

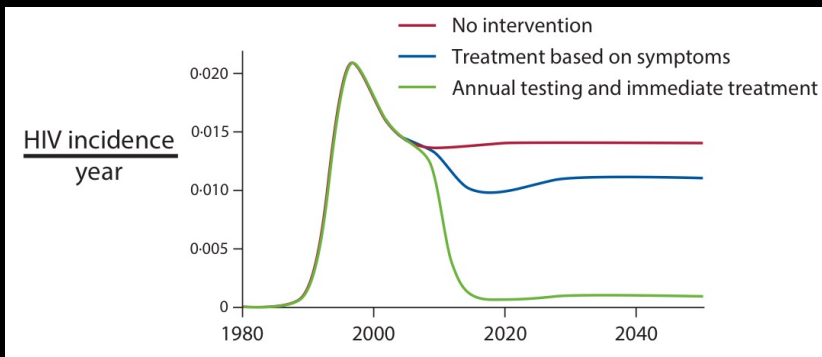
Addressing biases in HIV infectivity estimates

Steve Bellan, PhD, MPH
Center for Computational Biology and Bioinformatics
The University of Texas at Austin

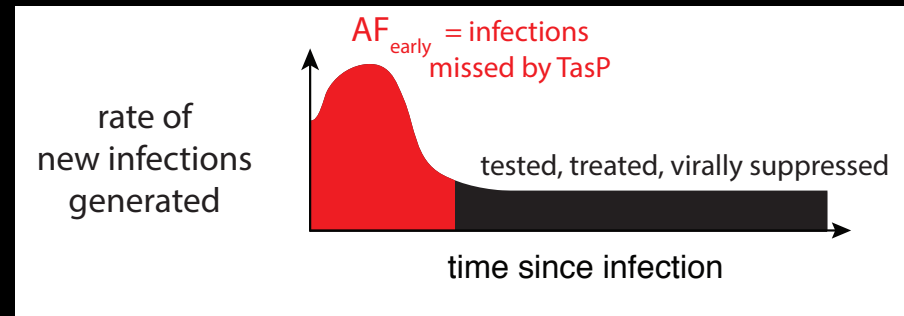
MMED 2016
AIMS, Muizenberg

Treatment as Prevention (TasP)

Treatment reduces infectiousness 96%



Early transmission is unblockable by TasP



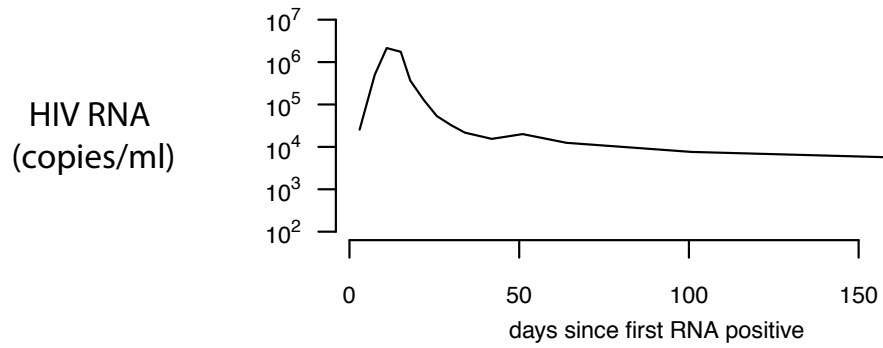
Cohen et al. (2011). *NEJM*
Granich et al. (2009). *Lancet*.

Review

HIV Treatment as Prevention: Debate and Commentary—Will Early Infection Compromise Treatment-as-Prevention Strategies?

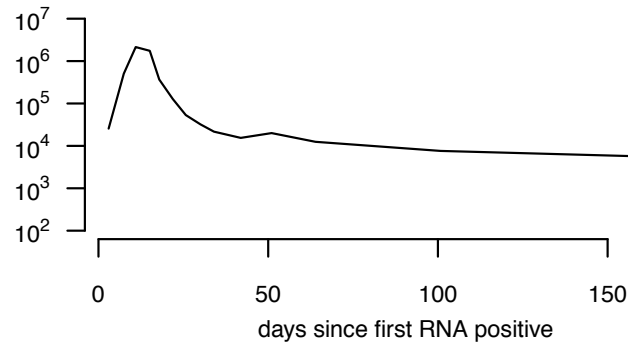
Myron S. Cohen^{1,2,3†}, Christopher Dye^{4†}, Christophe Fraser^{5†*}, William C. Miller^{2,3†},
Kimberly A. Powers^{2,3†*}, Brian G. Williams^{6†*}

Early Transmission

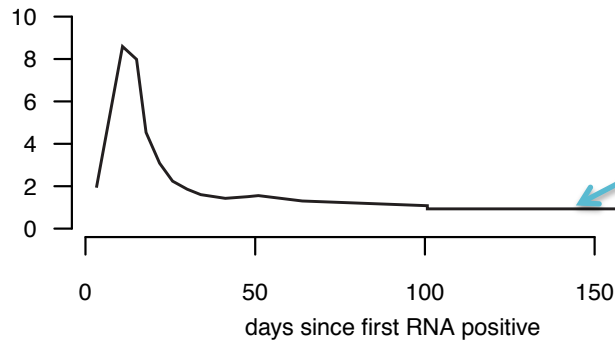


Early Transmission

HIV RNA
(copies/ml)



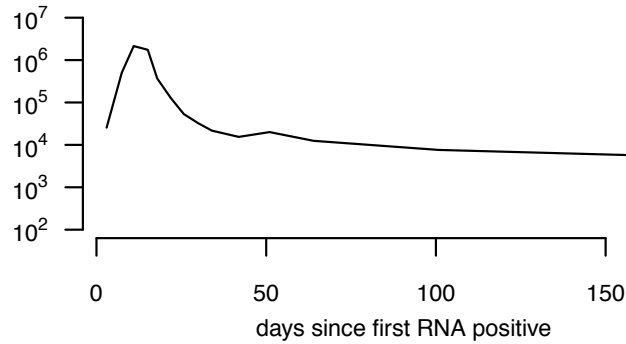
relative infectivity



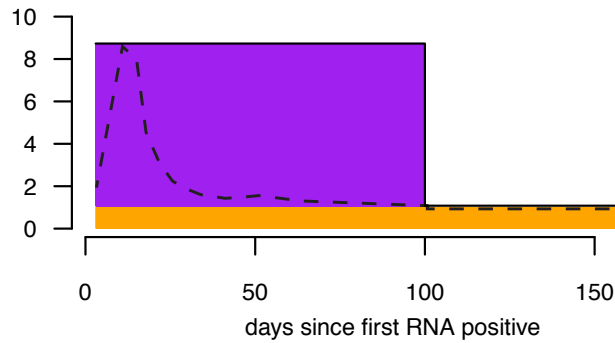
1/300 per heterosexual sex act

Early Transmission

HIV RNA
(copies/ml)



relative infectivity



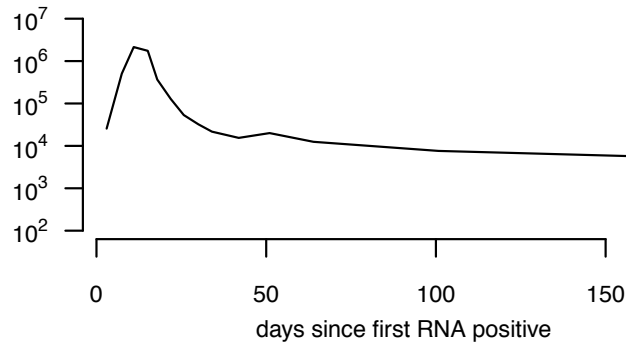
excess hazard-months = 25
attributable to acute phase

9x as infectious for 3 months

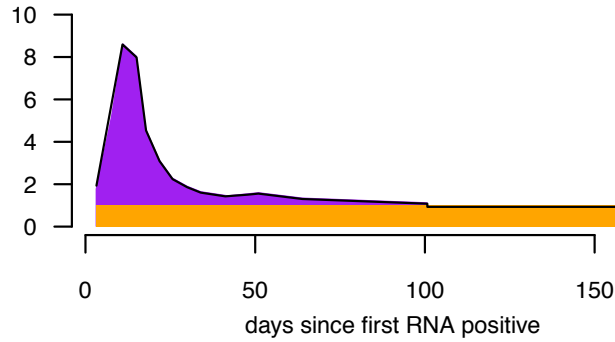


Early Transmission

HIV RNA
(copies/ml)

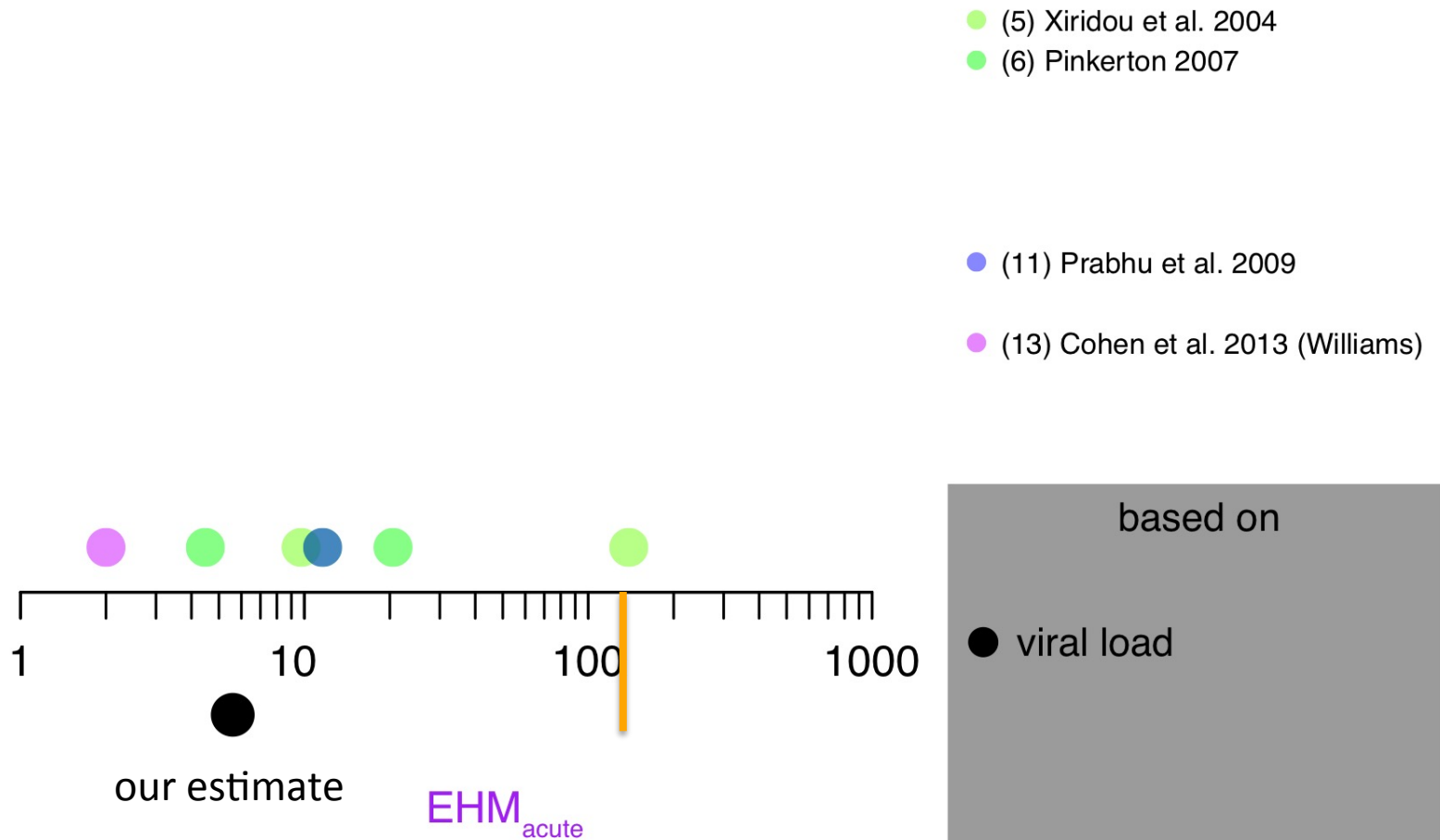


relative infectivity

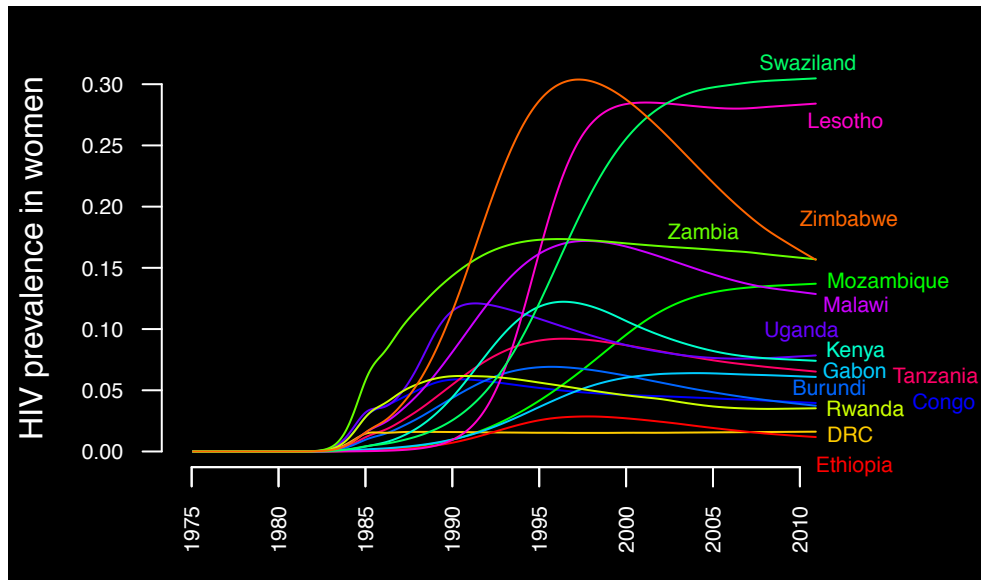


excess hazard-months = 5.6
attributable to acute phase

Variation in EHM_{acute} Estimates

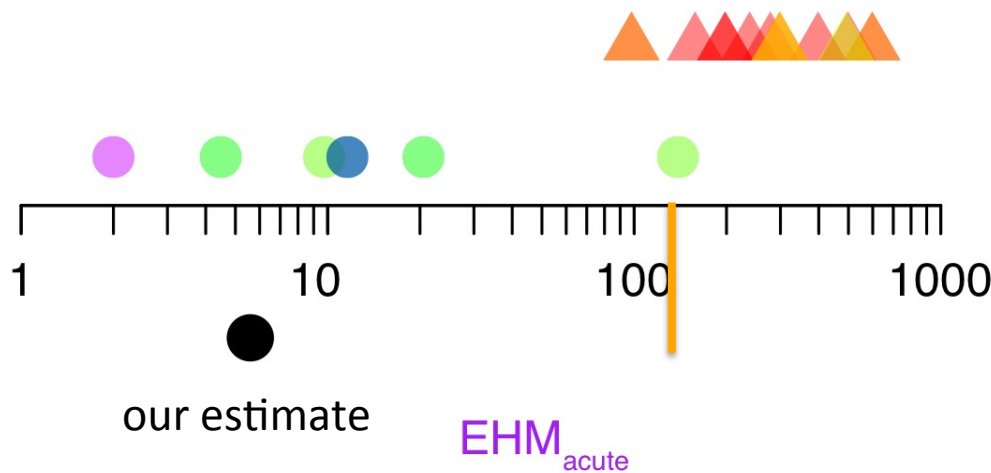


Variation in EHM_{acute} Estimates



- ▲ (1) Jacquez et al. 1994
- ▲ (2) Pinkerton and Abramson 1996
- ▲ (3) Koopman et al. 1997
- ▲ (4) Kretzschmar & Dietz 1998
- (5) Xiridou et al. 2004
- (6) Pinkerton 2007

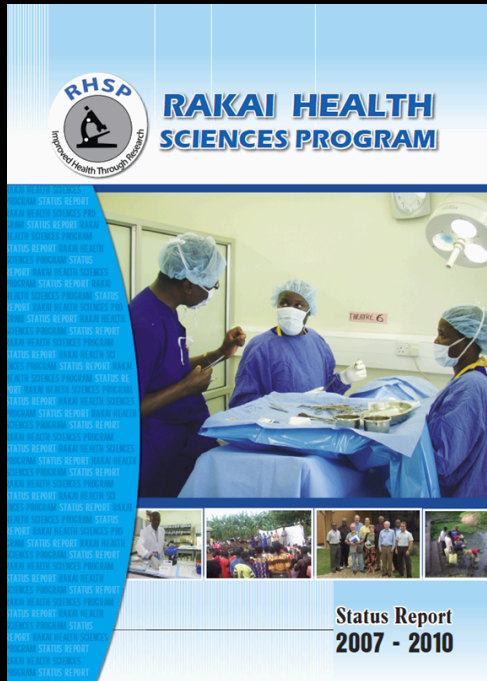
- (11) Prabhu et al. 2009
- (13) Cohen et al. 2013 (Williams)



based on

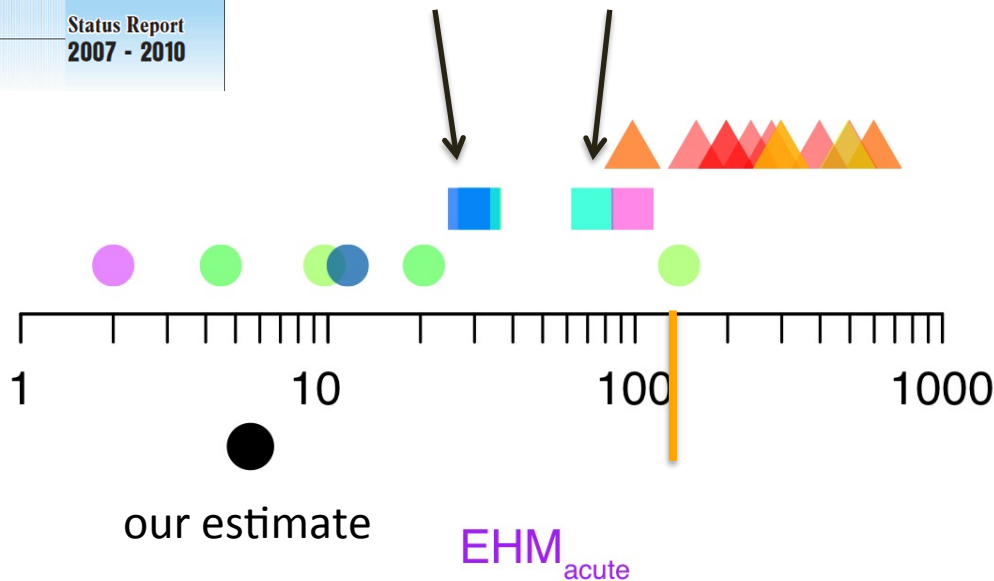
- ▲ epidemic curve
- viral load

Variation in EHM_{acute} Estimates



Directly measured by
Rakai Community
Cohort Study, Uganda

$EHM_{acute} = 30$ and 70

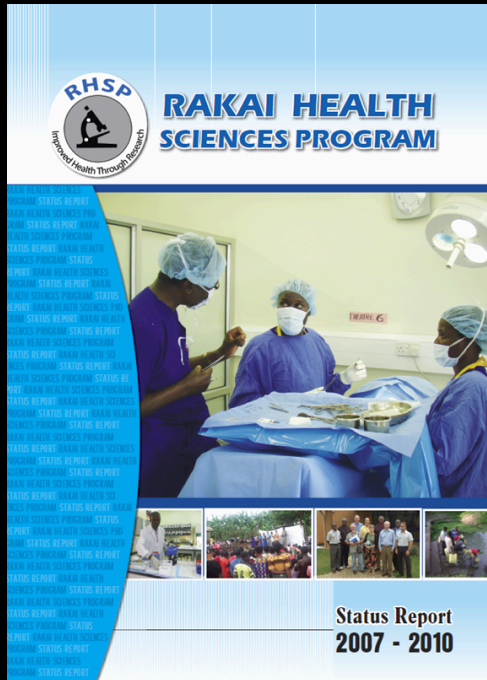


- ▲ (1) Jacquez et al. 1994
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- ▲ (4) Kretzschmar & Dietz 1998
- (5) Xiridou et al. 2004
- (6) Pinkerton 2007
- (7) Hayes et al. 2006
- (8) Hollingsworth et al. 2008
- (9) Abu-Raddad et al. 2008
- (10) Salomon & Hogan 2008
- (11) Prabhu et al. 2009
- (13) Cohen et al. 2013 (Williams)
- (14) Romero-Severson et al. 2013

based on

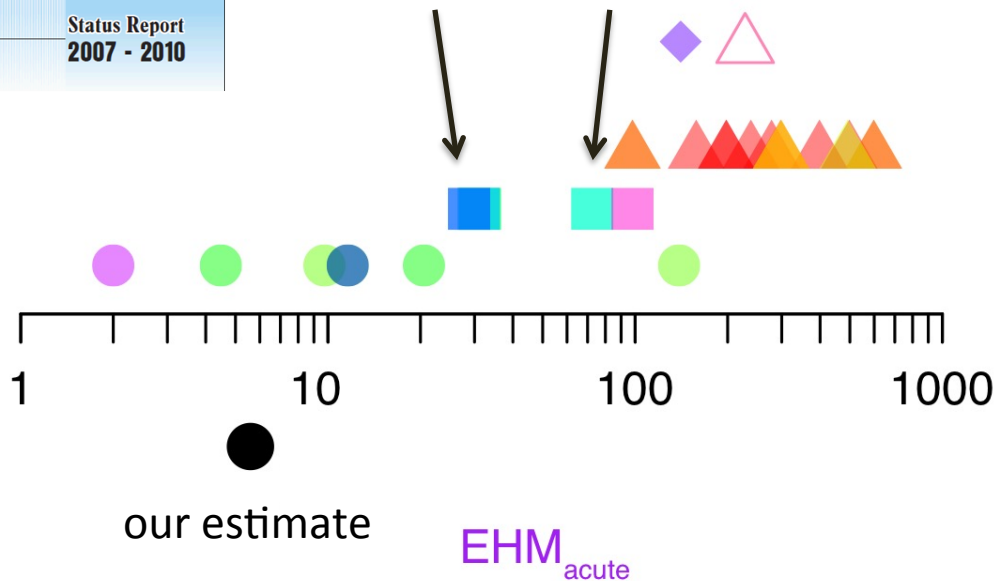
- ▲ epidemic curve
- viral load
- Rakai

Variation in EHM_{acute} Estimates



Directly measured by
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$EHM_{acute} = 30$ and 70

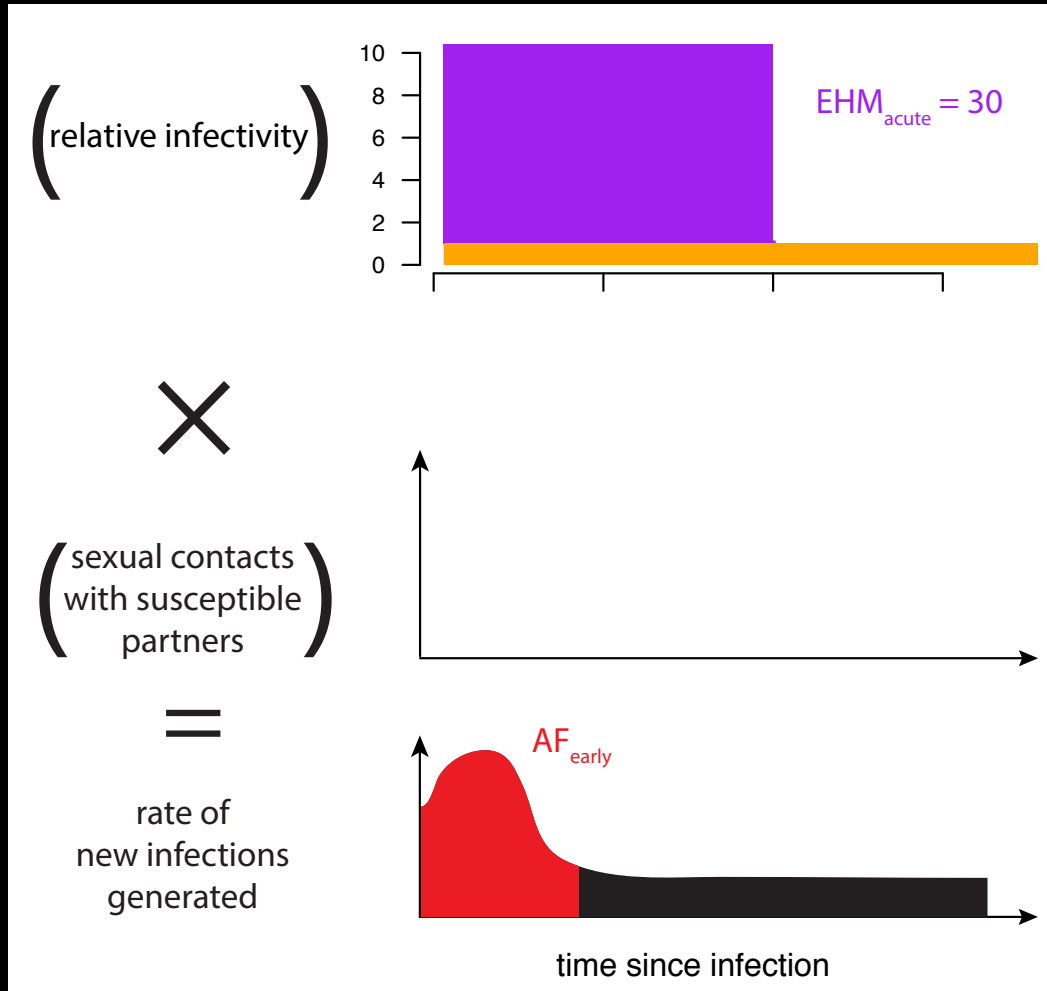


- ▲ (1) Jacquez et al. 1994
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- ▲ (3) Koopman et al. 1997
- ▲ (4) Kretzschmar & Dietz 1998
- (5) Xiridou et al. 2004
- (6) Pinkerton 2007
- (7) Hayes et al. 2006
- (8) Hollingsworth et al. 2008
- (9) Abu-Raddad et al. 2008
- (10) Salomon & Hogan 2008
- (11) Prabhu et al. 2009
- ◆ (12) Powers et al. 2011
- (13) Cohen et al. 2013 (Williams)
- (14) Romero-Severson et al. 2013
- △ (15) Rasmussen et al. 2014

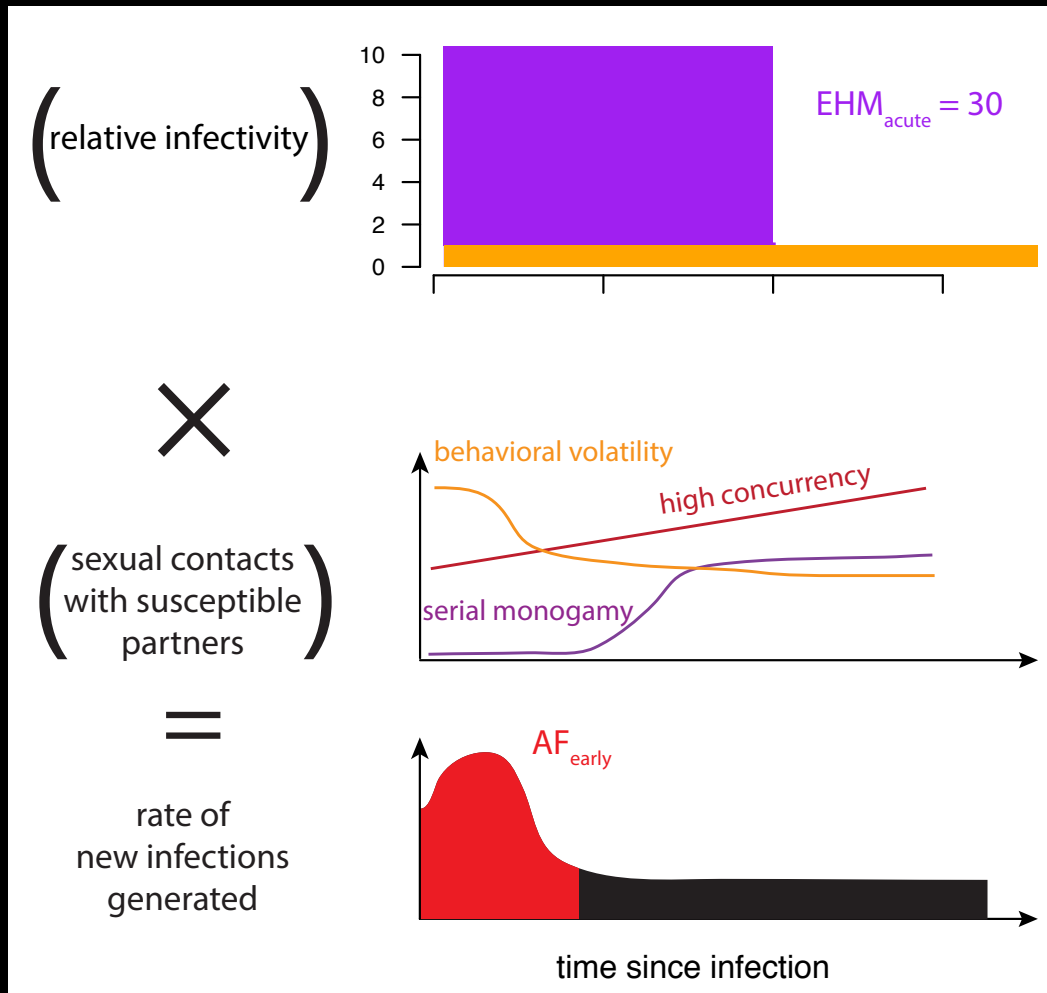
based on

- ▲ epidemic curve
- viral load
- Rakai
- ◆ Rakai & epidemic curve
- △ phylogenetics

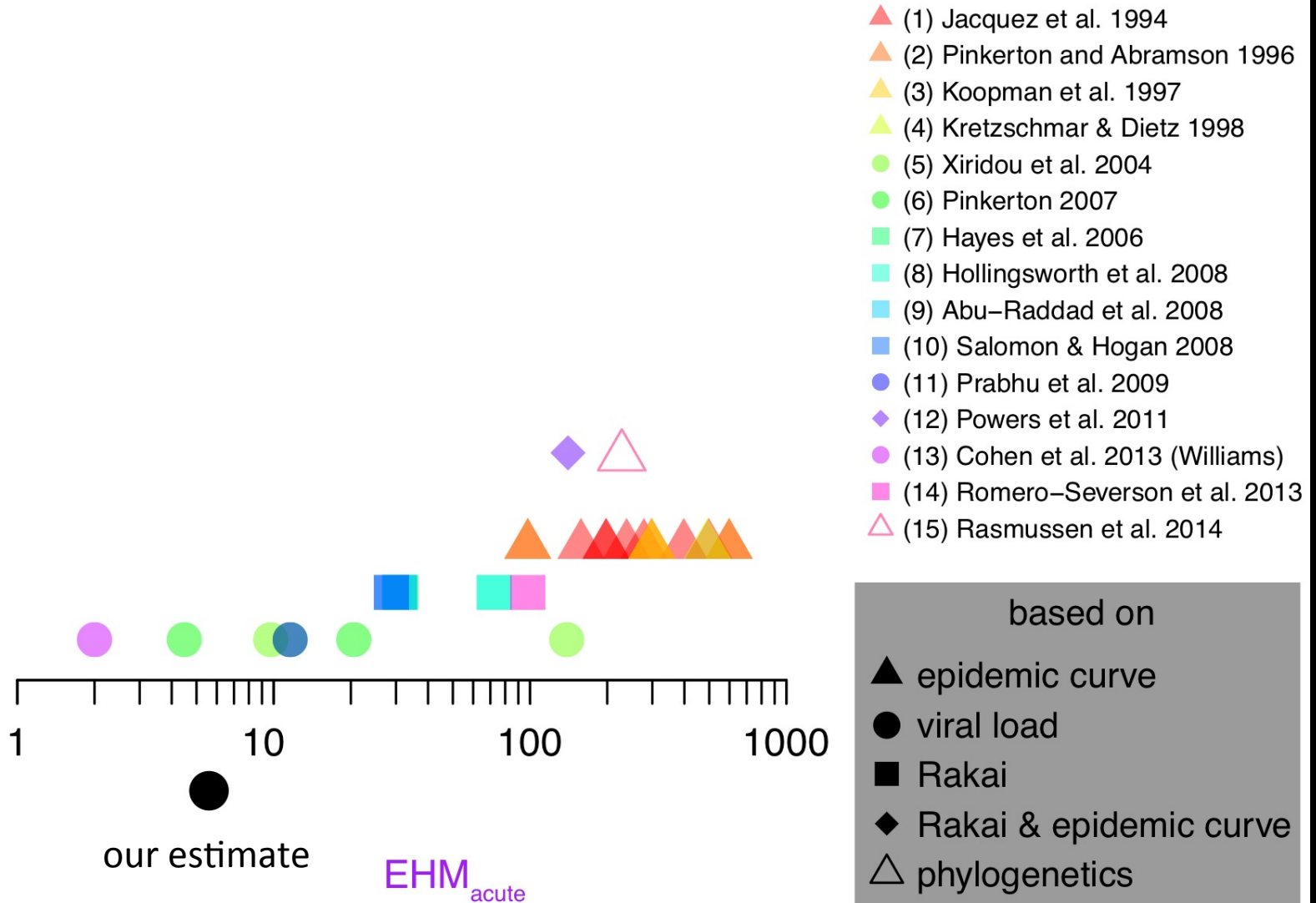
Infectivity only matters during sex with susceptible partners



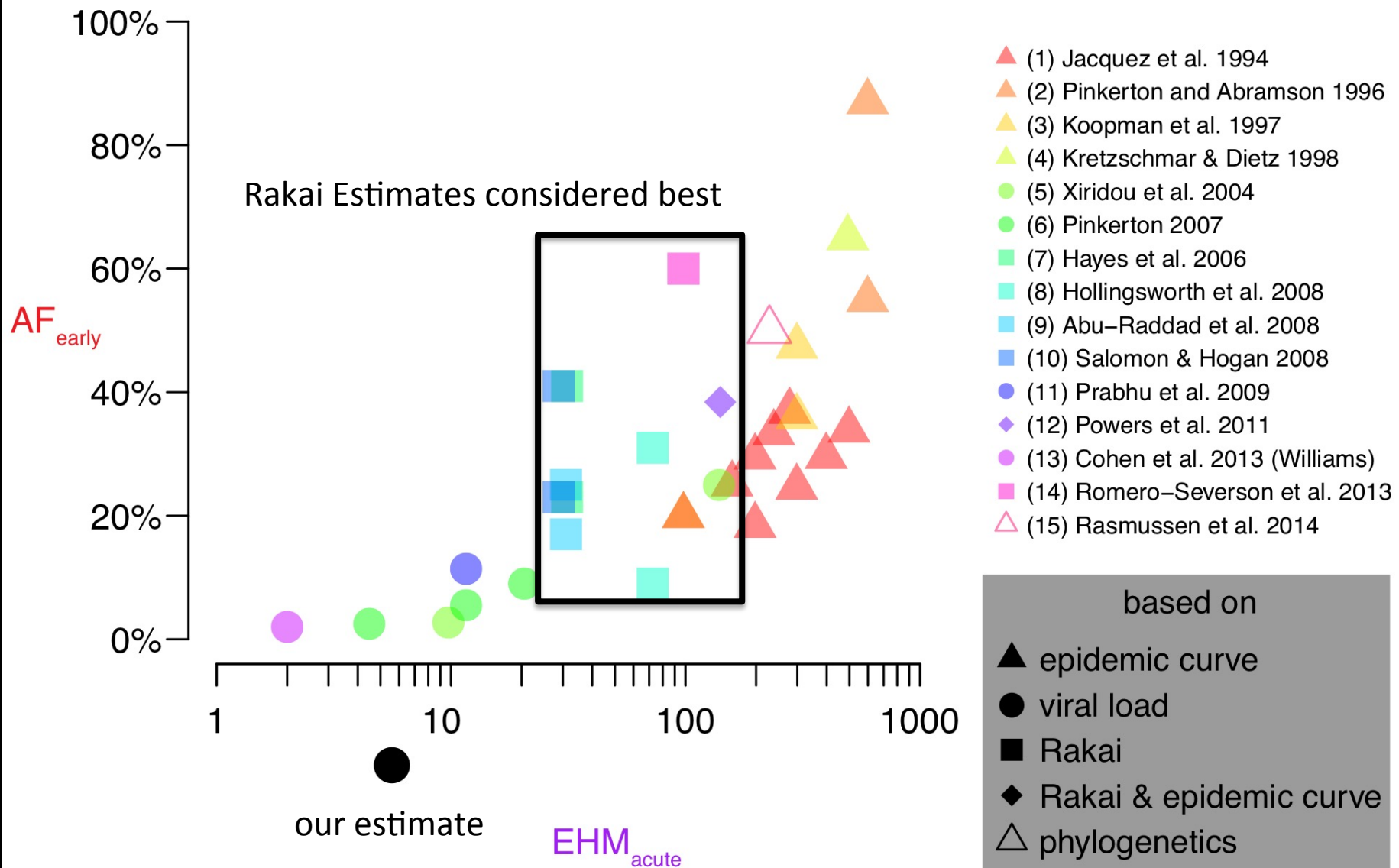
Infectivity only matters during sex with susceptible partners



Variation in EHM_{acute} Estimates



Variation in AF_{early} Estimates



Reassessment of HIV-1 Acute Phase Infectivity: Accounting for Heterogeneity and Study Design with Simulated Cohorts

Steve E. Bellan^{1*}, Jonathan Dushoff², Alison P. Galvani^{3,4}, Lauren Ancel Meyers^{5,6}

PLOS Medicine | DOI:10.1371/journal.pmed.1001801 March 17, 2015

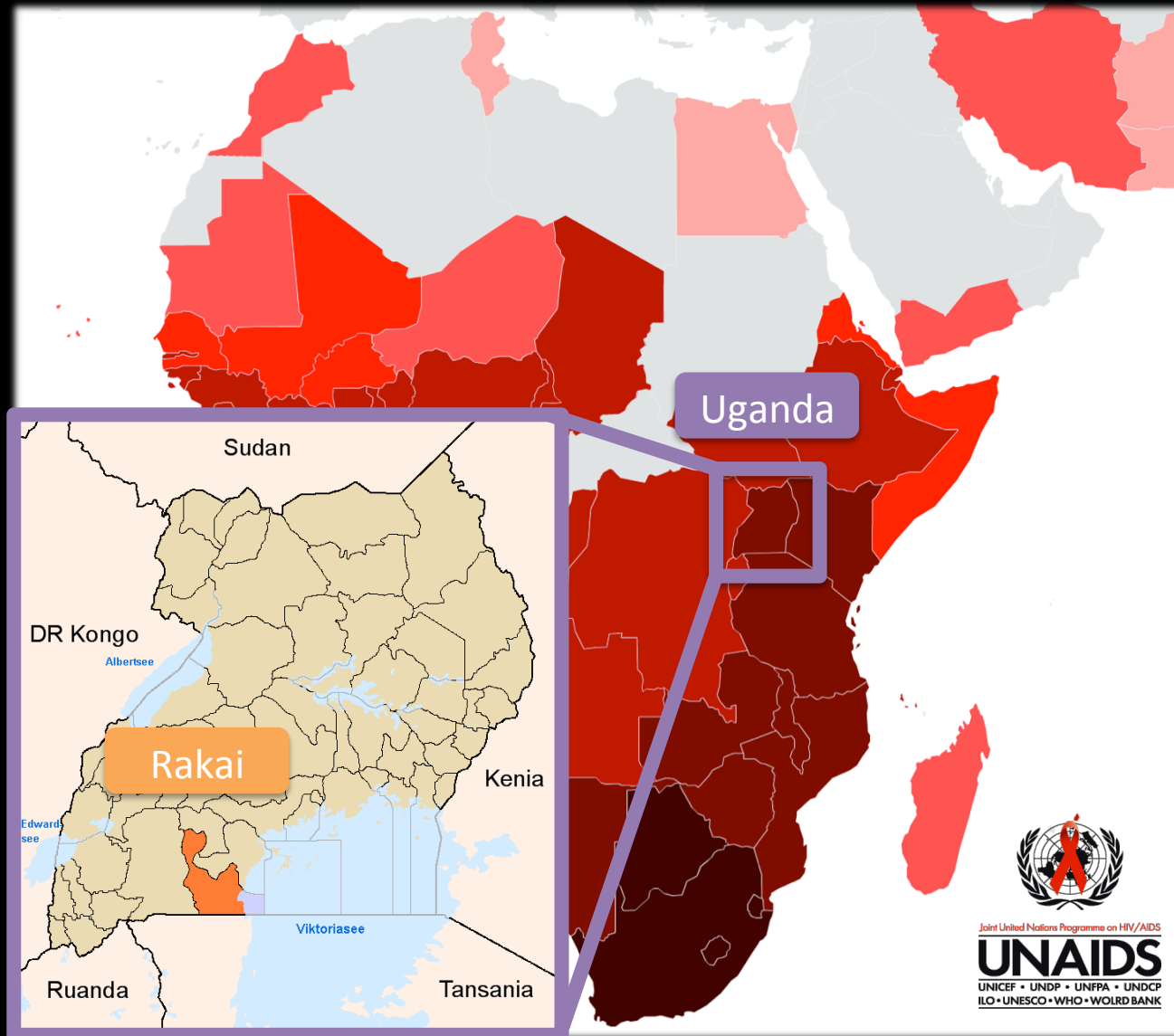
Rakai estimates are substantially upwards-biased.

**Identified biases by simulating
transmission & study design.**

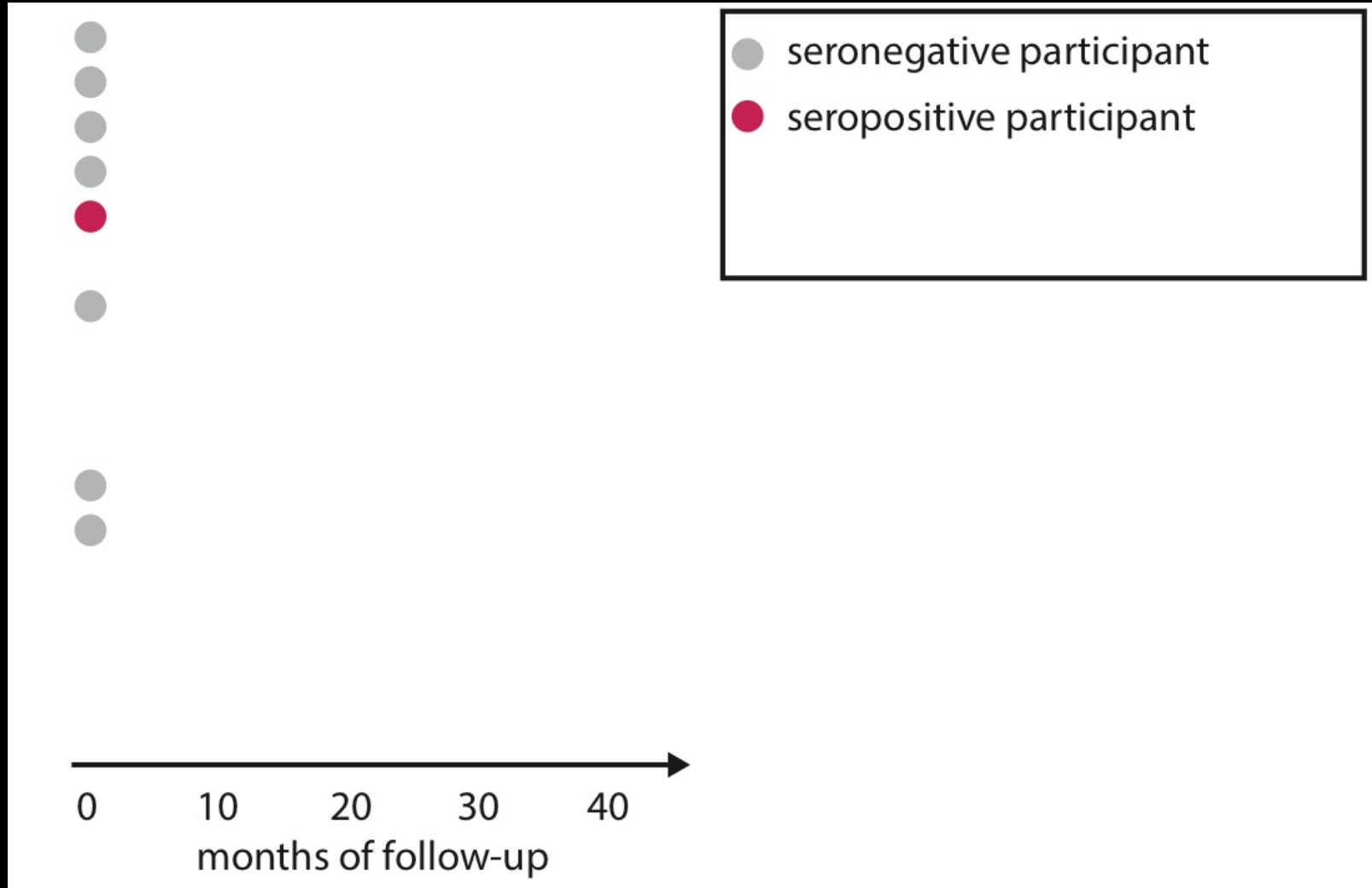
How to measure acute infectivity?

- Identify recently infected individuals
- Observe rate at which they infect sexual partners
- Must be switching between partners
- Moral imperative to intervene

Rakai Community Cohort Study



Rakai *Retrospective Couples* Cohort



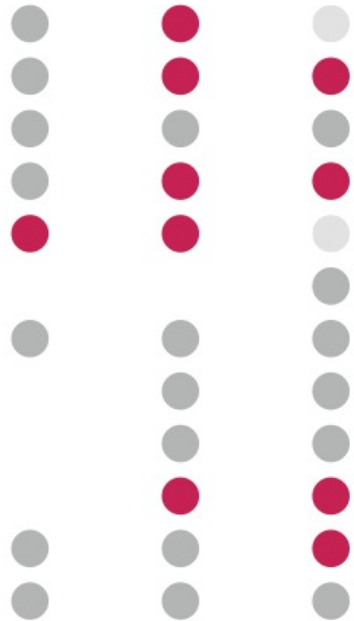
Rakai *Retrospective Couples* Cohort



● seronegative participant
● seropositive participant

0 10 20 30 40
months of follow-up

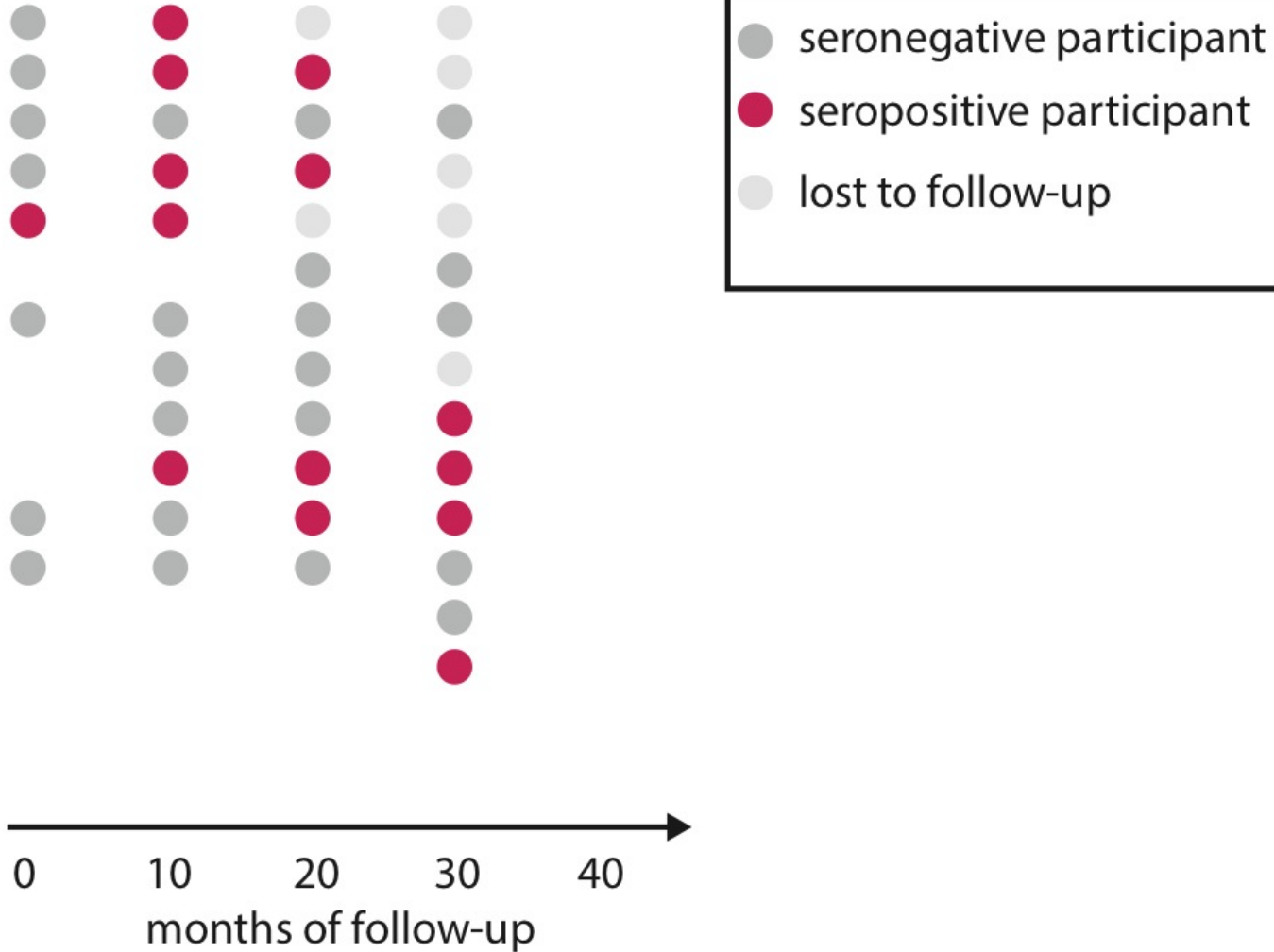
Rakai *Retrospective Couples* Cohort



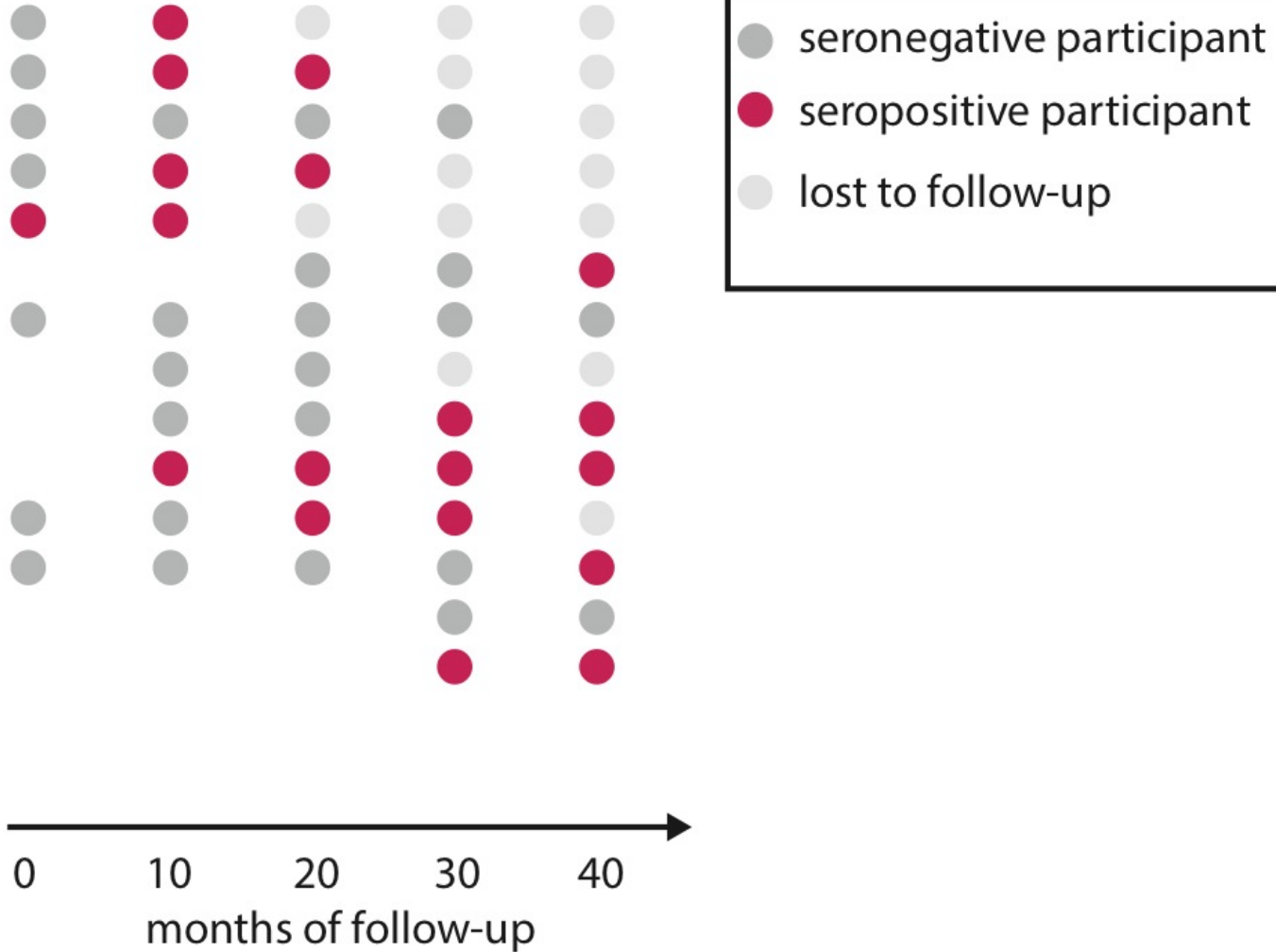
- seronegative participant
- seropositive participant
- lost to follow-up

0 10 20 30 40
months of follow-up

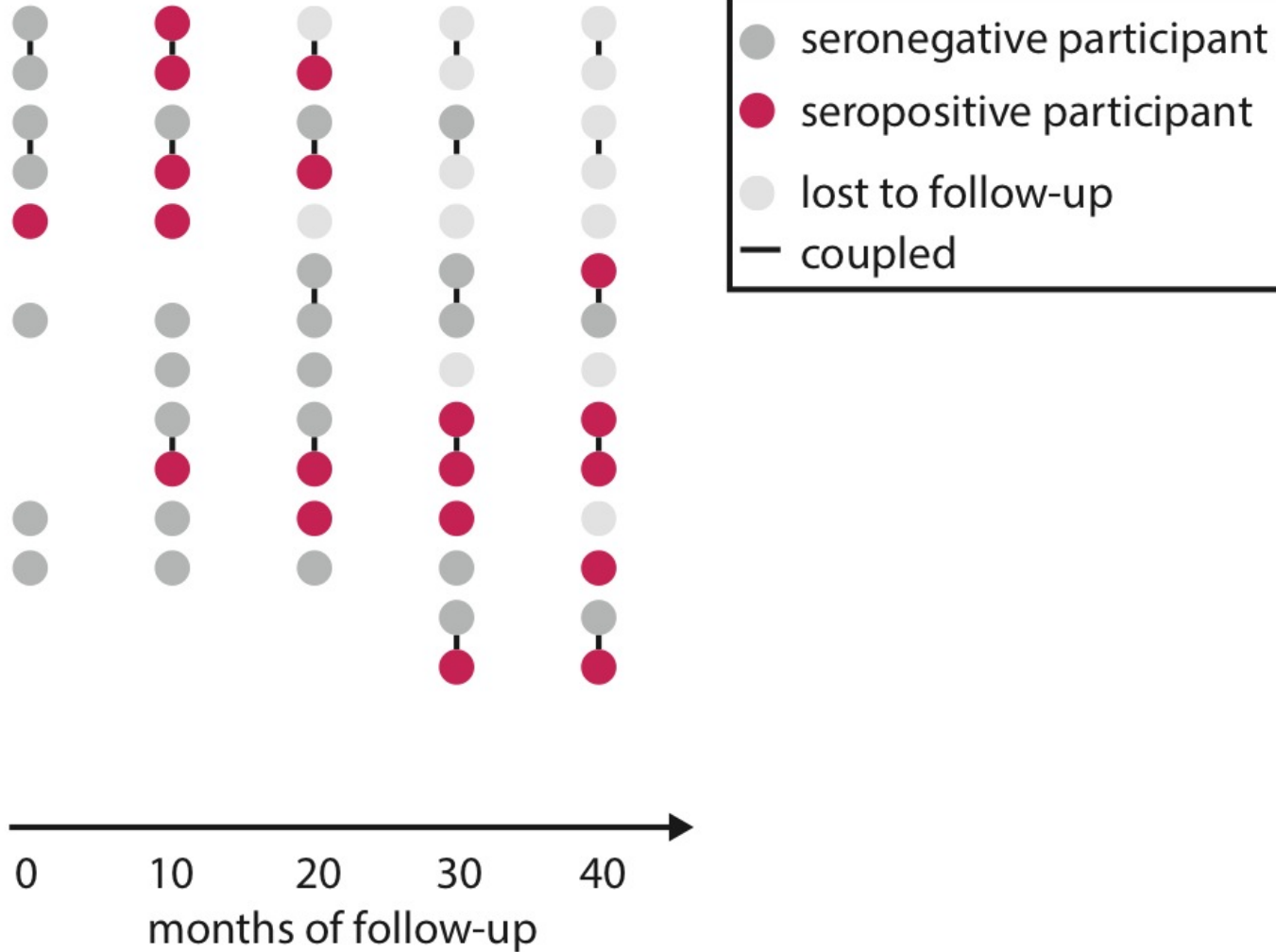
Rakai *Retrospective Couples* Cohort



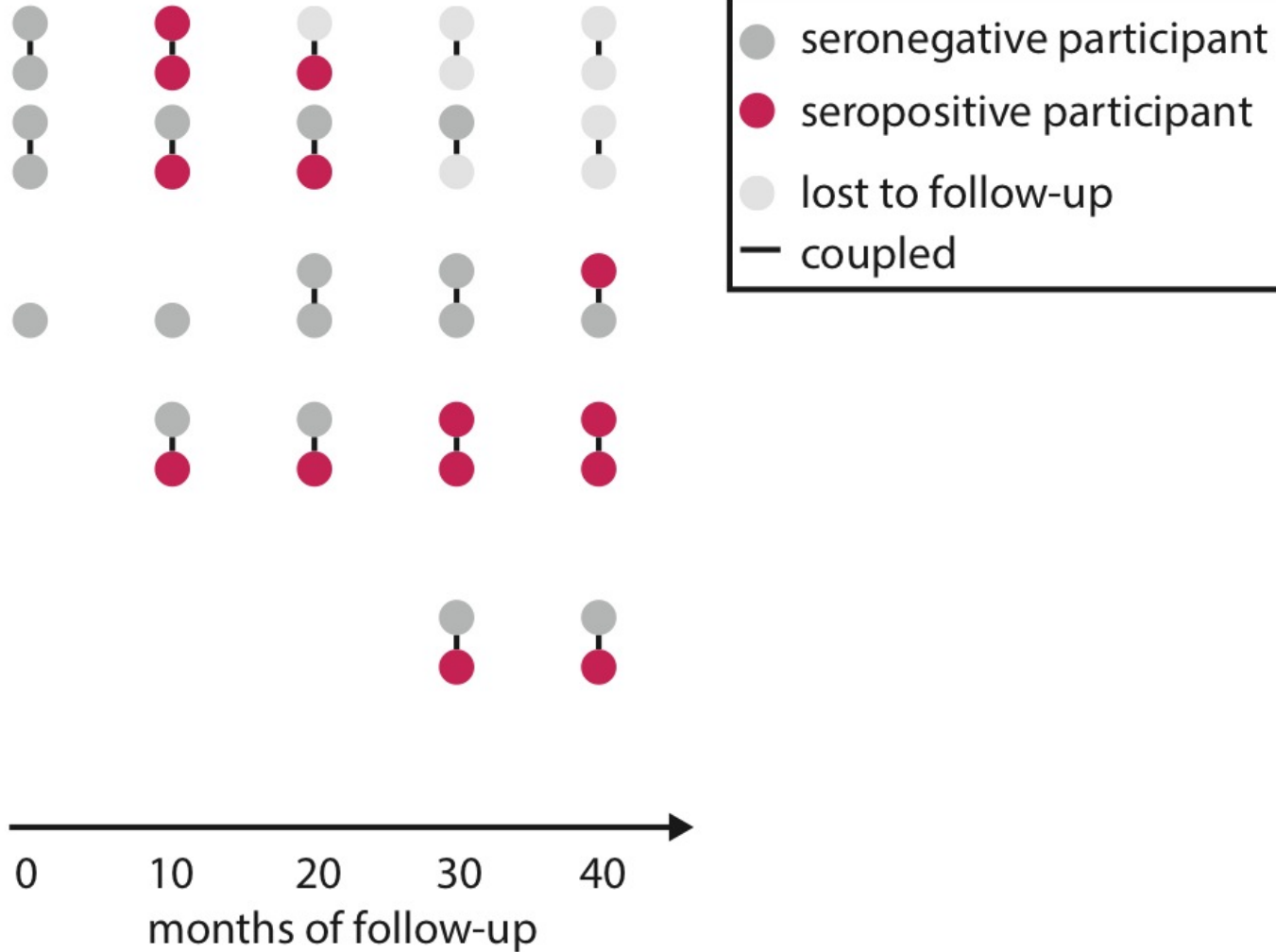
Rakai *Retrospective Couples* Cohort



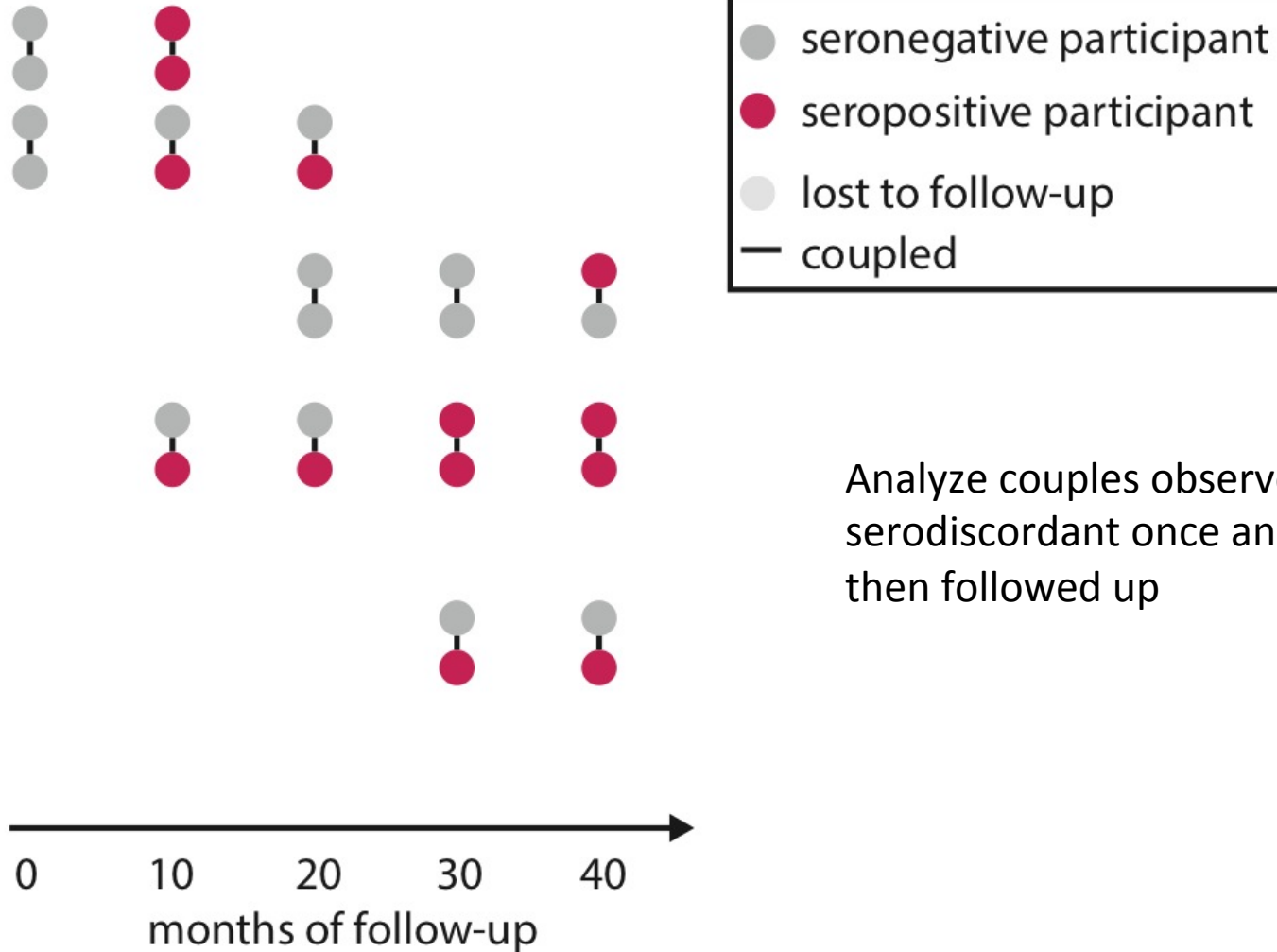
Rakai *Retrospective Couples* Cohort



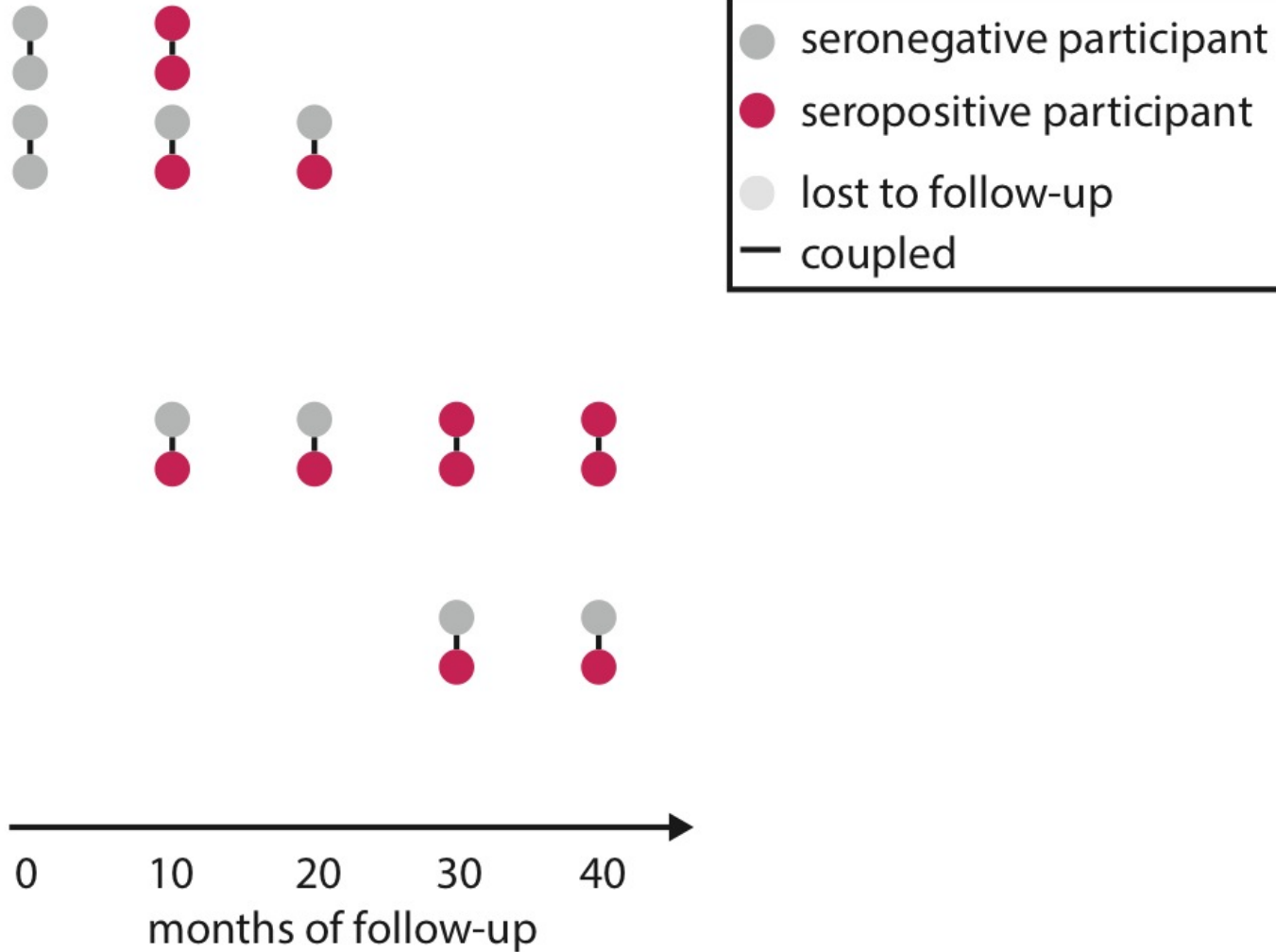
Rakai *Retrospective Couples* Cohort



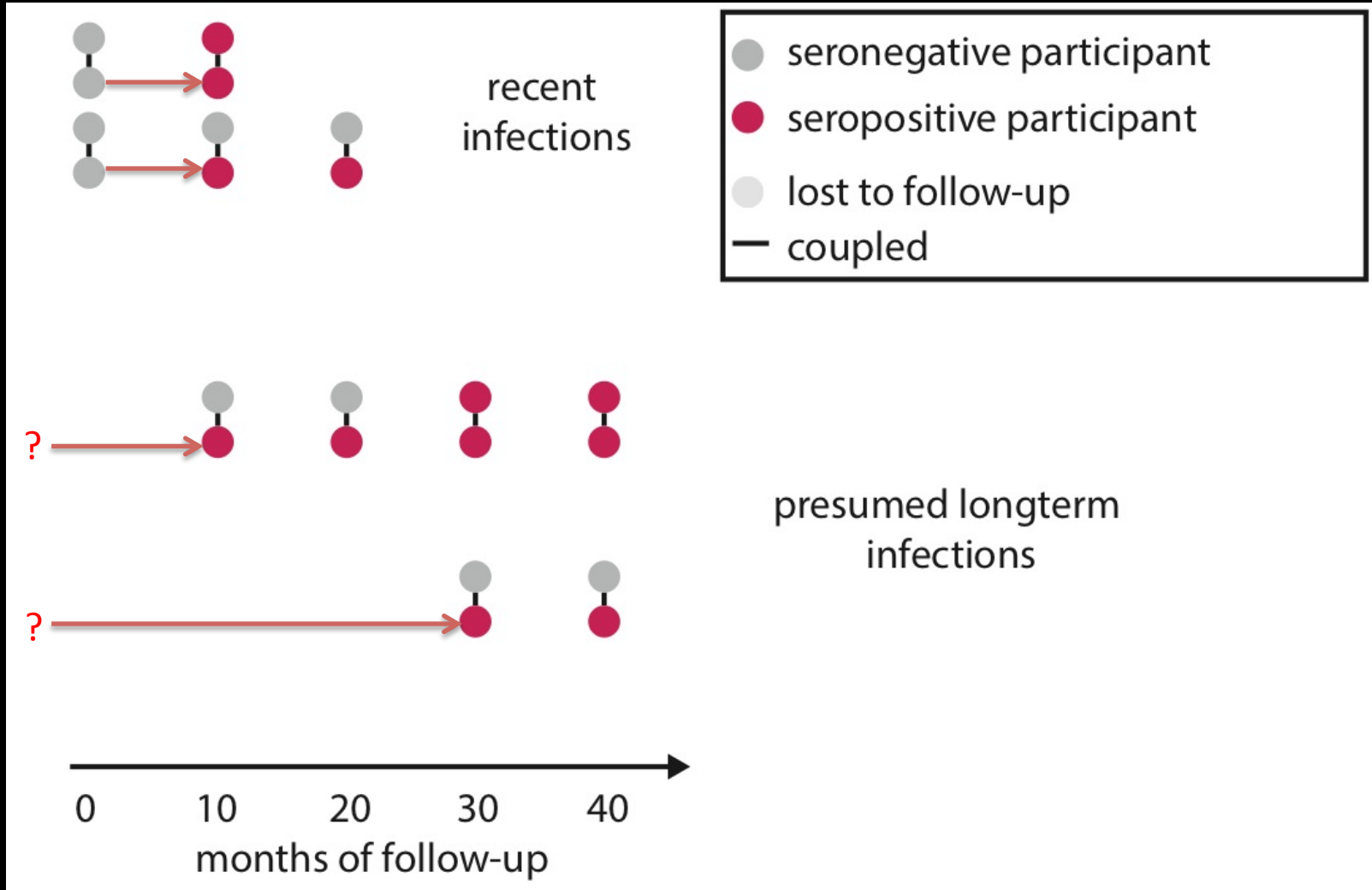
Rakai *Retrospective Couples Cohort*



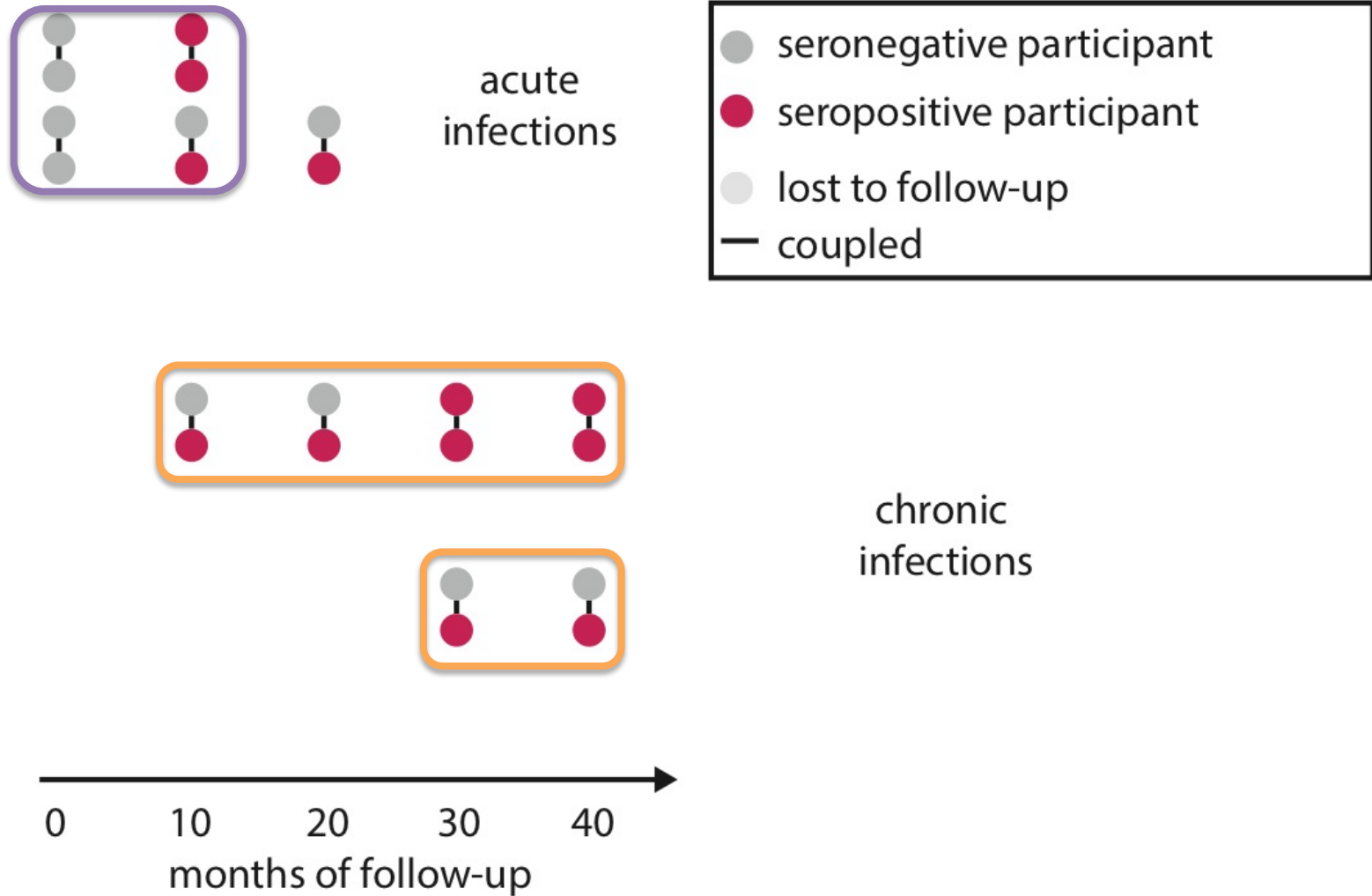
Rakai *Retrospective Couples* Cohort



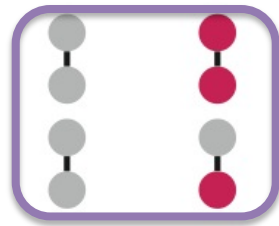
Rakai *Retrospective Couples* Cohort



Rakai *Retrospective Couples* Cohort



Rakai *Retrospective Couples* Cohort

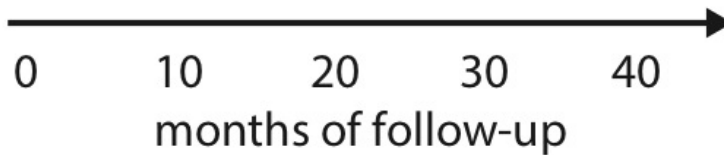


acute
infections

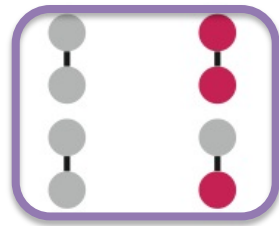
- seronegative participant
- seropositive participant
- lost to follow-up
- coupled



chronic
infections



Rakai *Retrospective Couples* Cohort



acute
infections

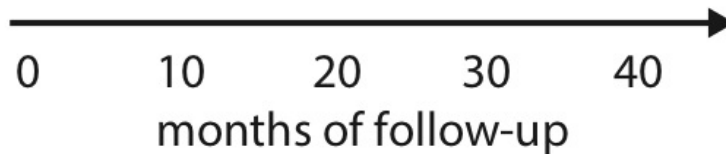
10/23 seroconverted

- seronegative participant
- seropositive participant
- lost to follow-up
- coupled



chronic
infections

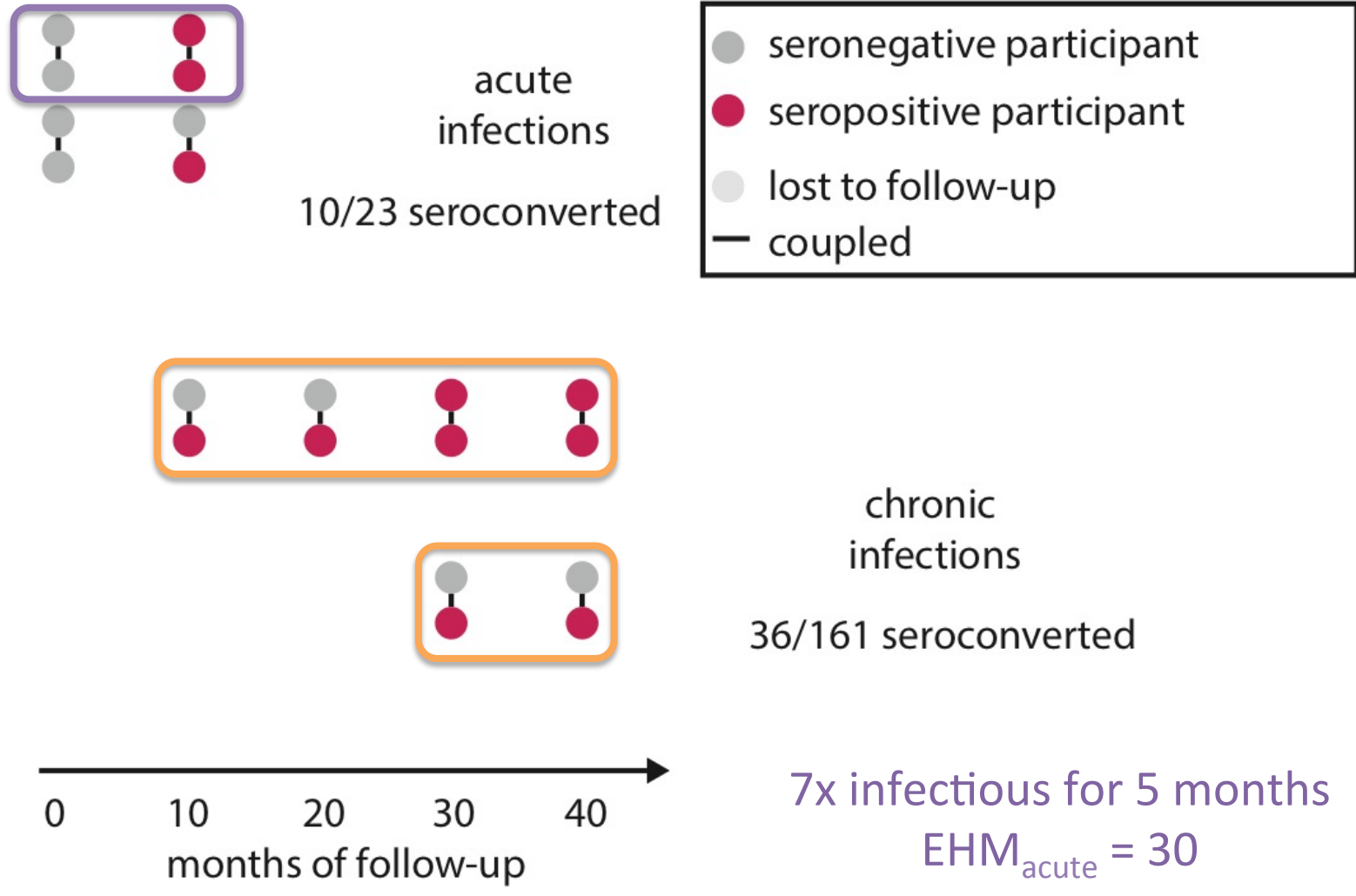
36/161 seroconverted



7x infectious for 5 months
 $EHM_{acute} = 30$

Rakai *Retrospective Couples* Cohort

Suggestive of HIGH acute infectivity



Why re-analyze these data?

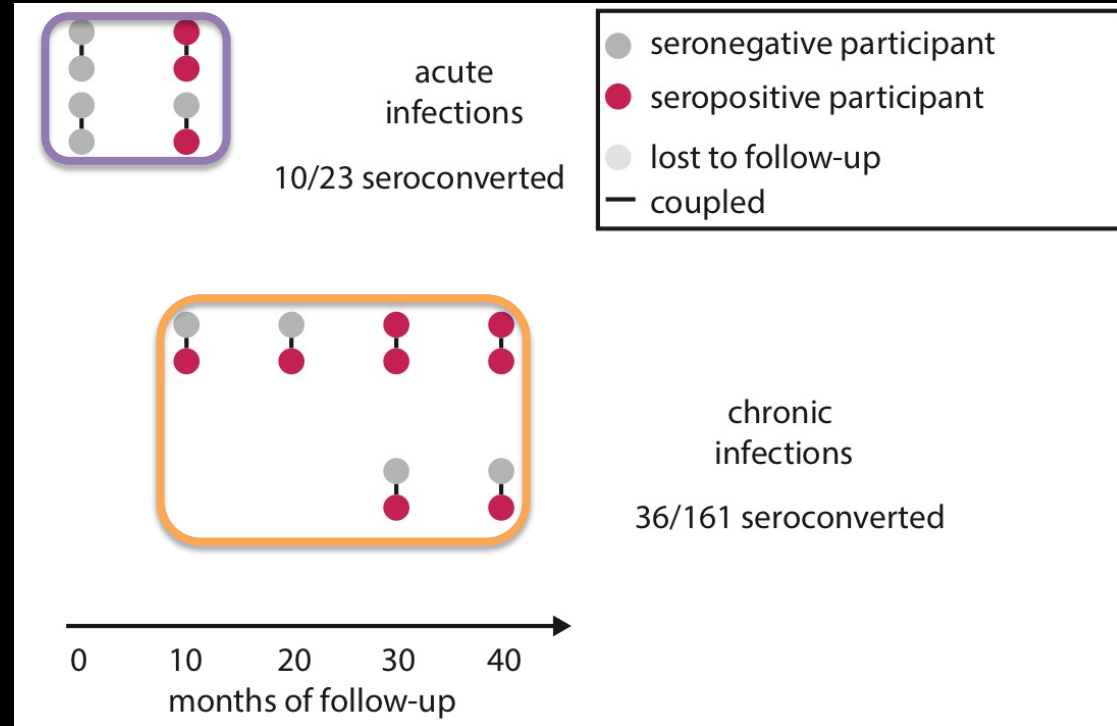
Heterogeneity in Transmission Rates

- Host genetics
- Circumcision
- Viral load
- Viral genotype
- Coital Rate
- Intercourse type (anal, dry, vaginal)
- Condom usage
- STIs
- Coinfections
- Nutrition

Bias 1: Unmodeled Heterogeneity

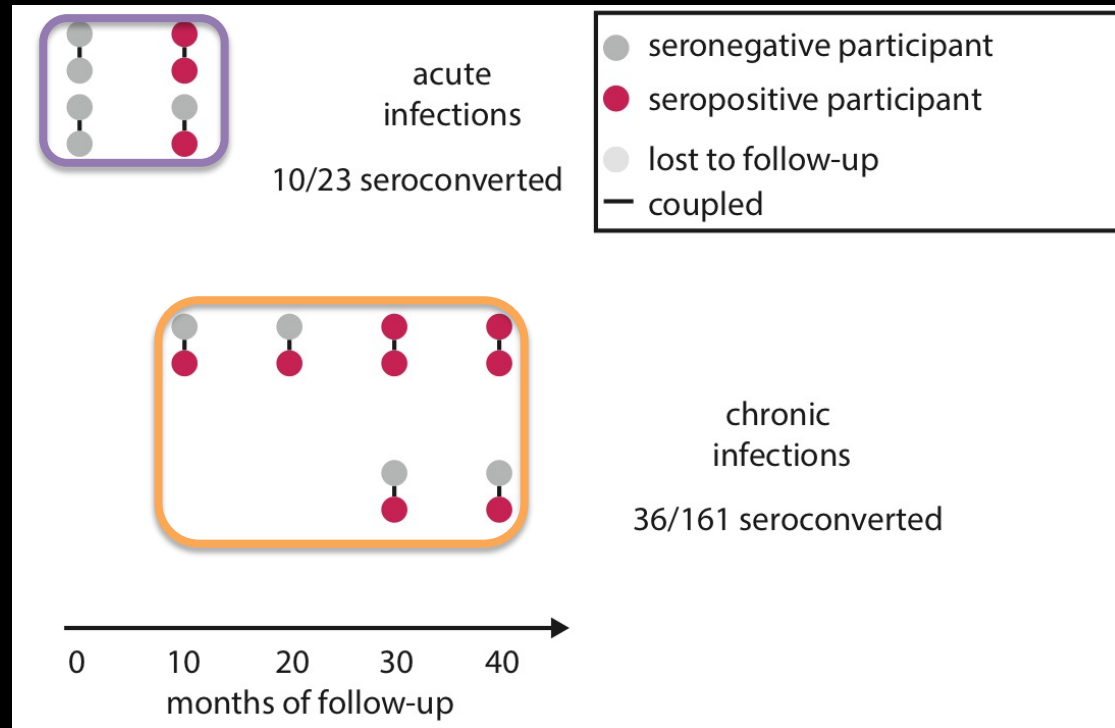
“Naïve” Couples.
Some are **high risk**

Persistently serodiscordant.
Selected to be **low risk**



Bias 1: Unmodeled Heterogeneity

Average risk
acutely infected partners

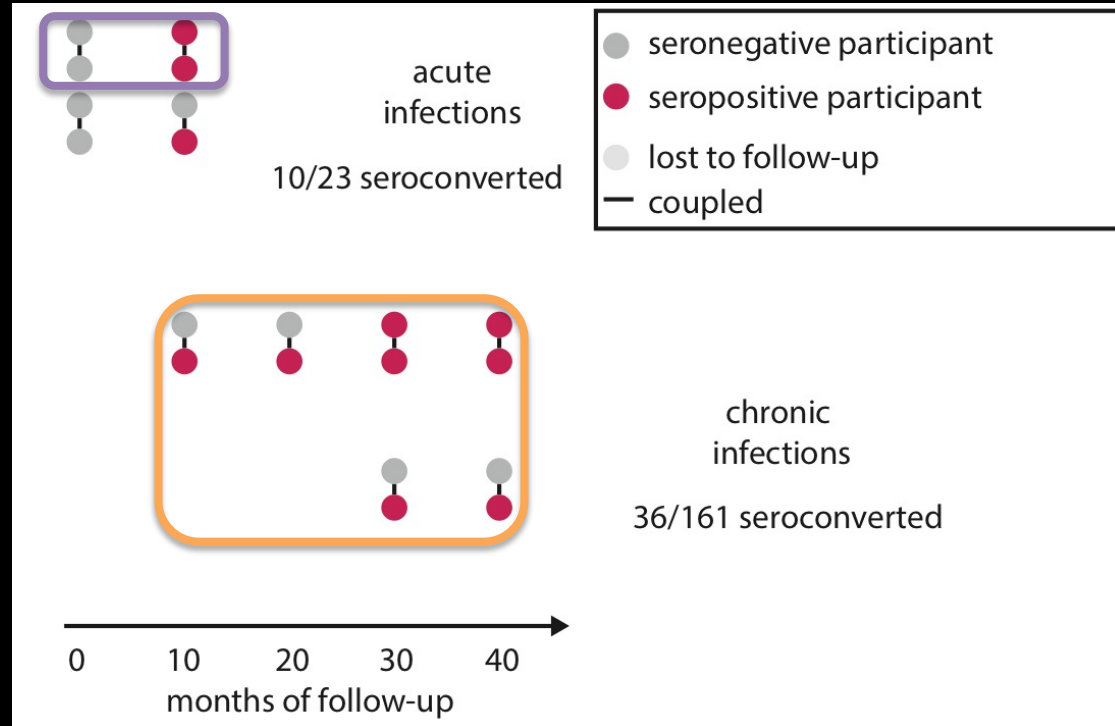


Low risk
chronically infected partners

Unmodeled heterogeneity might
bias EHM_{acute} upwards

Bias 2: Inclusion Criteria

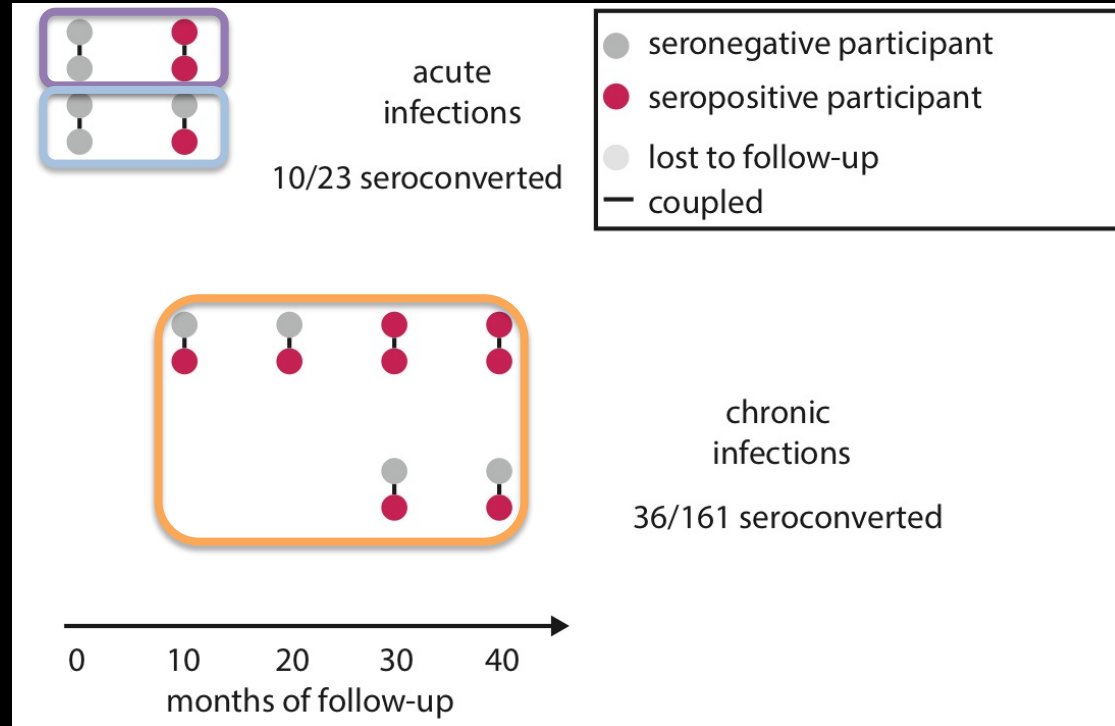
HIGH acute infectivity



Bias 2: Inclusion Criteria

HIGH acute infectivity

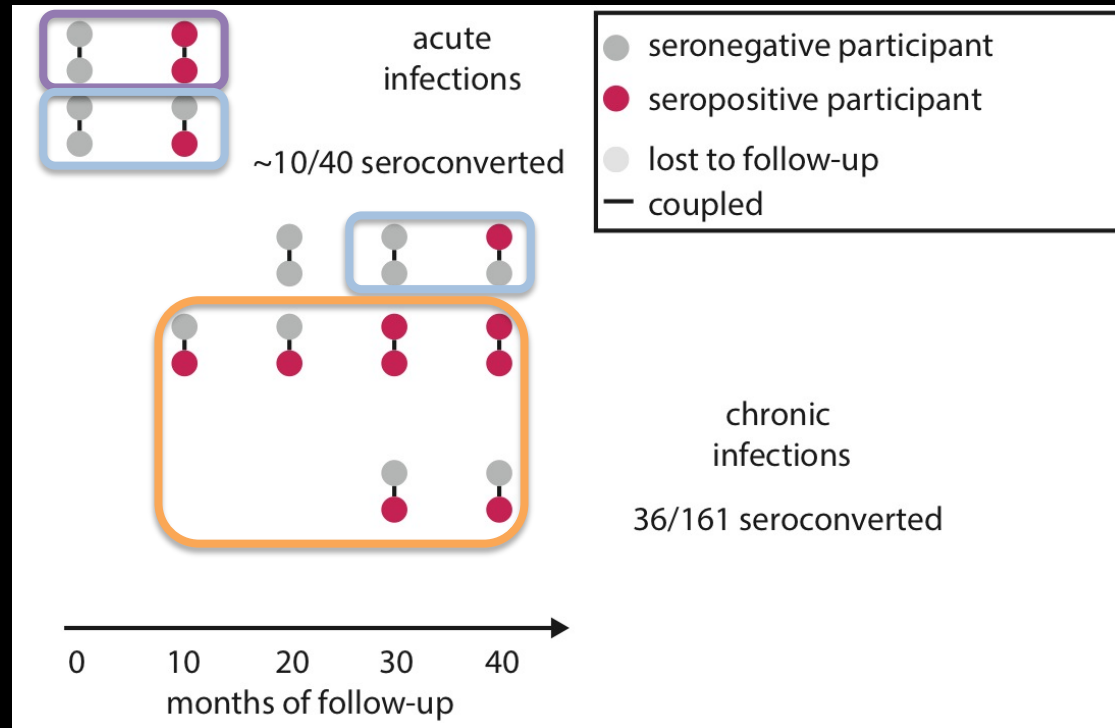
LOW acute infectivity



Bias 2: Inclusion Criteria

HIGH acute infectivity

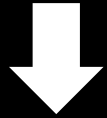
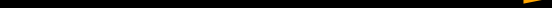
LOW acute infectivity



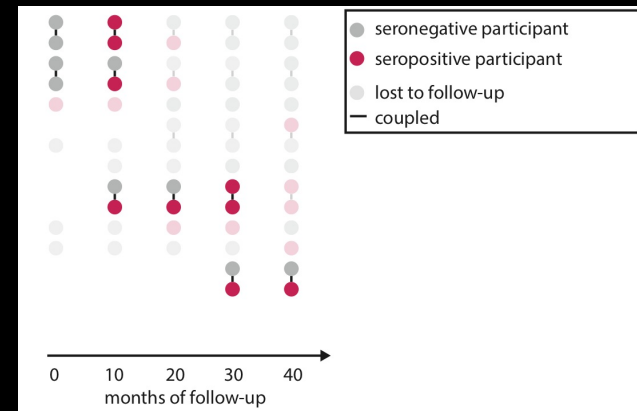
Accidentally excluded
~17 couples suggestive of low infectivity

Simulating Rakai Transmission & Observation

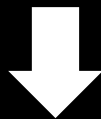
Input EHM_{acute}



1. Simulate transmission
2. Replicate Rakai study design



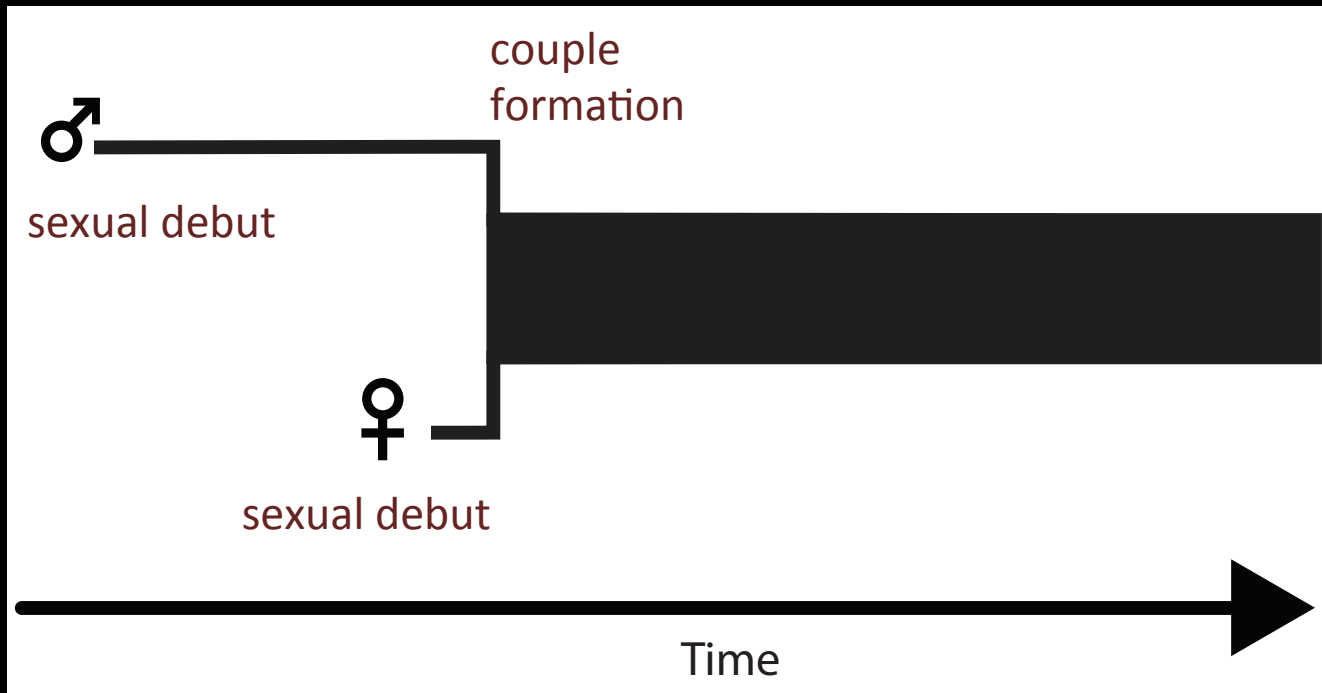
3. Apply published analyses to simulated data.



Estimated EHM_{acute}

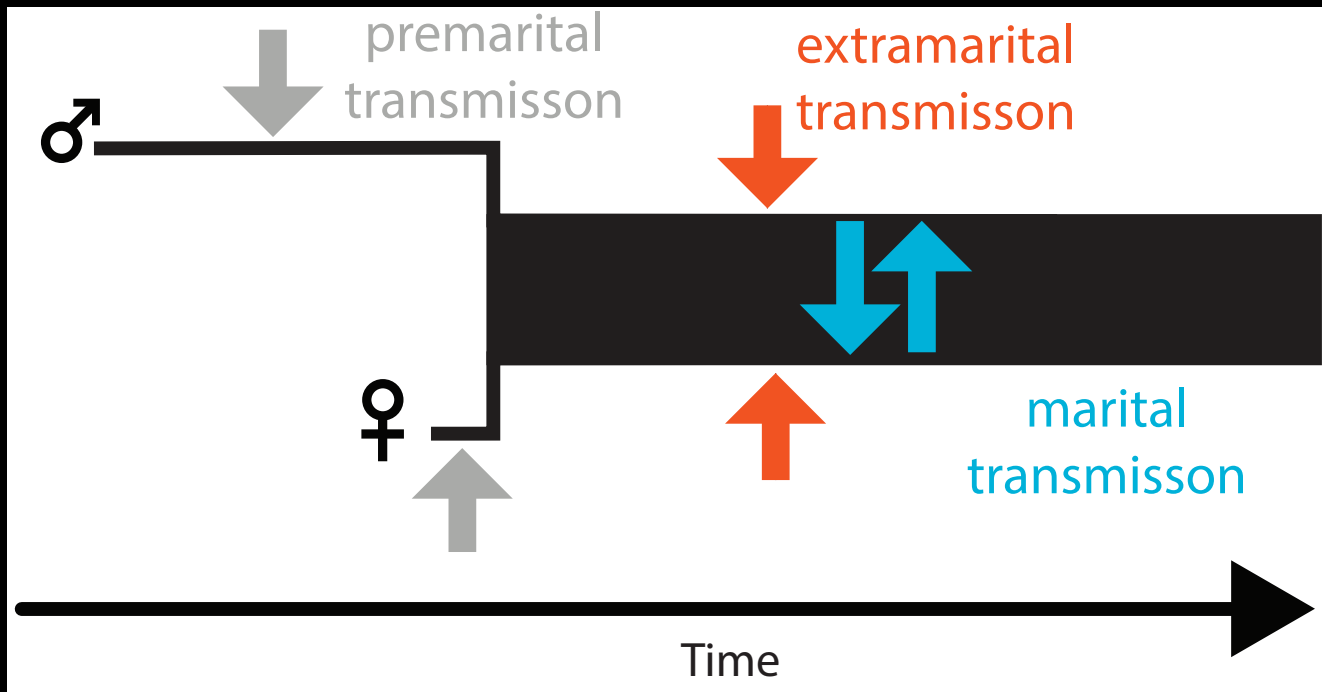


Couple Transmission Model

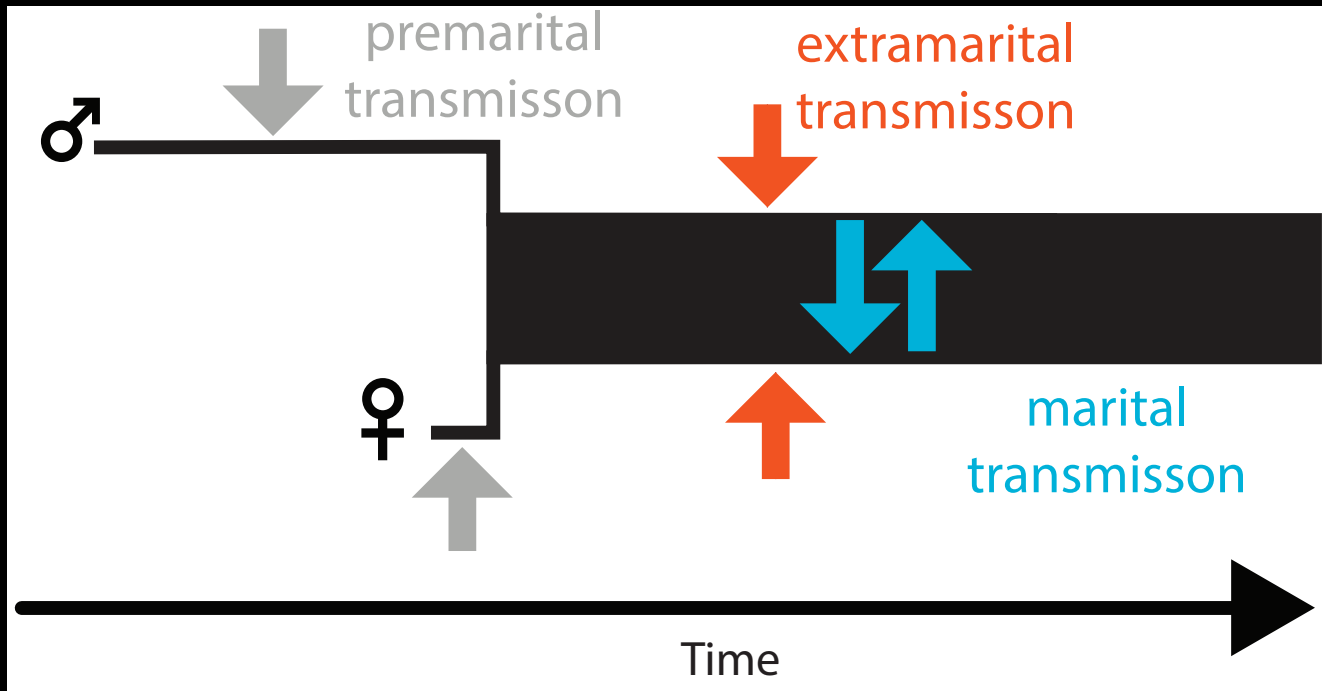


example relationship history

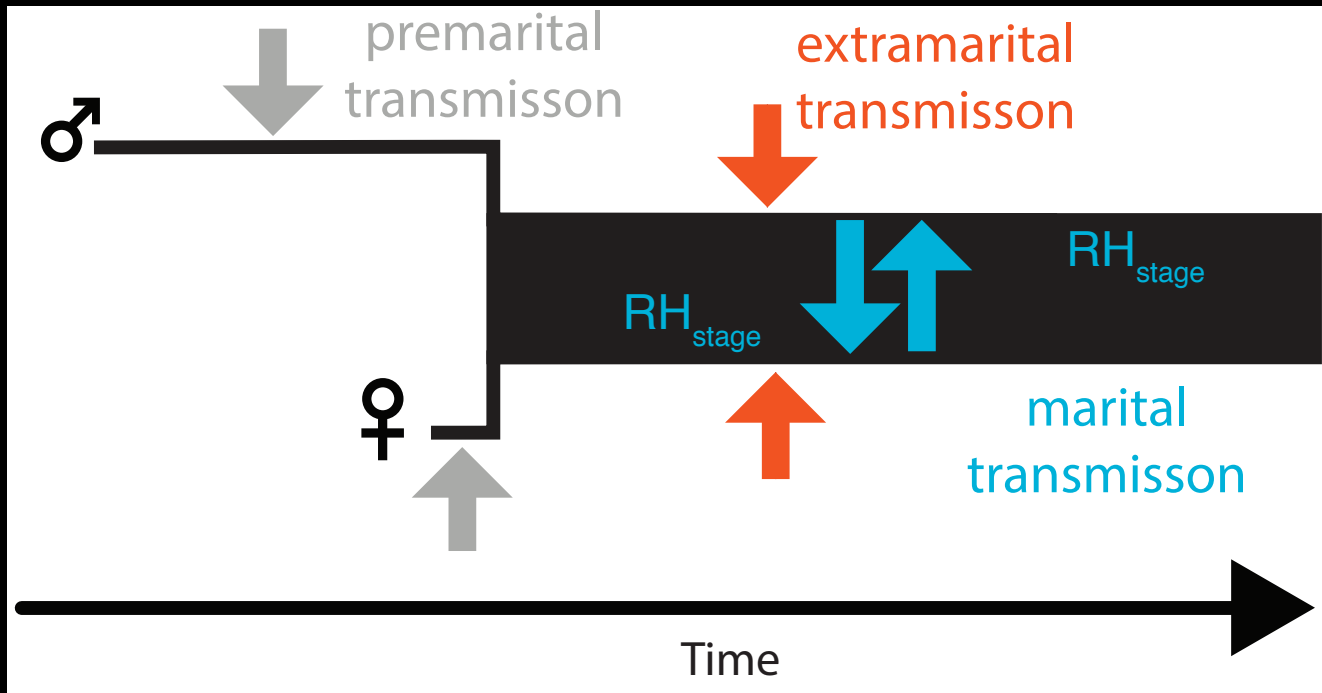
Couple Transmission Model



Couple Transmission Model



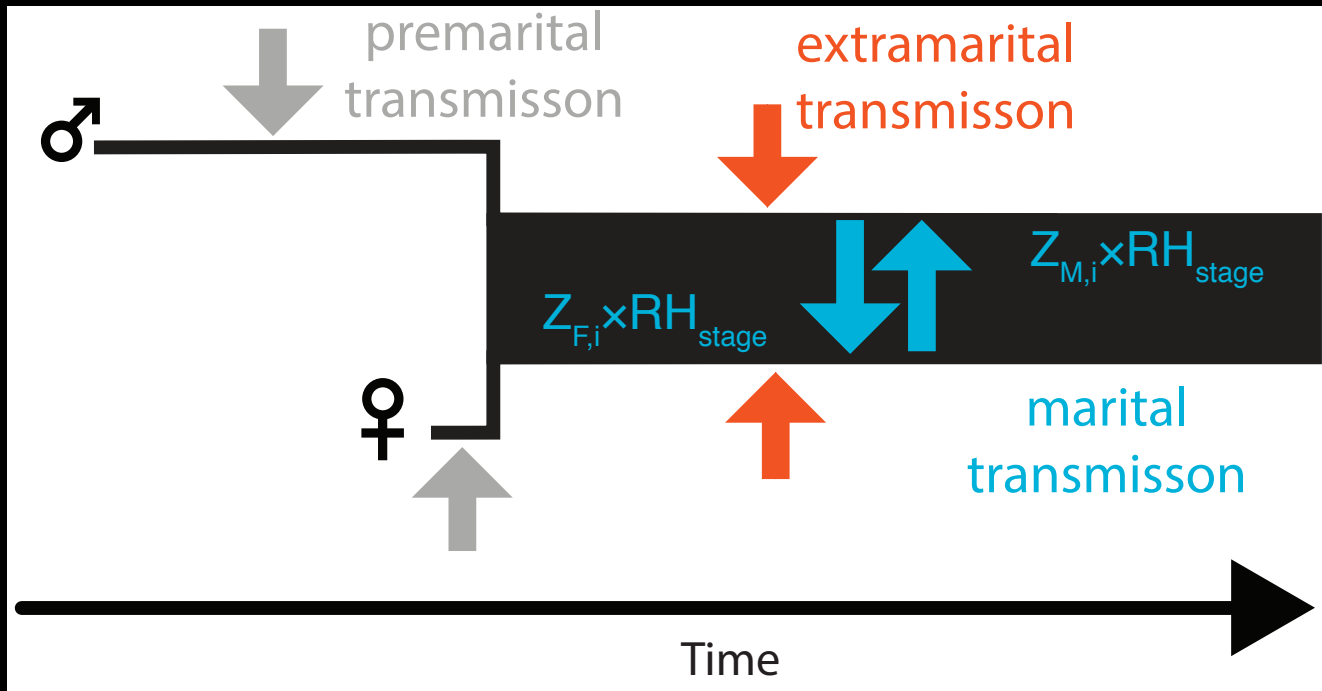
Couple Transmission Model



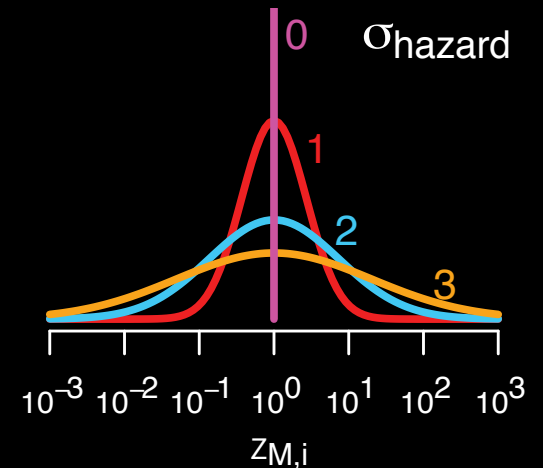
relative hazard (RH) varies by HIV stage



Couple Transmission Model



Heterogeneity



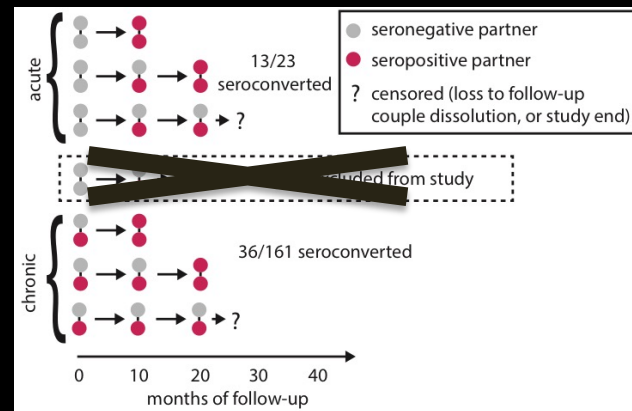
Simulating Rakai Transmission & Observation



1. Simulate transmission in couples cohort ← process-centric

2. Replicate Rakai study design

data-centric →

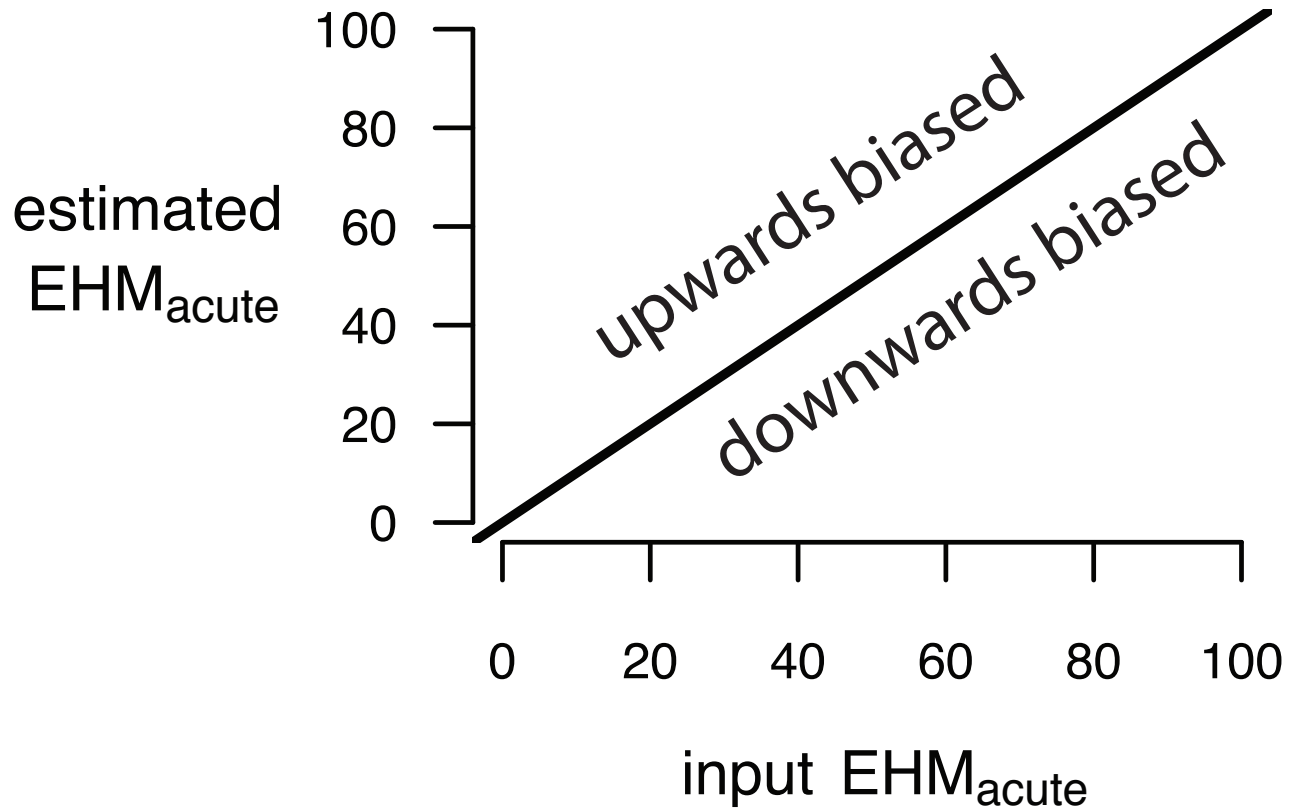


3. Apply published analyses to simulated data.

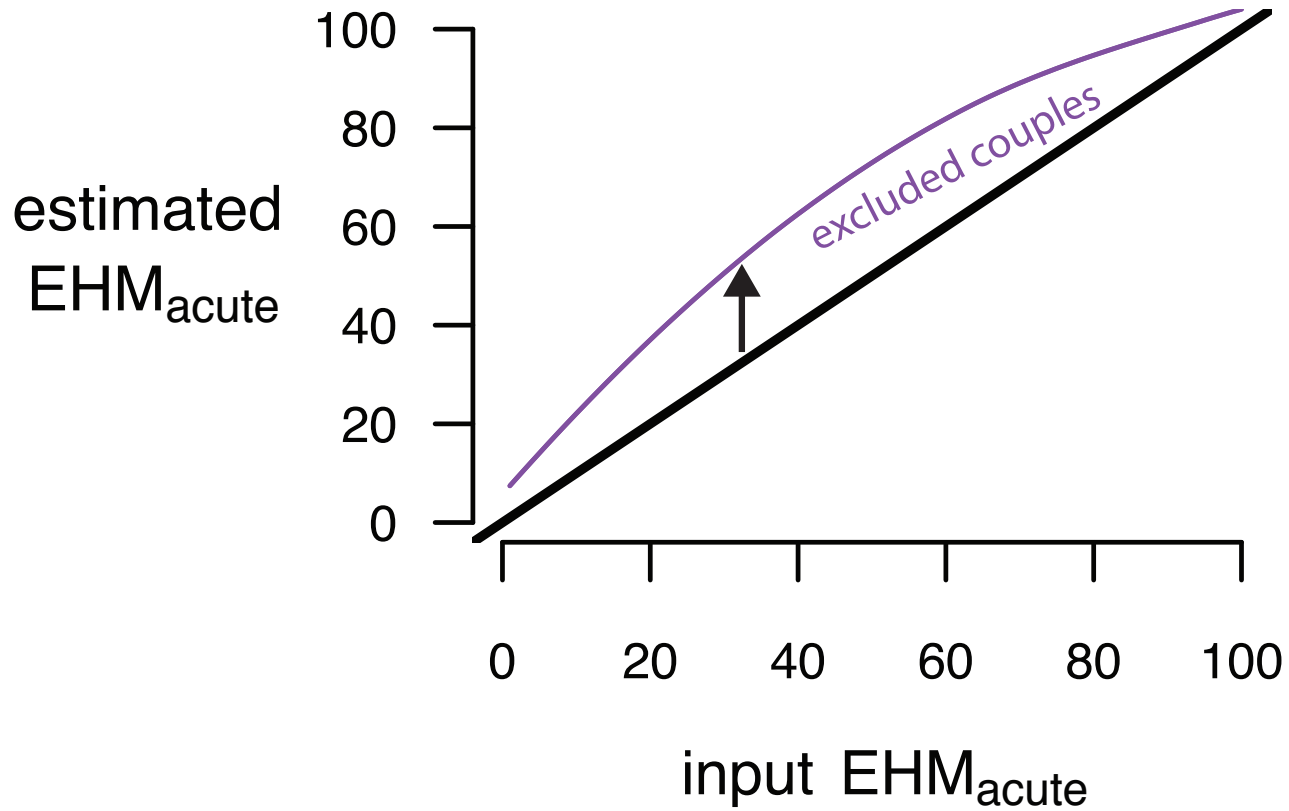
Estimated EHM_{acute}



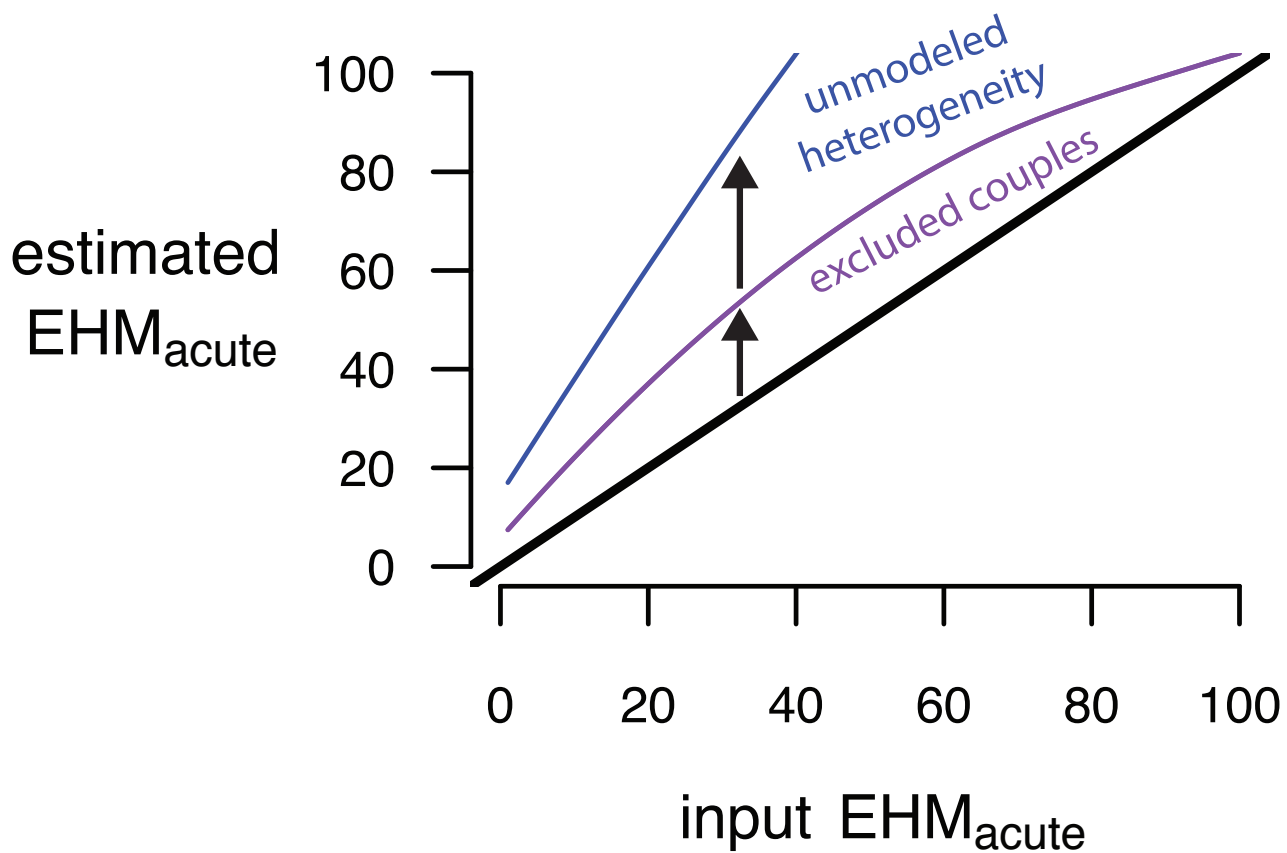
Bias Analysis



Bias Analysis



Bias Analysis



Bias-Adjusted Estimates (ABC-SMC)

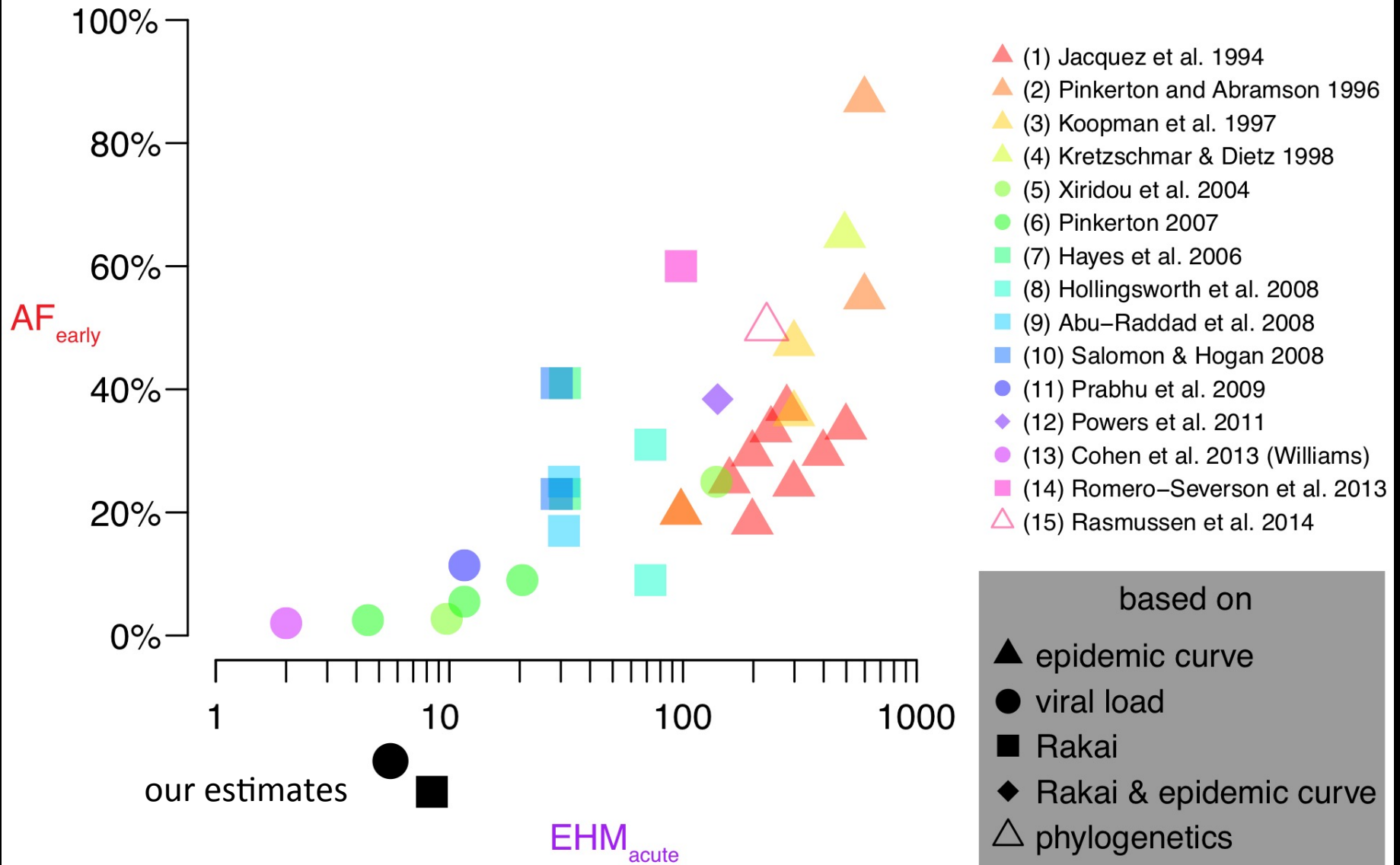
Estimation

What inputs consistent with Rakai data?

$$EHM_{acute} = 8.4$$


~~$$EHM_{acute} = 30 - 70$$~~

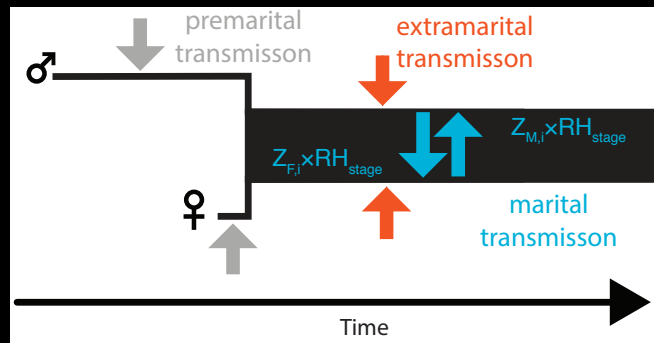
Variation in AF_{early} Estimates



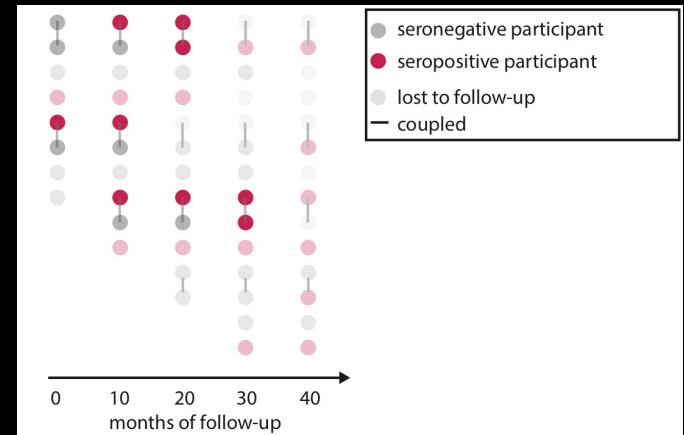
Conclusions

- Acute infectivity substantially overestimated
- Early transmission less likely to undermine Treatment as Prevention
- Importance of heterogeneity

process-centric



data-centric



Acknowledgements

- Lauren Ancel Meyers, Jonathan Dushoff, Juliet Pulliam, Carl Pearson, Alison Galvani, Manoj Gambhir, Ben Lopman, Travis Porco, Rieke van der Graaf, David Champredon, Spencer Fox, Laura Skrip
- Meyers Lab
- International Clinics on Infectious Disease Dynamics and Data (ICI3D)
- GA Tech Conference: Modeling the Spread & Control of Ebola in W Africa

