

# Hormonal contraception and HIV Risk: Evidence and Unknowns

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# Contraception

- Safe and effective contraception is essential to health and development of women, children, and families worldwide
- Hormonal forms of contraception are used by >140 million women worldwide
- In many settings, the unmet need for contraception is large
- Contraceptives have known “non-contraceptive” side effects (cancer, BMD, thromboembolism)



# The question

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# The question(s)

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- Does using hormonal contraceptives change a woman's risk of acquiring (or, if she is HIV+, transmitting) HIV?
  - Is that driven by a biologic effect, or it is mediated through changes in sexual behavior? Some of both?
  - If there is increased HIV risk, is it for all contraceptives or just some?
  - If there is increased HIV risk, how to weigh that within a context of other risks incurred by changing contraceptive options/choices?

# Biology

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# Non-human primate studies

## Progesterone implants enhance SIV vaginal transmission and early virus load

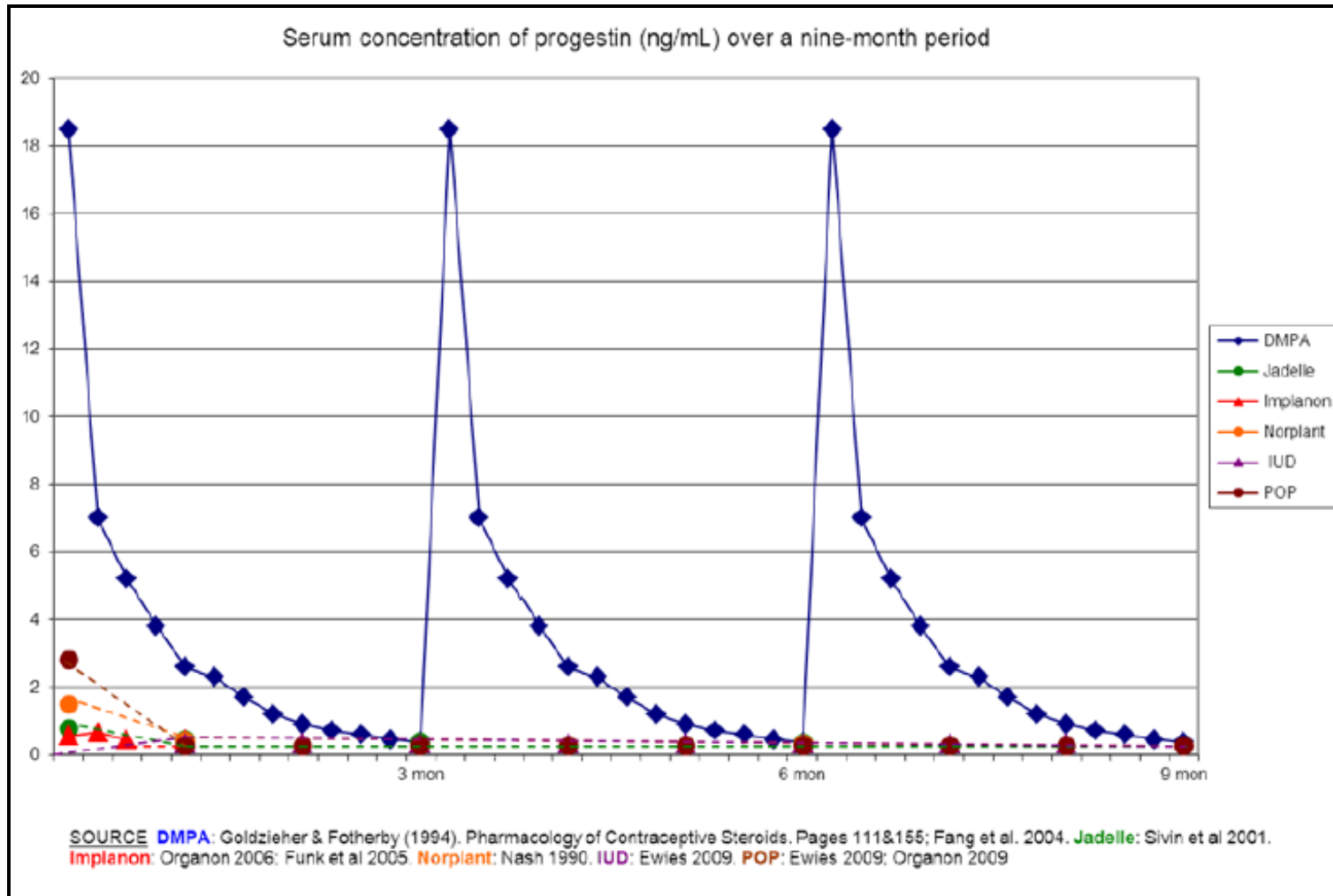
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- Summary

- High-dose progesterone
- Increased SIV transmission risk >7-fold
- Thinned vaginal epithelium (mechanism?)
- Also resulted in higher viral load in plasma
- *For many subsequent evaluation studies of vaccines and microbicides, pre-treatment with progestin is used to enhance transmission risk.*

# Serum progesterin levels in different hormonal contraceptives



# Possible biologic mechanisms

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- 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....*



# Epidemiologic studies

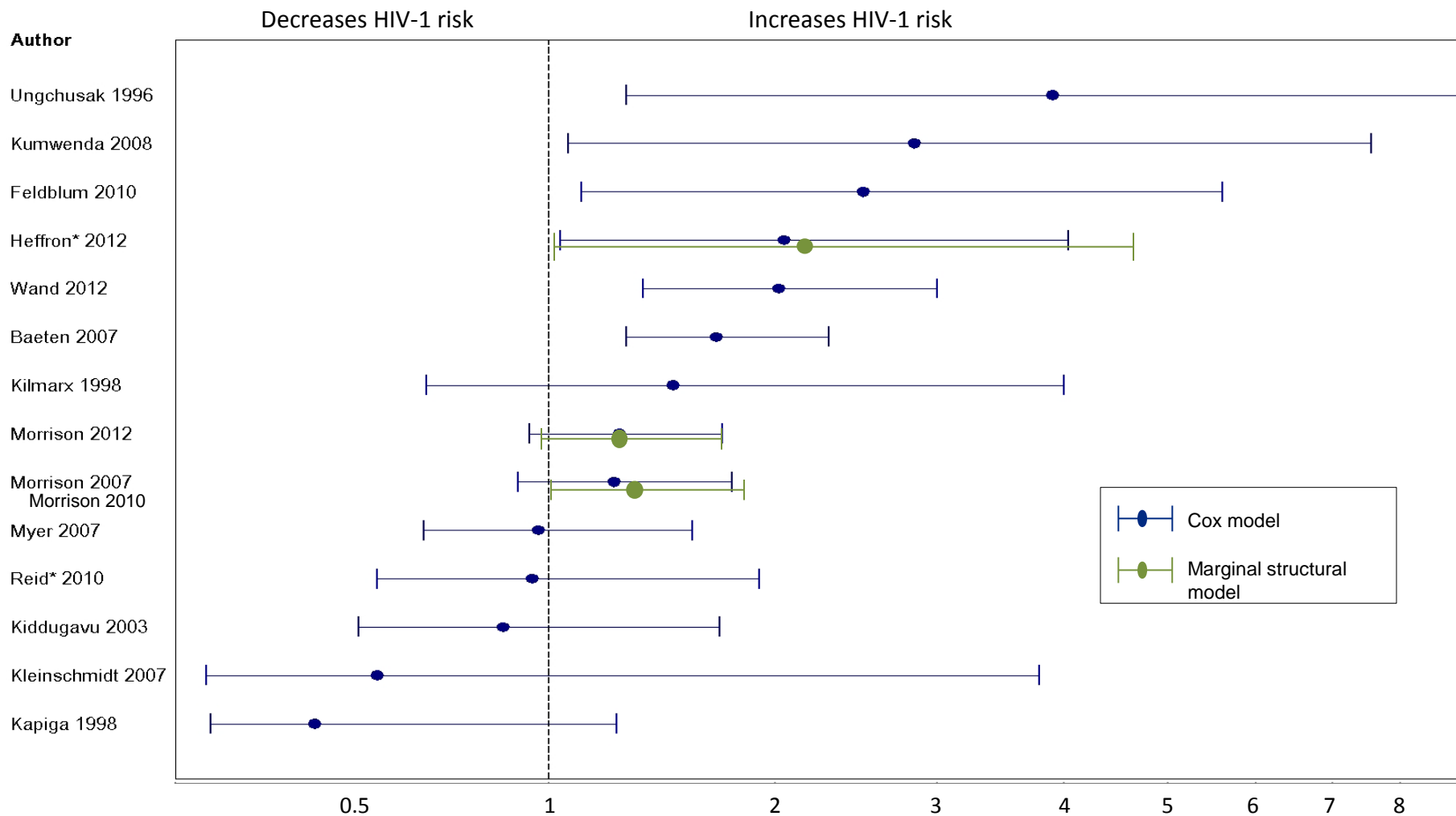
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# Epidemiologic studies

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- Some epidemiologic studies have suggested that hormonal contraceptives may alter HIV-1 susceptibility in women
  - Evidence seems strongest for injectable progestin contraception
  - Results are inconsistent and study quality varies tremendously

# Published studies of injectable contraceptive use and HIV-1 risk



\*Includes 2 types of injectables – DMPA and Net-En; All other studies include only injectable DMPA

# Limitations

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- Small sample size
- Long follow-up time between study visits
- Poor follow-up rates
- Inability to distinguish between types of hormonal contraceptives (oral v. injectable, etc.), or lack of a comparison group
- No or limited adjustment for confounding factors; insufficient adjustment
- Self-report of contraceptive use and sexual behavior

# Looking at just 3 of the observational studies...

	Population	Results	Limitation
<b>Mombasa</b> <i>Lavreys 2004</i> <i>Baeten 2007</i>	<b>Sex workers</b> <i>Kenya</i>	OCPs HR 1.46, p=0.05 DMPA HR 1.73, p<0.001	Sex workers
<b>Rakai</b> <i>Kiddugavu 2003</i>	<b>Community cohort</b> <i>Uganda</i>	OCP aIRR 1.12, p=NS injectable aIRR 0.84, p=NS	Infrequent follow-up (10-12 months)
<b>HC-HIV</b> <i>Morrison 2007</i> <i>Morrison 2010</i>	<b>FP clinic attendees</b> <i>Uganda, Zimbabwe</i>	Overall increased HIV for DMPA HR 1.48, p=0.04	Marginal statistical significance

# Recent data

## 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 Ngunjiri, 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  
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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](#)



# Methods

- Prospective cohort study of 3790 HIV-1 discordant couples from 7 countries in East and southern Africa (Partners in Prevention HSV/HIV Transmission Study)
- Quarterly HIV-1 testing, contraceptive measurement, sexual behavior questionnaire
- Adjusted analyses (age, unprotected sex, HIV+ plasma VL, pregnancy)
  - Cox proportional hazards and marginal structural models



# HIV-1 acquisition

- Overall, 21.2% of HIV-1 seronegative women used hormonal contraception at least once during follow up
  - Injectable contraception used at least once by 16.0% of women
  - Oral contraception used at least once by 6.7% of women
- There were a total of 73 incident HIV-1 infections
  - HIV-1 incidence rate: 4.09 per 100 person years





# Contraception and HIV-1 acquisition in women

	Incidence rate*	Adjusted** Cox PH regression analysis		Adjusted** marginal structural model analysis	
		HR (95% CI)	p-value	OR (95% CI)	p-value
No hormonal contraception	3.78	1.00		1.00	
Injectable	6.85	2.05 (1.04-4.04)	0.04	2.19 (1.01-4.74)	0.05

\*per 100 person years  
 \*\*Adjusted for age, enrollment plasma viral load level of the HIV-1 infected partner and time dependent unprotected sex and pregnancy.

Heffron et al. *Lancet Infectious Diseases*. 2012



# 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





# 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*...

Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential.

## Hormonal contraception and HIV Technical statement

### Executive summary

Following new findings from recently published epidemiological studies, the World Health Organization (WHO) convened a technical consultation regarding hormonal contraception and HIV acquisition. The group concluded 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. Expansion of contraceptive method mix and further research on the relationship between hormonal contraception and HIV infection is essential.

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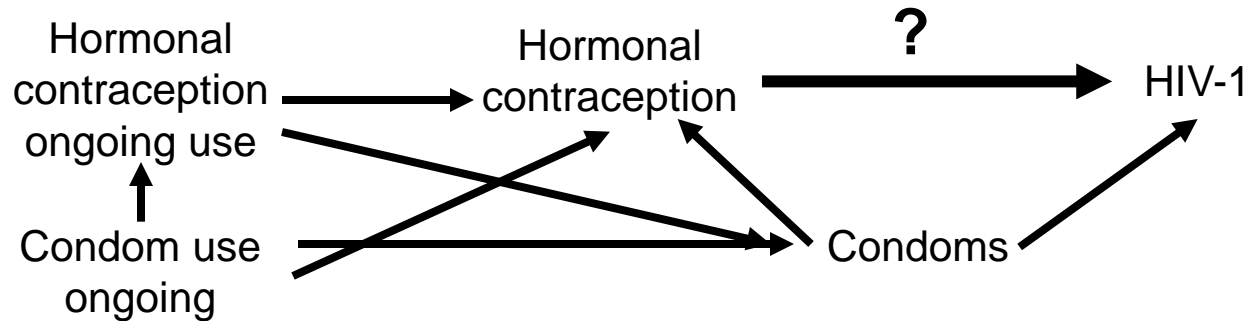
Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition, other studies do not show this association. A WHO expert group reviewed all the available evidence and agreed that the data were not sufficiently conclusive to change current guidance. 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 strongly advised to also always use condoms, male or female, as hormonal contraceptives are not protective against HIV transmission or acquisition.



# Why is this topic so difficult?

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# Relationship of hormonal contraception, condoms, and HIV-1



# Principles of observational epidemiology

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- Observational epidemiology is completely about:
  - Exposure (*contraception*)
  - Outcomes (*HIV acquisition*)
  - Confounders (*sexual behavior, etc.*)

# Principles of observational epidemiology

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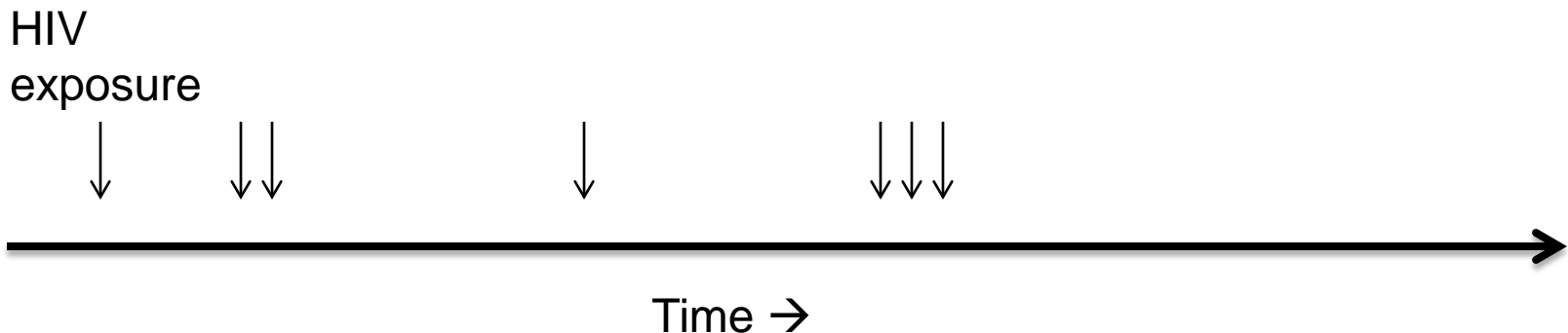
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Time →

# Principles of observational epidemiology

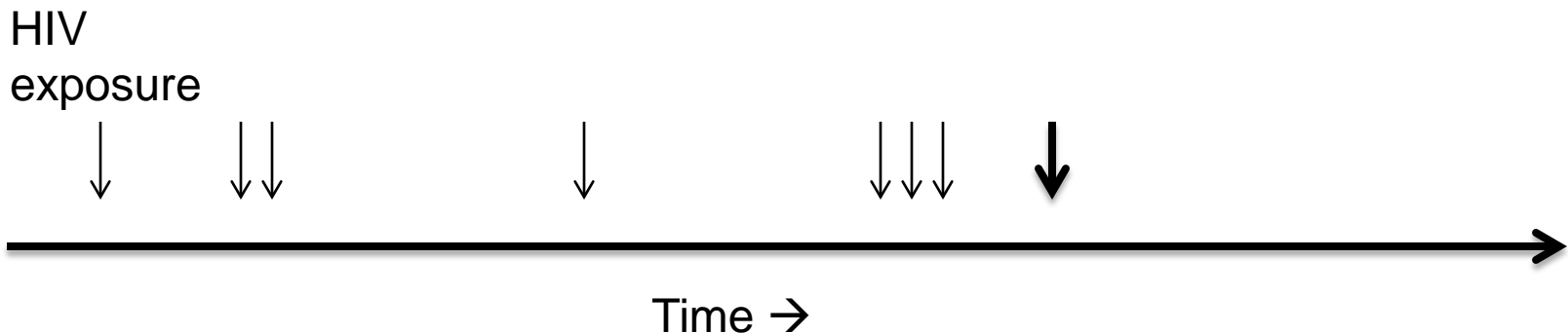
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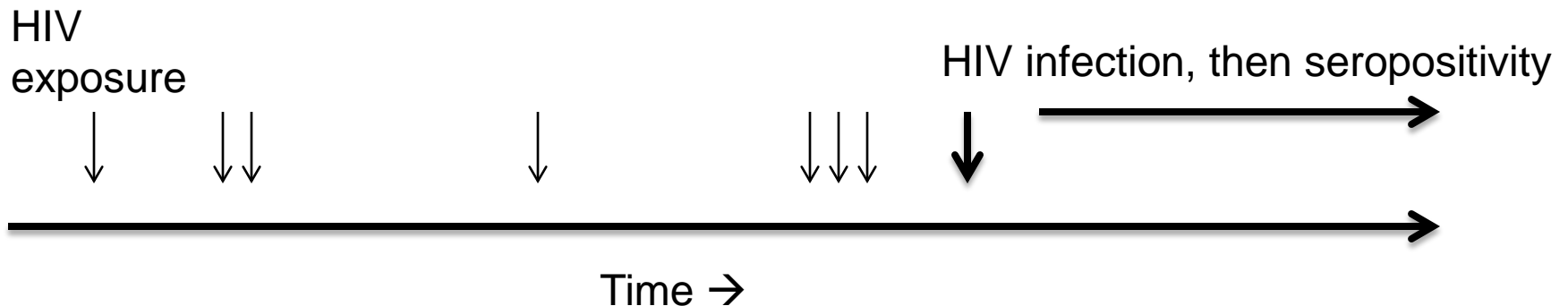
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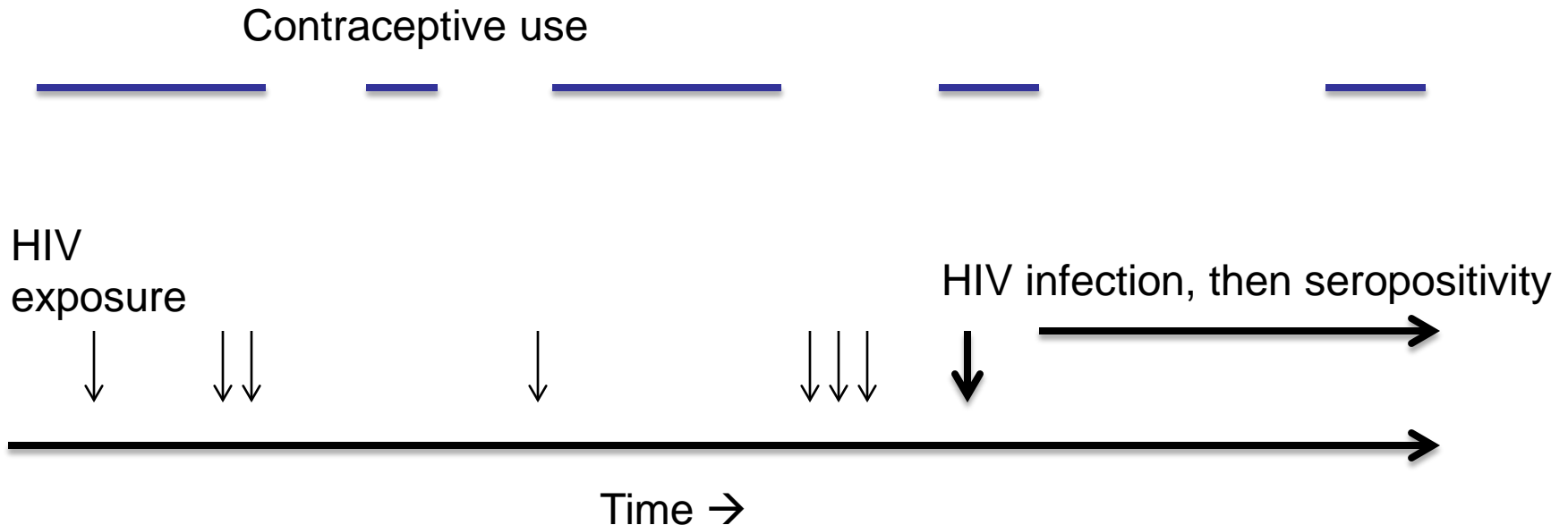
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# Principles of observational epidemiology

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- Observational epidemiology is completely about:
  - Exposure (*contraception*)
  - Outcomes (*HIV acquisition*)
  - Confounders (*sexual behavior, etc.*)
- Exposures measurement needs precision
  - Poor measurement of contraceptive exposure (both accuracy of reporting and precision of timing) risks bias towards the null

# Principles of observational epidemiology

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- Observational epidemiology is completely about:
  - Exposure (*contraception*)
  - Outcomes (*HIV acquisition*)
  - Confounders (*sexual behavior, etc.*)
- Outcome measurement must be done carefully  
HIV seroconversion is objective, but its temporal relationship to exposures and confounders is not trivial

# Principles of observational epidemiology

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- Observational epidemiology is completely about:
  - Exposure (*contraception*)
  - Outcomes (*HIV acquisition*)
  - Confounders (*sexual behavior, etc.*)
- Confounders are tough to measure
  - Particularly self-reported sexual behaviors

# Limitations of secondary analyses of prevention RCT datasets

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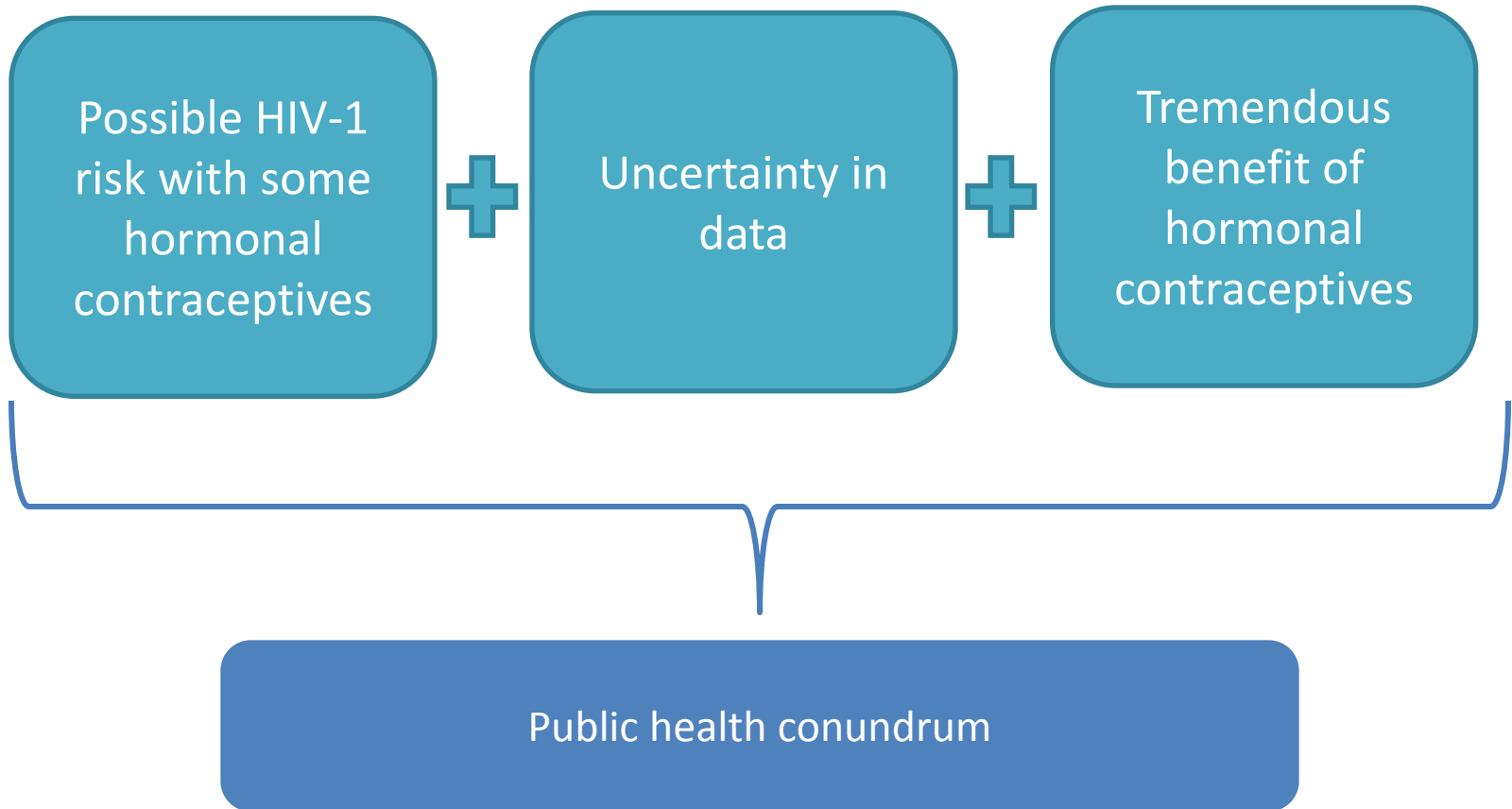
- Careful measurement of contraceptive method was not a primary goal of these studies
- *Many women in microbicide trials are unexposed to HIV and hard to know if that is related to contraceptive choice (in which case would be a huge confounder)*
- Contraception often required for study entry
  - Possibility of limited/no “control” group
  - Accuracy of exposure is a potential concern – women may inaccurately self-report use in order to stay in the trial

# What do we do?

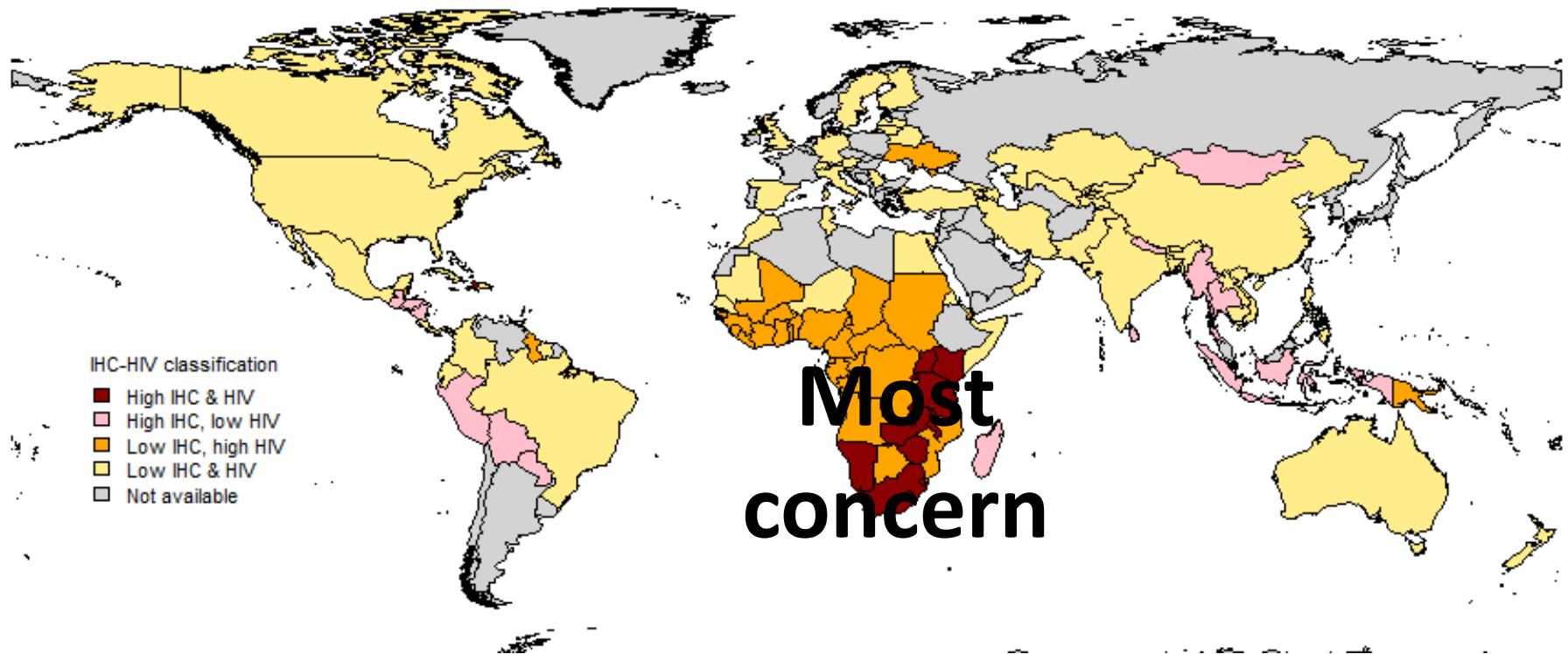
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# Summary of current understanding



# Intersection of injectable hormonal contraceptive use and HIV-1 prevalence



# What do we need to do to get a more clear answer?

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- More research
  - Randomized trial
  - Observational analyses
  - Biologic studies
- More action
  - Change the method mix
  - Increase HIV-1 testing
  - More access to effective HIV-1 prevention strategies
  - Integrated family planning and HIV-1 services

# Answering important questions

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- Arguably, the key question here is what are the individual and public health risks and benefits for different contraceptive options:
  - HIV-1, unintended pregnancy, important side effects, related morbidity and mortality
- For women deciding among different contraceptive options, data and messaging regarding the relative risks and benefits are needed.
  - I would argue that the key questions are comparisons between different contraceptive methods – DMPA versus nothing is not really a choice.

# Concluding Point

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- 25 years of epidemiologic and biologic studies have attempted to assess the relationship between contraceptive use and HIV-1 acquisition (and transmission)
- For areas of highest HIV-1 risk, this question is of incredible importance.

*Can we continue to make important public health decisions realizing that we may have to operate without certainty?*

# Acknowledgements

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## Partners in Prevention HSV/HIV Transmission Study Team

University of Washington Coordinating Center and Central Laboratories - Seattle, WA

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