Contraception and HIV Risk: Evidence and Unknowns

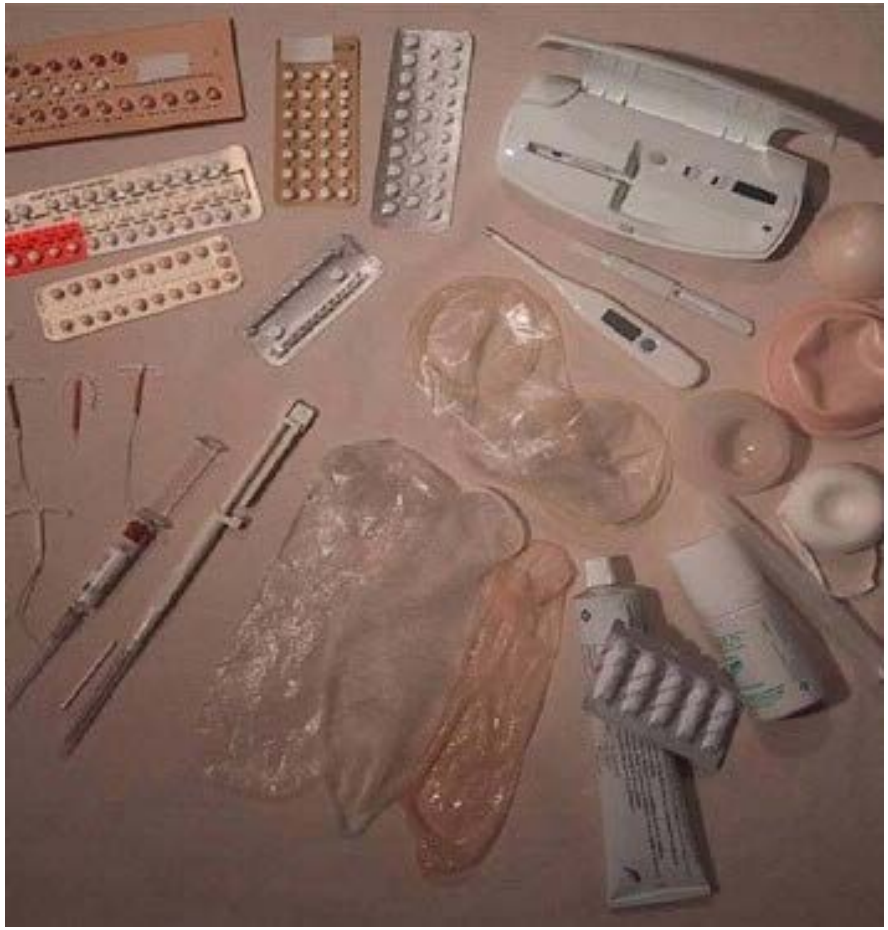
Jared Baeten MD PhD
Departments of Global Health and Medicine
University of Washington

MTN Annual Meeting
February 2012

Contraception

- Safe and effective contraception is essential to health and development of women, children, and families worldwide

- Contraceptives have known “non-contraceptive” side effects (cancer, BMD, thromboembolism)



The question

- Does using hormonal contraceptives change a woman's risk of acquiring (or, if she is HIV+, transmitting) HIV?

The question(s)

- 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?

Non-human primate studies

Progesterone implants enhance SIV vaginal transmission and early virus load

PRESTON A. MARX[1,2], ALEXANDER I. SPIRA[1,2], AGEGNEHU GETTIE[1], PETER J. DAILEY[3], RONALD S. VEAZEY[4], ANDREW A. LACKNER[4], C. JAMES MAHONEY[5], CHRISTOPHER J. MILLER[6], LEE E. CLAYPOOL[7], DAVID D. HO[1] & NANCY J. ALEXANDER[8]

- Summary
  - High-dose protesterone
  - 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 transmision risk.*

Marx Nature Medicine 1996

Possible biologic mechanisms

- 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

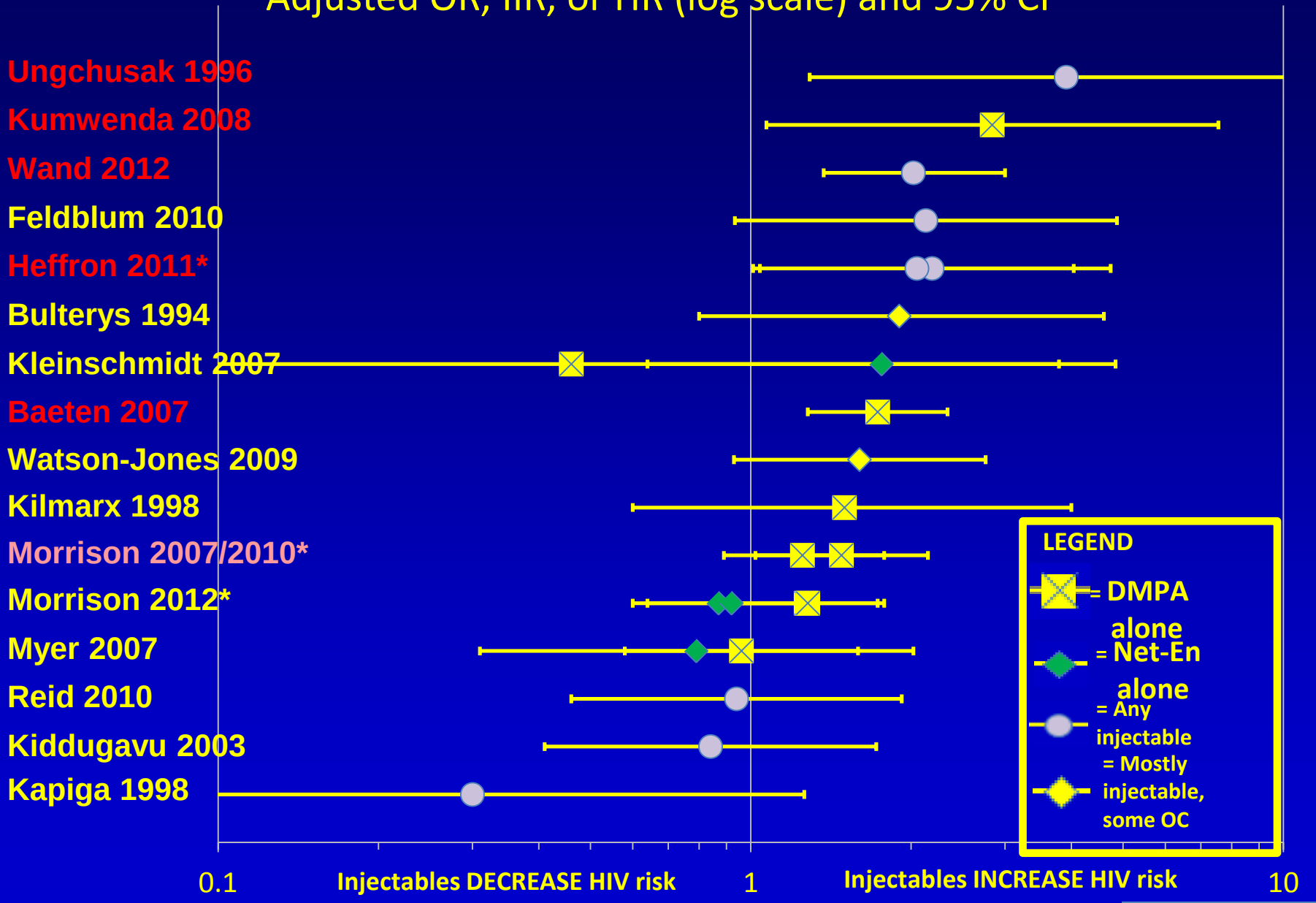
- *However, data are often sparse or potentially could point in different directions, and, most importantly, no laboratory study would be sufficient for this question….*

Epidemiologic studies

- 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

Prospective, observational studies of injectables & HIV acquisition

Adjusted OR, IIR, or HR (log scale) and 95% CI



* includes MSM and Cox estimates

Slide: Chelsea Polis

Limitations

- 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
Mombasa *Lavreys 2004* *Baeten 2007*	**Sex workers** *Kenya*	Increased risk OCPs (HR 1.46, p=0.05) DMPA (HR 1.73, p<0.001)	Sex workers
Rakai *Kiddugavu 2003*	**Community cohort** *Uganda*	No increased risk OCP aIRR 1.12 injectable aIRR 0.84	Infrequent follow-up (10-12 months)
HC-HIV *Morrison 2007* *Morrison 2010*	**FP clinic attendees** *Uganda, Zimbabwe*	Overall increased HIV for DMPA (HR 1.48, p=0.04) **Marked subgroup differences - - among **age <25**: OCP HR 2.02, DMPA HR 2.76 among those **HSV-2 neg**: DMPA HR 4.49	Risk only in subgroup

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 Ngure, 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

Objective

- Compare HIV-1 incidence rates among women using and not using hormonal contraceptives
  - HIV-1 acquisition among women
  - HIV-1 transmission from women to men

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

HIV-1 acquisition

	Incidence rate*	Adjusted Cox PH regression analysis HR (95% CI)	p-value	Adjusted marginal structural model analysis OR (95% CI)	p-value
No hormonal contraception	3.78	1.00		1.00	
Any hormonal contraception	6.61	1.98 (1.06-3.68)	0.03	1.84 (0.98-3.47)	0.06
Injectable	6.85	2.05 (1.04-4.04)	0.04	2.19 (1.01-4.74)	0.05
Oral	5.94	1.80 (0.55-5.82)	0.33	1.63 (0.47-5.66)	0.44

*per 100 person years

HIV-1 transmission

- Overall, 33.3% of HIV-1 seropositive female partners used hormonal contraception at least once during follow up
  - Injectable contraception used at least once by 26.8% of women
  - Oral contraception used at least once by 8.9% of women
- There were 59 HIV-1 seroconversions in initially-HIV-1 seronegative men that were genetically linked to their female study partner
  - HIV-1 incidence rate: 1.75 per 100 person years

HIV-1 transmission

	Incidence rate*	Adjusted Cox PH regression analysis HR (95% CI)	p-value	Adjusted marginal structural model analysis OR (95% CI)	p-value
No hormonal contraception	1.51	1.00		1.00	
Any hormonal contraception	2.61	1.97 (1.12-3.45)	0.02	2.05 (1.12-3.74)	0.02
Injectable	2.64	1.95 (1.06-3.58)	0.03	3.01 (1.47-6.16)	0.003
Oral	2.50	2.09 (0.75-5.84)	0.16	2.35 (0.79-6.95)	0.12

*per 100 person years

Injectable users also had small increase HIV-1 RNA in cervical swabs: +0.19 log copies/swab

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

Why is this topic so difficult?

Principles of observational epidemiology

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

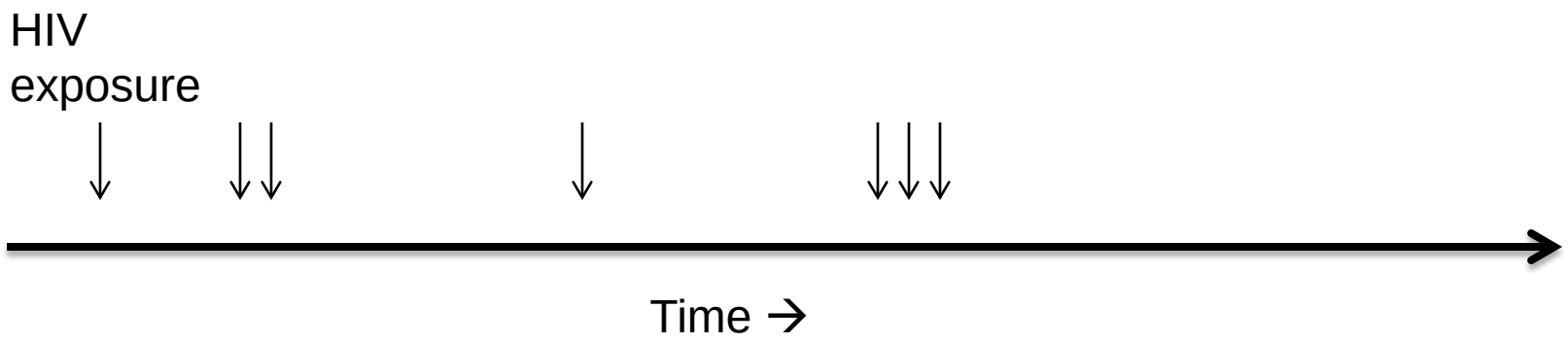
Principles of observational epidemiology

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

Time →

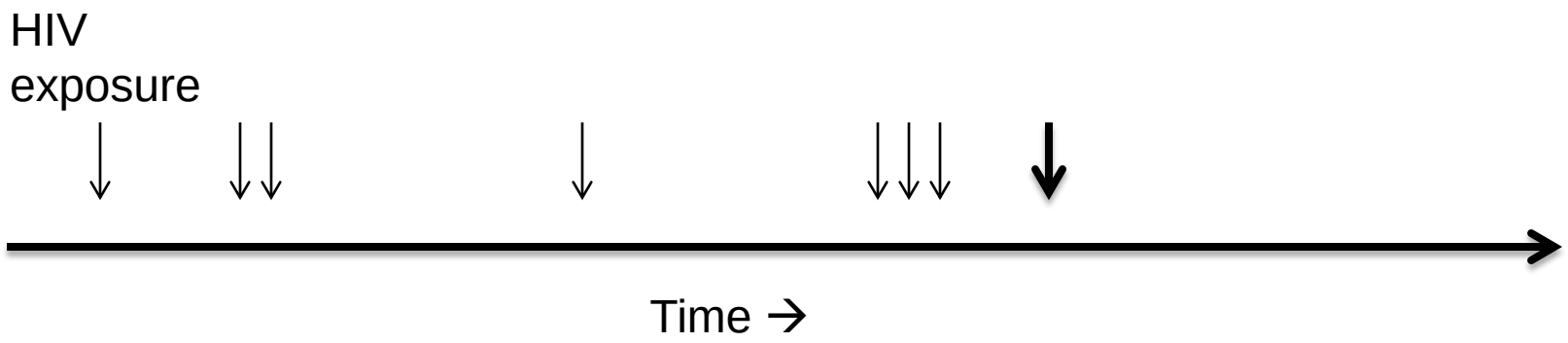
Principles of observational epidemiology

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



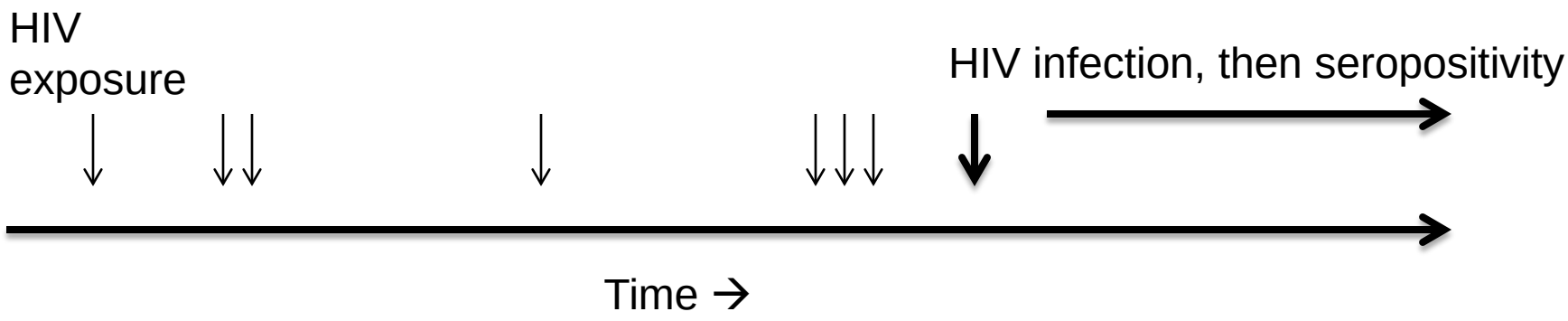
Principles of observational epidemiology

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



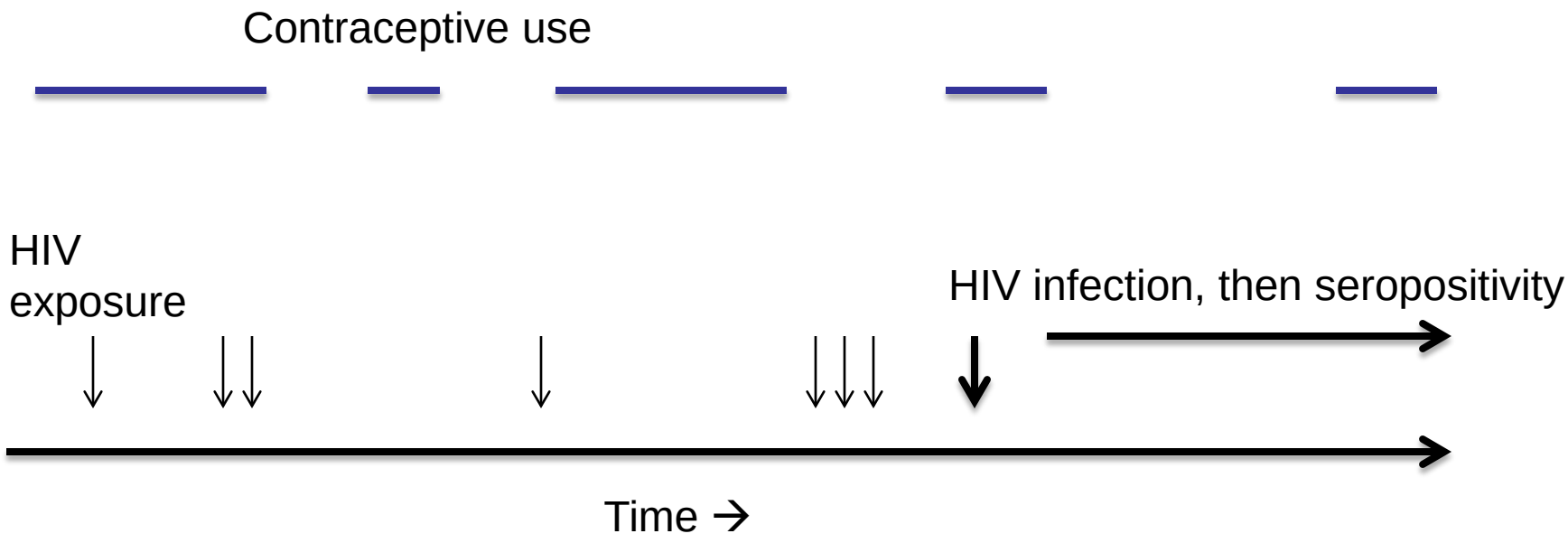
Principles of observational epidemiology

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



Principles of observational epidemiology

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



Principles of observational epidemiology

- 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

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

- Outcome measurement is potentially easier
  - HIV seroconversion is objective, but its temporal relationship to exposures and confounders is not trivial

Principles of observational epidemiology

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

- Confounders are tough to measure
  - Particularly self-reported sexual behaviors

Principles of observational epidemiology

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

- Relative risk estimates <2 are extremely difficult to measure
  - Lots of opportunity for both imprecision and bias to result in spurious findings

Strengths of available observational data

- Large studies, low loss to follow-up
- Multinational populations
- Multiple risk groups
- Frequent measurement of contraceptive exposure and HIV outcome
- Measurement of confounding factors

Strengths of available observational data

- Large studies, low loss to follow-up
- Multinational populations
- Multiple risk groups
- Frequent measurement of contraceptive exposure and HIV outcome
- Measurement of confounding factors

Thus, available data have many of the design characteristics we'd like

What else would be the ideal?

- Perfect capture of contraceptive use
- Fully accurate characterization of confounding factors, particularly sexual behavior
- Capture of all potential confounding factors
- Large number of HIV seroconversions, including by different contraceptive types and within subgroups, so that study power is not limiting

What else would be the ideal?

- Perfect capture of contraceptive use
- Fully accurate characterization of confounding factors, particularly sexual behavior
- Capture of all potential confounding factors
- Large number of HIV seroconversions, including by different contraceptive types and within subgroups, so that study power is not limiting

These may be difficult to achieve

New sources of data…

- Large randomized trials of novel HIV prevention strategies (PrEP, microbicides) could be analyzed for this question:
  - *Large sample sizes, geographic diversity*
  - *Very complete and careful collection of HIV outcomes*
  - *Prospective (but not necessarily good) measures of sexual behavior*

Limitations of prevention RCT datasets

- 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

And what about an RCT?

Challenges of an RCT (1)

- RCTs answer 1 question
  - *It is not clear whether the field has a single question here (beyond the too-vague "is DMPA bad?")*
    - DMPA vs. IUD
    - DMPA vs. IUD vs. implant
    - Etc.

Challenges of an RCT (2)

- RCTs maintain their integrity when they are well-conducted:
  - High retention
  - High protocol and product adherence (no switching!)
  - Non-differential confounding (which is only likely protected by full blinding)

- Or might just end up analyzing as an observational study

Concluding Point

- 25 years of epidemiologic and biologic studies have attempted to assess the relationship between contraceptive use and HIV-1 acquisition (and transmission)

- The fact that there remains uncertainty today suggests that this is a question for which it is tough provide absolute clarity

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

Acknowledgements

- Funding sources:
  - National Institutes of Health (R03 HD068143, R01 AI083034, P30 AI027757)
  - Bill & Melinda Gates Foundation
  - University of Washington STD/AIDS Research Training Grant Program, T32 AI007140

Partners in Prevention HSV/HIV Transmission Study Team

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

Connie Celum, Anna Wald, Jairam Lingappa, Jared Baeten, Mary Campbell, Lawrence Corey, Robert Coombs, James Hughes, Amalia Magaret, M.Juliana McElrath, Rhoda Morrow, James Mullins

Site Principal Investigators

Botswana: Max Essex, Joseph Makhema

Kenya: Elizabeth Bukusi, Kenneth Fife, James Kiarie, Nelly Rwamba Mugo, Edwin Were, Craig Cohen, Carey Farquhar, Grace John-Stewart

Rwanda: Etienne Karita, Kayitesi Kayitenkore, Susan Allen

South Africa: David Coetzee, Guy de Bruyn, Sinead Delany-Moretlwe, Glenda Gray, James McIntyre, Helen Rees

Tanzania: Rachel Manongi, Saidi Kapiga

Uganda: Elly Katabira, Allan Ronald

Zambia: Mubiana Inambao, William Kanweka, Bellington Vwalika, Susan Allen

UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER
PARTNERS IN PREVENTION