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HORMONAL CONTRACEPTIVE METHODS AND HIV: EPIDEMIOLOGICAL AND MODELING DATA

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USAID/PEPFAR/CDC technical brief on hormonal contraception & HIV



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TECHNICAL BRIEF HORMONAL CONTRACEPTION AND HIV

September 2013

BACKGROUND

This brief was produced in collaboration with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Office of Population and Reproductive Health at the U.S. Agency for International Development (USAID).

What is the purpose of this brief?

To summarize current epidemiological evidence regarding use of hormonal contraception (HC) and:

- Whether HIV-negative women will acquire HIV
- Whether women living with HIV will transmit HIV to their male sex partner(s)
- Whether women living with HIV will experience faster HIV disease progression
- Whether women living with HIV using antiretroviral therapy (ART) will experience drug-drug interactions

Who should read this brief?

- National policy makers responsible for HIV and/or family planning programming
- U.S. Government family planning and HIV program managers at headquarters and in the field
- HIV and family planning implementing partners

COMMON METHODS OF HORMONAL CONTRACEPTION

| Type of Contraceptive | Provision Frequency |
|---------------------------------------------------|-------------------------|
| Oral contraceptive pills | |
| Combined oral contraceptive pill ("the pill") | Taken daily |
| Progestin-only pill (POP) | Taken daily |
| Progestagen-only injectables | |
| Depo medroxyprogesterone acetate (DMPA) | Injected every 3 months |
| Norethisterone enanthate (NET-EN) | Injected every 2 months |
| Long-acting contraceptive methods | |
| Implant | Can last up to 5 years |
| Levonorgestrel intrauterine device (hormonal IUD) | Can last up to 5 years |

EVIDENCE AND RECOMMENDATIONS

What published evidence and recommendations are available regarding use of HC among HIV-negative women?

- HC use does not protect against HIV acquisition; all individuals at risk of HIV should be encouraged to use condoms consistently and correctly.
- The most recent World Health Organization (WHO) guidance (2012)¹ recommends no restriction on the use of any HC method for women at high risk of HIV, and it contains a special clarification for women at high risk of HIV who use progestogen-only injectable contraception, such as DMPA or NET-EN.

1. Does use of an HC method increase a woman's risk of HIV acquisition?

- Due to the inconclusive nature of the body of evidence on possible increased risk of HIV acquisition with use of progestogen-only injectable contraception,² women at high risk of HIV using progestogen-only injectable contraception should be strongly advised also to use condoms (male or female) consistently and correctly and to take other HIV preventive measures.⁴
- Available data do not suggest an increased risk of HIV acquisition with use of oral contraceptive pills.²
- There are limited data on whether methods such as contraceptive implants, patches, rings, or hormonal IUDs may or may not impact the risk of HIV acquisition.²
- Improving and reinforcing messaging on dual method use (i.e., use of a condom plus a highly effective contraceptive) to simultaneously prevent unintended pregnancy and acquisition/transmission of sexually transmitted infections including HIV is critical.
- Additional relevant evidence^{3,7} that has become available since the 2012 WHO guidance and that is published in the peer-reviewed literature will be reviewed at the next WHO technical consultation, planned for 2014. This evidence will include:

- Several sensitivity analyses conducted by Hefron et al. to address concerns that their original estimates (which suggested a doubling of risk in HIV acquisition with use of injectable contraception) may have been due to certain types of confounding bias. The sensitivity analyses supported their original findings.⁴



Do specific methods of hormonal contraception increase risk of:

HIV-
negative
women

1. HIV acquisition in uninfected women?

Women
living
with HIV

2. HIV transmission to uninfected male partners?

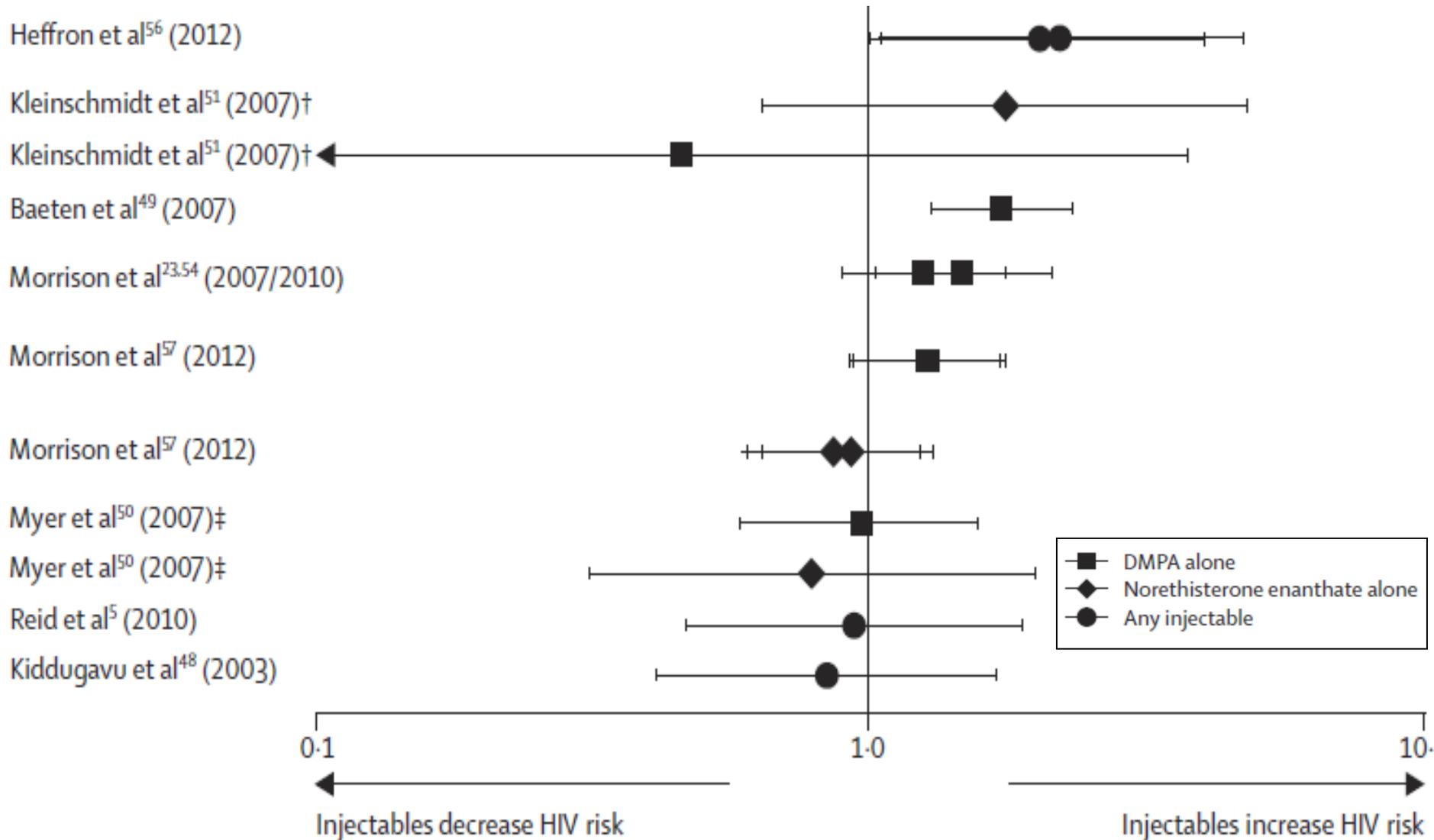
3. HIV disease progression in HIV-infected women?

4. Interaction with antiretroviral therapy?

- Systematic search identified 20 relevant studies (published or in press by Dec 15, 2011)
- Most available studies assessed oral contraceptive pills and contraceptive injectables
- We developed minimum quality criteria to distinguish between lower vs. higher quality studies
 - Although some studies were methodologically stronger than others, all available studies are observational, thus vulnerable to confounding bias

Injectables & HIV acquisition

Studies meeting minimum quality criteria



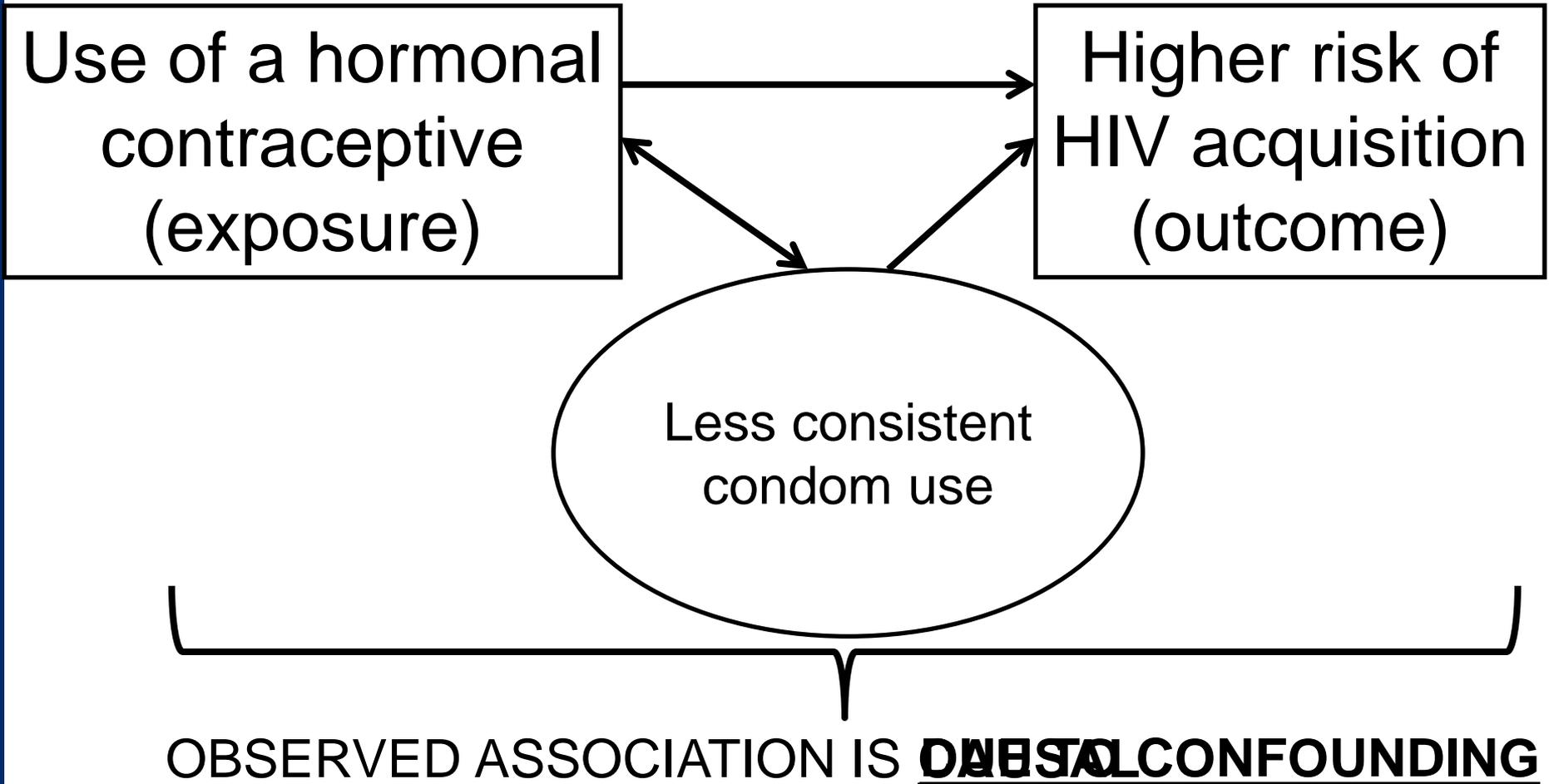
Selected key challenges in observational HC-HIV analyses

- Measurement of HC exposure, HIV exposure, & HIV outcome
 - Disaggregation of HC methods, which may have different effects
 - Contraceptive switching is common; measuring/analyzing it is complex
 - Measuring timing of HIV acquisition requires frequent, repeated testing
 - Unknown levels of underlying exposure to HIV risk
- Defining the comparison group
 - HC users often compared against women using either no contraception or a non-hormonal method (e.g., condoms, IUD); confounding likely
- Residual or uncontrolled confounding
 - Self-reported data about sexual behavior and FP use subject to error
 - Such information may be inadequate for thorough statistical adjustment
 - Other confounders may be unmeasured



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Causal vs. confounded associations: condom use example





- **OCPs:** data do not suggest an increased risk of HIV
- **NET-EN:** data are limited, do not suggest increased risk
- **Implants, patches, rings, hormonal IUDs:** limited/no data
- **DMPA:** substantial uncertainty, some of the higher quality studies suggest a potential increased risk of HIV acquisition
 - Magnitude unclear: if association is real, could range from modest effect to 2-fold
 - Must be balanced against risks of unintended pregnancy (maternal death, morbidity, unsafe abortion, infant mortality), and potential risk of HIV acquisition associated with pregnancy
 - *We must assist women and couples to make an informed choice*



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2012 WHO HC-HIV statement: Medical Eligibility Criteria for Contraceptive Use

Statement



Hormonal contraception and HIV

Technical statement

16 February 2012

Executive summary

Following new findings from recently published research, the World Health Organization (WHO) convened a technical consultation on hormonal contraception and HIV acquisition, progression and transmission. This was likely to be of particular concern in countries where hormonal contraceptive methods constitute a large proportion of all contraceptive use. In these countries, mortality rates remain high. The meeting was held in Geneva between 31 January and 1 February 2012, and involved 75 individuals from 25 countries. Specifically, the group considered whether the current Medical Eligibility Criteria for Contraceptive Use, Fourth edition 2009 (MEC) should be updated in light of new evidence.

After detailed, prolonged deliberation, informed by the scientific evidence and presentations on biological and epidemiological evidence, the group concluded that the current MEC should be updated to recommend that there are no restrictions for the use of hormonal contraceptive methods for women living with HIV. The group recommended that a new clarification (underlining) be added to the MEC regarding the use of progestogen-only injectable contraception.

Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition. A WHO expert group reviewed all the available evidence and concluded that the evidence was not sufficiently conclusive to change the MEC. However, because of the inconclusive nature of the body of evidence on possible increased risk of HIV acquisition, women using progestogen-only injectable contraception should be advised to *also always use condoms, male or female, and other HIV preventive measures...*

Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection will be continually reviewed in light of new evidence.

The group further wished to draw the attention of policy-makers to the potential seriousness of the issue of HIV acquisition. The group noted the importance of continued research on the relationship between hormonal contraception and HIV infection for public health and emphasized the need for continued research on the relationship between hormonal contraception and HIV infection. The group also recommended that women using hormonal contraception should *also always use condoms, male or female, and other HIV preventive measures...* against HIV transmission or acquisition.

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 (at high risk of HIV) using progestogen-only injectable contraception should be strongly advised to *also always use condoms and other HIV preventive measures...*

Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential. These recommendations will be continually reviewed in light of new evidence.



Updated systematic review presented at March 2014 MEC

- MEC HC-HIV guidance to be released July 2014
- Review submitted for publication; includes new published data
 - Heffron et al. sub-analyses (LID 2013)
 - McCoy et al. analysis of MIRA data (AIDS 2013)
 - Lutalo et al. analysis of serodiscordant couples in Rakai (AIDS 2013)

Presentations (unpublished data; not yet included in review)

- Chirenje et al. analysis of HPTN 035 (Microbicides 2012)
- Crook et al. analysis of MDP 301 (CROI 2013)
- Morrison et al. IDP meta-analysis (North American Forum on FP 2013)
- Noguchi et al. analysis of DMPA vs. NET-EN in VOICE (CROI 2014)

Future studies being discussed

- Randomized trial

Progress: analytic recommendations for future observational analyses

Table 1. Considerations and recommendations for future observational analyses of hormonal contraception and HIV acquisition.

| Considerations for observational analyses of hormonal contraception and HIV acquisition | Recommendations for design, analysis, or reporting to minimize potential limitations and improve study quality |
|------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Multiple types of hormonal contraception | Disaggregate hormonal contraceptive methods by distinguishing between pills, injectables, implants, IUDs, etc. Where possible, further distinguish by hormonal content and formulation (e.g., DMPA vs. NET-EN, progestin-only methods, pills, injectables, implants, hormone-releasing IUDs) (e.g., et al.) and intramuscular DMPA vs. lower- |
| | Use appropriate analytic techniques to cumulative exposures contraceptive method hormonal contraception exposure, intervals are preferable the comparison group comparison group and a comparison (d), if sample size and study power affects or direct effects consistency of condom use over time x), age, and others listed in Figure 1 and on available literature, especially reporting different sexual behaviors (and with reduced rates; report e of measurement error) semen exposure (Y chromosome or) reporting during recent sex not no condom use (by censoring at) using no condom use may be less) concomitant medications (log) with decreased pregnancy rates, we lower rates; report results within |
| Pregnancy | main paper to describe possible degree of measurement error Ideal approaches remain unclear; sensitivity analyses using multiple approaches are recommended to examine whether primary results are robust |
| Level of HIV-1 exposure | Describe the rationale for analytic choices made regarding pregnancy Conduct studies among serodiscordant couples when possible If data are available on male partner HIV status (and HIV viral load), consider adjusting for this in the analysis Test stored female genital swab specimens for HIV DNA to determine exposure to HIV If serodiscordant data are unavailable, consider adjusting for behavioral data (or conducting subgroup analyses) on partner risk, recognizing that such measures may have limitations and should be validated to the extent possible |
| Statistical techniques | Determine whether Cox proportional hazards modeling, marginal structural modeling with IPWs, or alternate g-methods are appropriate for the data and question of interest Analytic method should be clearly prespecified to avoid data-dredging Multiple approaches can act as sensitivity analyses; e.g., MSM and g-formula |
| Missed study visits and missing data | Ideal approaches for handling missing data due to women who are not lost to follow-up but who miss specific follow-up visits remain unclear; sensitivity analyses using multiple approaches are recommended to examine whether primary results are robust |
| Loss to follow-up | Compare contraceptive use and sexual behavior characteristics at enrollment between women retained and lost to follow-up Determine whether loss to follow-up is differential by arm If loss to follow-up exceeds 20%, consider whether the data are appropriate for the analysis |
| Study power | Determine study power for each outcome a priori and report it in the article If study power is low, consider whether the data are appropriate for analysis, or focus on interpretation of direction and magnitude of point estimates, rather than emphasizing statistical significance or lack thereof |
| Publication bias | Both significant and nonsignificant results should be published in the scientific literature |
| DMPA, depot-medroxyprogesterone acetate; HSV-2, herpes simplex virus type-2; IUD, intrauterine device; NET-EN, norethisterone enanthate. | |

Assessing the effect of hormonal contraception on HIV acquisition in observational data: challenges and recommended analytic approaches

Chelsea B. Polis^{a,*}, Daniel Westreich^{b,c,*}, Jennifer E. Balkus^{d,e,*},
Renee Heffron^{e,*}, participants of the 2013 HC-HIV
Observational Analysis Meeting

We must not forget about contraceptive services for women living with HIV

- Women living with HIV report high rates of unintended pregnancy and unmet need for family planning.
- Unintended pregnancy among women living with HIV carries significant risks for mothers and babies.
- Reducing unintended pregnancies to women living with HIV is an essential, cost-effective, and under-emphasized component of preventing mother-to-child HIV transmission
 - ***At the same level of expenditure, contraception averts 28.6% more HIV-positive births than single-dose NVP.***



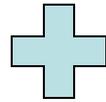
Overview of all HC methods & all HIV-related risks

| | HIV-negative | Living with HIV | |
|---------|----------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| | Acquisition | Progression | Transmission |
| OCPs | No current concern | No current concern | No current concern (based on very few studies) |
| DMPA | Some concern , more research warranted | No current concern (potentially protective effect based on very few studies) | Some concern (based on very few studies), more research warranted |
| NET-EN | Limited concern (based on very few studies) | No current concern (based on very few studies) | Limited concern (based on very few studies), more research warranted |
| LNG-IUD | No data available | No current concern (based on very few studies) | No current concern (based on very few studies) |

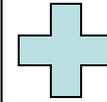
- No data available for contraceptive implants, contraceptive patches, contraceptive rings, or emergency contraception.
- Some ART medications (NNRTIs and ritonavir-boosted PIs) may reduce efficacy of some HC methods (COCs, implants).
- No drug interactions expected between ART medications and DMPA; this may be an important option for women living with HIV.

Current understandings about injectables in women at risk of HIV acquisition

Possible HIV-1
acquisition risk
with some
hormonal
contraceptives



Uncertainty in
data

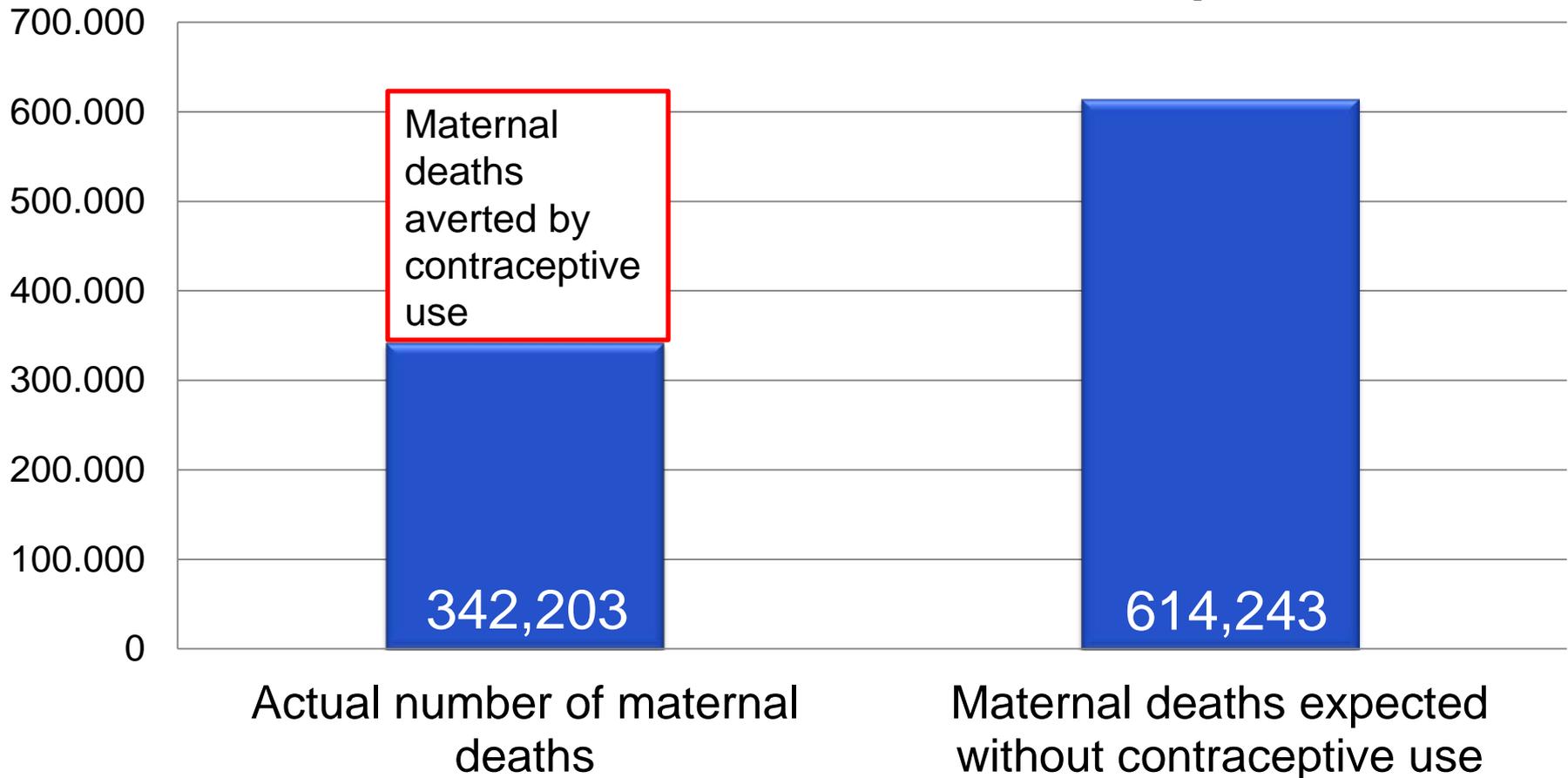


Life-saving
benefits of
hormonal
contraceptives

Public health conundrum

Contraceptive use prevents 44% of maternal deaths worldwide

Number of maternal deaths in 2008: actual and estimated without contraceptive use





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Maternal deaths: the tip of the iceberg



“For every woman who dies, there are 20 to 30 others who survive childbirth but suffer debilitating injuries.”

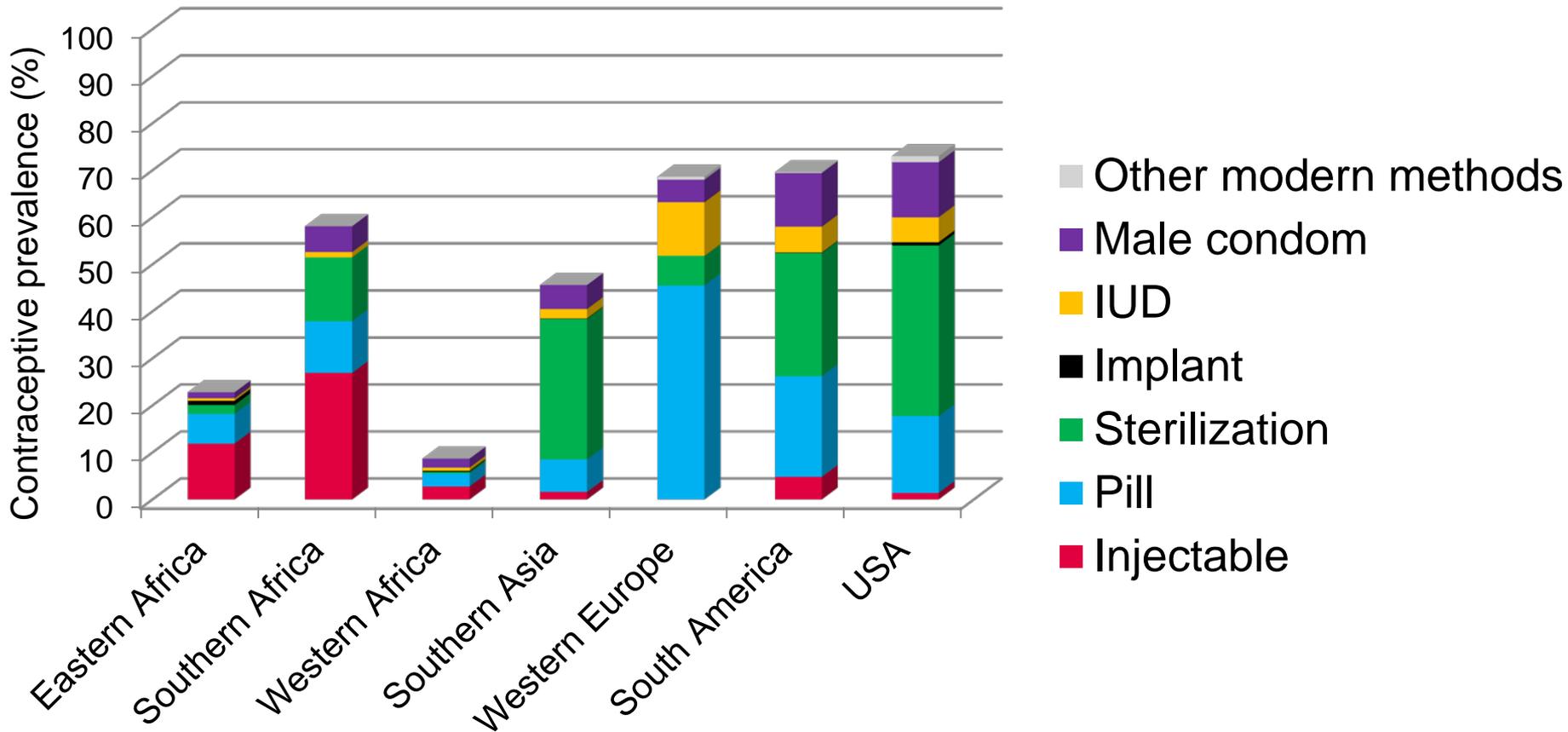
UNFPA Executive Director
Thoraya Ahmed Obaid

April 2007



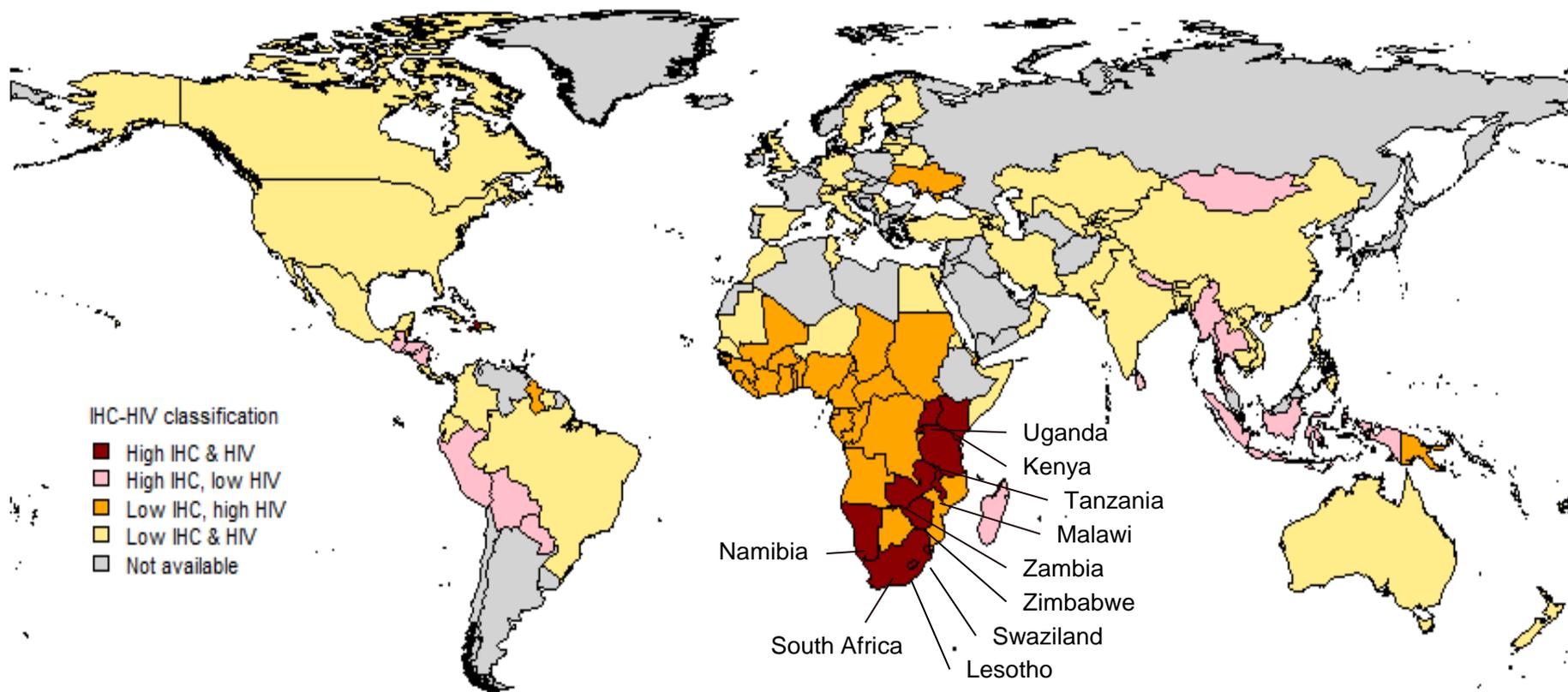
Contraceptive prevalence and method mix varies greatly by region

Regional modern contraceptive prevalence and method mix among women married or in union



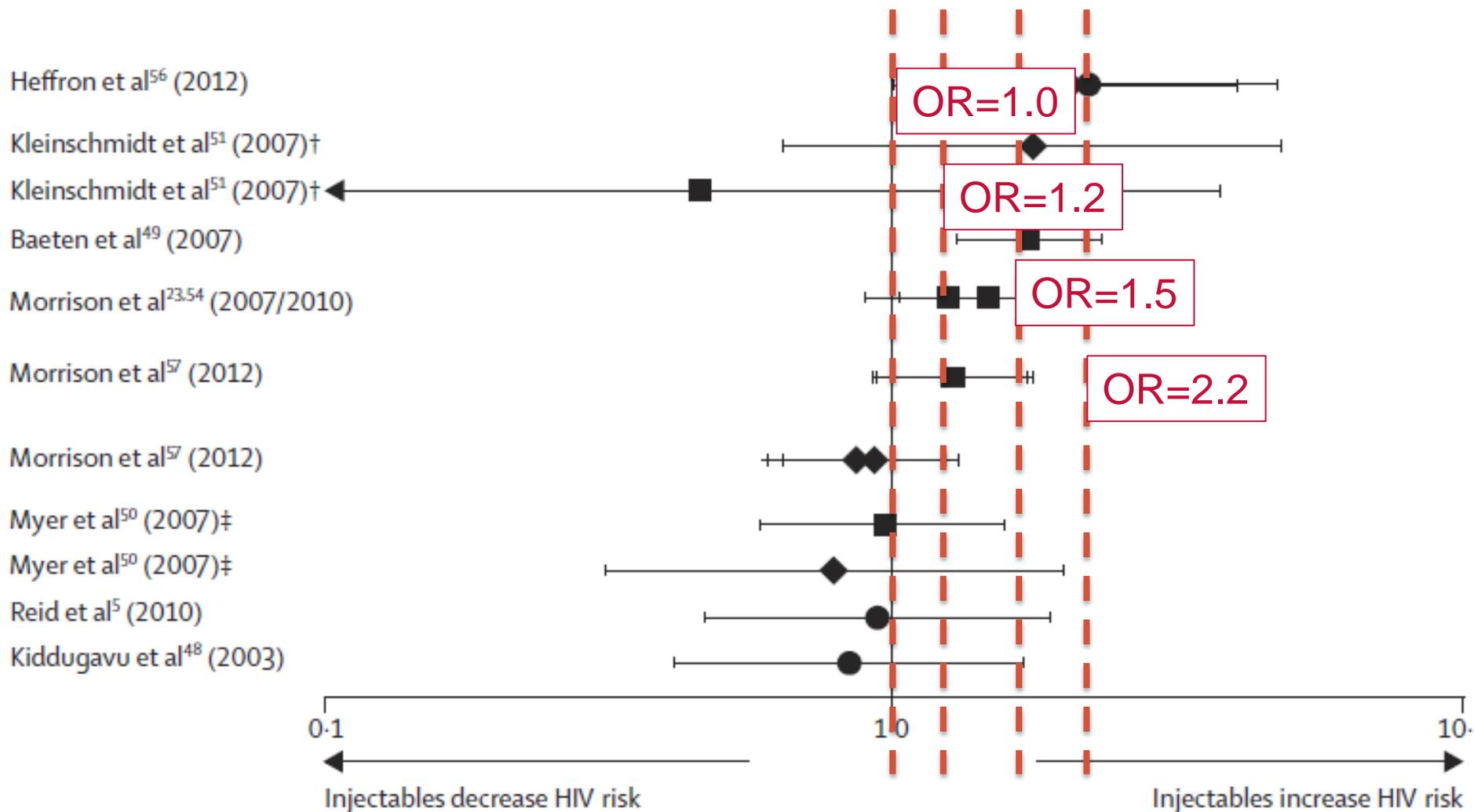
High rates of HIV coincide with high use of injectables in E. and S. Africa

HIV prevalence and use of injectables



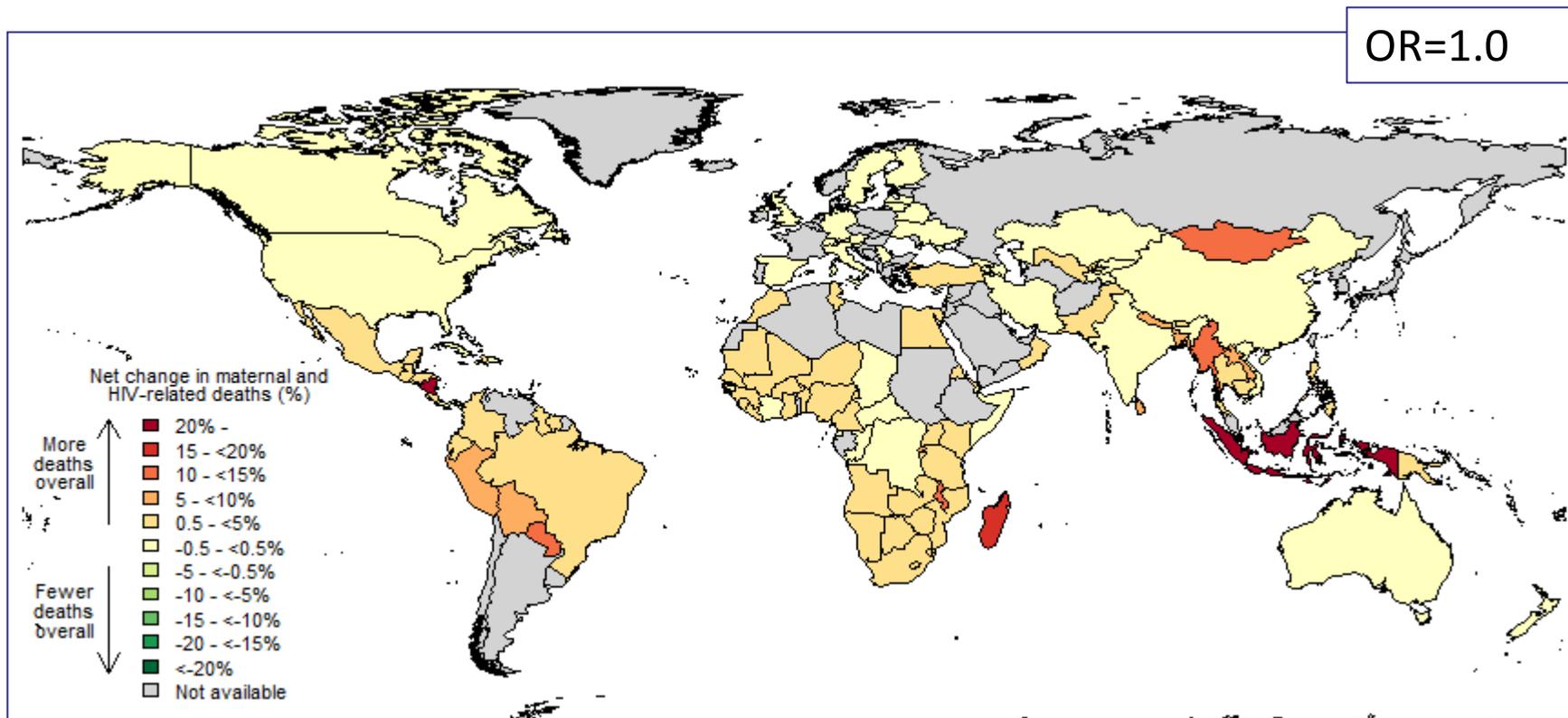
HIV 'high' = > 1% IHC 'high' = upper quartile

Modeling study: various assumptions about actual HIV risk of injectables



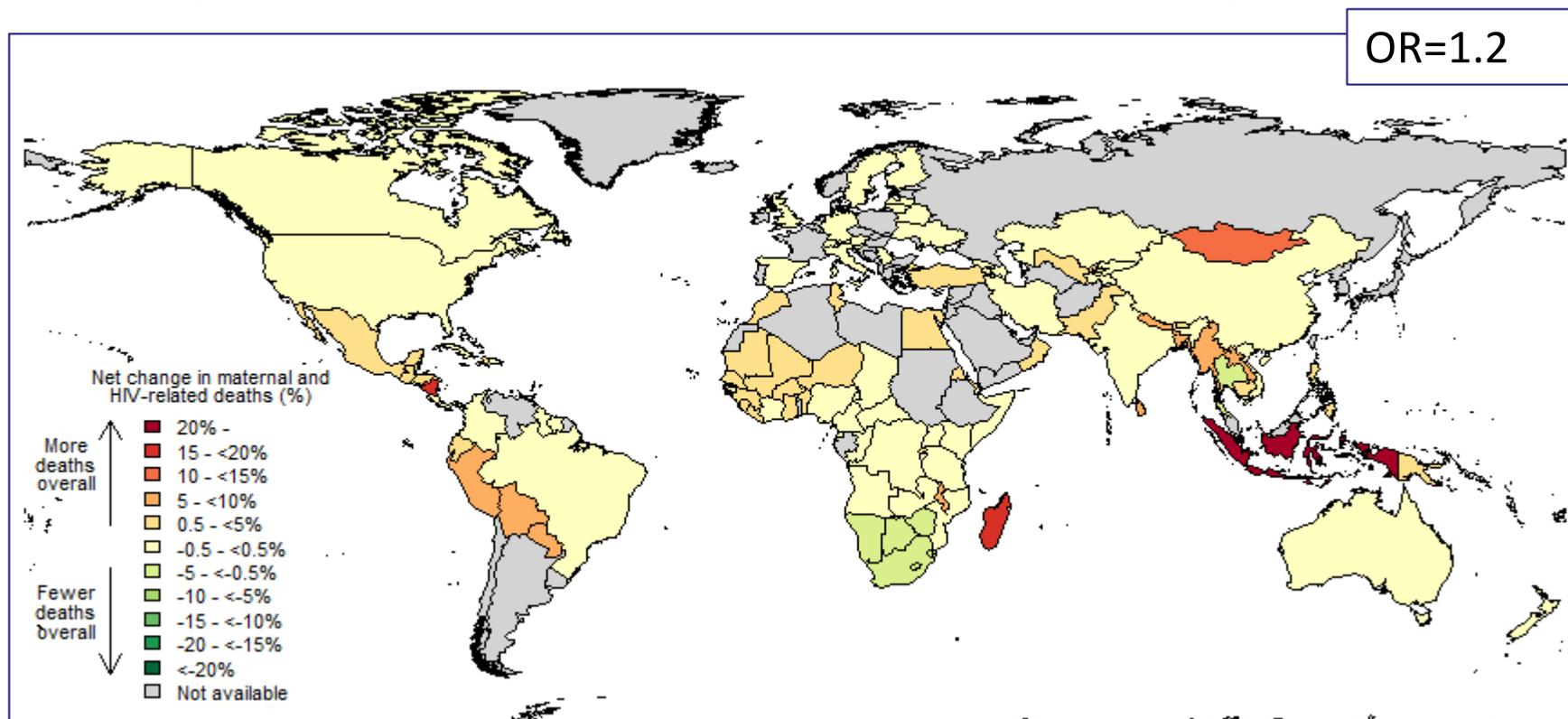
Balance of increasing maternal deaths and decreasing HIV-related deaths (%)

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



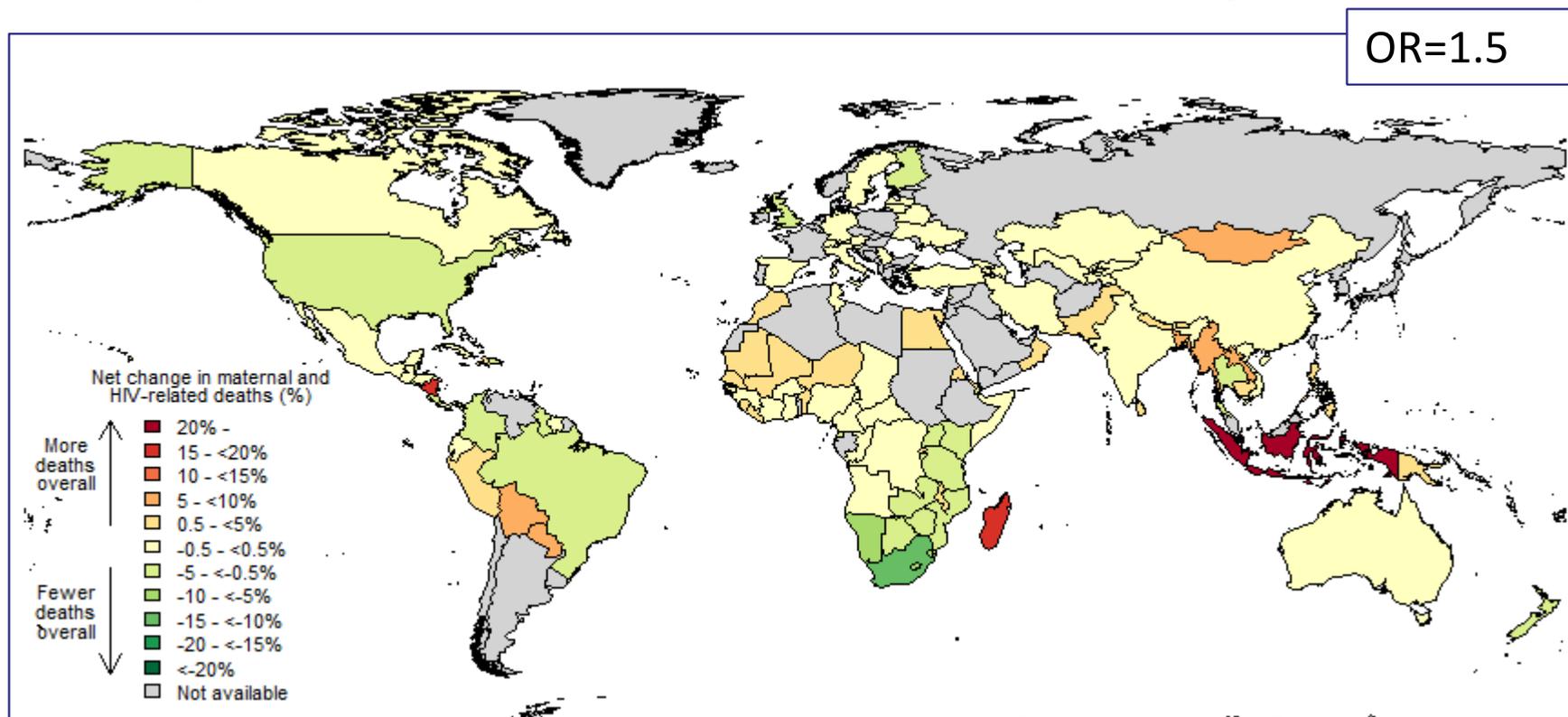
Balance of increasing maternal deaths and decreasing HIV-related deaths (%)

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



Balance of increasing maternal deaths and decreasing HIV-related deaths (%)

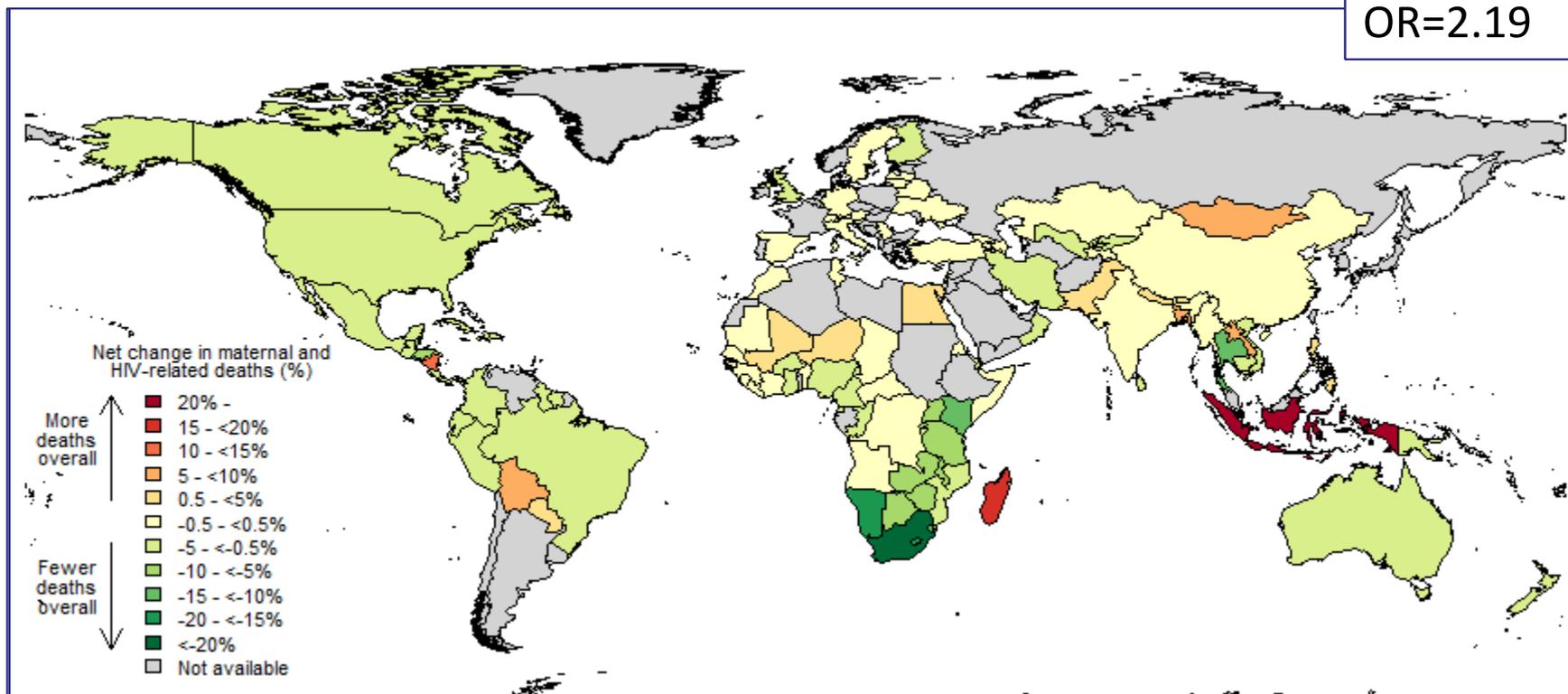
% change in net maternal and AIDS deaths on cessation of injectable HC use



Balance of increasing maternal deaths and decreasing HIV-related deaths (%)

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

OR=2.19





- Overlap of high HIV incidence and high injectable use in southern and eastern Africa
- If we assume that injectables increase risk of HIV, reducing injectable use may both:
 - Reduce HIV infections in areas of high HIV incidence
 - Increase maternal deaths in areas of high maternal mortality
- Public health impact depends on the true effect size (and on assumptions about contraceptive alternatives)
 - Strong IHC-HIV interaction: overall reduction in deaths with reduced IHC use in southern and eastern Africa
 - Weak IHC-HIV interaction: no public health argument for reduction in IHC use, except perhaps South Africa



- Programmatic priorities
 - Ensure counseling of risks and benefits of all contraceptive methods
 - Expand contraceptive method mix to ensure choice
 - Increase HIV testing, explore ART-based prevention strategies, etc.
 - Innovative interventions to increase dual method use?
- Need for additional data
 - Future observational analyses can consider analytic recommendations
 - Biological/immunological data to understand potential mechanisms
 - Application of modeling studies to various epidemiological contexts
 - Is a randomized trial feasible? Will it provide clear answers?
- Development of multipurpose prevention technologies
- *Build shared understanding within the public health community, so we can best serve girls, women, and couples.*



Acknowledgements

- The women and men who have participated in studies advancing our understanding on this complex subject
- Colleagues including (but not limited to) those at:
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 - Imperial College London
 - FHI 360
 - Johns Hopkins Bloomberg School of Public Health
 - The Bill and Melinda Gates Foundation
 - And many others...

