

Confounded by Contraception

Ward Cates

MTN Regional Meeting

October 13, 2011

Acknowledgments

Colleagues from:

- FHI 360
- USAID
- University of Witwatersrand
- University of Washington
- And many more...

Hormonal Contraception and HIV

- 1.75 billion women of reproductive age
- 16 million women HIV-infected; 80% in Sub-Saharan Africa
- Hormonal contraception used >150 million women (COCs: >100 million; DMPA: >50 million)
- Injectable progestin (DMPA and Net-En) use increasing rapidly, especially Southern Africa

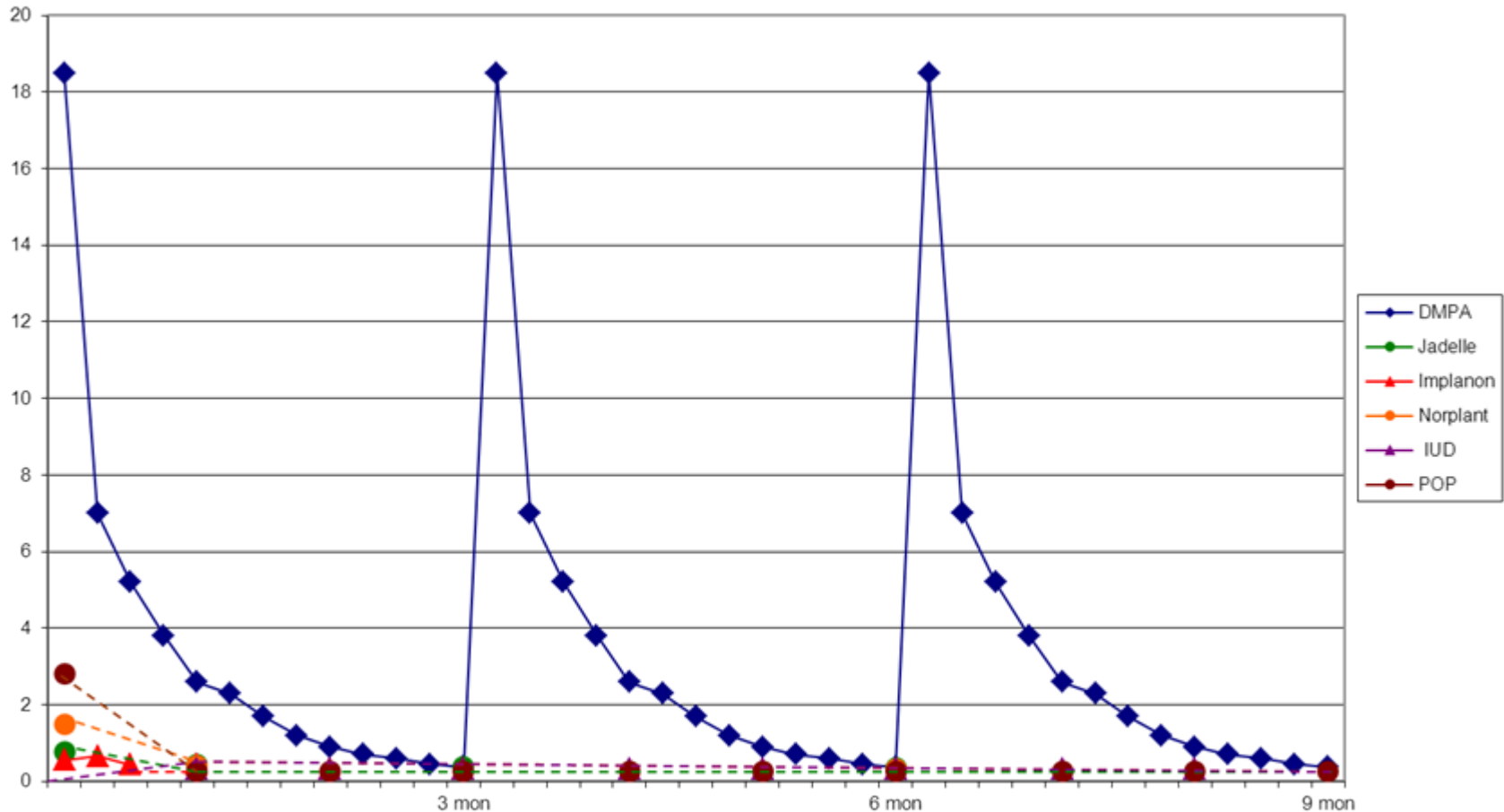
Hormones and HIV

Possible Mechanisms

- Vaginal and cervical epithelium (ectopy, etc.)
- Cervical mucus
- Menstrual patterns
- Vaginal and cervical immunology
- Viral (HIV) replication
- Acquisition of other STI

Serum Levels in Progestin Contraceptives

Serum concentration of progestin (ng/mL) over a nine-month period

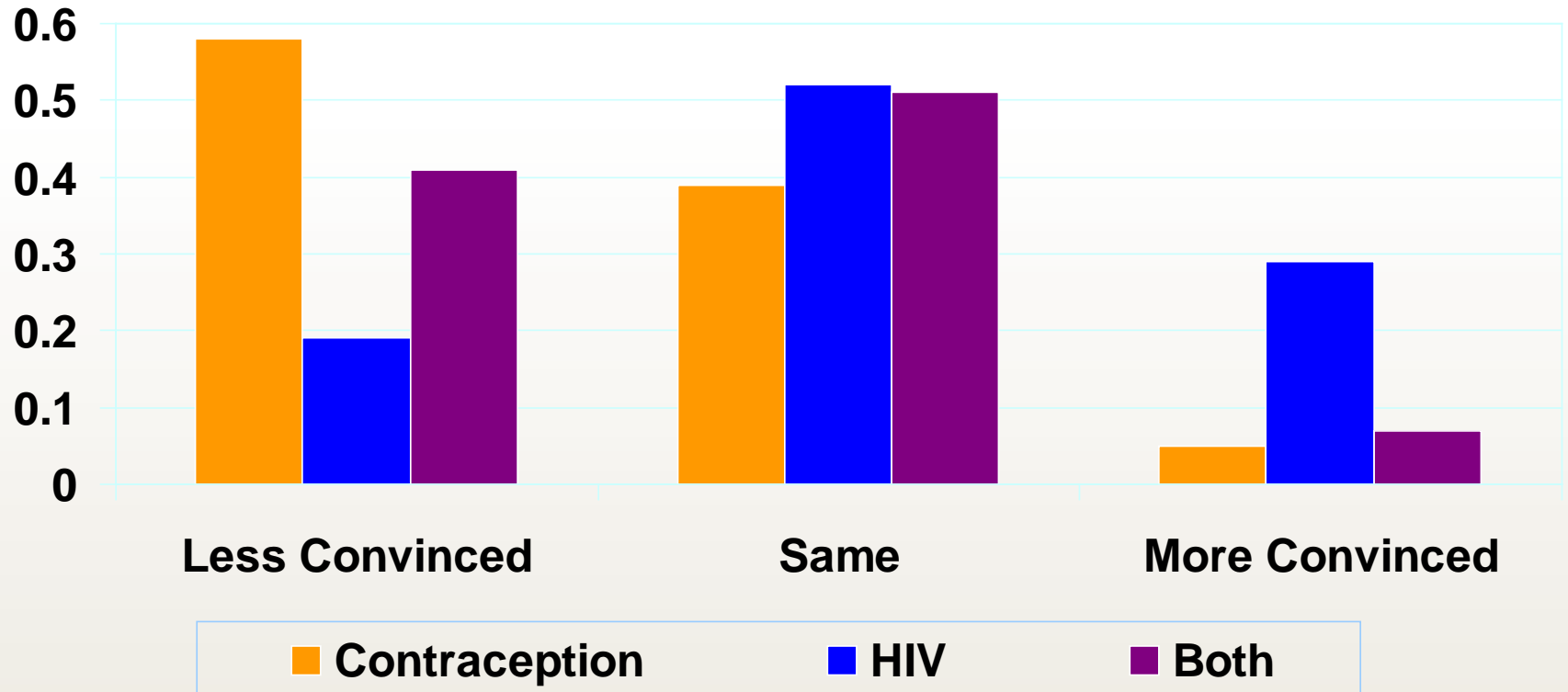


SOURCE DMPA: Goldzieher & Fotherby (1994). Pharmacology of Contraceptive Steroids, Pages 111&155; Fang et al. 2004. Jadelle: Sivin et al 2001. Implanon: Organon 2006; Funk et al 2005. Norplant: Nash 1990. IUD: Ewies 2009. POP: Ewies 2009; Organon 2009

HC/HIV Acquisition Research Timeline

- 1987 – Plummer IAS presentation
- 1988-on – Multiple secondary analyses
- 1996 – Marx monkey model/NIH review

Different Views on Hormone/HIV Association - 1996



HC/HIV Acquisition Research Timeline

- 1998 – HIVNET 021 → FHI's HC/HIV study
- 2007 – 1st WHO HC/HIV Consultation
- 2009 – FHI's External Consultation
- 2012 – 2nd WHO HC/HIV Consultation

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

Africa study suggests hormonal contraceptive tied to HIV infection



13 hours 44 min ago - health

Female hormonal contraceptive linked to higher HIV risk



Women who use hormonal control are roughly twice as likely to become infected with HIV or pass on the AIDS virus to their partner, according to a study published on Tuesday.

The research was carried out among 3,700 heterosexual couples in Africa where one partner had the human immunodeficiency virus (HIV) and the other was uninfected.

Birth control method blamed for HIV risk



PHOTOFILE Last week, the US Federal Drug Administration warned over the potentially high risk of blood clots in women using birth control pills containing the hormonal chemical called drospirenone. It is marketed under various brand names in Kenya. BUCO's product is registered with the Pharmacy and Poisons Board as well.

Health

Contraceptive Used in Africa May Double Risk of H.I.V.

By PAM BELLUCK
Published: October 3, 2011

The most popular contraceptive for women in eastern and southern Africa, a hormone shot given every three months, appears to double the risk the women will become infected with [H.I.V.](#), according to a large study published Monday. And when it is used by H.I.V.-positive women, their male partners are twice as likely to become infected than if the women had used no [contraception](#).

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World news

HIV could spread if birth control injections increase, warn scientists

Researchers call for new guidelines for women using family planning services in Aids-hit areas

Miguna Miguna

Uhuru won propaganda war but lost legal battle



Comment: Page 24



Property: Page 38

Building online

Nairobi Council starts e-Construction permits

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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 study is the strongest. "We want to make sure that we when there is a real need to warn, but the same time we don't want to con with a hasty judgement that would far-reaching severe consequences fo

CONTINUED ON P

Contraceptives double HIV risk

FROM PAGE 1

sexual and reproductive health of women," said Mary Lyn Gaffield, an epidemiologist in the World Health Organisation's department of reproductive health and research quoted in the *New York Times*.

Kenya's Ministry of Public Health says they are waiting for direction from the WHO.

There may however be a policy change to promote alternative family planning solutions for women.

Injectables have been the most popular form of contraception in Kenya and are used by 48 percent of married women, according to the 2008 Kenya Demographic and Health Survey.

About 16% of total users prefer the pill while women using implants account for about 14 percent of total users.

The *Lancet* study says that women using hormonal contraception through injectables became infected at a rate of 6.61 per 100 person-years, compared with 3.78 for those not using them.

Transmission of HIV to men occurred at a rate of 2.61 per 100 person-years for women using hormonal contraception compared with 1.51 for those who did not.

Researchers have been trying to explain the link between contraceptive use and HIV infection.

They said it is possible

hormonal contraception causes biological changes, such as changes to the cells that line the vagina or cervix and that influence susceptibility to HIV.

Renee Heffron, an epidemiologist and co-author of the study, however said research examining whether the hormone changes genital tissue or vaginal mucous had been inconclusive.

"It could be that progestin in injectables causes immunologic changes in the vagina and cervix or could increase the HIV's ability to replicate," Charles Morrison, senior director of clinical sciences at FHI 360, an NGO whose work includes researching the intersection of family planning and HIV told the US media.

Injectable contraceptives in Kenya include Depo Provera. Pfizer, the US-based manufacturer of the branded version of Depo-Provera, declined to comment to the *New York Times* on the study, saying officials had not yet read it.

The study's authors however said the injectables used by the African women were probably generic versions. Depo Provera has never been approved for use as a contraceptive in the US. It is controversial because it reportedly can cause heavy bleeding, weight gain, headaches, nervousness and depression.



RISKY: A nurse shows one of the most widely used contraceptives

Researchers also found that there was more HIV in the genital fluid of those using hormonal contraception than those who were not, which could explain why men might have increased risk of infection from women using injectables.

The researchers also found that oral contraceptives increased risk of HIV infection and transmission, but the number of pill users in the study was too small.

Others suggested that women on birth control often are careless in using condoms for protection.

The study however recorded condom use, thus excluding the possibility that increased infection occurred because couples using contraceptives were less likely to use condoms.

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Partners/HSV Study: HC/HIV Analysis

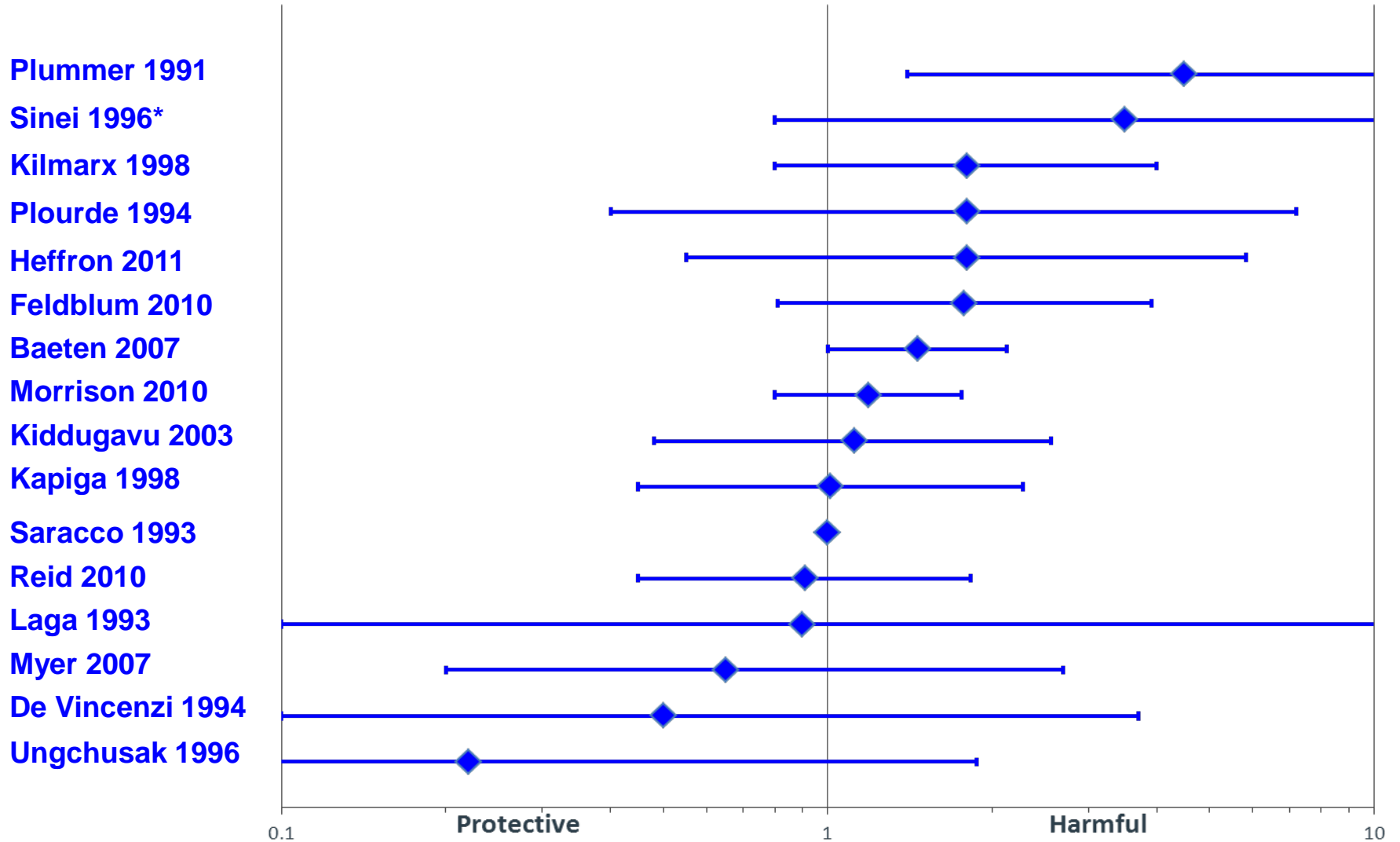
- 7 African countries, 14 sites
- 3321 Discordant Couples
 - Followed for 1-2 years
 - 2/3 couples – woman HIV-positive
- Overall Linked HIV Incidence
 - Male → Female – 4.1/100 p-y
 - Female → Male – 1.7/100 p-y

Source: Heffron (2011))

Partners/HSV Study: HC/HIV Acquisition – HIV-negative Women

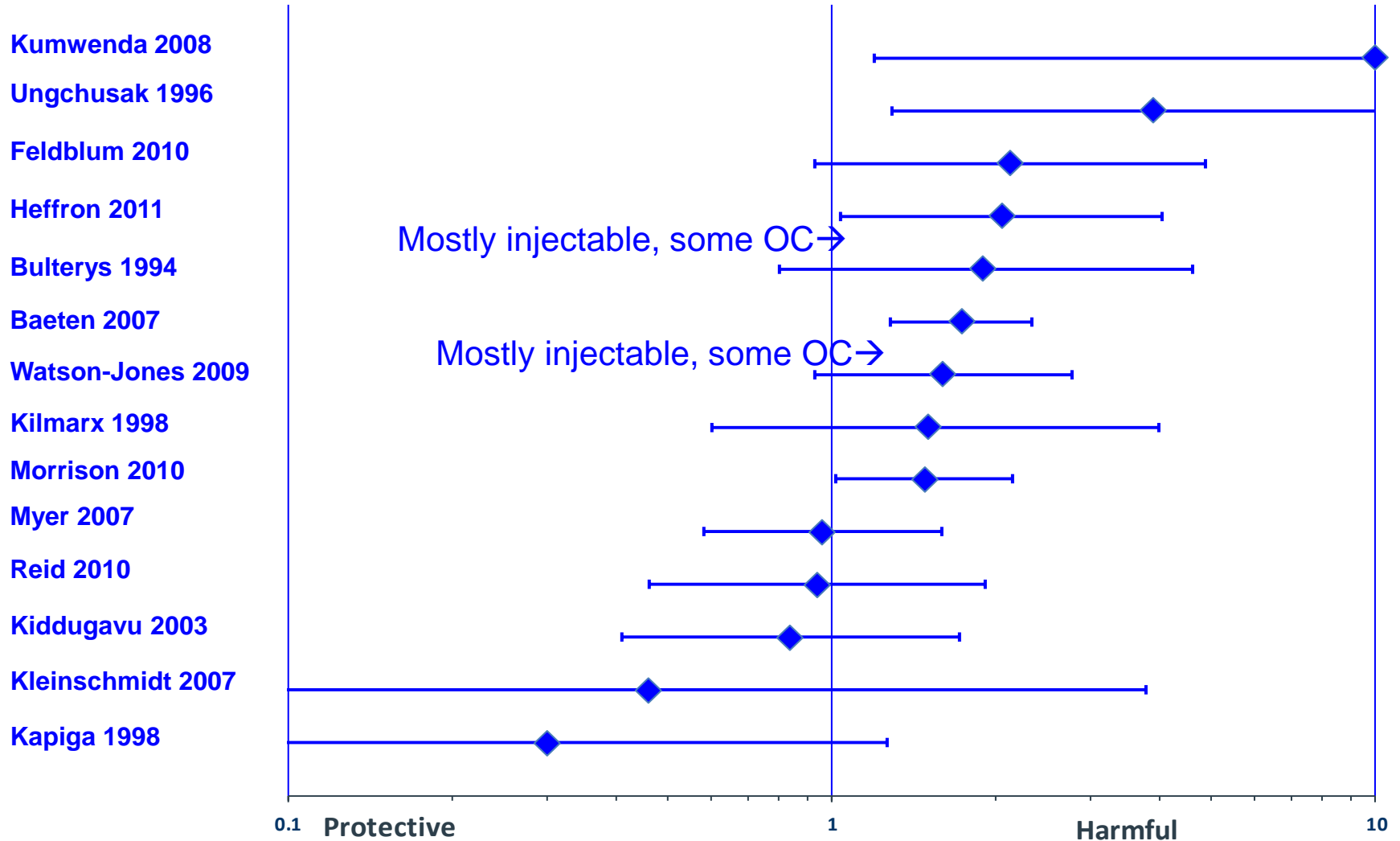
- 1314 HIV-neg women – 7% COCs, 16% DMPA
- HIV+ male: transmission to HIV- female
 - HIV Incidence: 4.1/100 p-y
 - Adjusted HR for COCs: 1.8 (0.6-5.8)
 - Adjusted HR for DMPA: 2.1 (1.0-4.0)

Prospective Studies of COCs & HIV Acquisition



Source: Adapted from Polis (2011)

Prospective Studies of Injectables & HIV Acquisition



Source: Adapted from Polis (2011)

HC/HIV Acquisition Summary – October, 2011

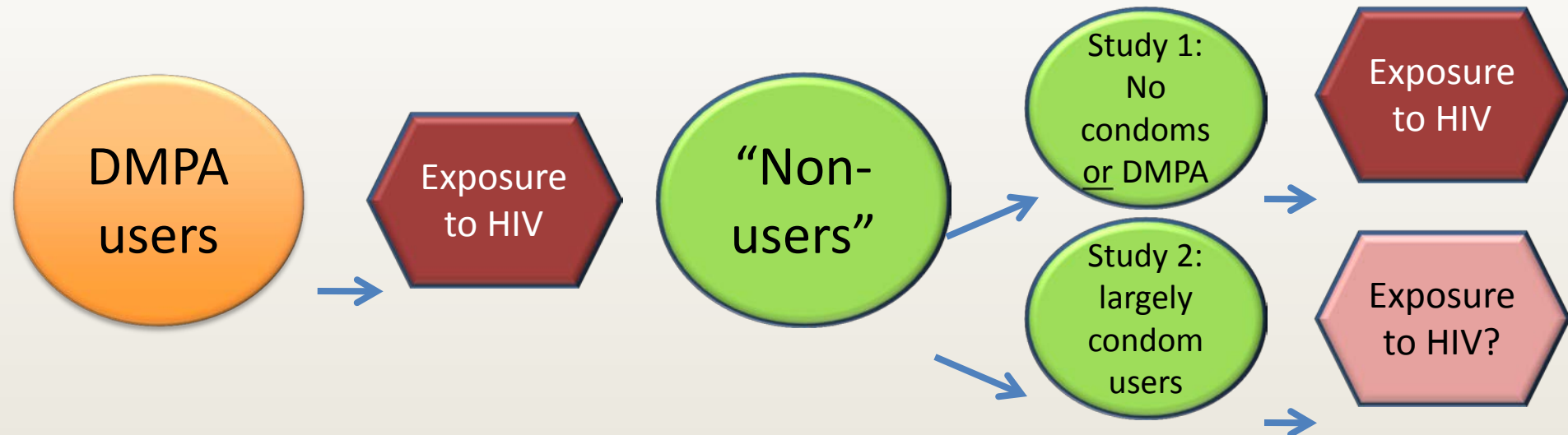
- OCs - 2/16 prospective studies found a significantly increased HIV risk
- DMPA – 5/14 prospective studies found significantly increased HIV risk
- Only 2 were designed to test hypothesis, others were secondary analyses

Limitations of HC/HIV Observational Studies

- Potential for unmeasured selection bias and confounding
- Hormonal contraceptive use not adequately documented
- Limited power - low HC use, few HIV+
- Non-hormonal comparison group has greater proportion of condom users

Potential Spurious Implications

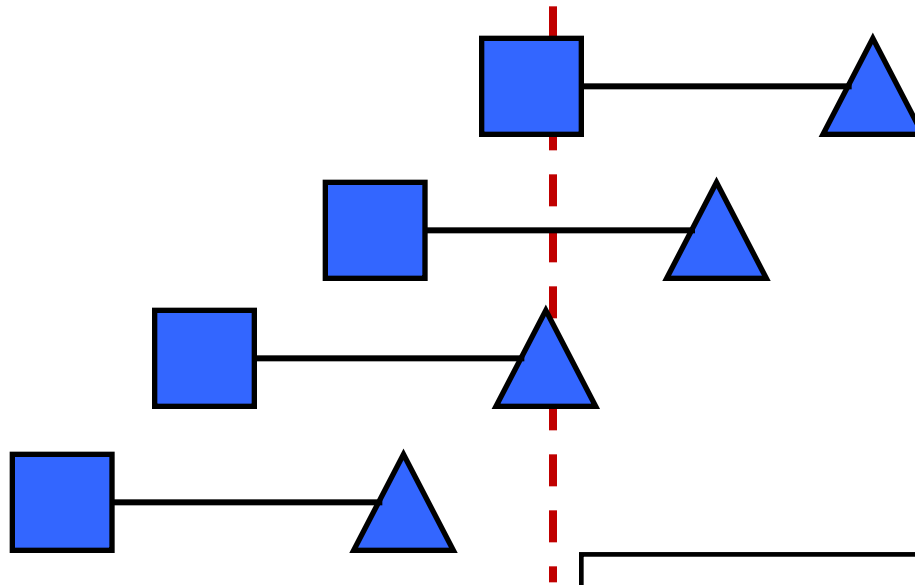
- Self-selection into HC use affects risk of HIV exposure
- HC users compared to “non-users”; definition of “non-users” varies, often includes condom-contraceptors



HC/HIV Results – What Do They Mean?

PROTECTIVE

HARMFUL



■ Non-Hormonal Group
– Greater condom use
– Higher partner risk score

▲ DMPA Group
– Less condom use
– Plausible biologic effect

Why an RCT Now?

- All previous studies observational – selection/confounding biases likely
- Macaque studies continue to find increased SIV transmission with DMPA
- HIV prevention trials have high HIV rates among young women; most using DMPA
- Recent HC/HIV findings have raised visibility
- We need to resolve this important global health issue once and for all

Design Issues for an HC-HIV RCT

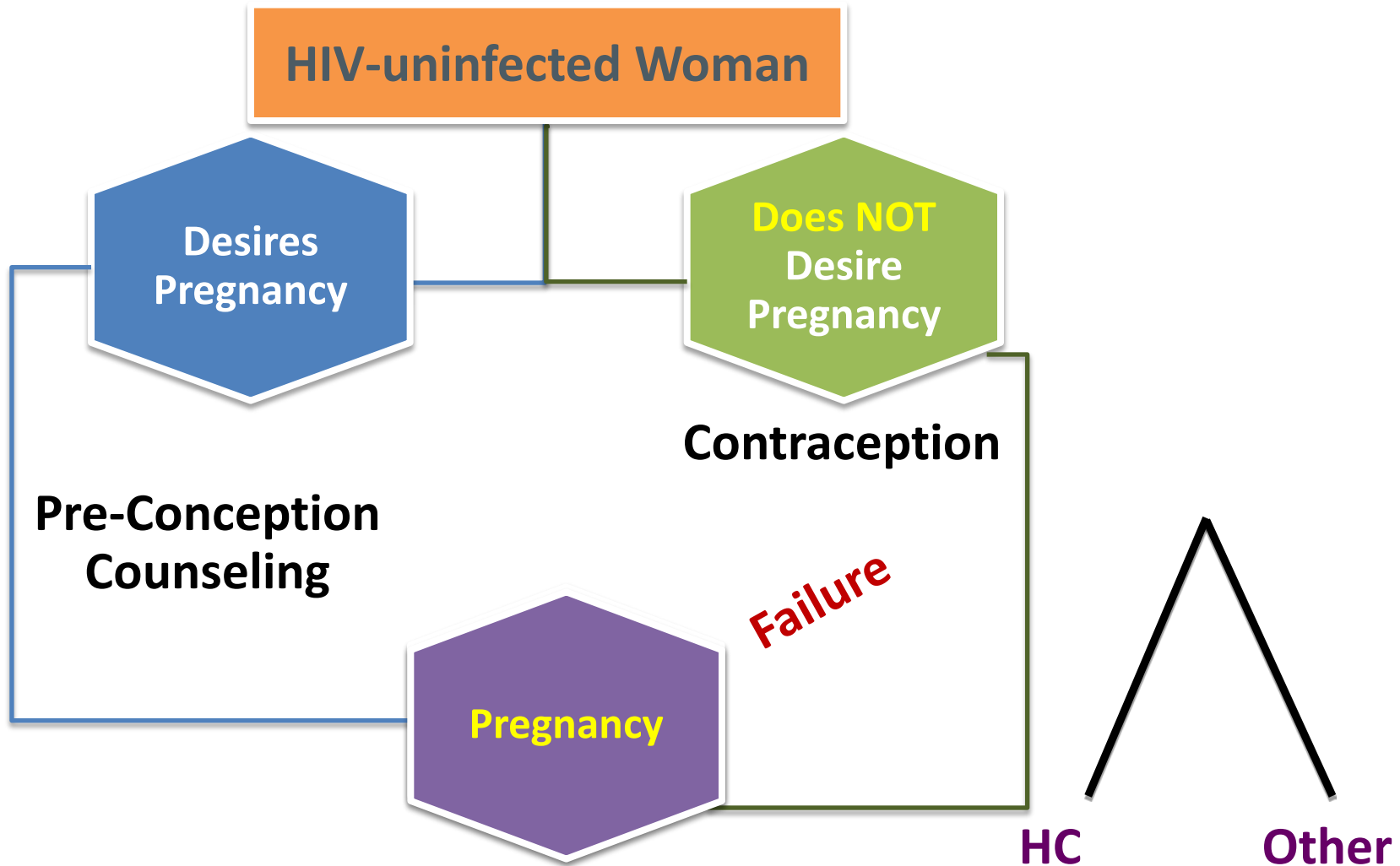
- How many arms should the study have, and what should those arms be?
- What should the target population be?
- Will women accept random assignment to dissimilar contraceptive methods?
- What age groups should we focus on?
- How do we maximize retention and adherence?

The ECHO Trial – An Ongoing RCT for HC/HIV

- **Location:** East London, South Africa
- **2 Arms:** DMPA cf IUD
- **Participants:** 9000 total, HIV-neg and HIV-pos women
- **Outcomes:** Contraceptive discontinuation, unintended pregnancy, HIV acquisition, HIV disease progression
- **Status:** Using local resources only, an estimated 10% have been enrolled

But Wait, There's Even More

Hormonal Contraception In Context



Does Pregnancy Affect HIV Risks?

- Partners HSV/HIV Trial - same database
- 7 African countries, 14 sites
- 3321 Discordant Couples
 - Followed for 1-2 years
 - 2/3 couples – woman HIV-positive
- Overall Linked HIV Incidence
 - Male → Female – 3.6/100 p-y
 - Female → Male – 1.7/100 p-y

Pregnancy/HIV Acquisition – HIV-negative Women

- 320 pregnancies in HIV- women – 29%
- HIV+ male: transmission to HIV-pregnant female
 - HIV Incidence: 7.4/100 p-y
 - Crude HR: 2.3 (1.2 – 3.7), $p = 0.003$
 - Adjusted HR: 1.5 (0.9 – 3.1), $p = 0.08$

So...What's An Uninfected Woman To Do?

- If she uses DMPA,
 - Less risk of pregnancy
 - More risk of HIV acquisition
- If she “falls” pregnant,
 - More risk of HIV acquisition
 - More risk of pregnancy M&M
- Tradeoffs

HC/HIV: Today's Conclusions

- Concerning DMPA findings from recent analyses
 - Point estimates higher than previous studies
- Intriguing pregnancy results
 - Reproductive choice tradeoffs
- Requires an RCT to answer more definitively
- Awaiting WHO consultancy and funders

Many Thanks