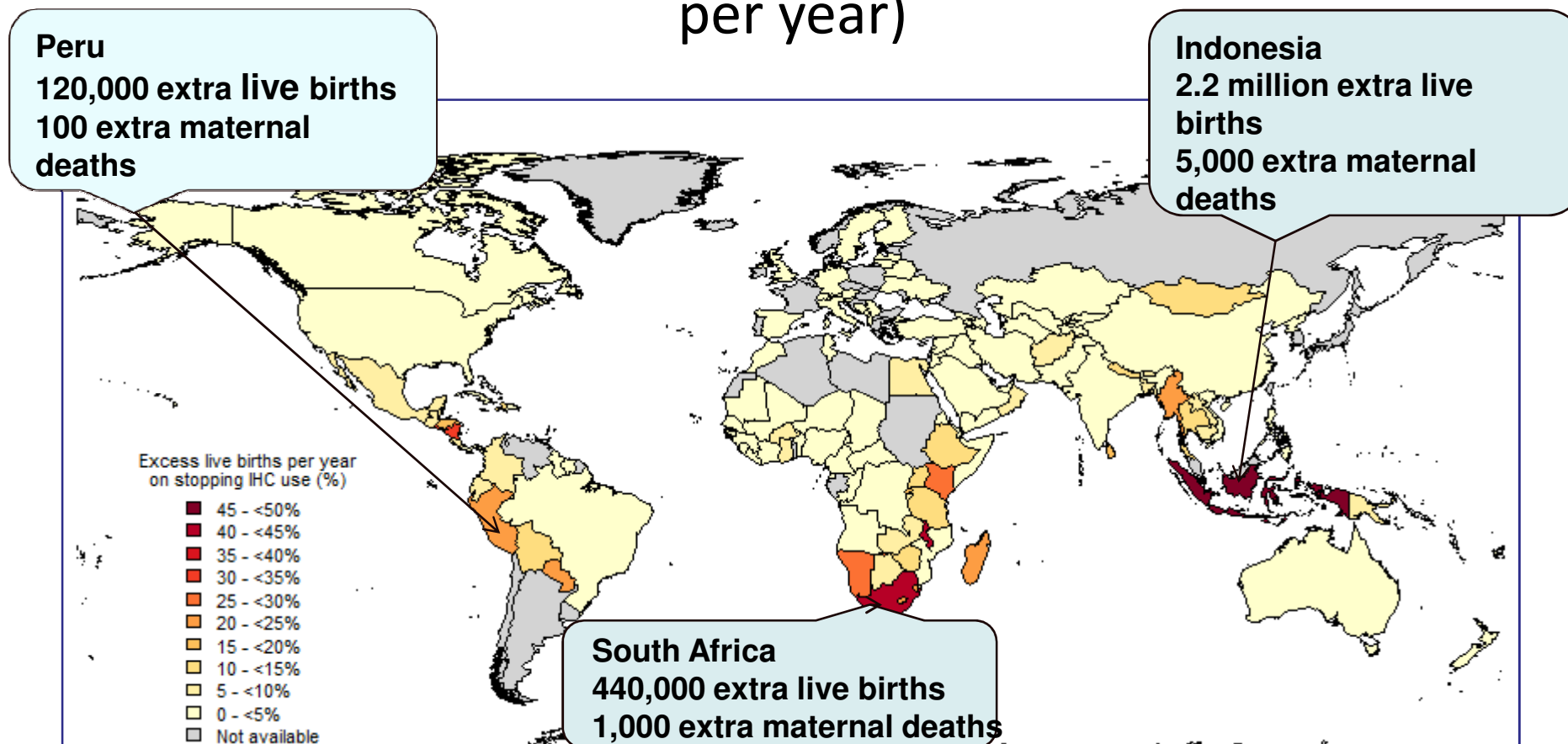
HIV infections attributable to hypothesised IHC-HIV interaction per year (% of total new infections)

OR=1.2



Regions with high HIV incidence and high IHC use have the largest percentage of infections attributable to injectable hormonal contraceptive use

Excess live births & maternal deaths per year on cessation of injectable HC use (% of current number per year)



Regions with a high birth rate and high IHC use have the largest % increase in live births on stopping IHC use

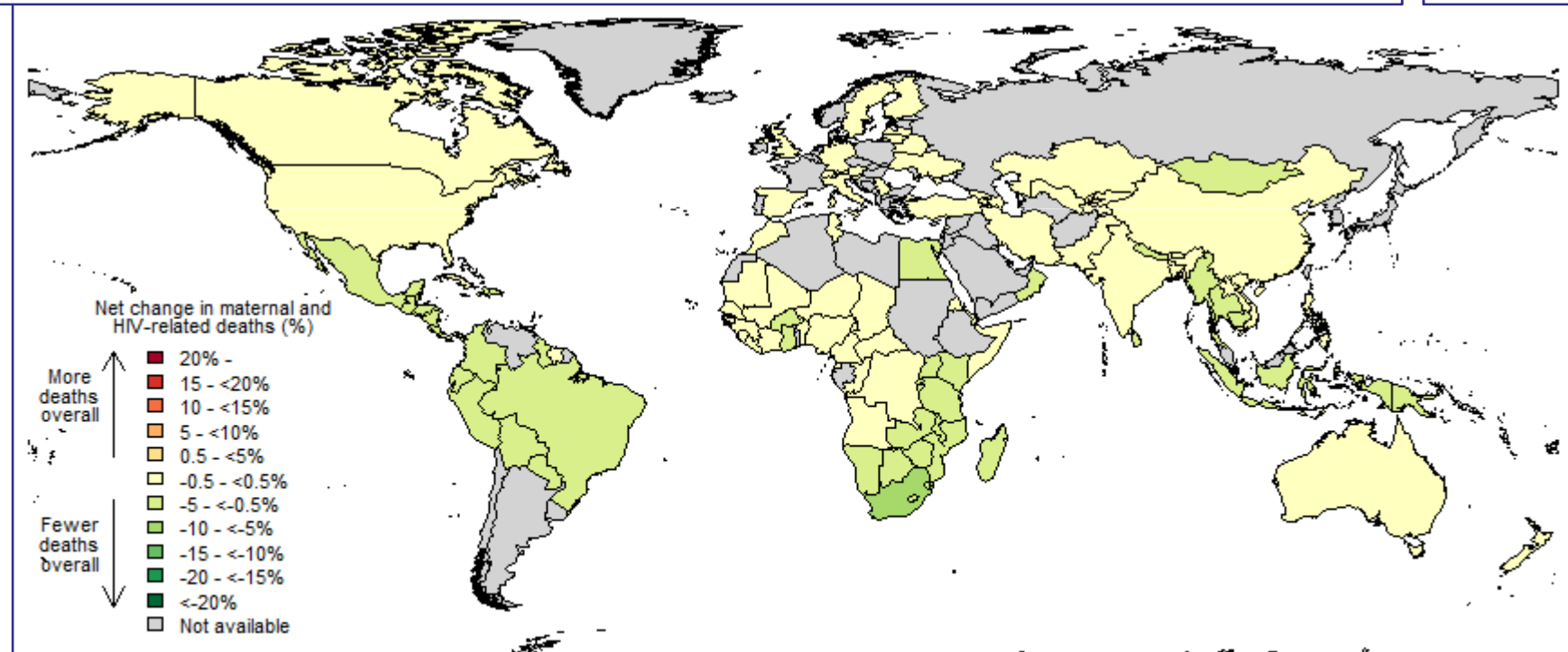
Regions with high maternal mortality and high IHC use have the largest % increase in maternal deaths on stopping IHC use

Net effect: 80% women stopping IHC are reassigned to effective alternative contraceptive

% change in net maternal and AIDS deaths on cessation of injectable HC use

Alternative contraceptive: 99.2% effective per year, similar to IUD

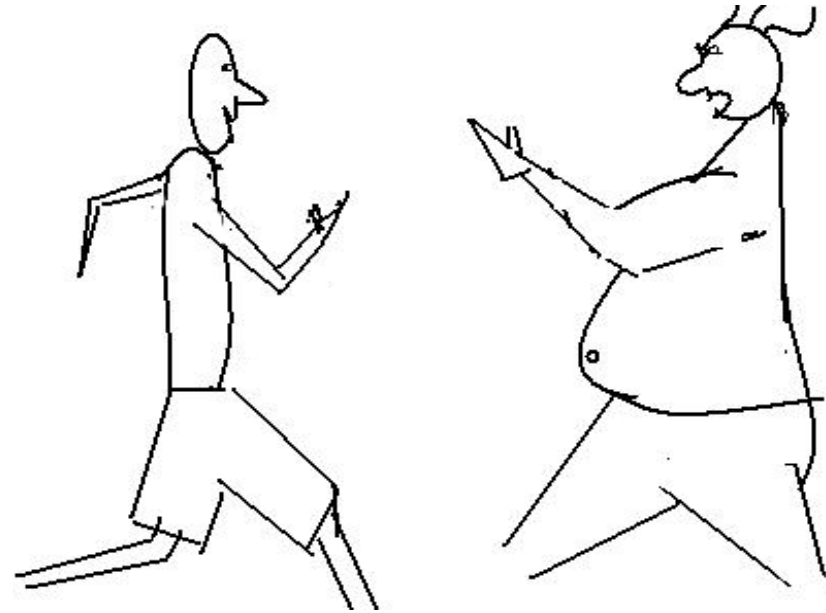
OR=1.2



Reduction in AIDS deaths outweighs changes in maternal deaths with highly effective alternative contraceptive.

Next Steps?

- More research
 - Randomized trial: other progestins including NET-EN, implants and DMPA
 - Observational analyses
 - Biologic studies
 - Combination prevention technologies
- More action
 - Change the method mix and reduce dependency on DMPA
 - Integrated family planning and HIV prevention and HCT
 - Messaging for women



Consider this hypothetical.....

statin when newer statins with the same efficacy and fewer side effects were available, and the higher dose made men.....

- Put on weight
- Made their hair temporarily stop growing
- And it took 9 months to return to normal
- AND may possibly increase HIV risk

How long would the marketplace tolerate this?

Thanks to.....

The many women who are willing to participate in research

Ward Cates & Charlie Morrison FHI 360

Jared Baeten, UW

The many donors and development partners



Women stop and start contraceptive methods

189 progestin injectable users followed up for 2 years
in family planning clinic in Soweto

Status	1 year		2 years	
	(%)	n	(%)	n
Continued	42	79	21	39
Lost to follow up	30	57	35	67
Discontinued	28	48	41	78
Withdrew	2	5	2	5

Of those who discontinued:

- 40% 'taking a break'
- >50% complained of side effects

Beksinska, Rees et al. Contraception 64(2001)

