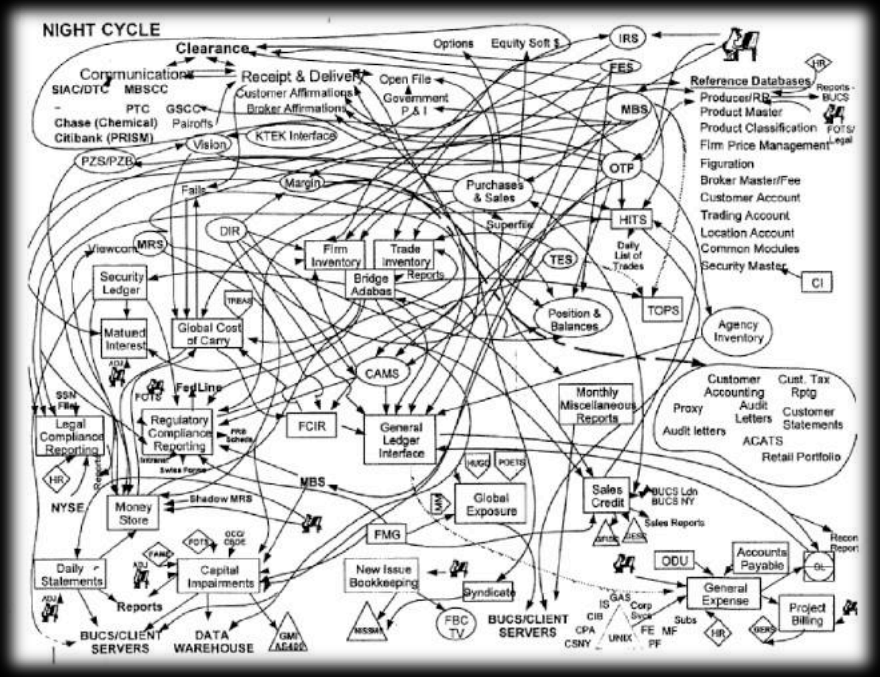
The Life Cycle of a Modeling Project: Estimating Acute HIV Infectivity



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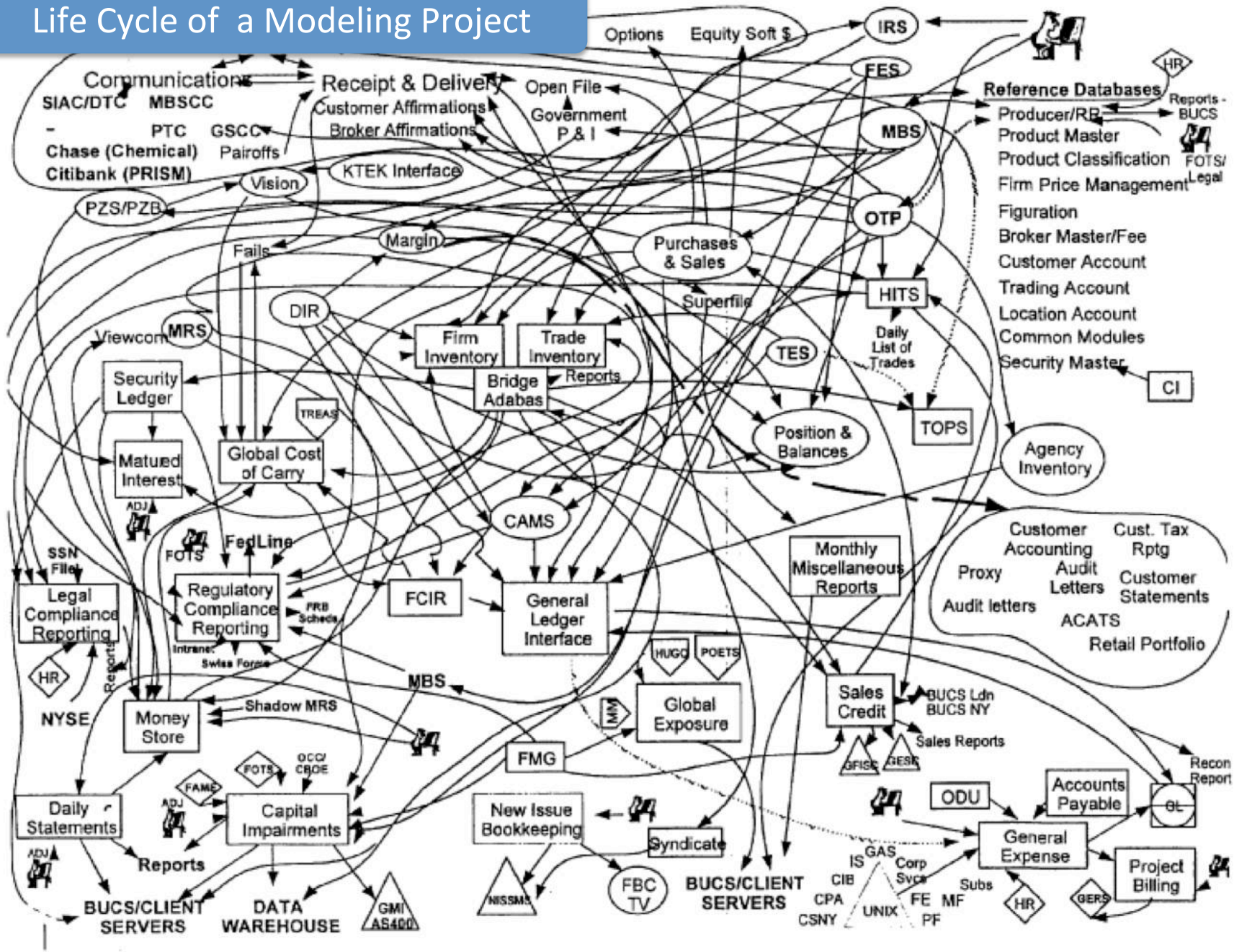
Dept. of Epidemiology & Biostatistics, College of Public Health
University of Georgia

DAIDD, White Oak Conservation
Wednesday December 7, 2016

Life Cycle of a Modeling Project



Units of Science

- Publications
- Policy Reports
- Dissertations
- Presentations
- Software

Why publish?

- Communication
- Career
- Peer Review

How do modeling projects differ?

- Not always necessary collect empirical data
- Rely more heavily on literature reviews

Development of Study Concept

- What is your question?
- Why is it interesting?
- Who is interested?
- Can it be narrowed down to a question about specific quantitative relationships?

Review of Literature & Available Data

- Who has tried to answer this before and how did they do it?
  - Empirical studies
  - Modeling studies (perhaps different pathogen)
- What are these studies short-comings?
- Find useful parameter estimates or data sets

Construction of Modeling Framework

- What drawbacks of previous studies can I mitigate (if applicable)

- What modeling elements are necessary for my question?
  - Stochasticity, time step size, compartmental structure, complexity of contact modeling

Writing the Model & Producing Output

- What are the 1-3 graphical outputs that will display the answer(s) to my question?
- Coding & debugging & commenting
- Version Control (Git)
- Simulation to verify methods & debug
- Write your methods at this stage!

Model Validation & Robustness

- Sensitivity analyses
- Model validation

  Out-of-sample prediction

  Outputs match patterns that weren't inputs

- Comparison to alternative models

Choose the Journal

- Where are the majority of your citations?
- Journal scope statement (on their website)
- Other articles in that journal
- Audience
- How mathematical will your article be?
- Text, figure, table limits

Write-Up of Results, Intro/Discussion

- State assumptions clearly

- Critique your own work
  as if you were a reviewer

Conclusion: HIV-1 acute infectivity has been substantially overestimated

PLOS | MEDICINE

RESEARCH ARTICLE

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

Steve E. Bellan[1*], Jonathan Dushoff[2], Alison P. Galvani[3,4], Lauren Ancel Meyers[5,6]

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

Lauren Meyers
UT Austin

Jonathan Dushoff
McMaster University

Alison Galvani
Yale University

Outline

1. Relevance: Treatment as Prevention (TasP)
2. Measuring excess infectivity with EHM_{acute}
3. Literature review of past estimates
4. Re-estimation of EHM_{acute} from viral load
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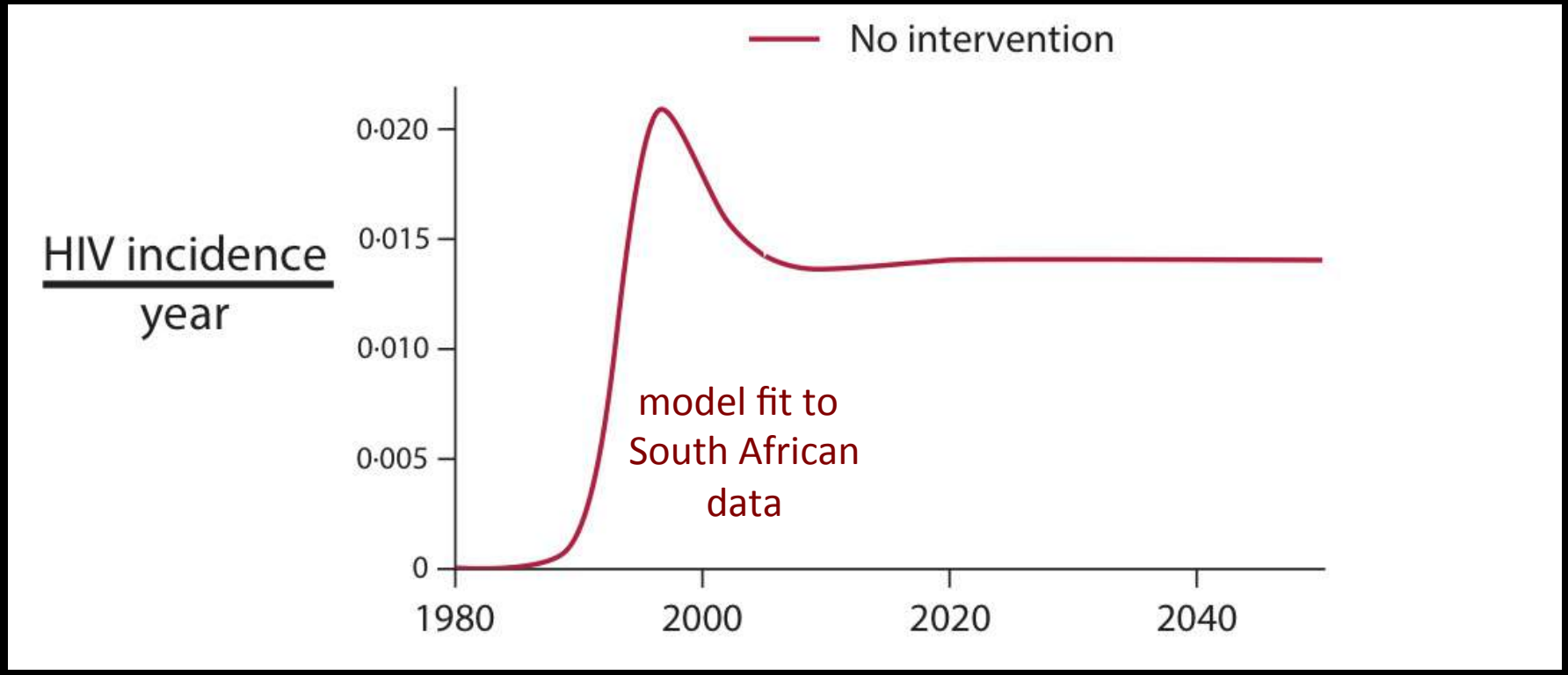
Treatment as Prevention (TasP)

Treated HIV-infected individuals
transmit 96% less than
untreated HIV-infected individuals

Cohen et al. (2011). *NEJM*.

Treatment as Prevention (TasP)



adapted from Granich et al. (2009). *Lancet*.

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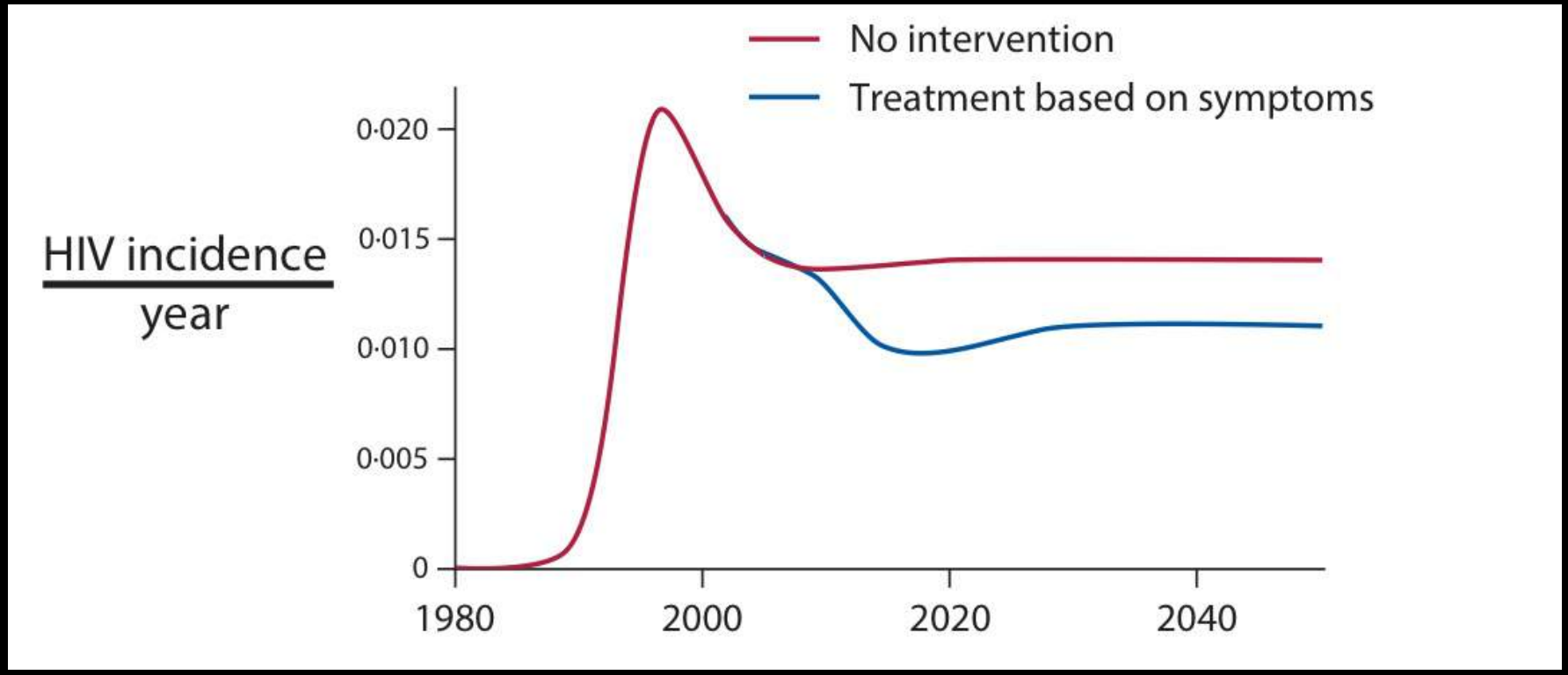

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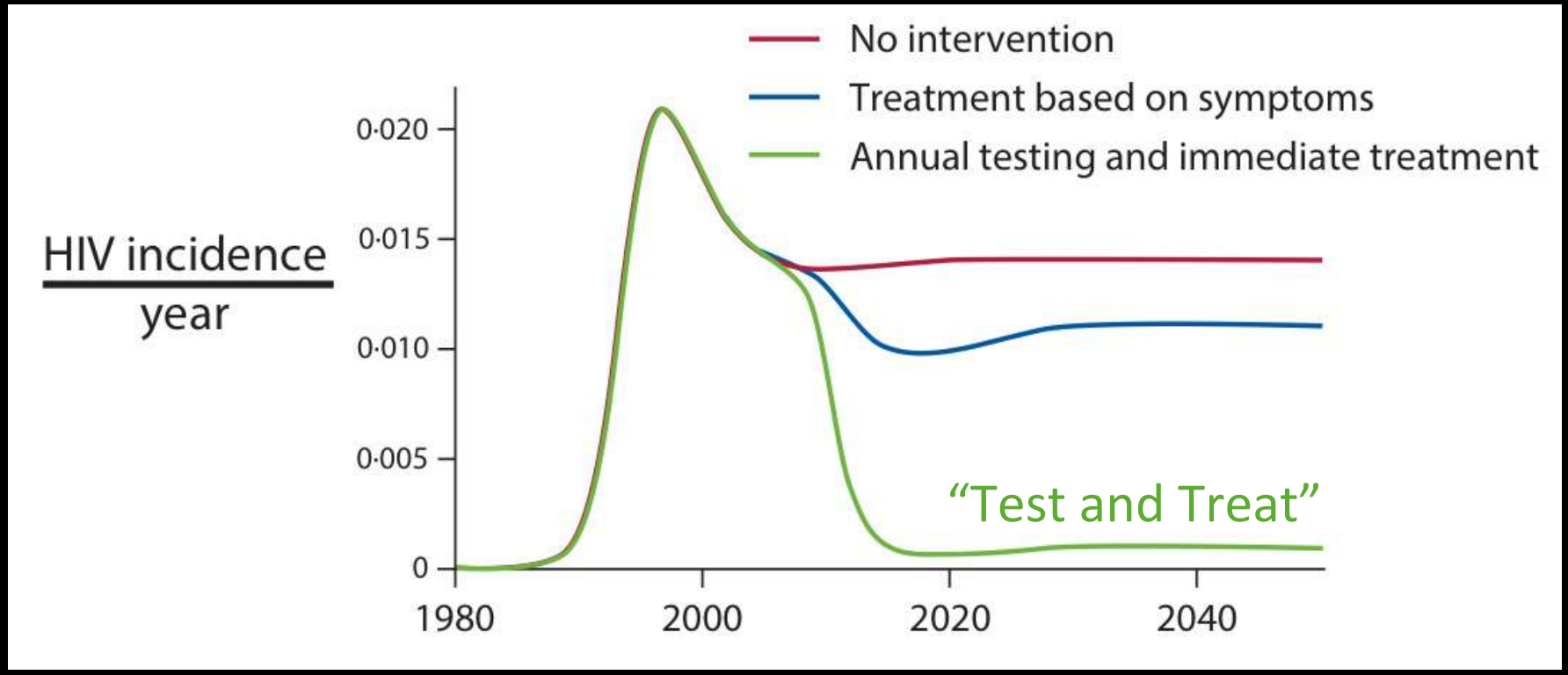
Universal Testing and Treatment



adapted from Granich et al. (2009). *Lancet*.

cluster randomized controlled trials underway

Will "Test and Treat" work?

- Logistics
- Uptake and adherence
- Drug Resistance
- Early Transmission

OPEN ACCESS Freely available online PLoS MEDICINE

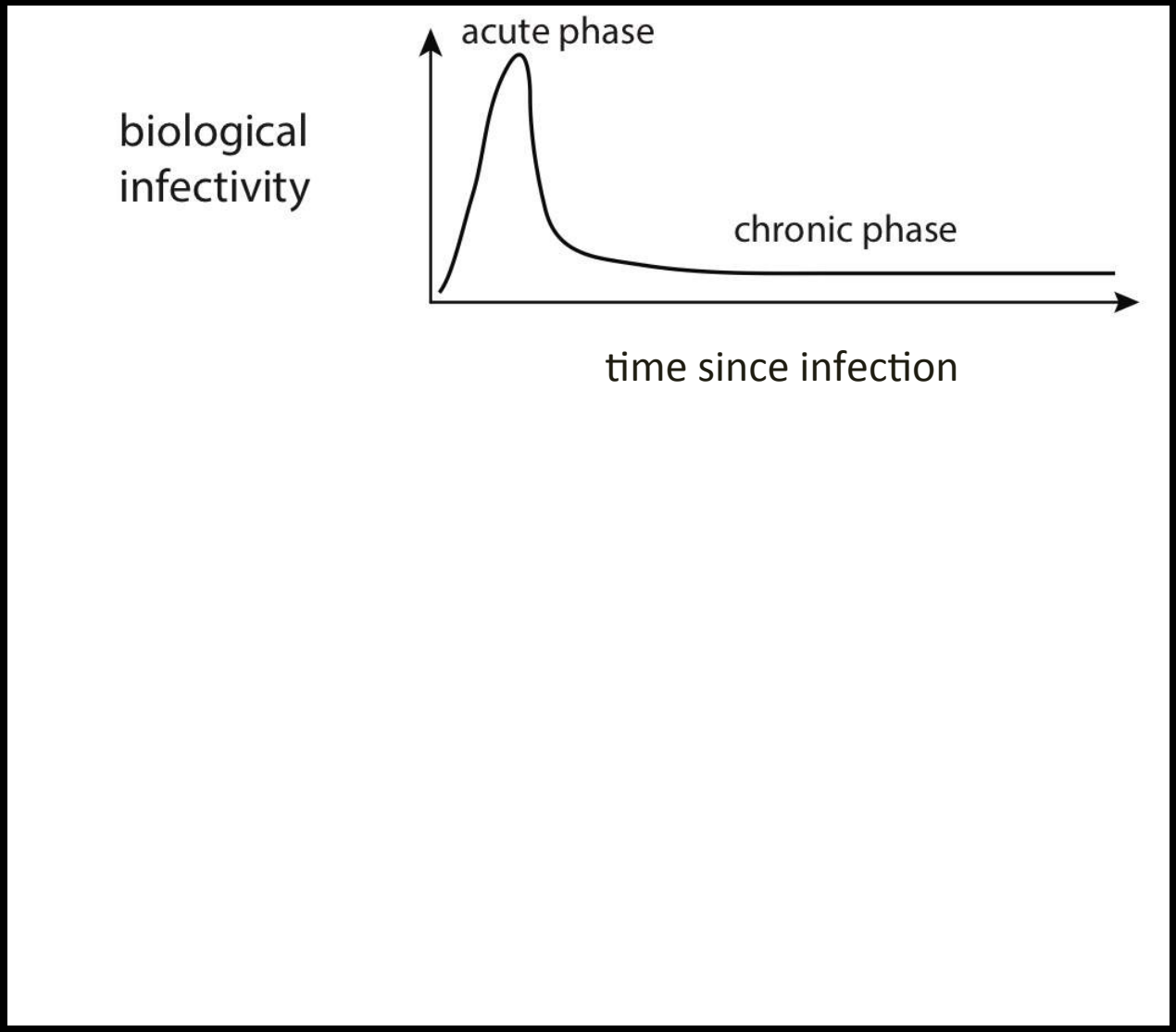
Review

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¶*]

How much transmission happens before diagnosis and treatment?

What proportion of transmission occurs early?



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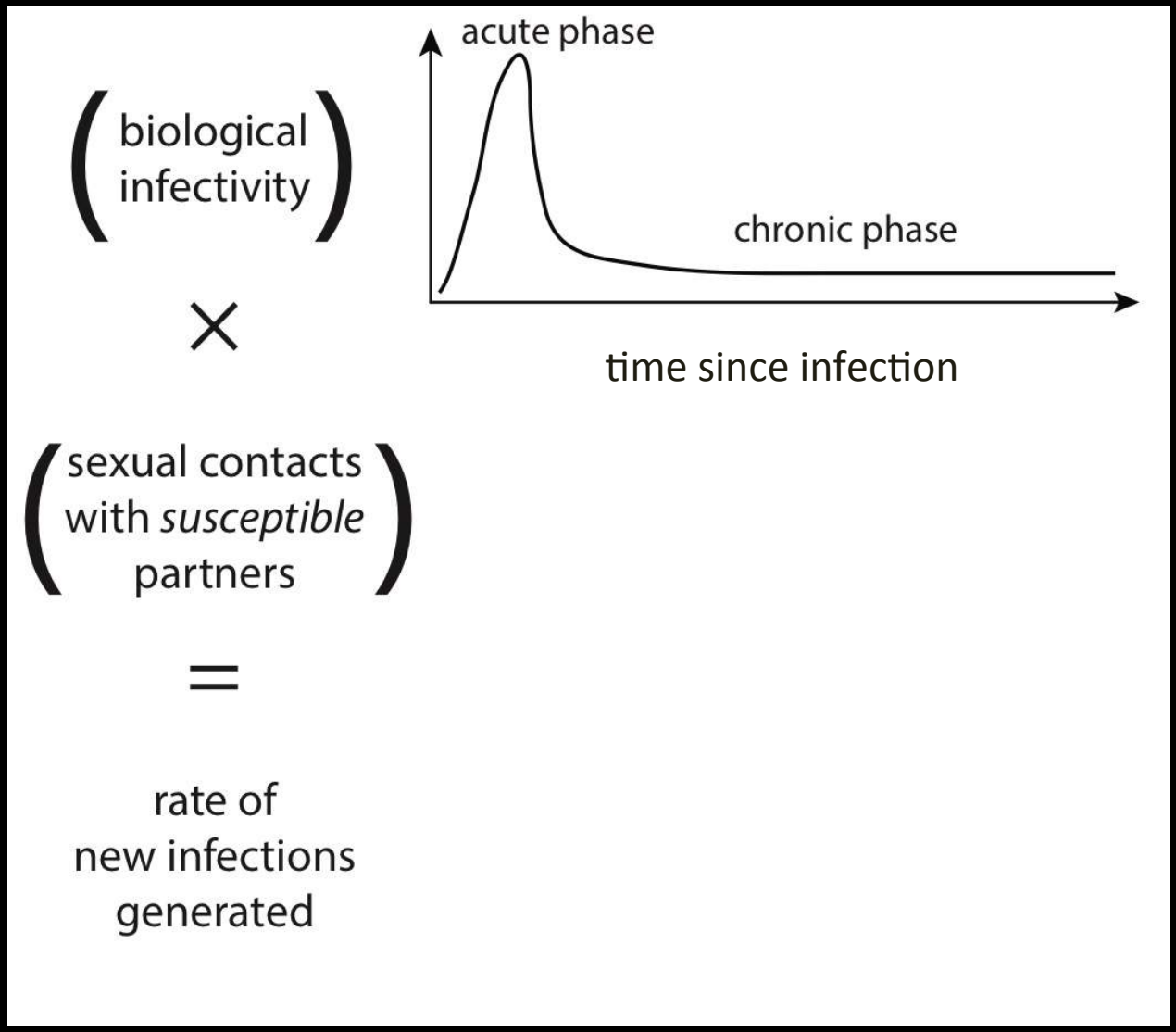

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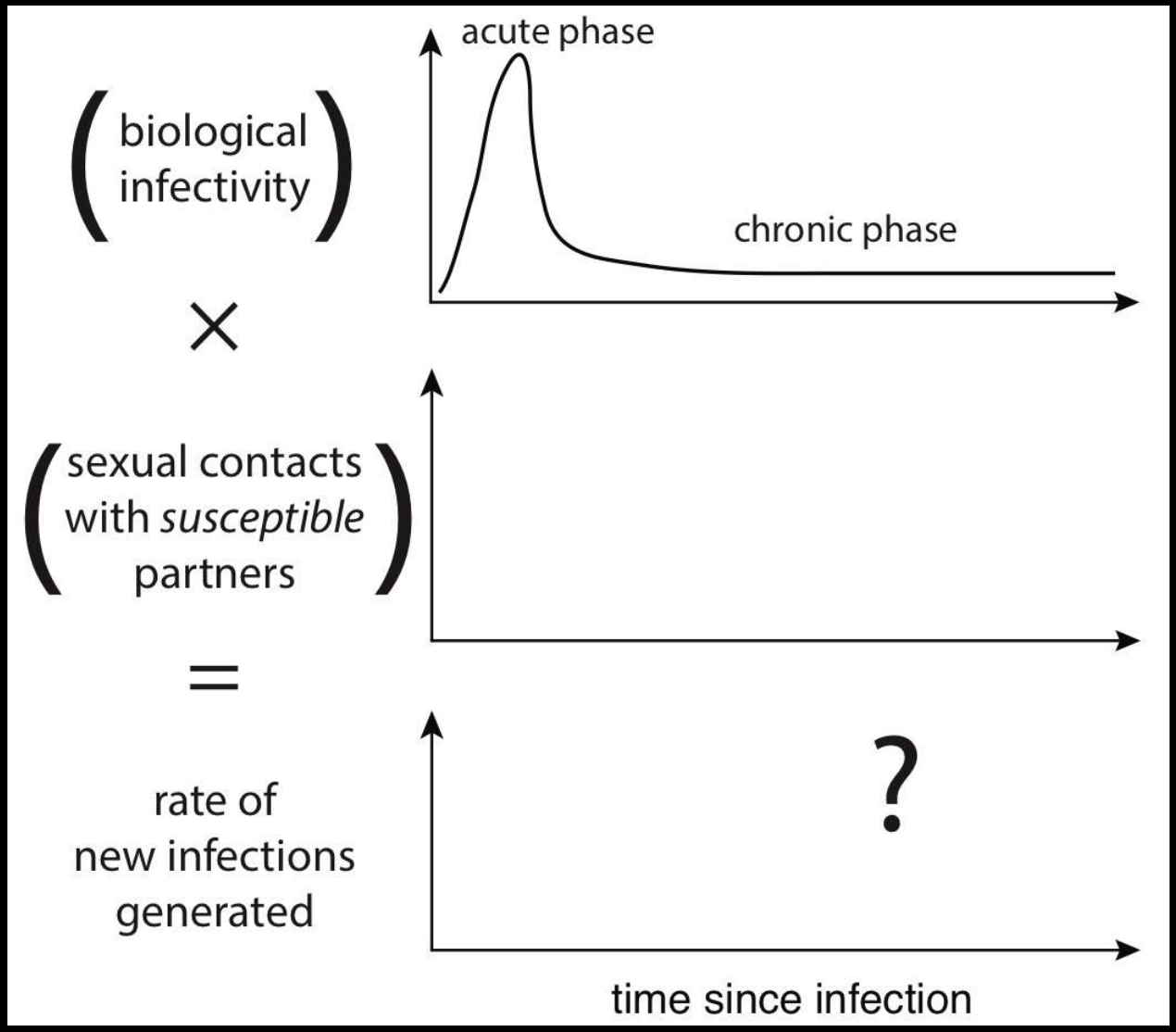

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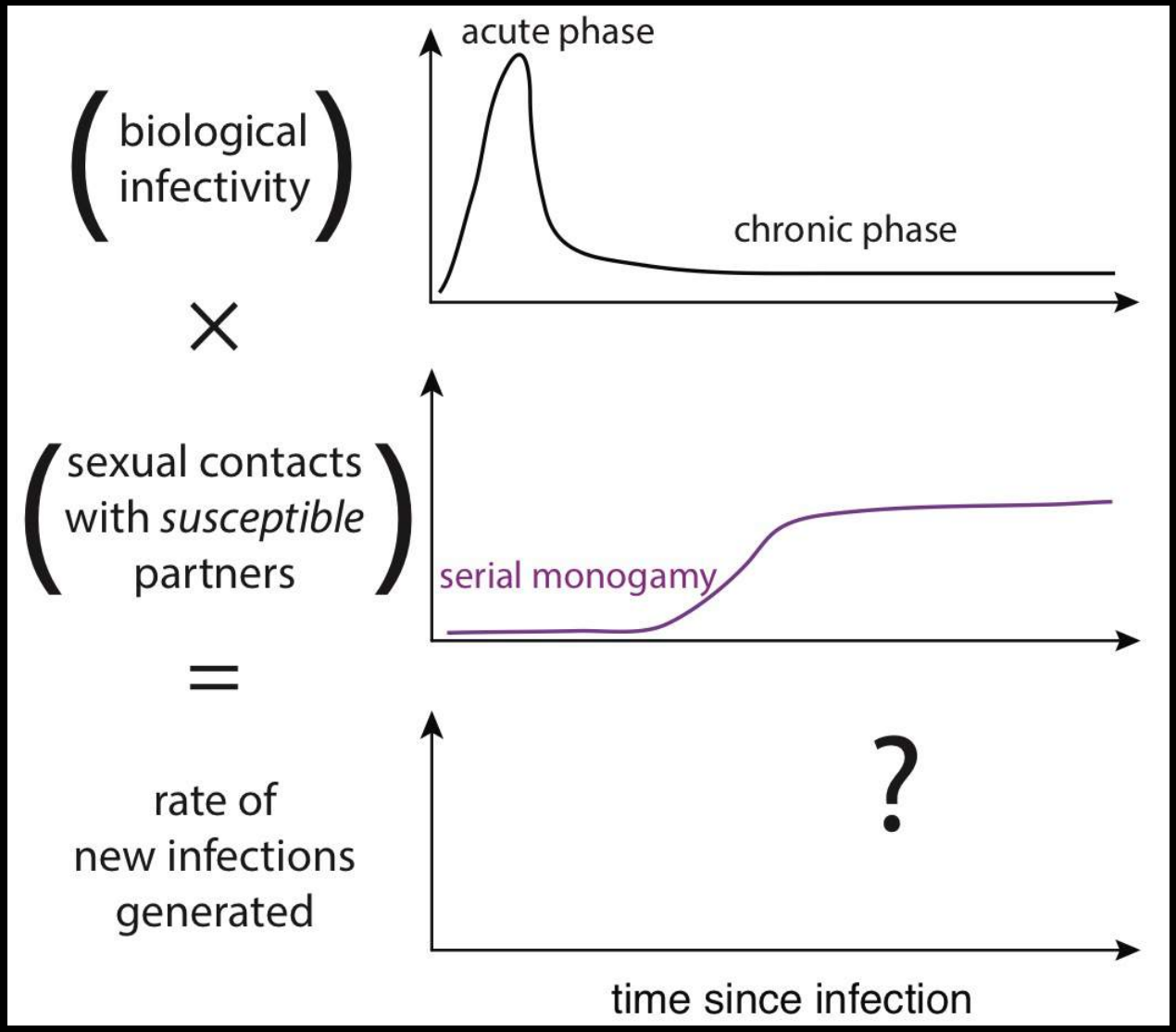

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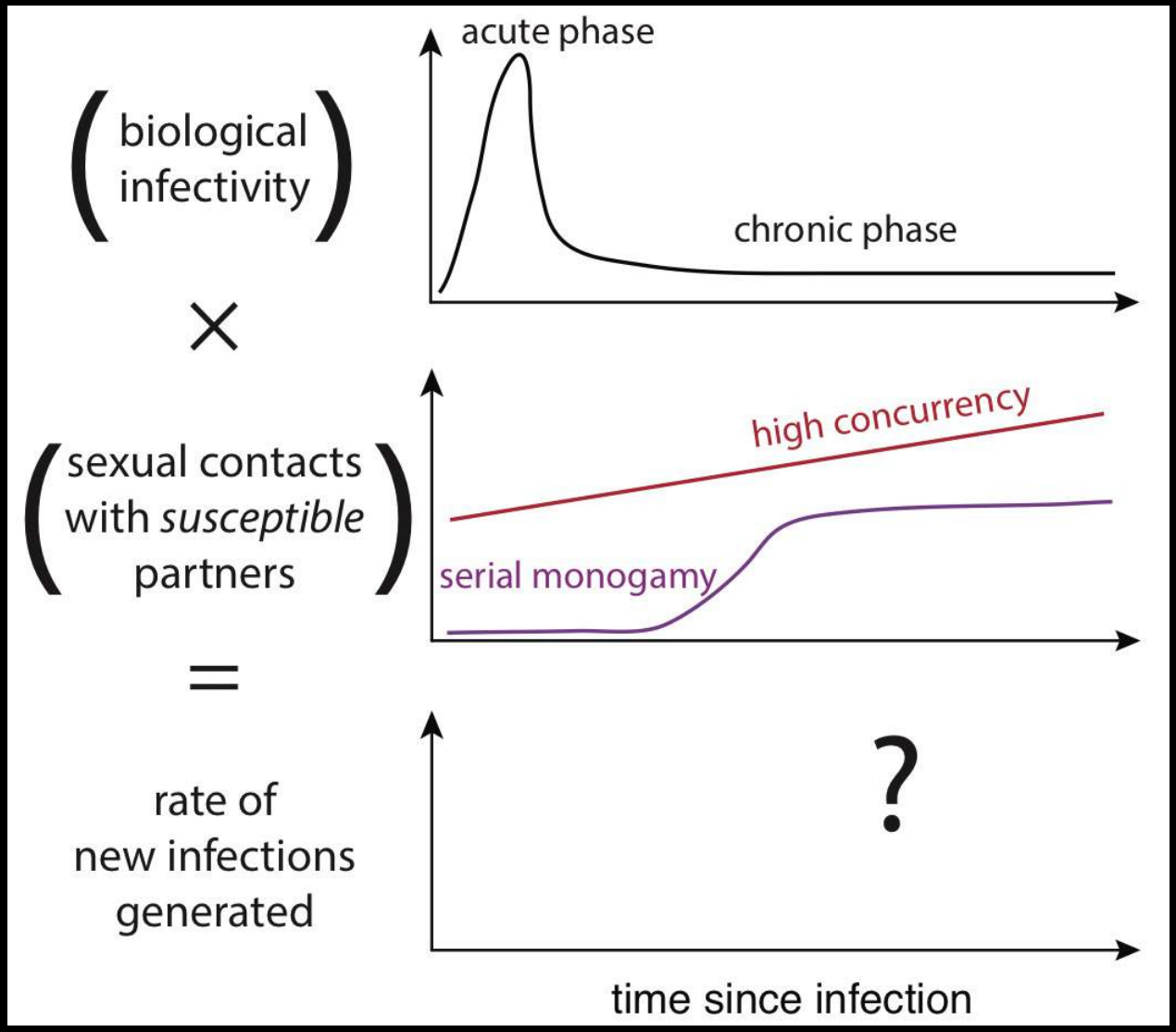

Eaton et al. 2011. *AIDS & Behavior*.

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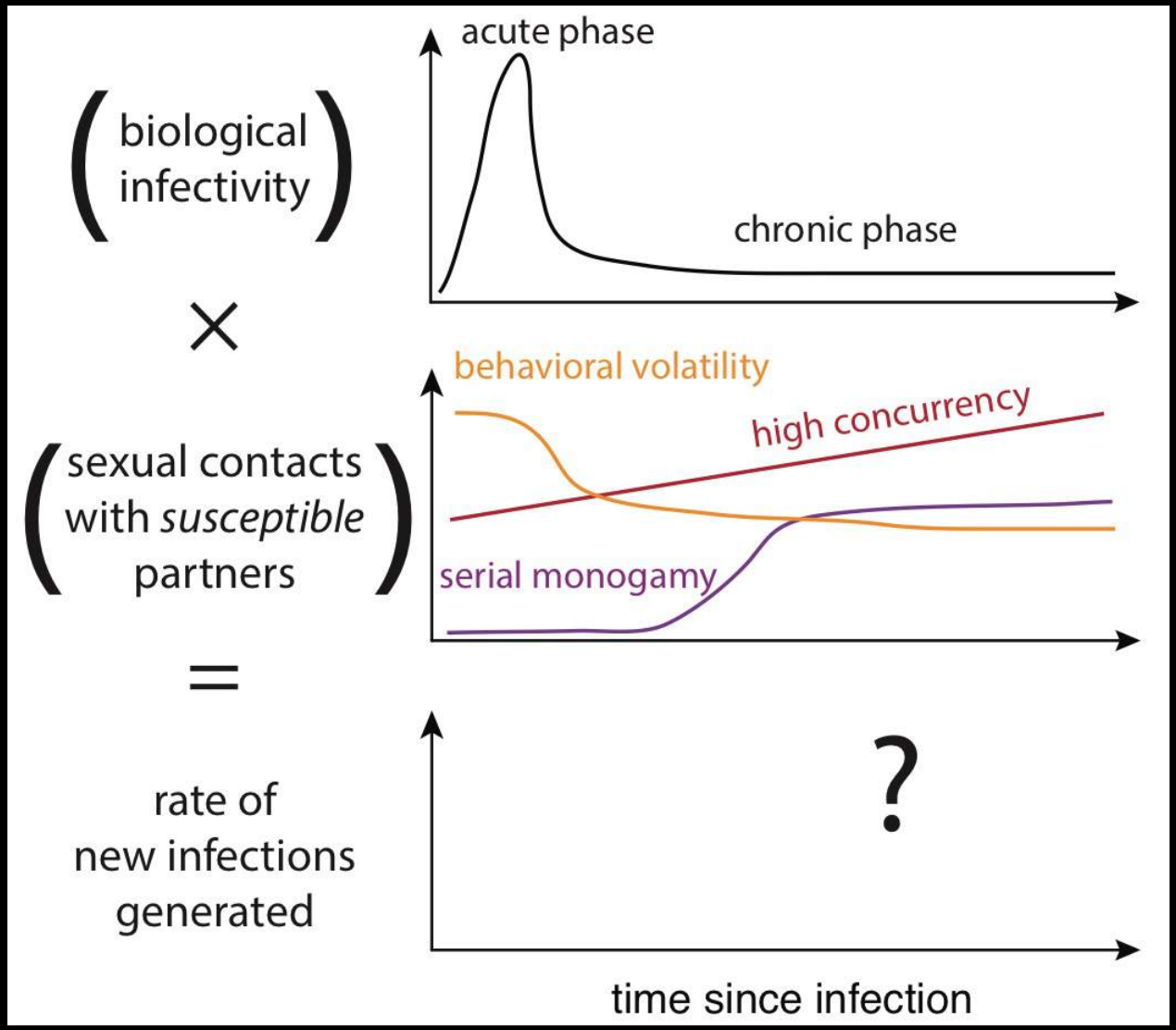

Eaton et al. 2011. *AIDS & Behavior*.

Alam et al. 2013. *Epidemics*.

Romero-Severson et al. 2013. *Epidemiolgy*.

Henry & Koopman. 2015. *Sci Reports*.

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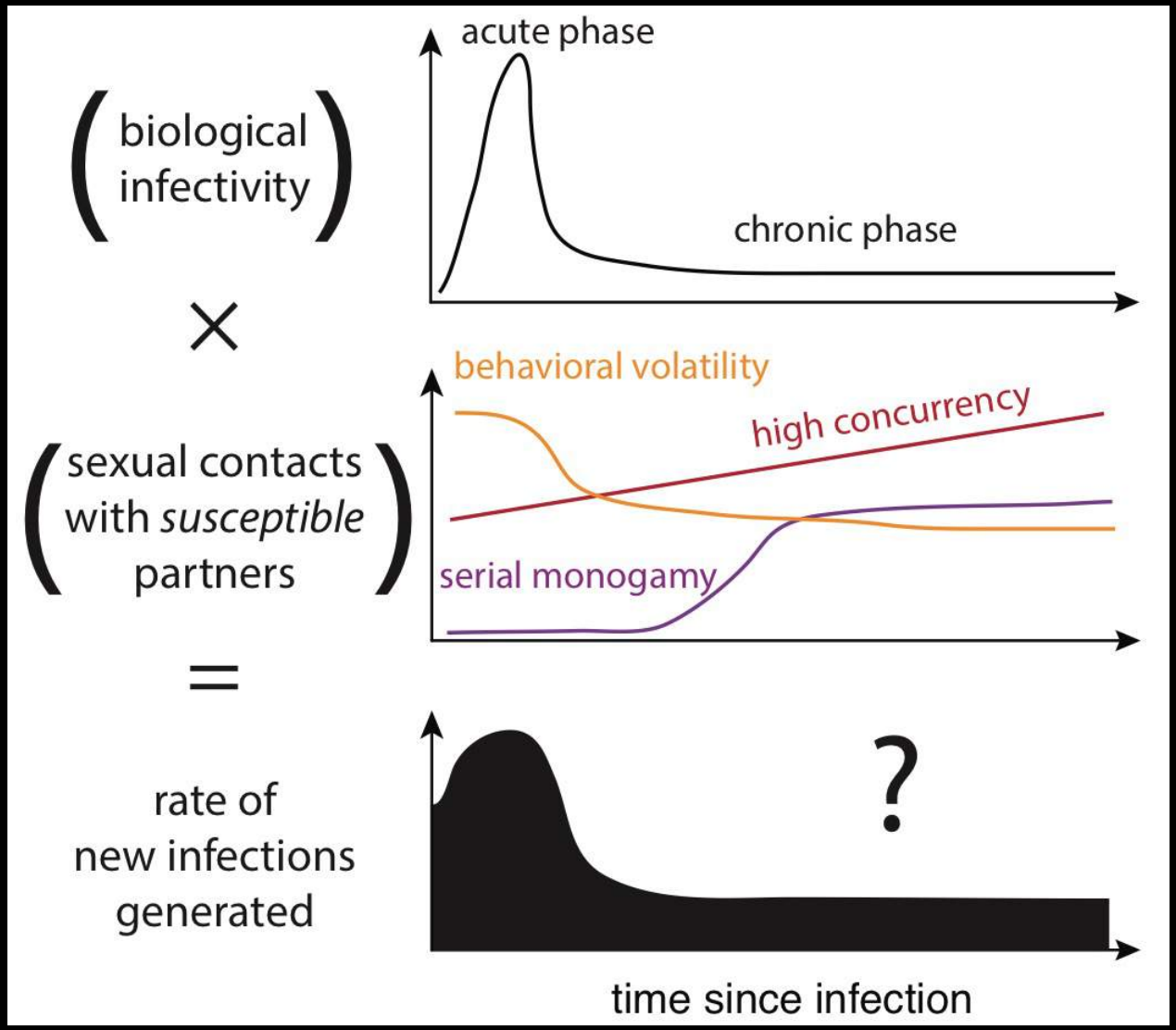

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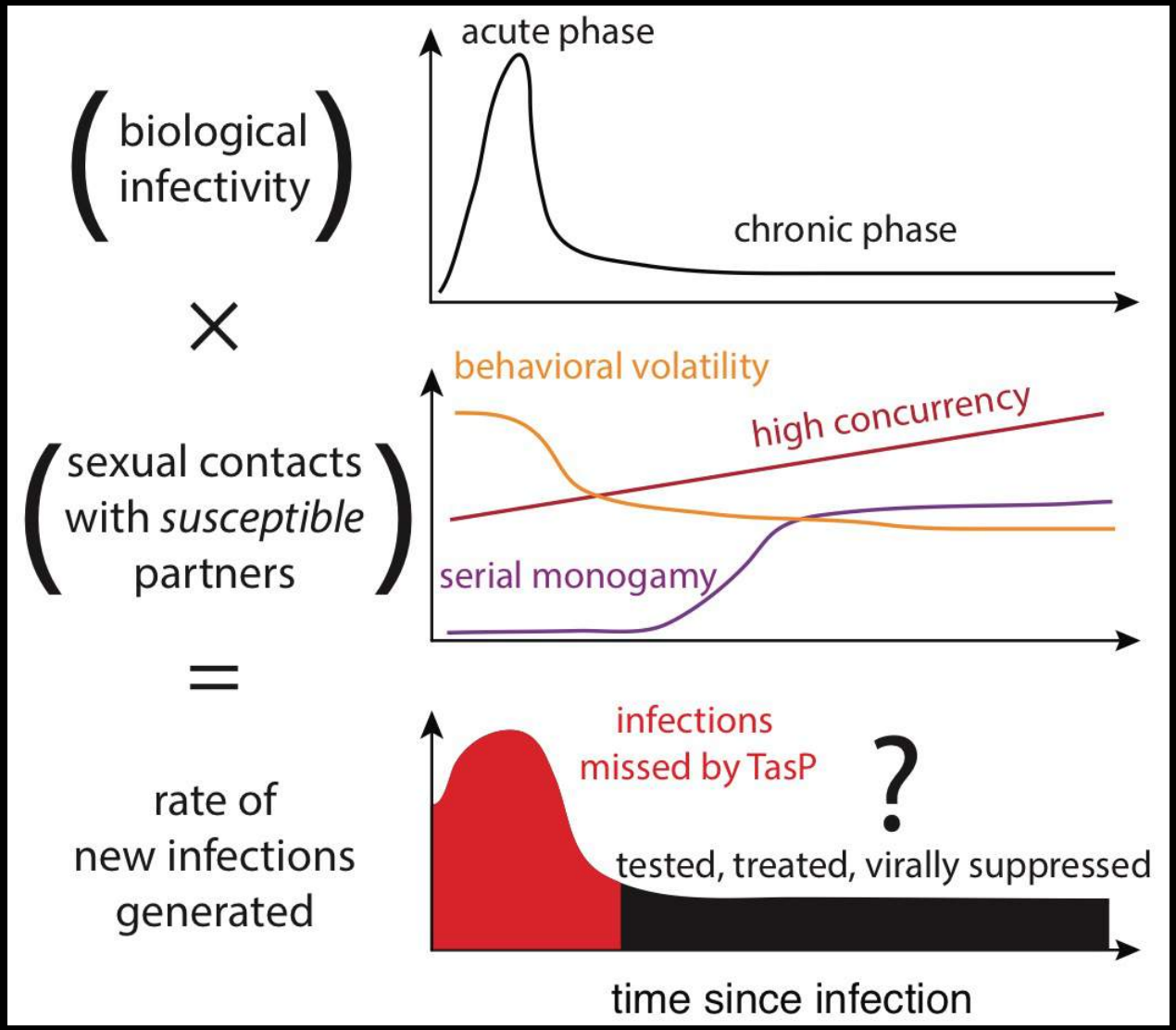

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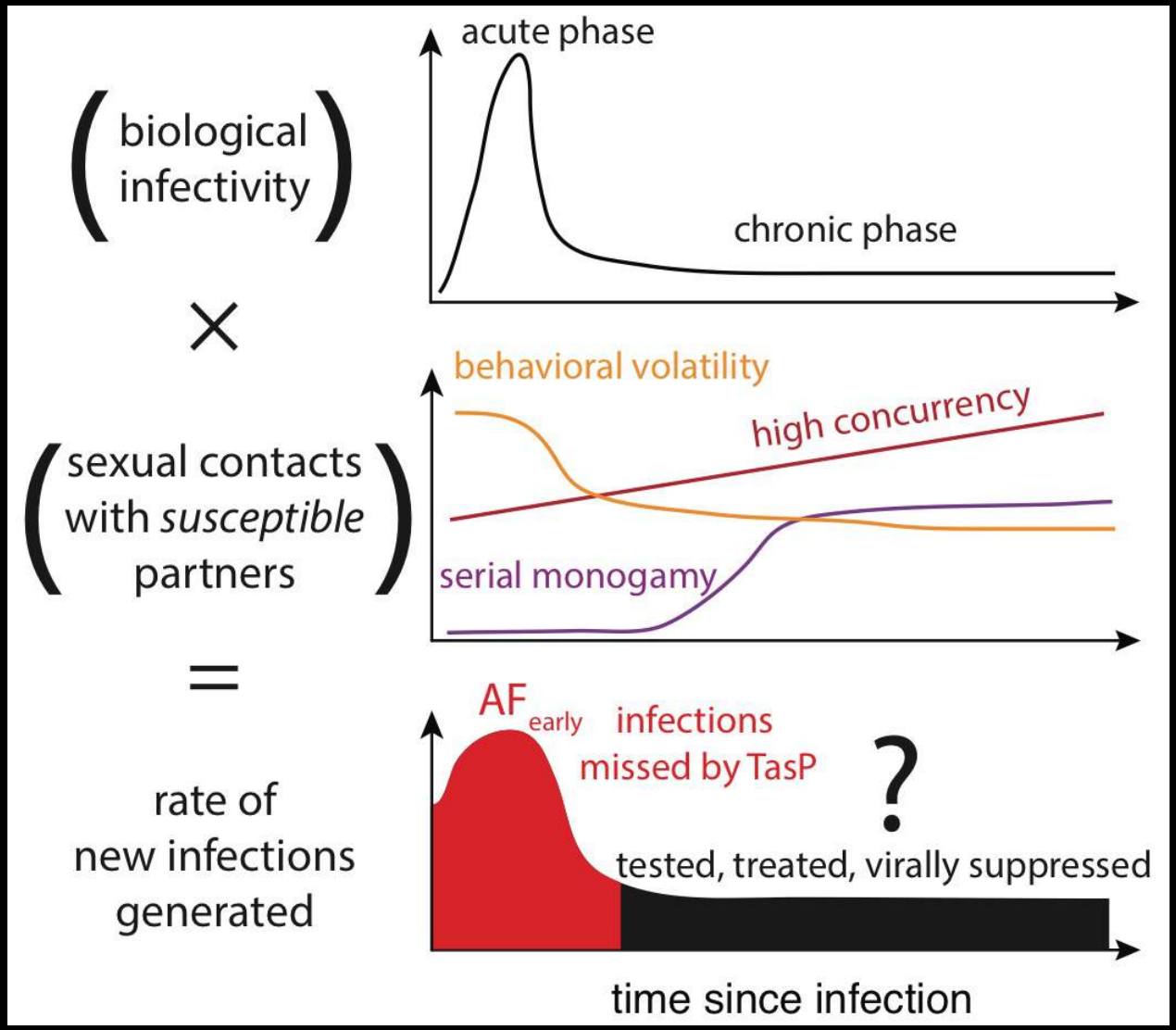
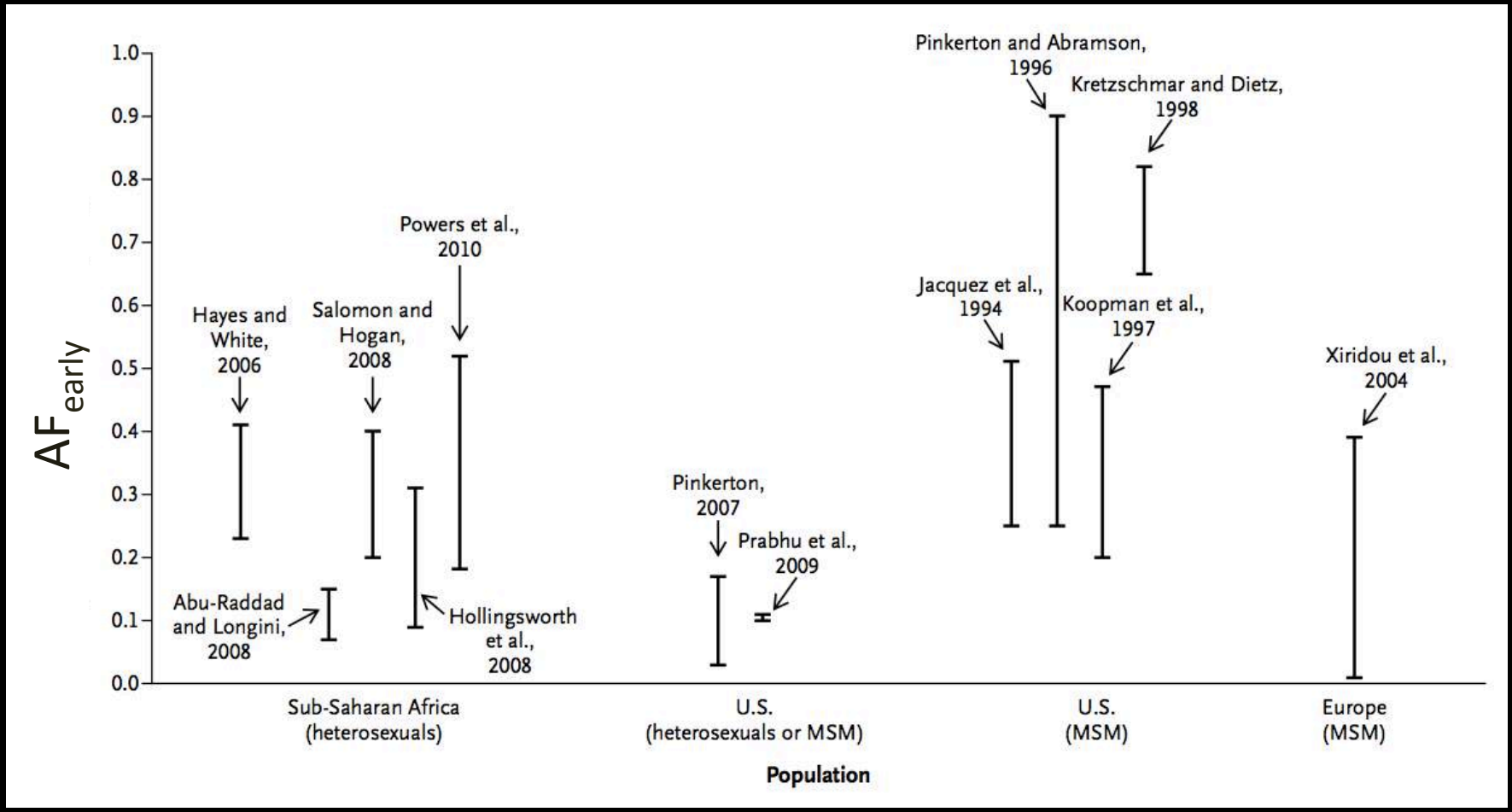


Estimates of AF_{early}: proportion of transmission < 1 yr post-infection



Cohen et al. (2011). *NEJM*.

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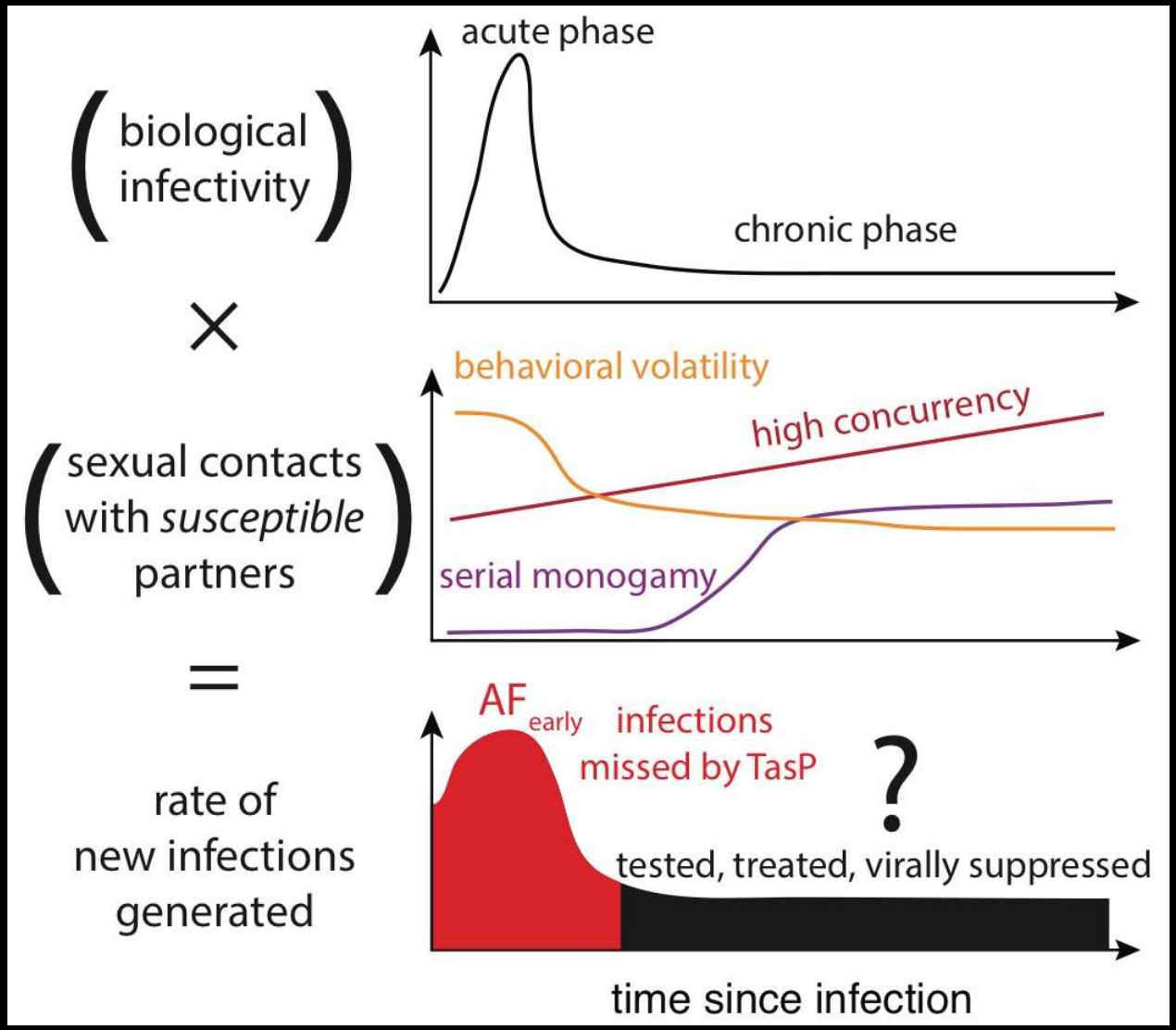

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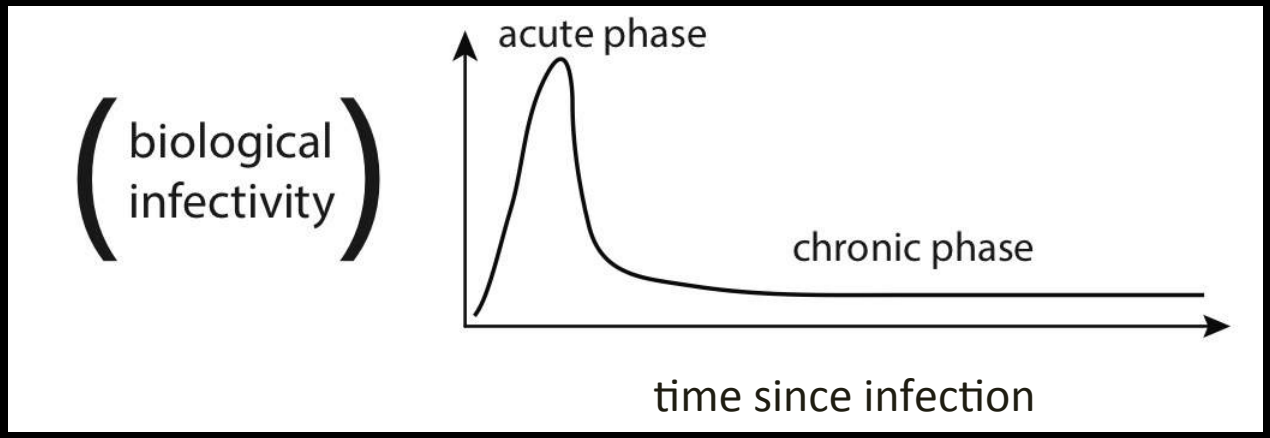

Here, we focus only on biological infectivity.

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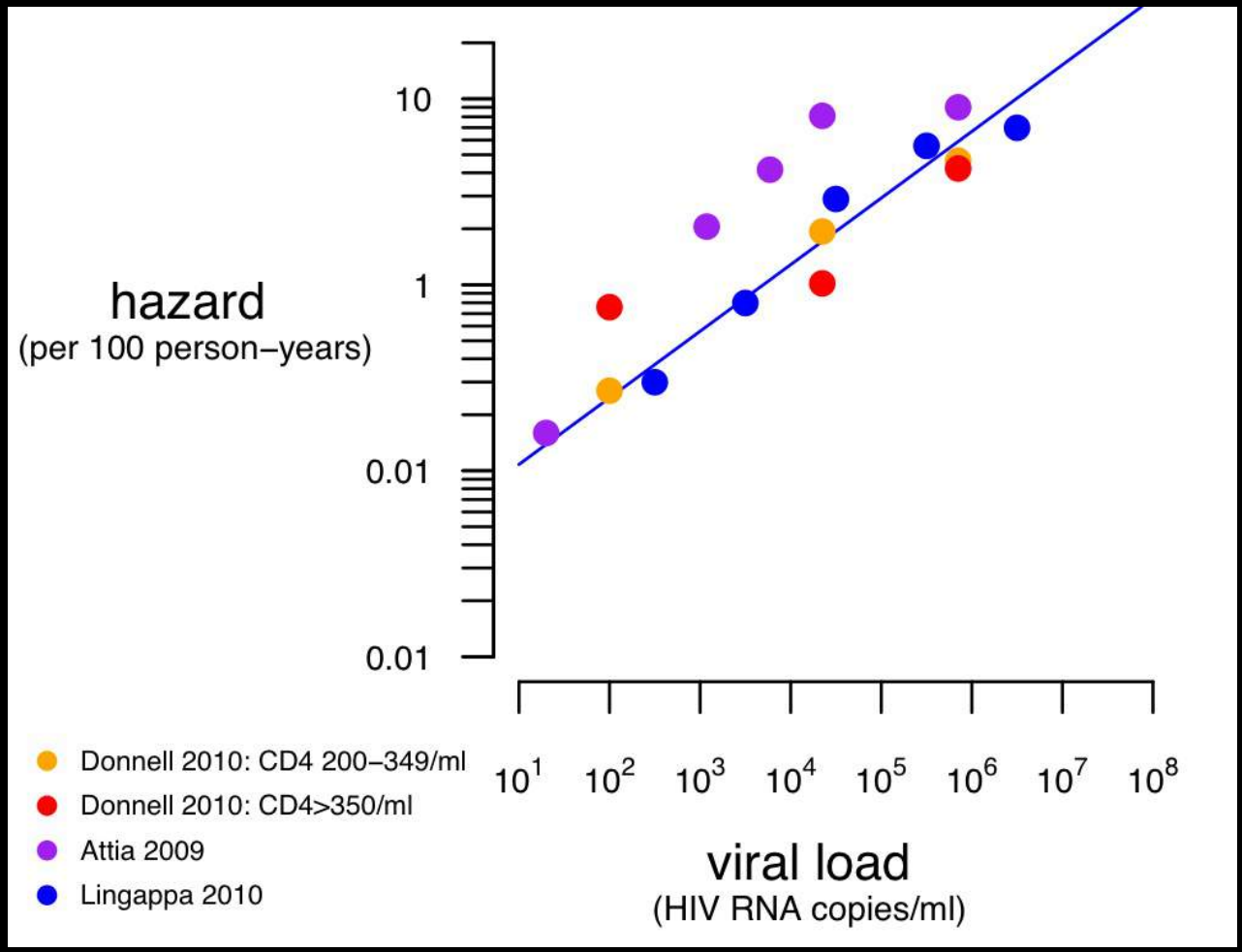
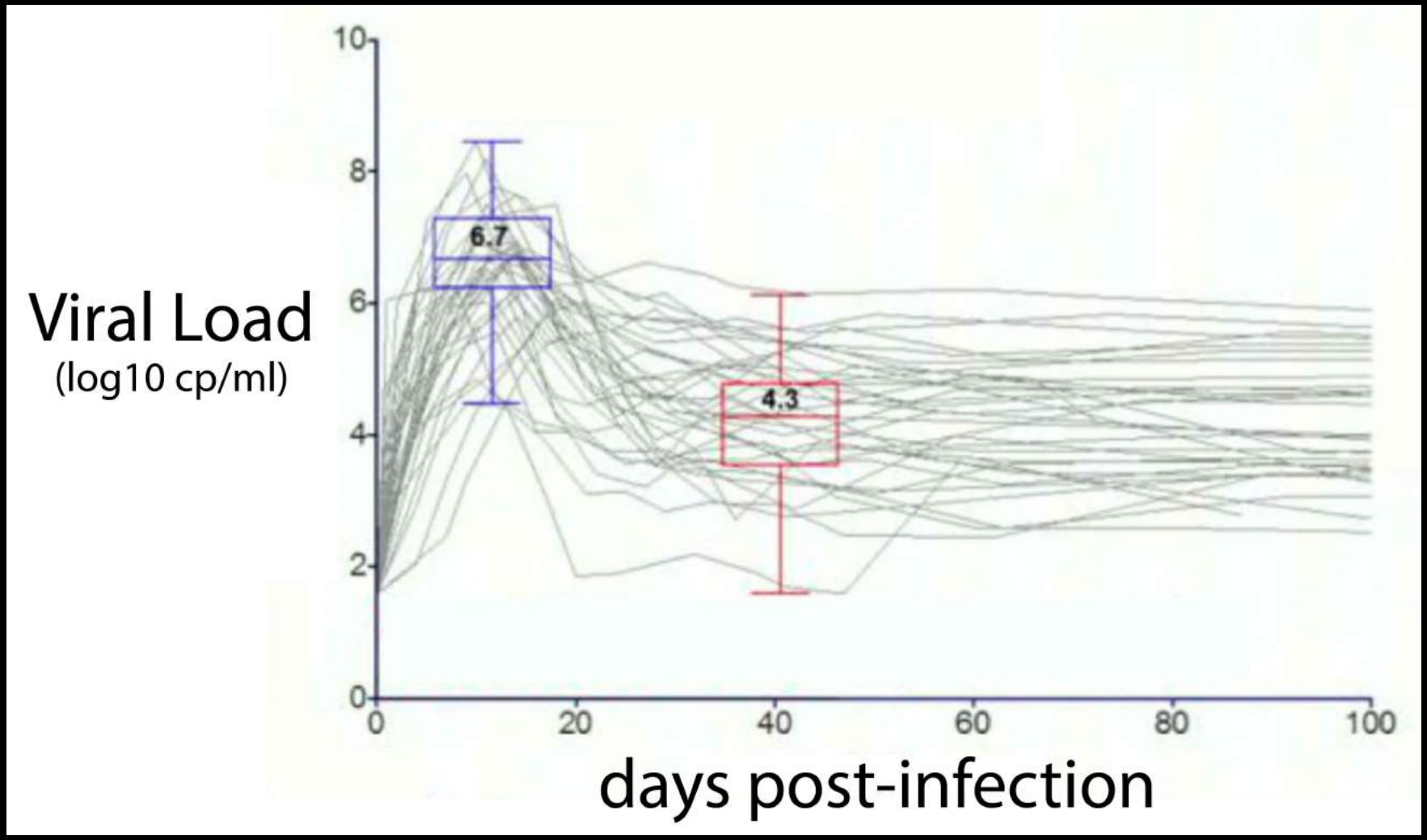
What affects biological infectivity?

2.5X infectivity / log10 viral load



Let's take the average viral load trajectory



Robb (2012). *AIDS Vaccine 2012*. PL02.02.

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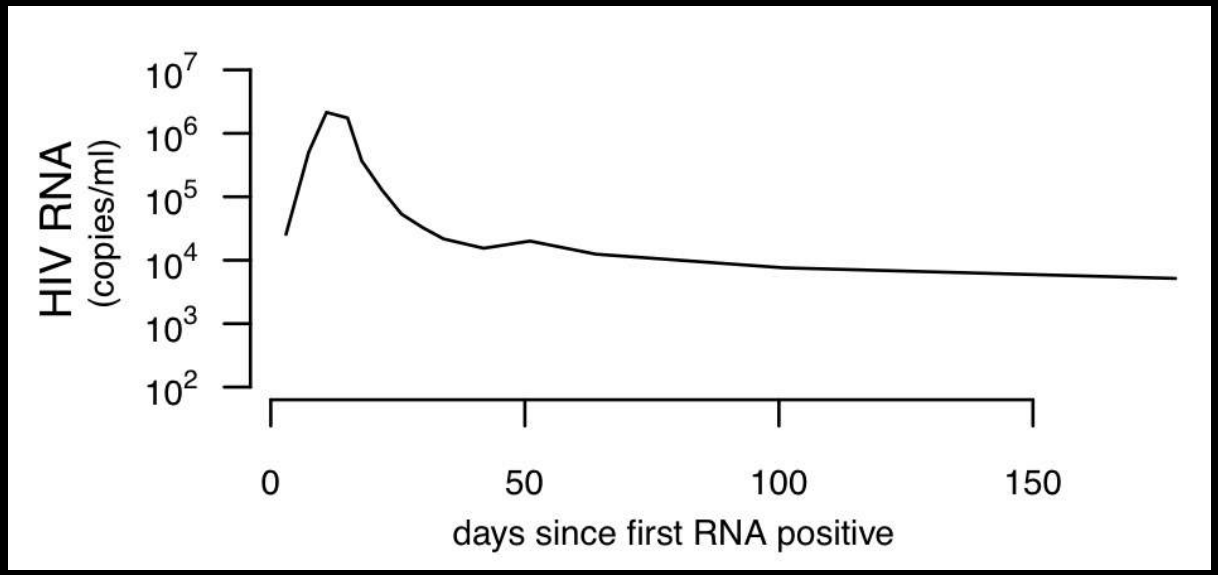
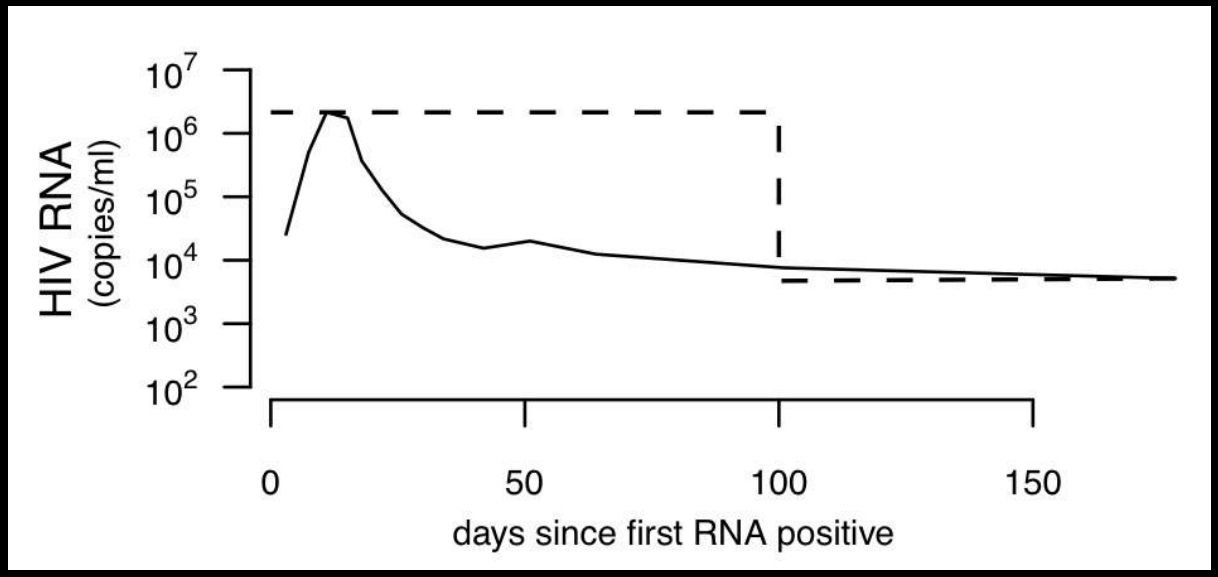


Determining a biological infectivity profile



All previous studies assumed discrete phases…

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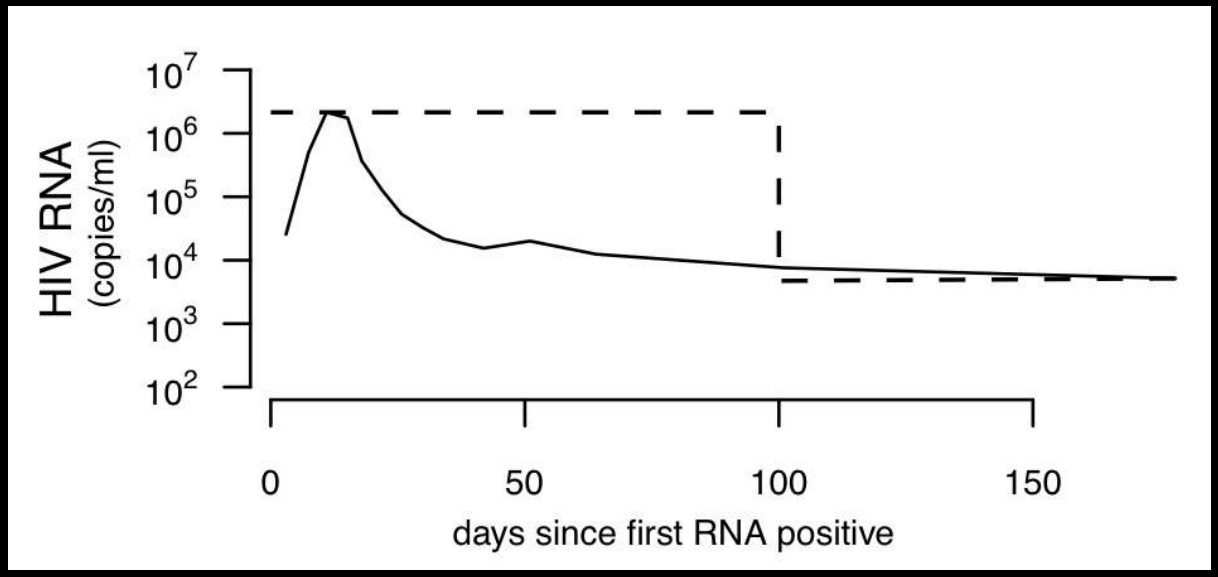

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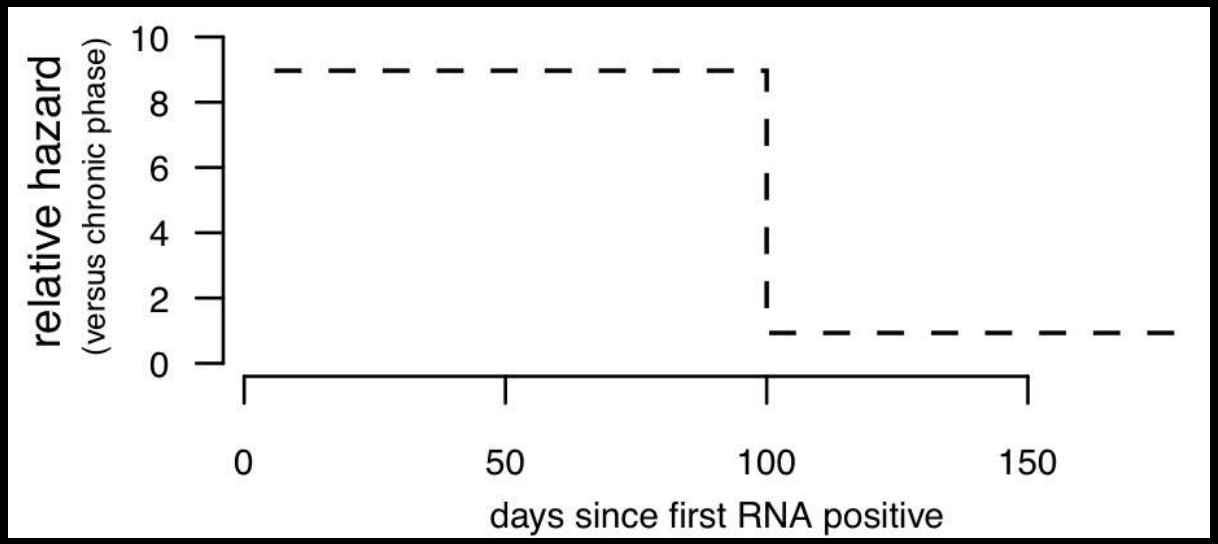

2.5X infectivity
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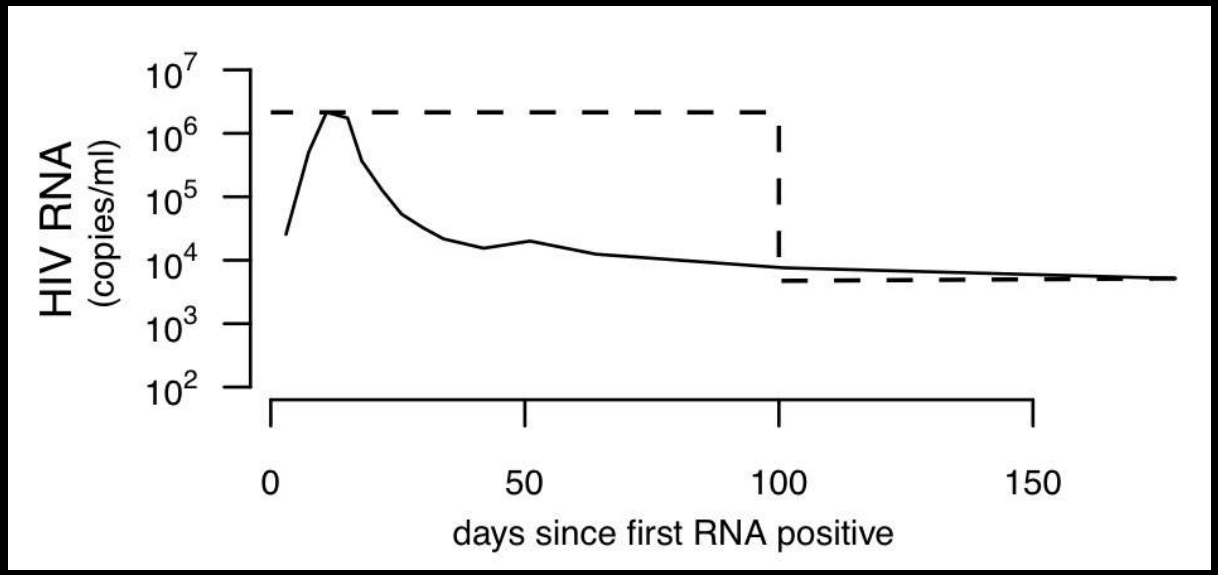

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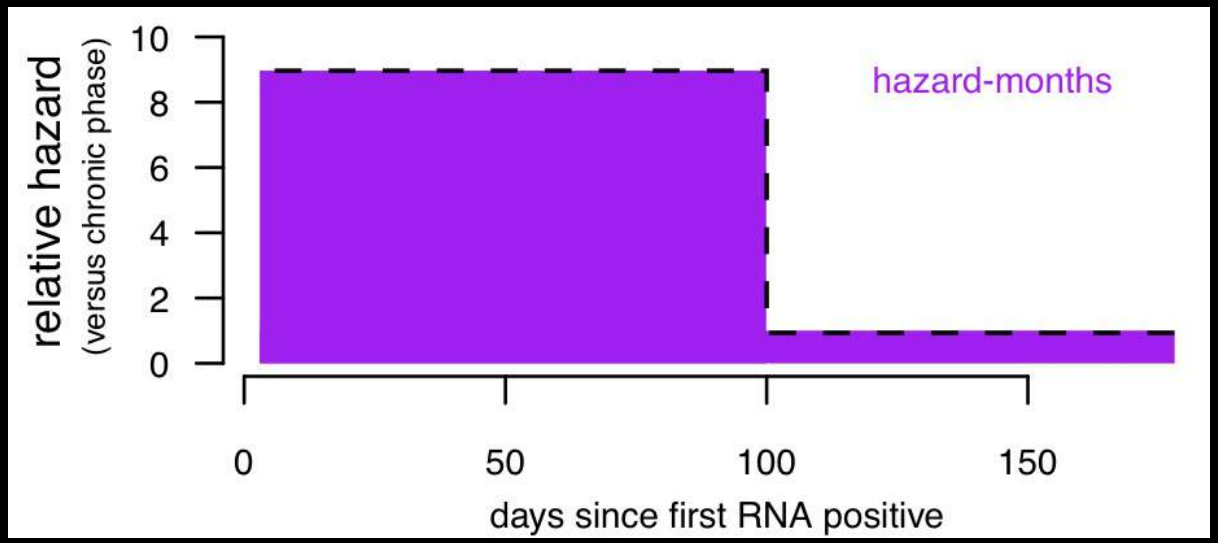

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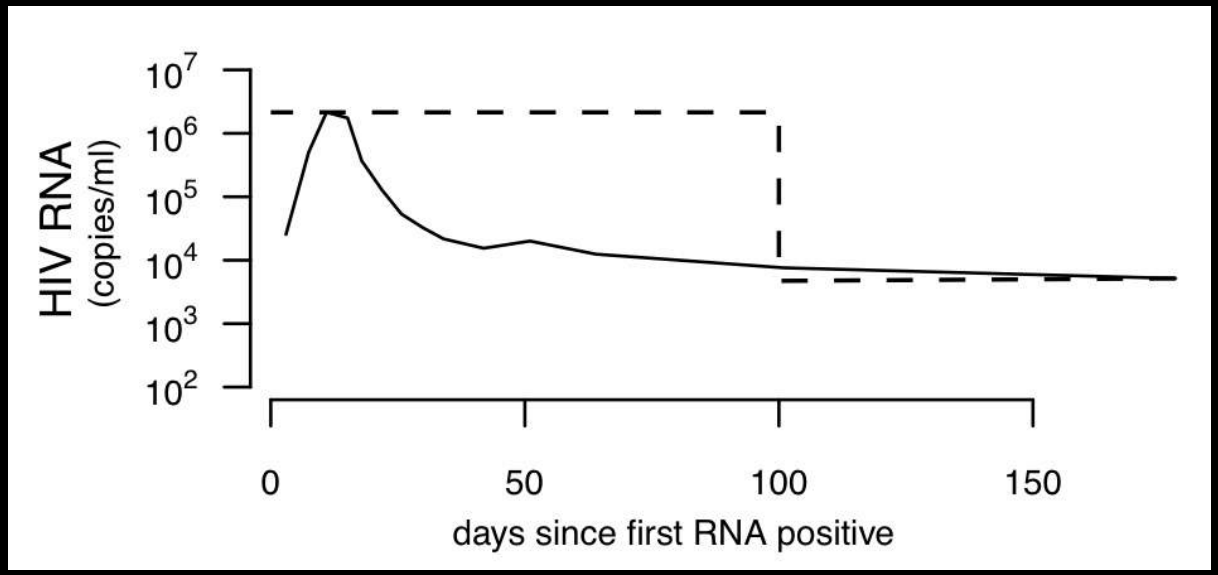

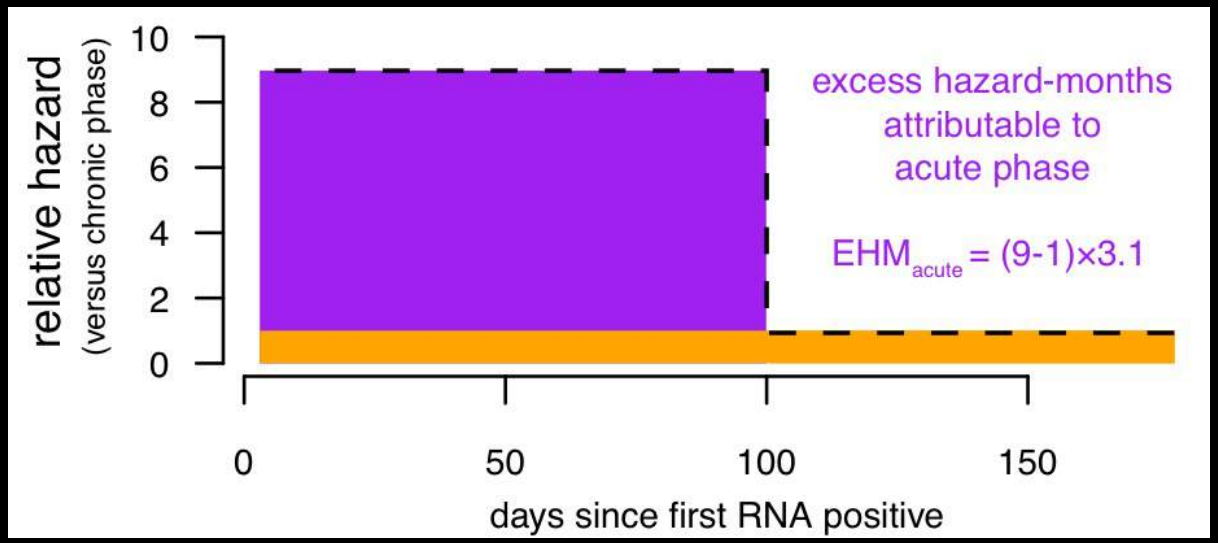

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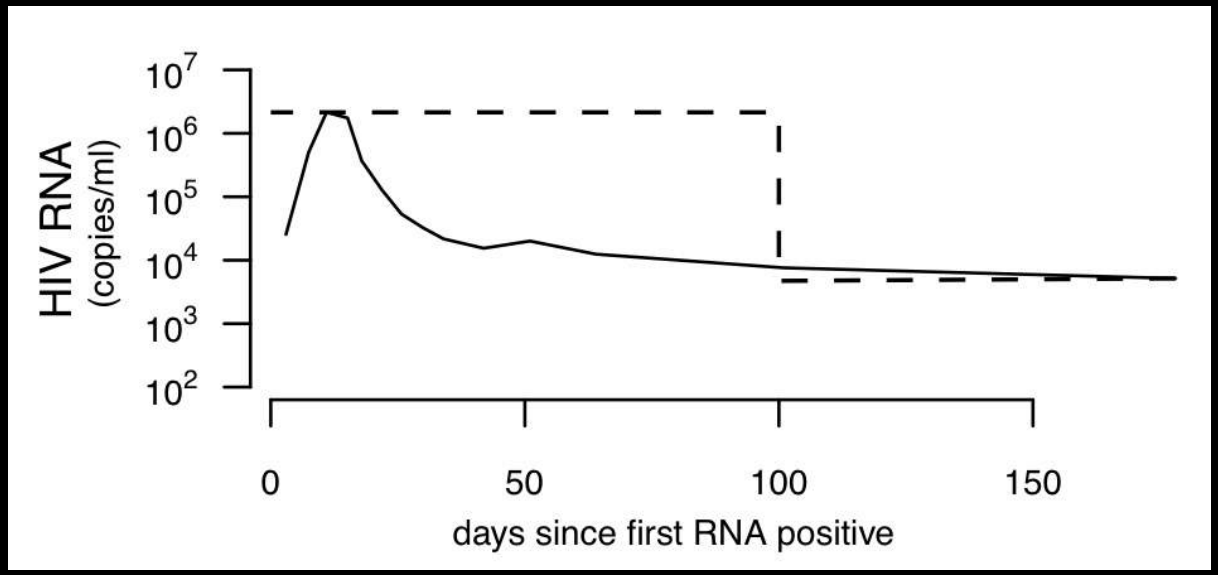
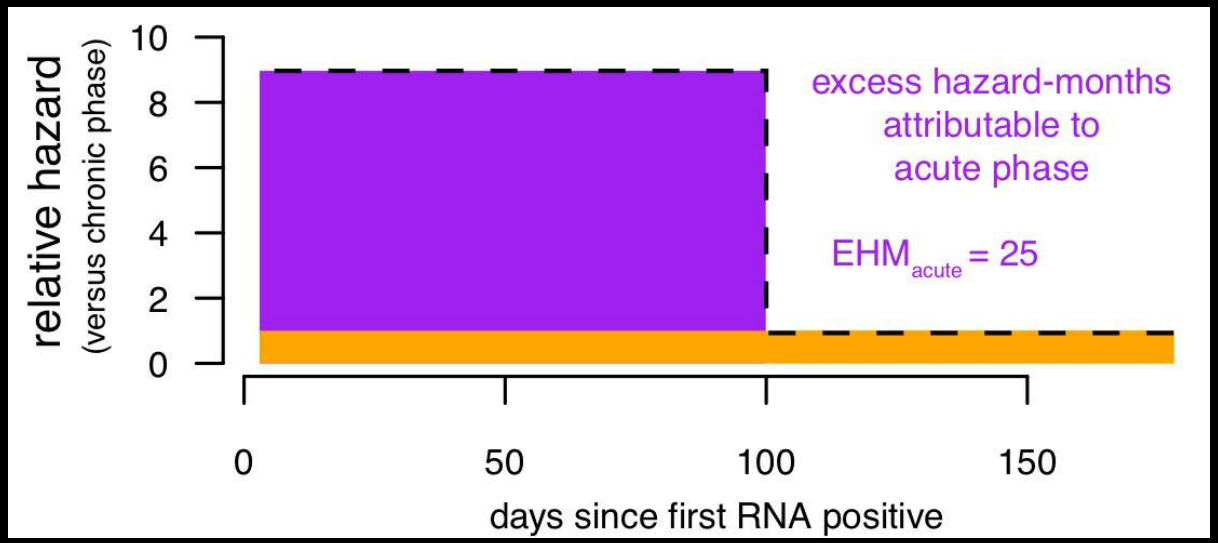
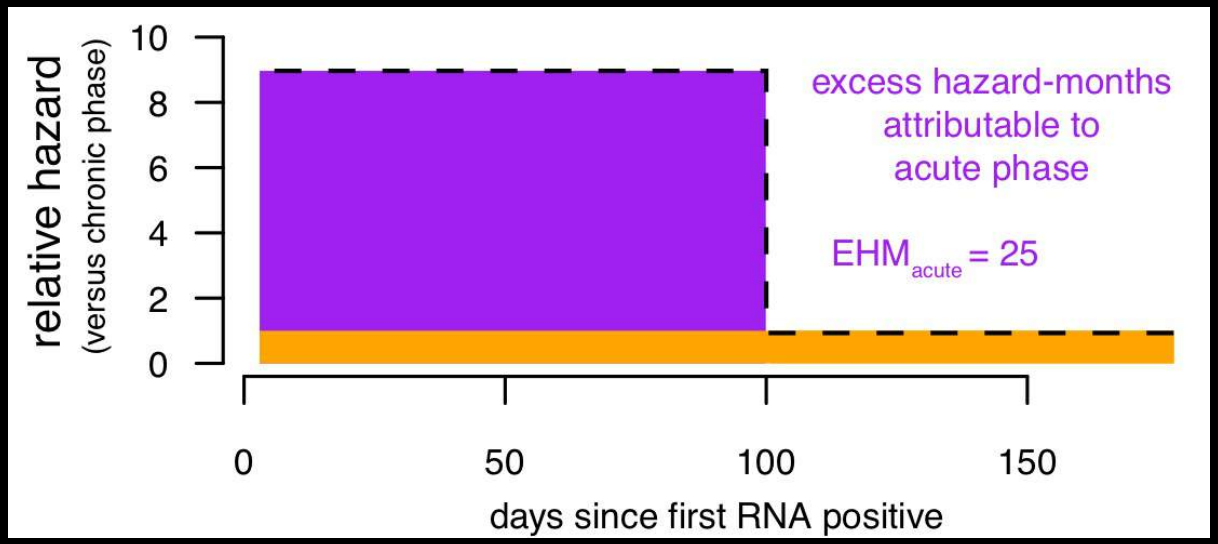




EHM_{acute}

25 compare to 120 hazard-months during 10 years of infection



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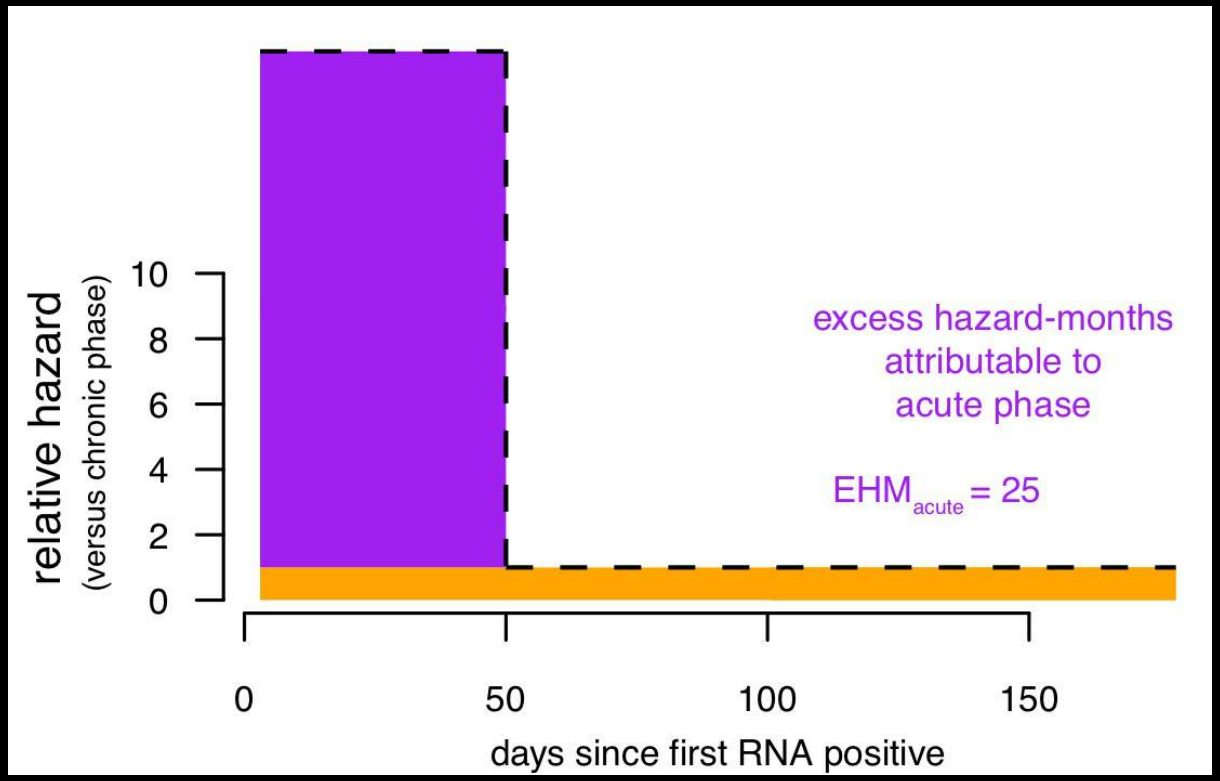

comparable across
different
acute phase durations

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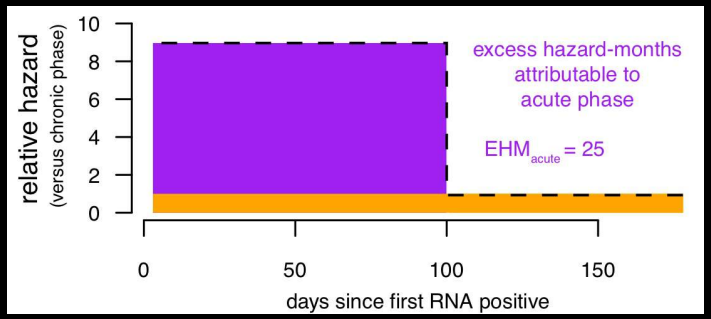
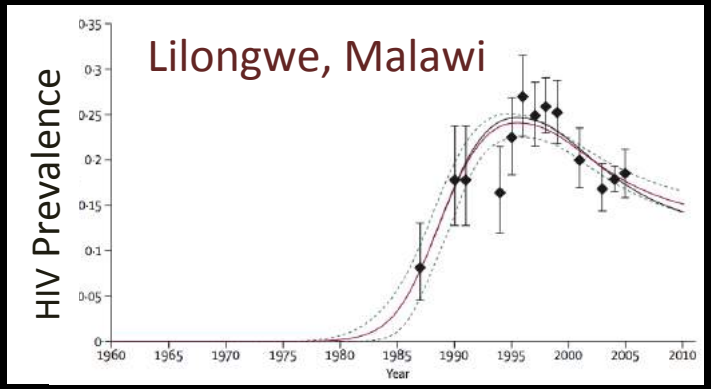
Estimating EHM_{acute} Indirectly

- Viral load trajectories

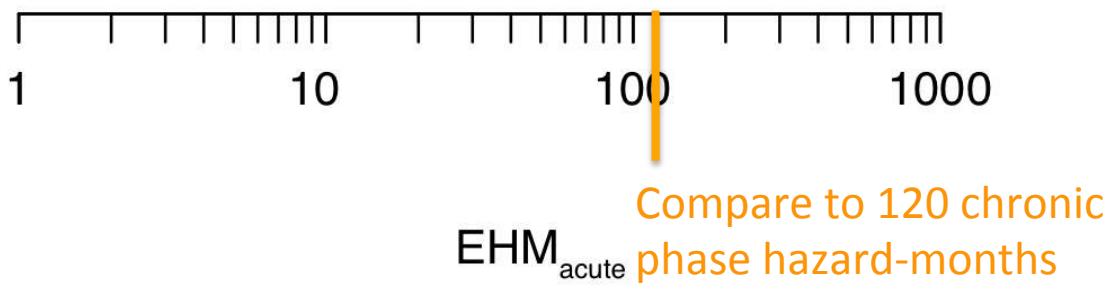


- Fast epidemic growth explainable by
  - early transmission



Powers et al. (2011). *Lancet*.

Variation in EHM_{acute} Estimates



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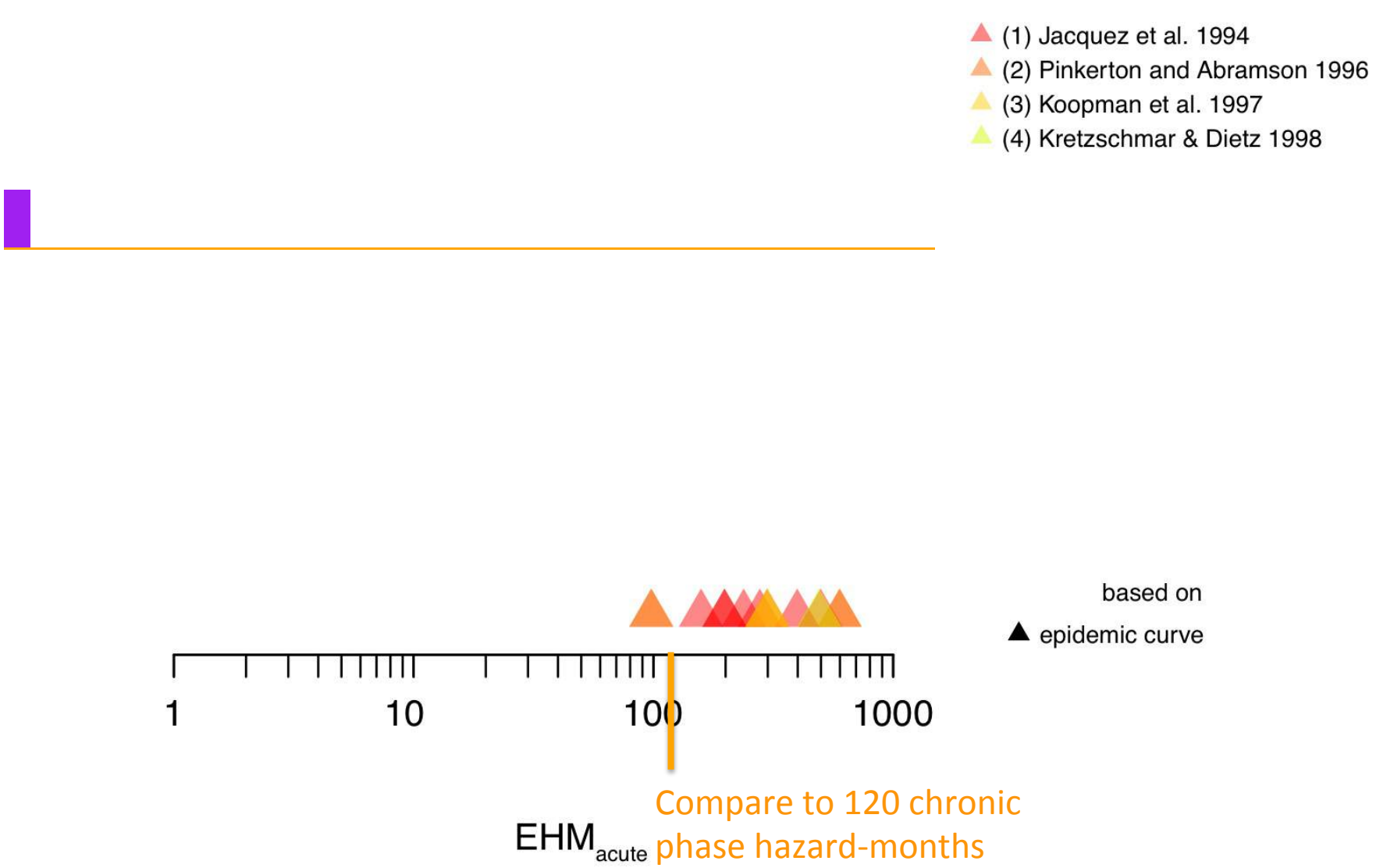

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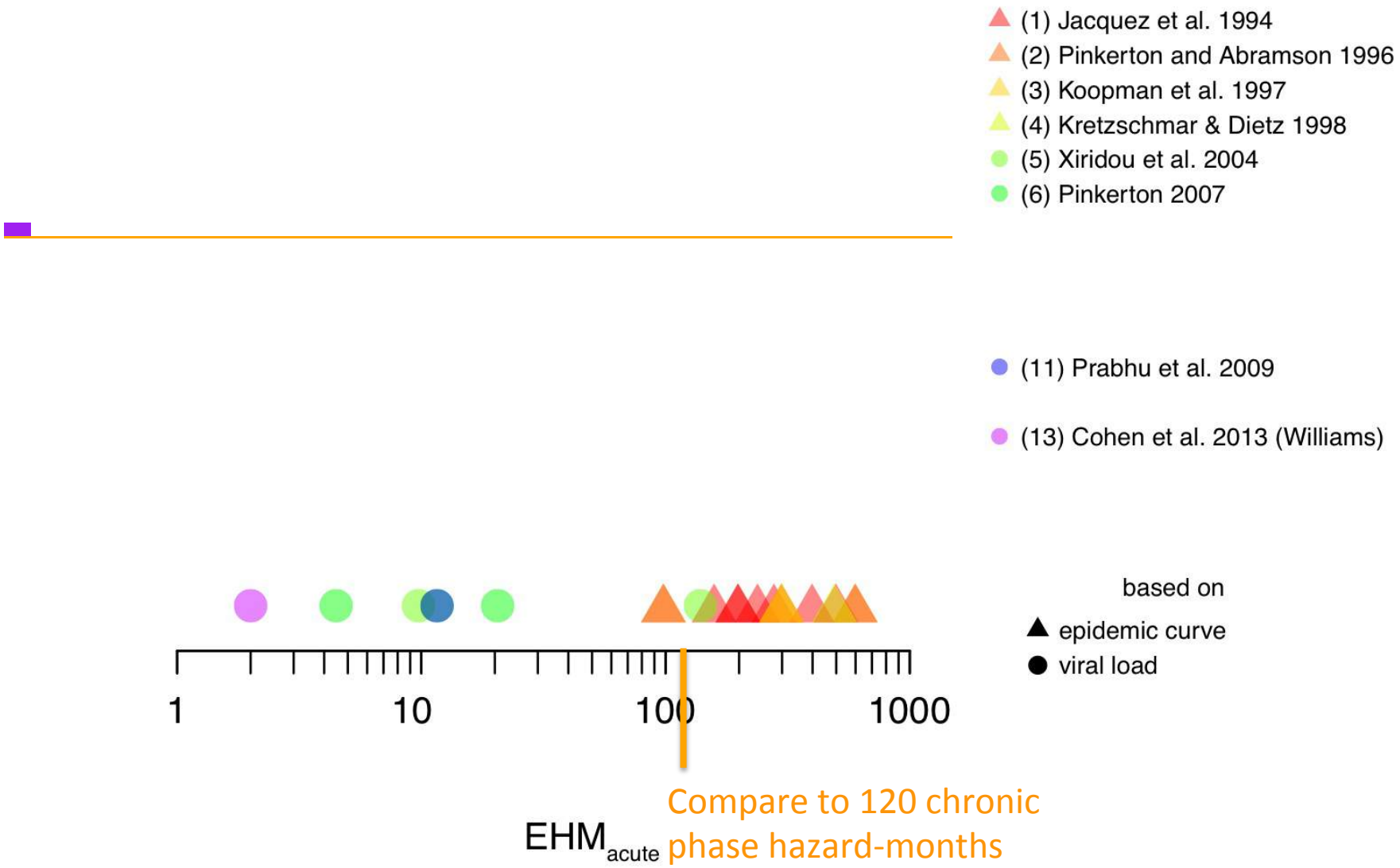


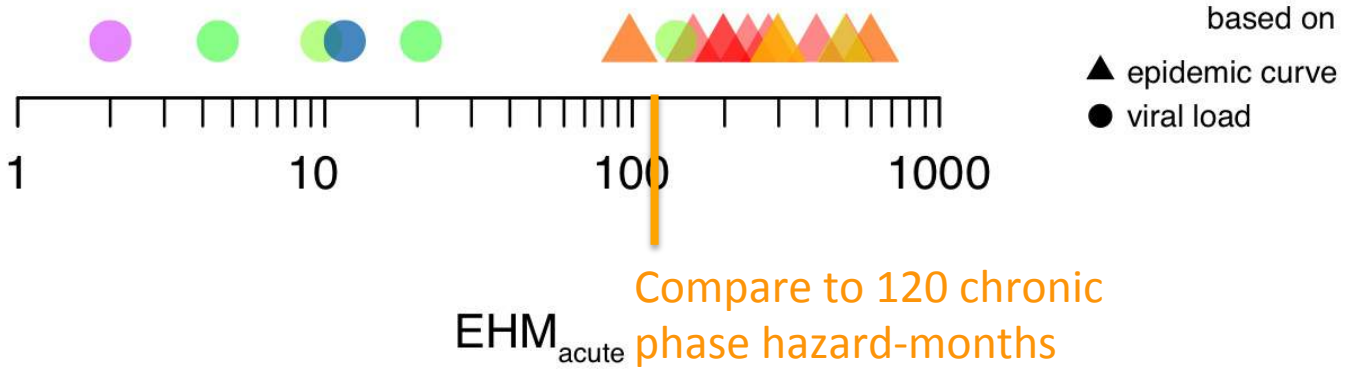
Variation in EHM_{acute} Estimates

Directly measured once by the
Rakai Community Cohort Study, Uganda

(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)



Variation in EHM_{acute} Estimates

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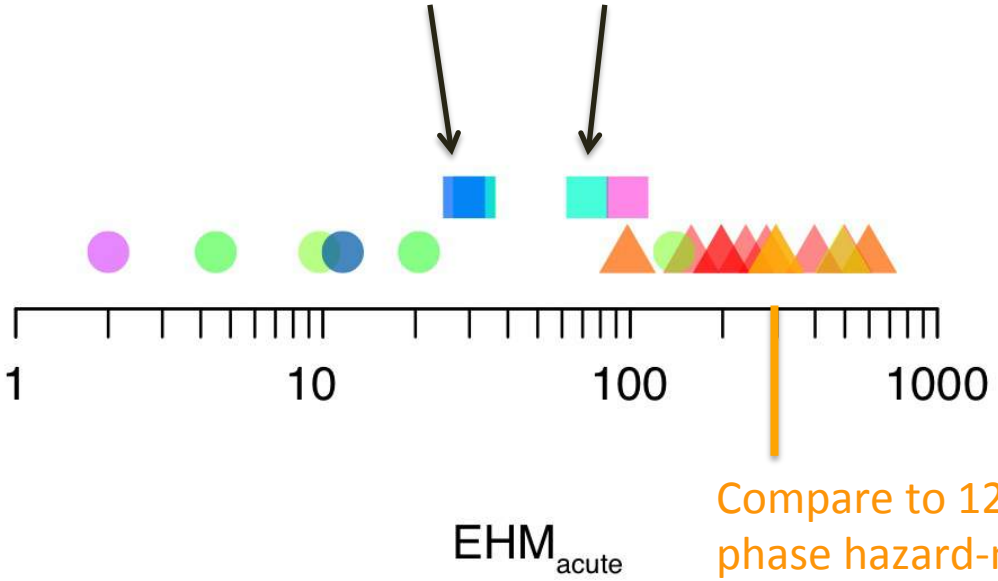
Most commonly cited estimates

EHM_{acute} = 35 and 71



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(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

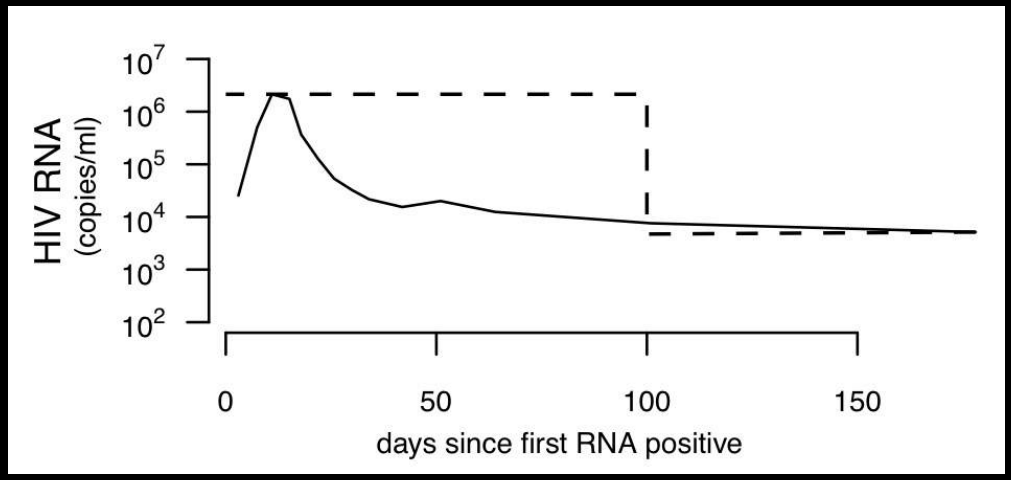
based on
epidemic curve
viral load
Rakai

Compare to 120 chronic phase hazard-months

Why reevaluate EHM_{acute} estimates?

- Viral Load

  Continuous trajectory
  instead of discrete phases



- Rakai Retrospective Cohort Study

  Biases due to (1) unmodeled heterogeneity
  (2) study design

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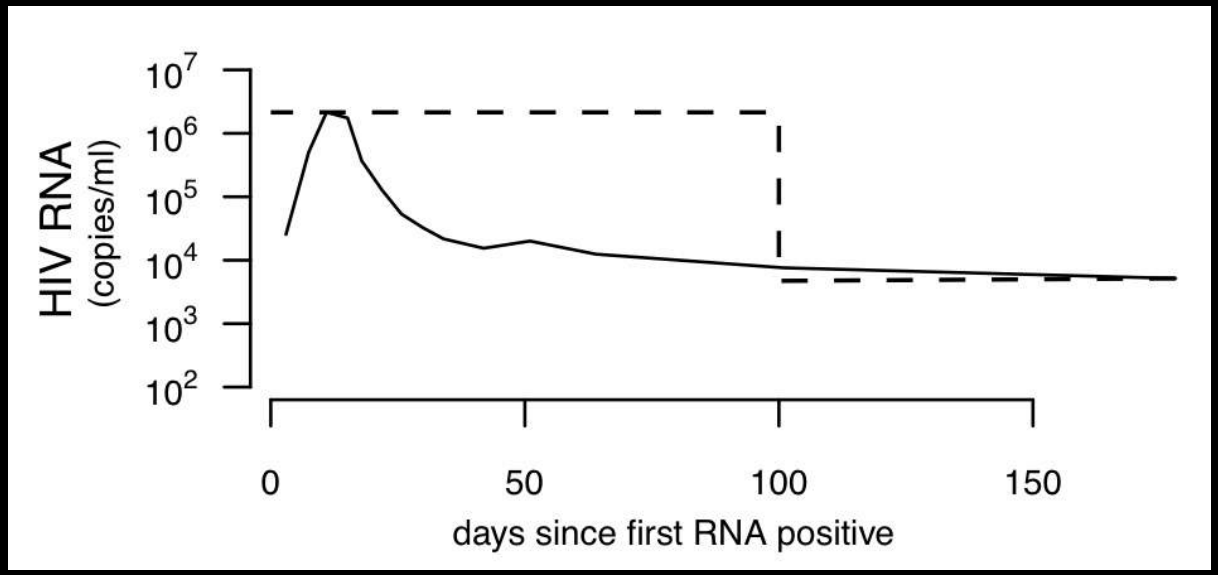
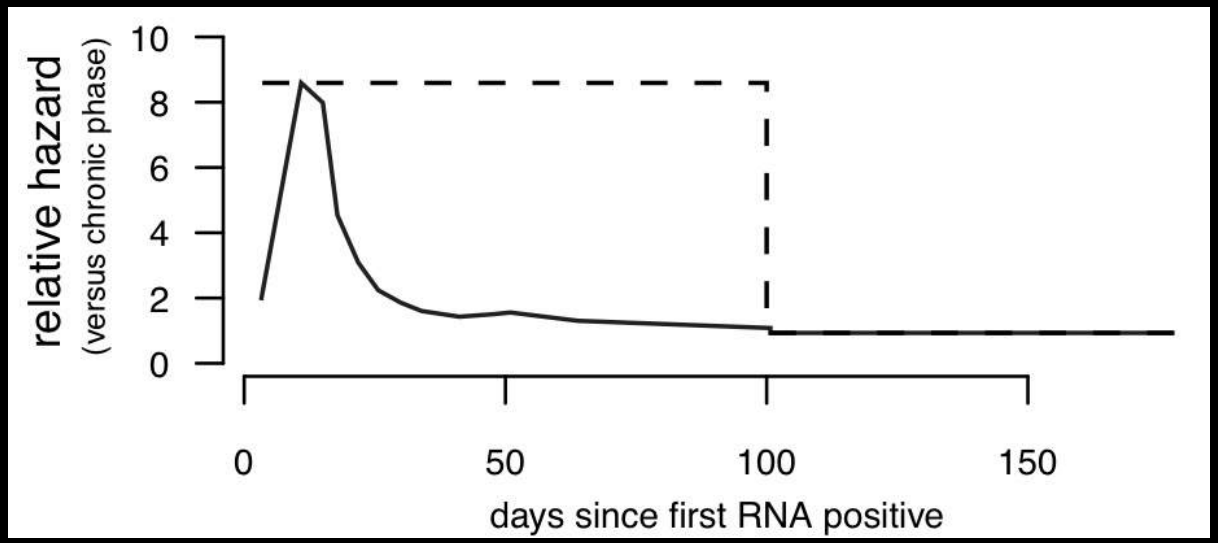
Determining a biological infectivity profile



continuous trajectory to avoid overestimation



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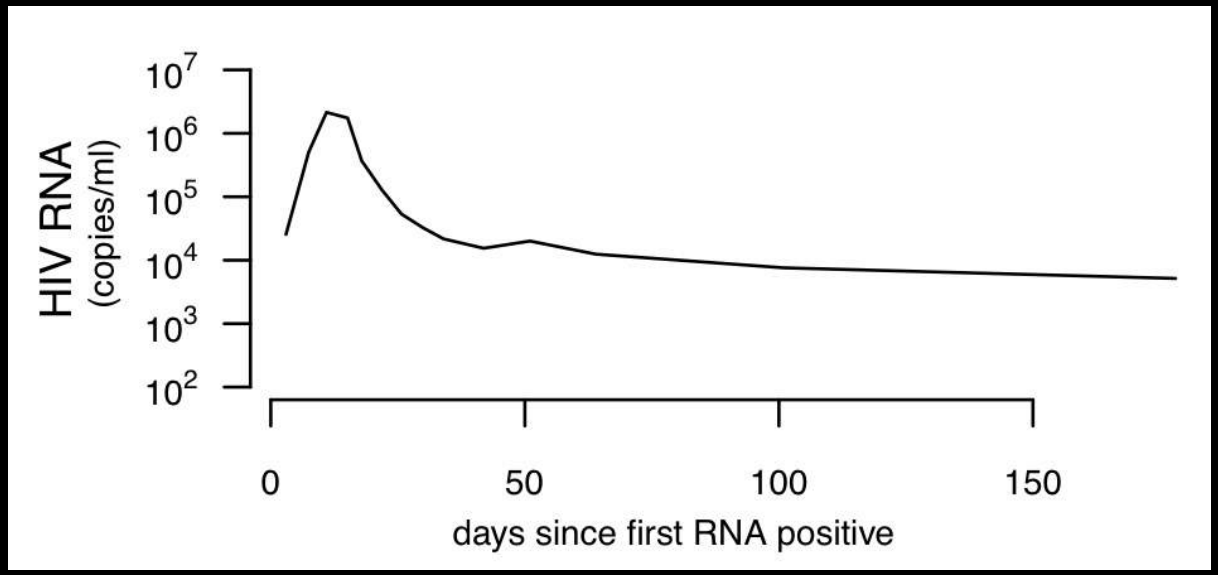

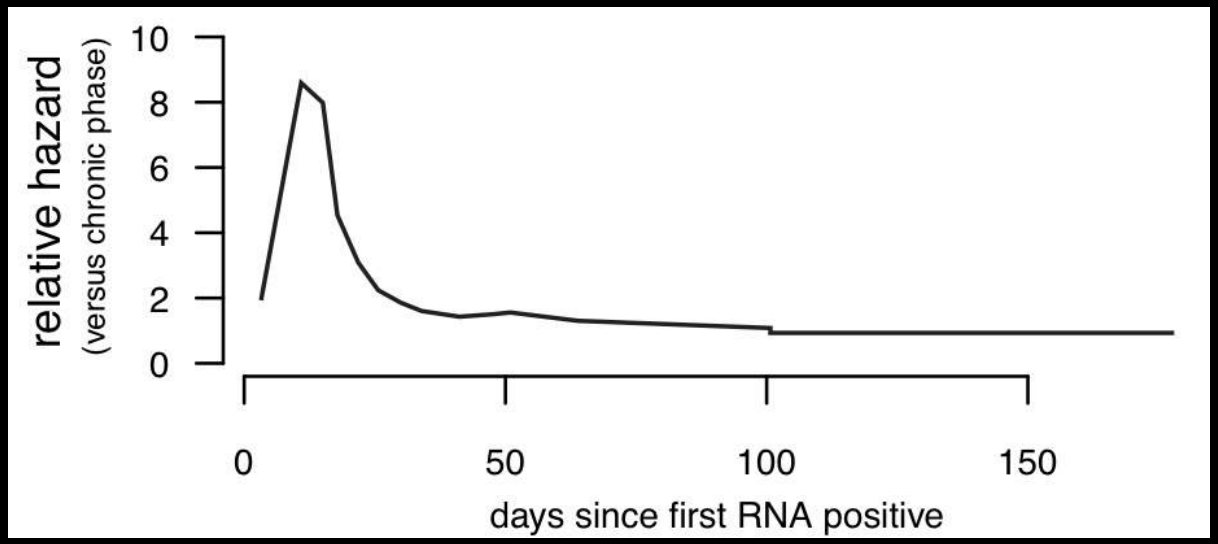

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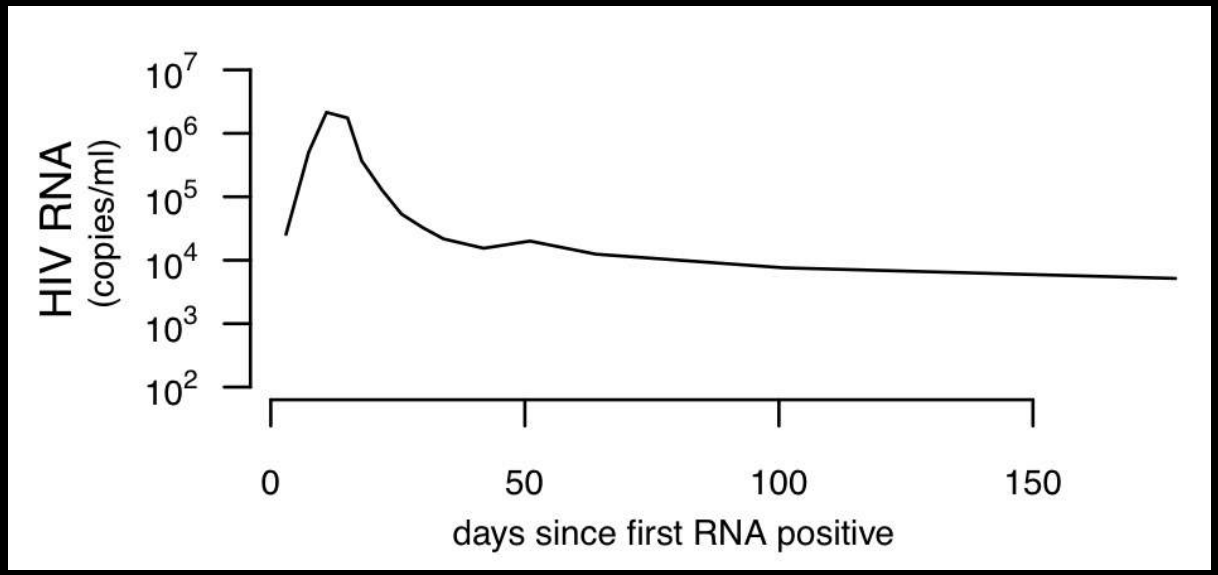
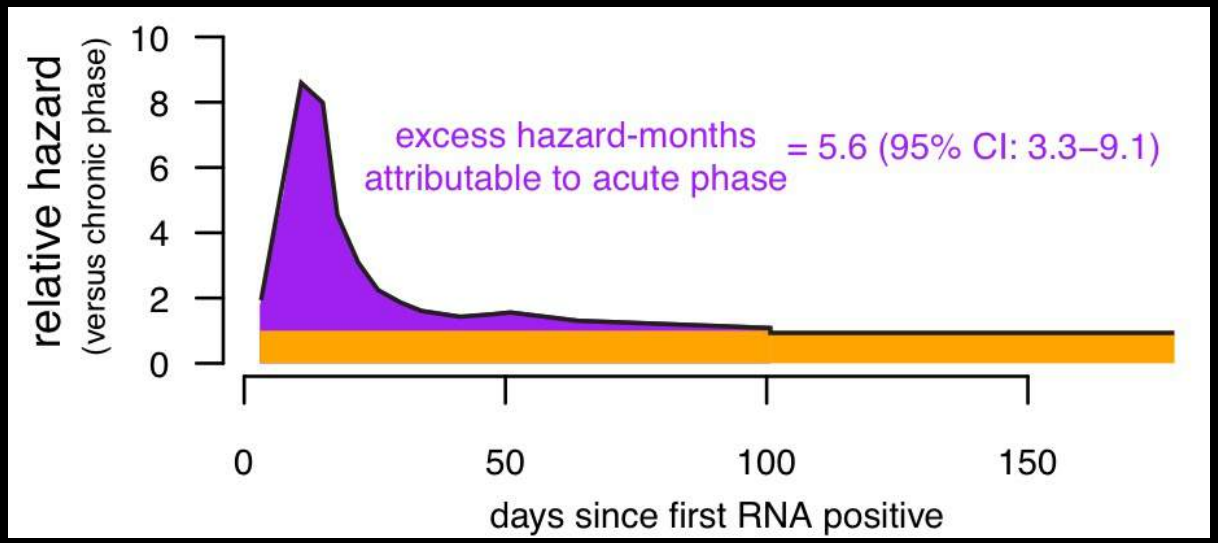
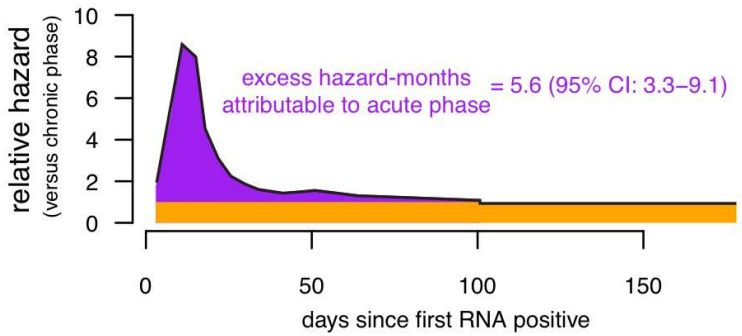
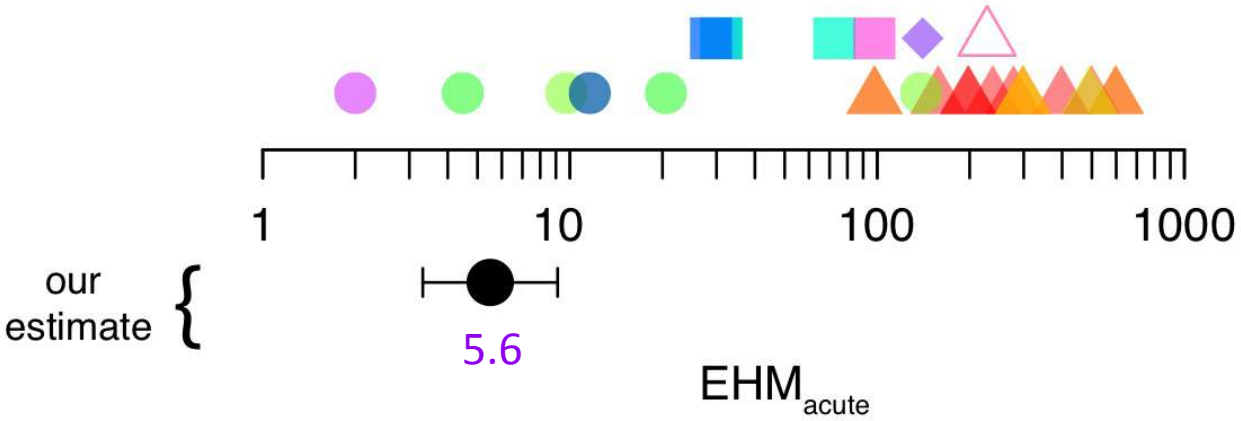




Variation in EHM_{acute} Estimates





- (1) Jacquez et al. 1994
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- (3) Koopman et al. 1997
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- (15) Rasmussen et al. 2014

based on

- epidemic curve
- viral load
- Rakai
- Rakai & epidemic curve
- phylogenetics

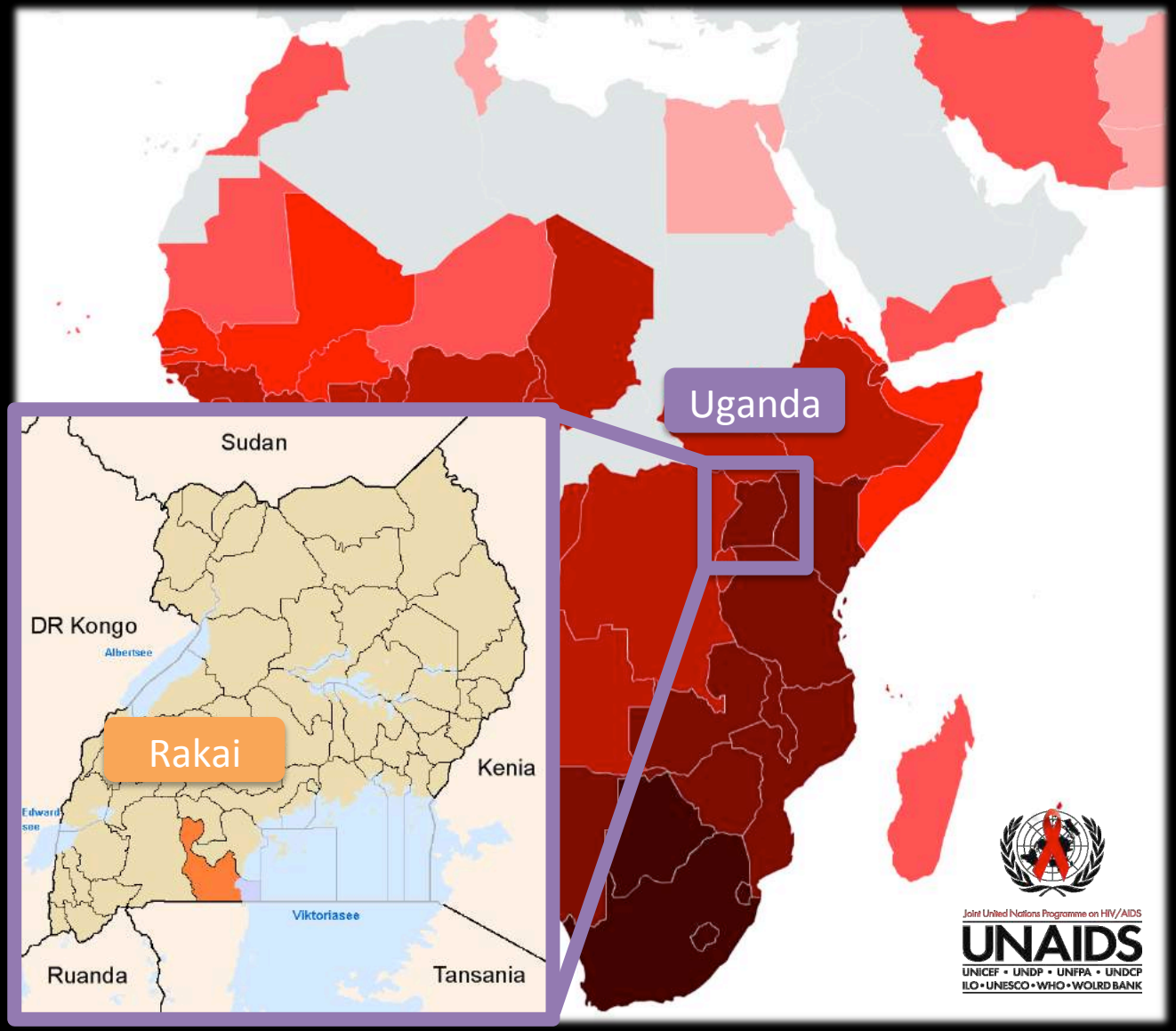
Outline

1. Relevance: Treatment as Prevention (TasP)
2. Measuring excess infectivity with EHM_{acute}
3. Literature review of past estimates
4. Re-estimation of EHM_{acute} from viral load
5. Re-estimation of EHM_{acute} from the Rakai cohort

How to *directly* 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



The Rakai Retrospective Cohort Study

In a prospective population cohort study 1994-1999

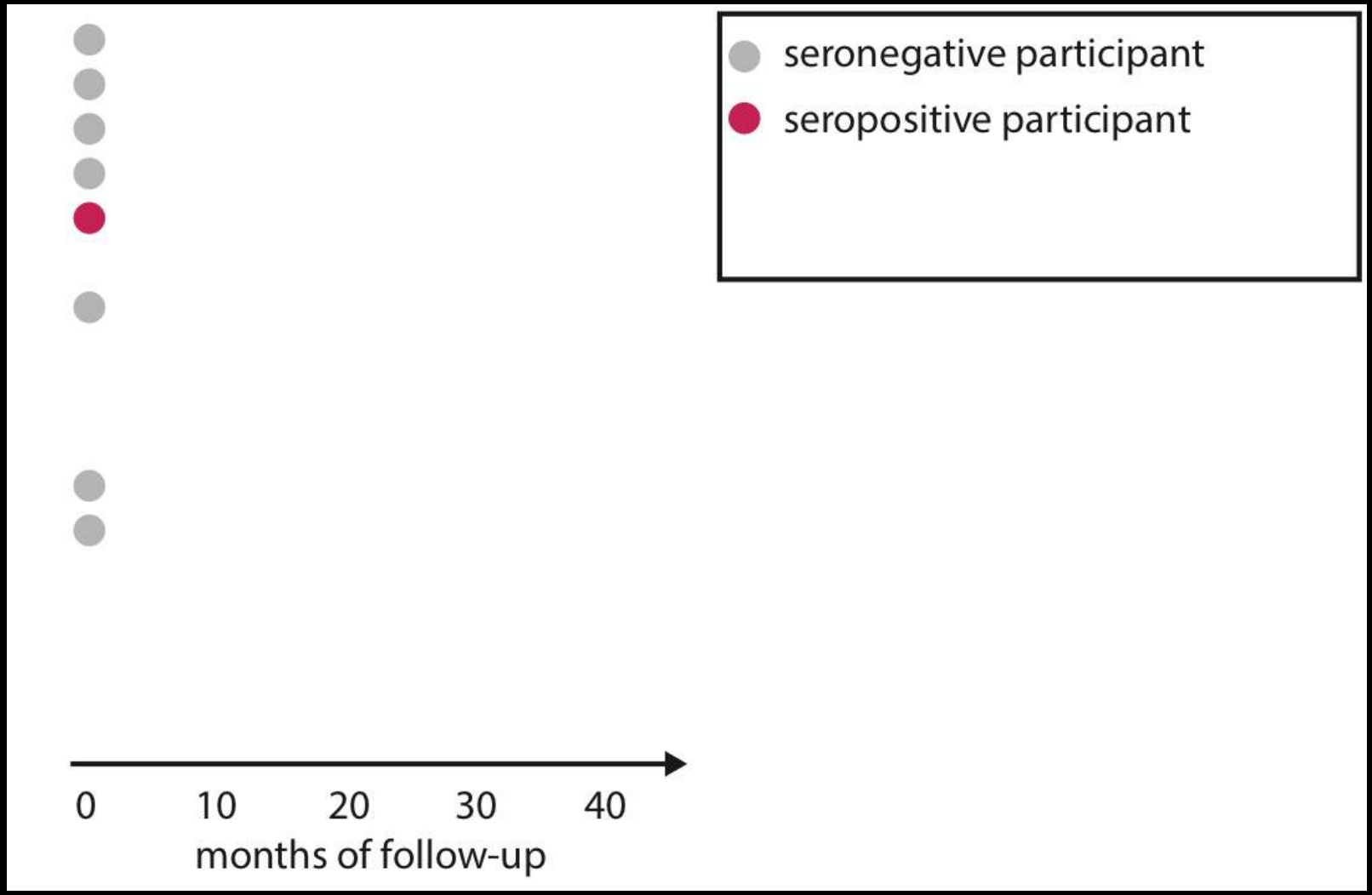
retrospectively identified

235 stable couples observed serodiscordant at least once

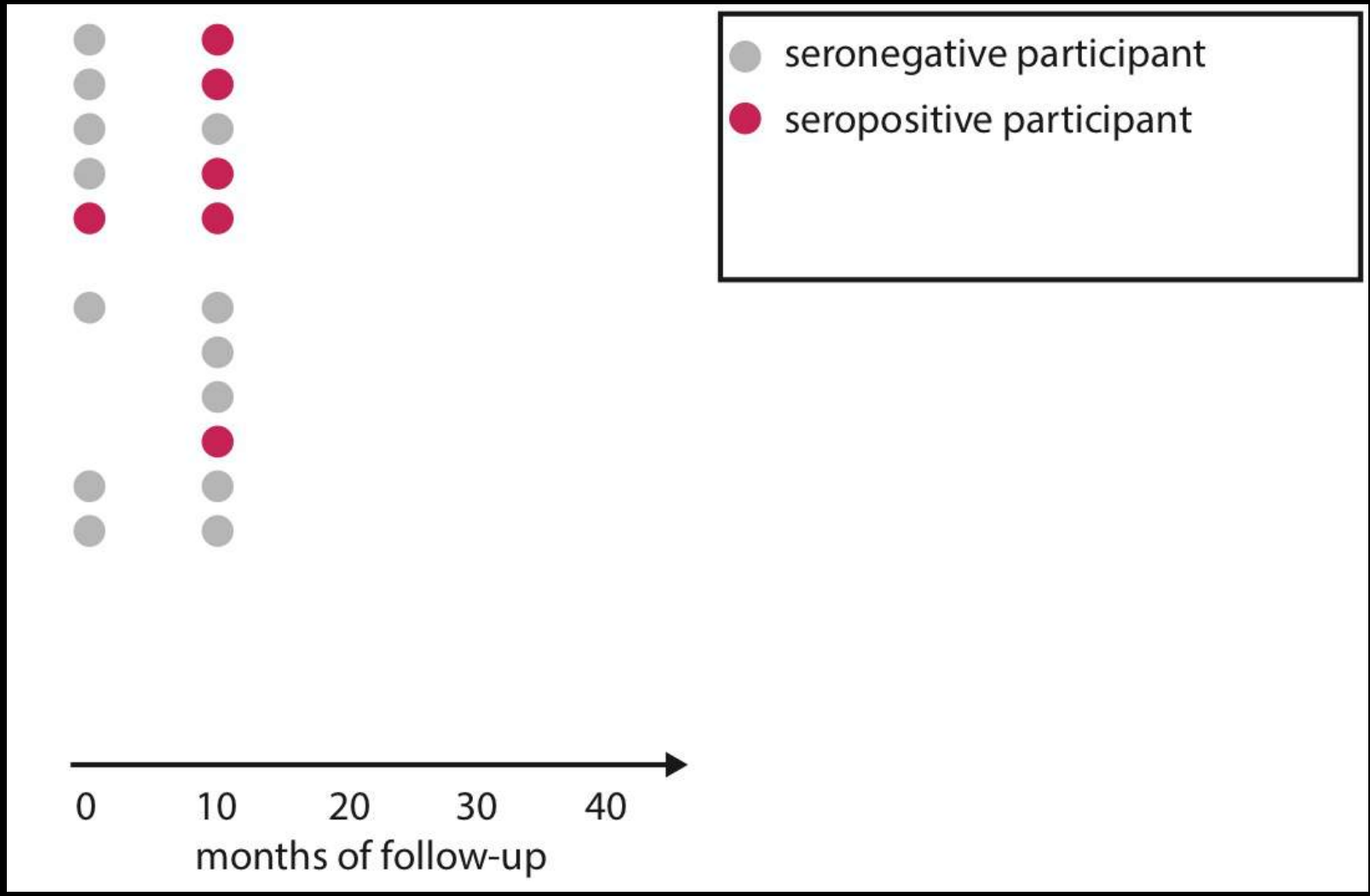
Do individuals infect their partners at
different rates
early vs. later in infection?

Wawer et al. (2005). *Journal of Infectious Disease*.

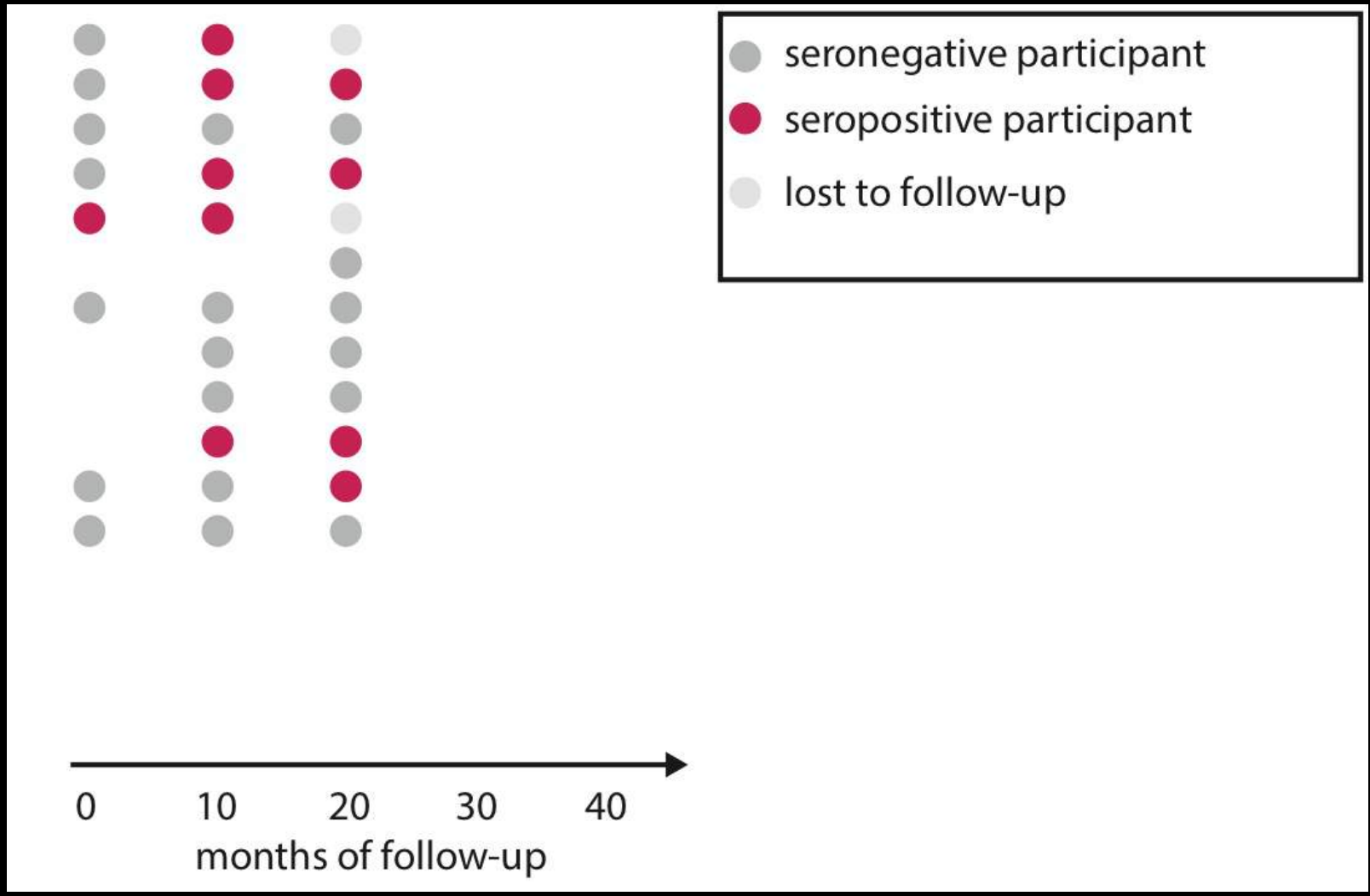
Rakai *Retrospective Couples* Cohort



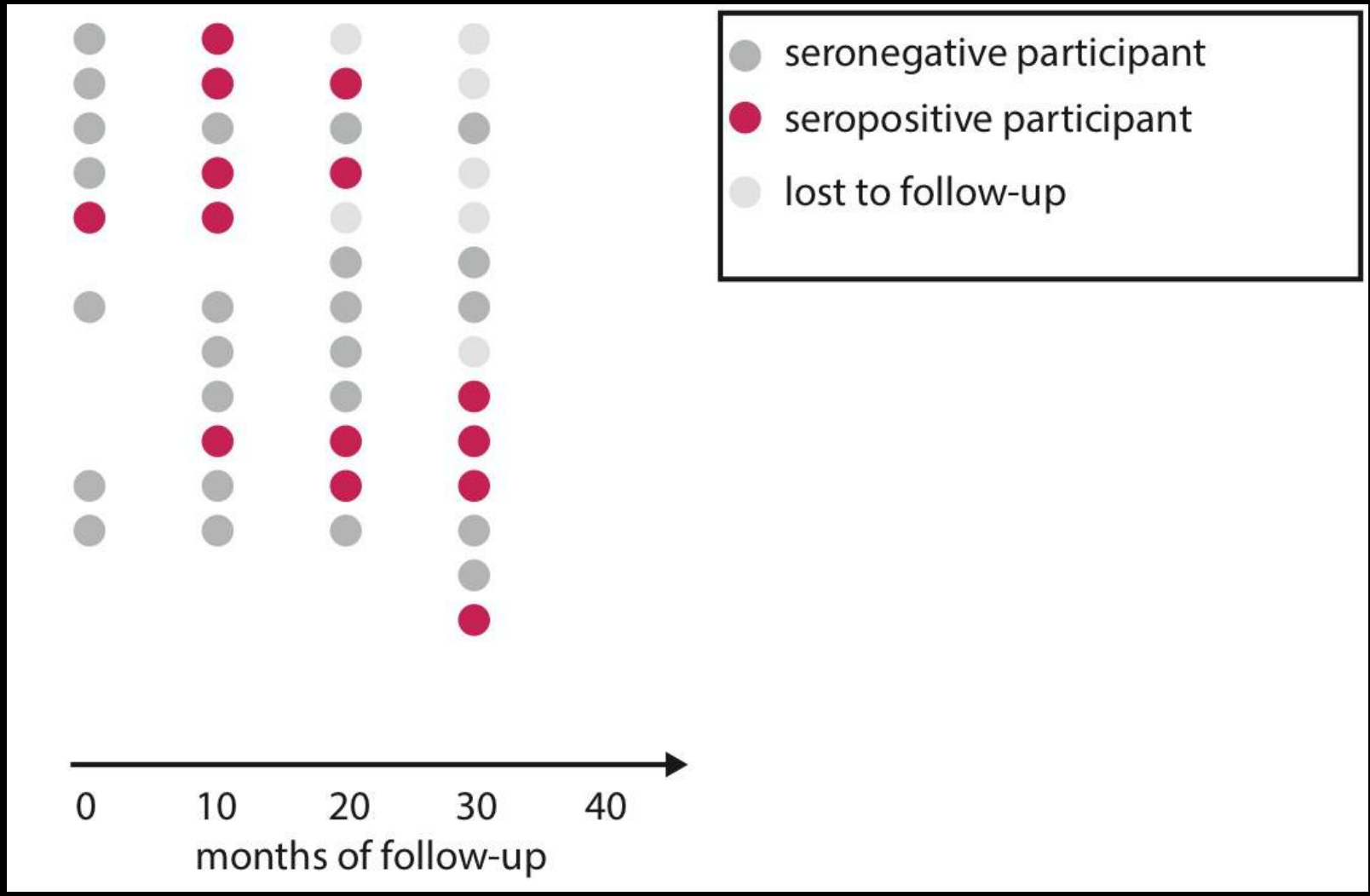
Rakai *Retrospective Couples* Cohort



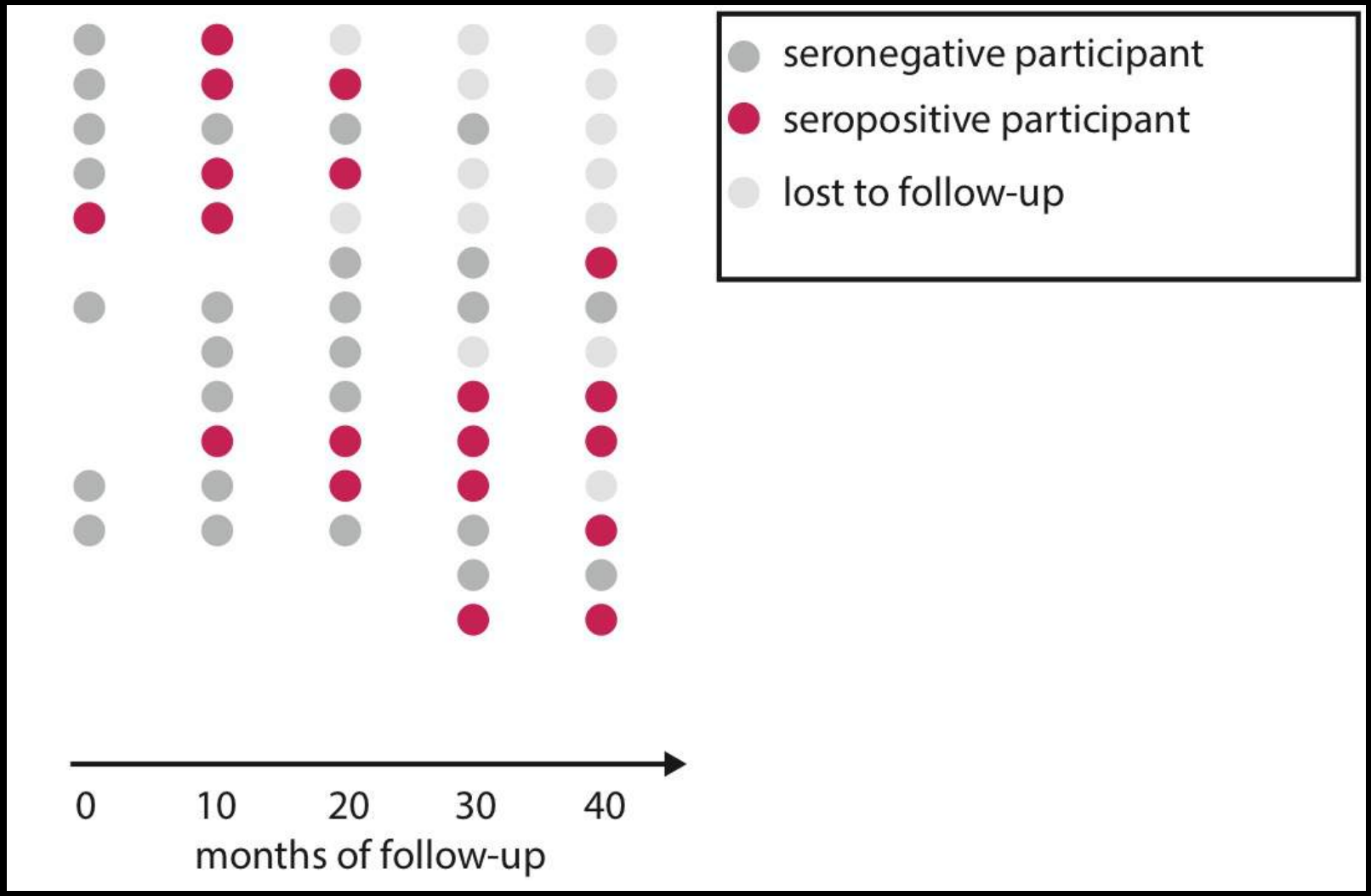
Rakai *Retrospective Couples* Cohort



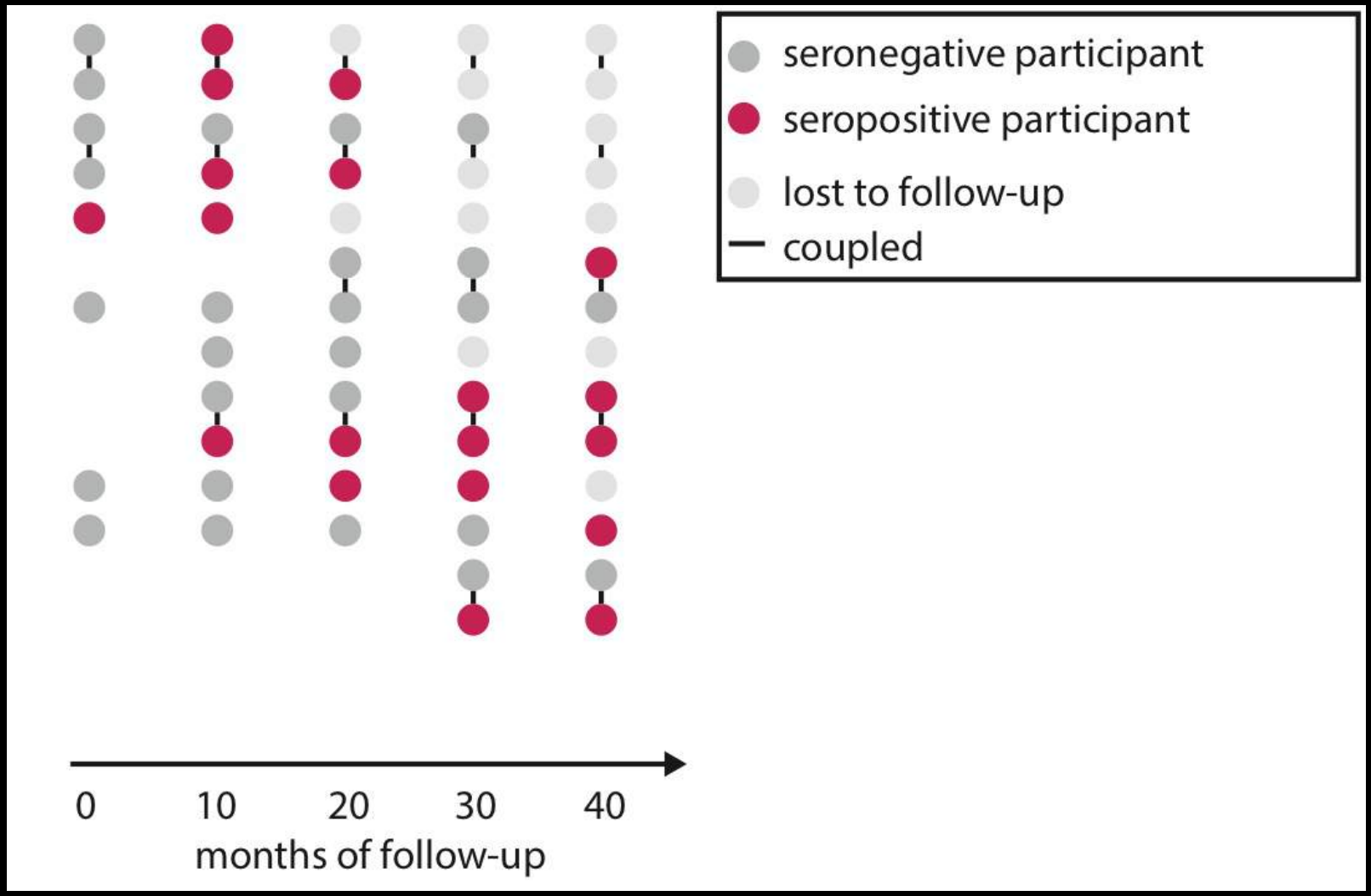
Rakai *Retrospective Couples* Cohort



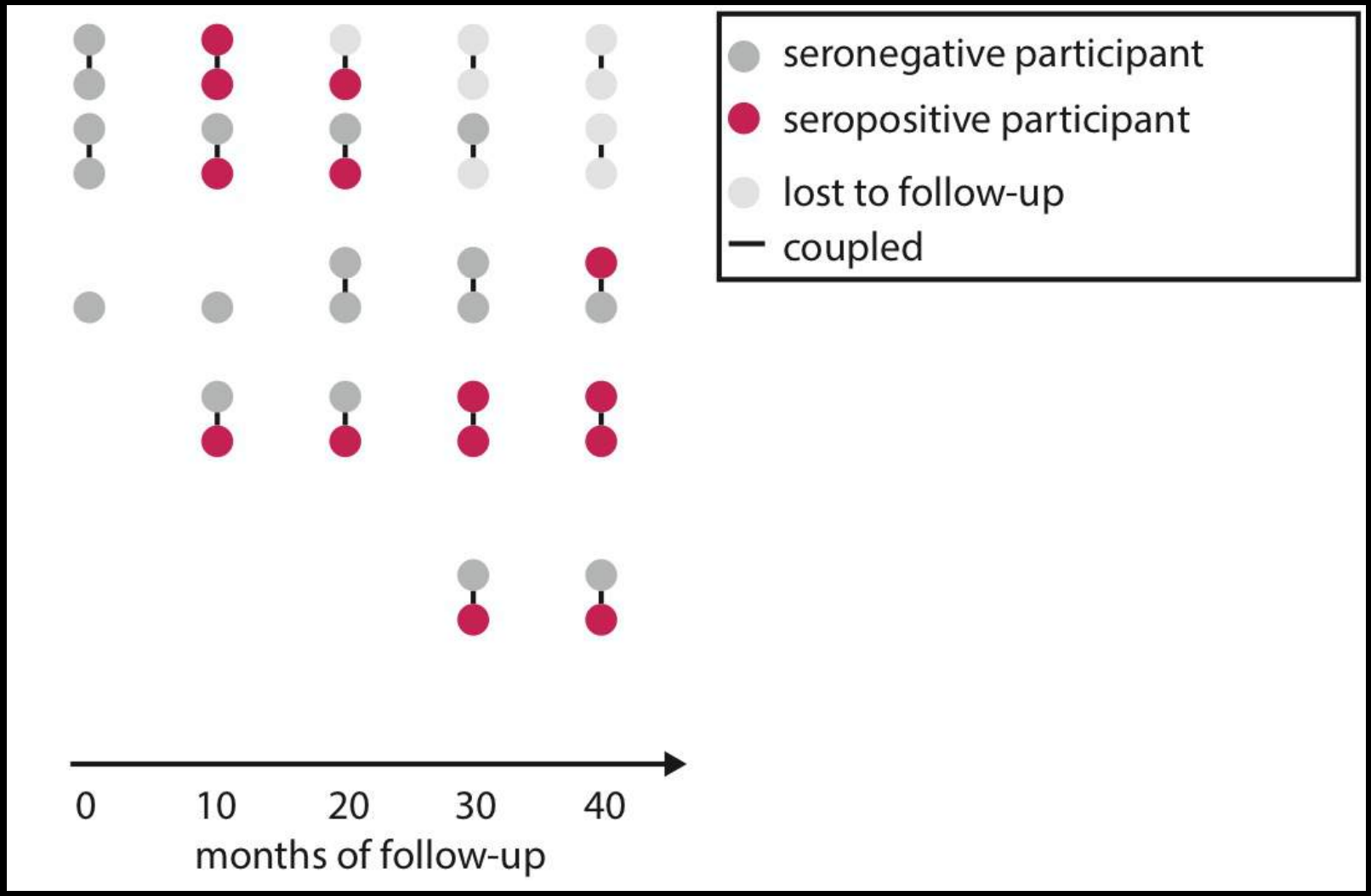
Rakai *Retrospective Couples* Cohort



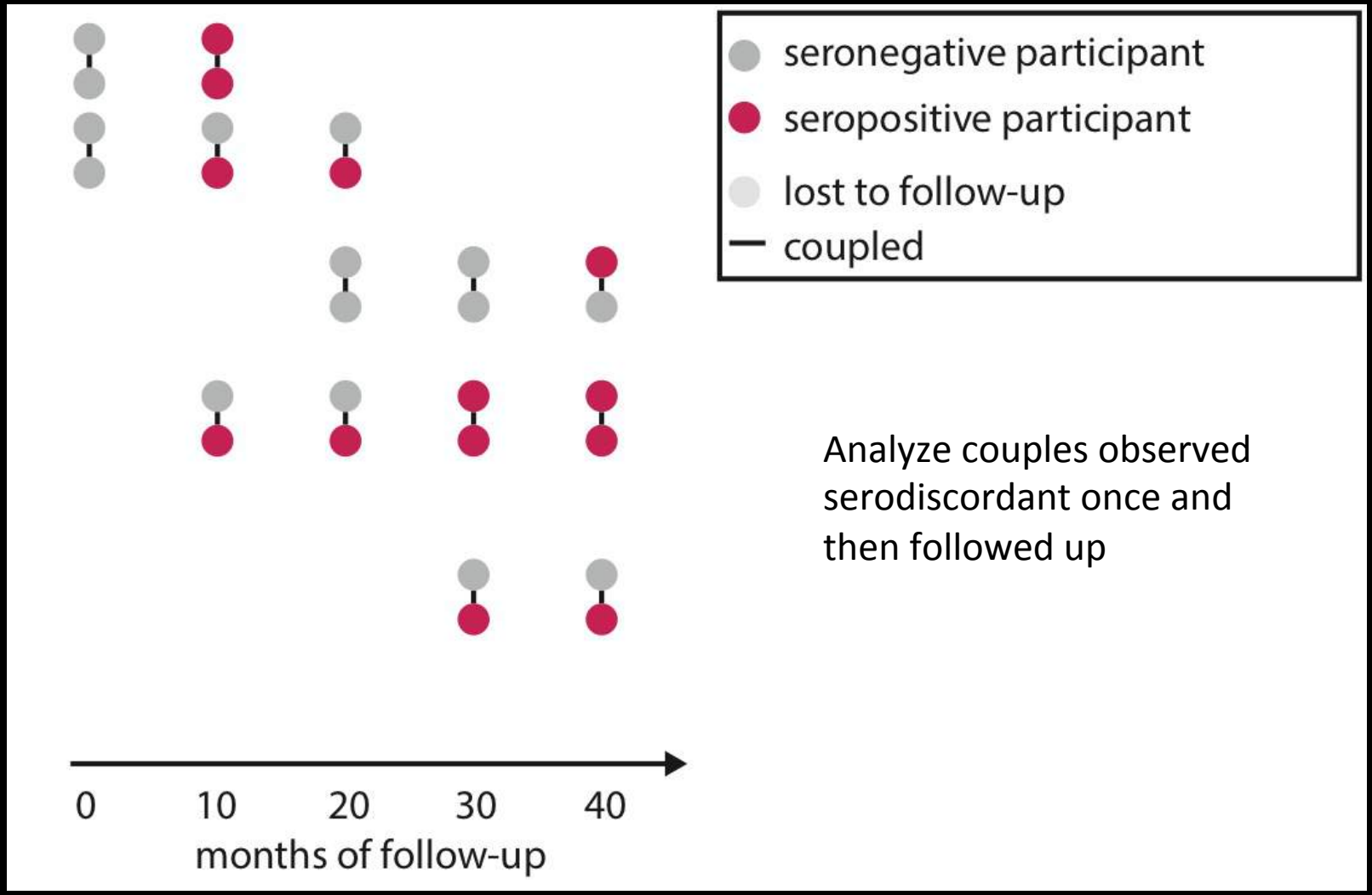
Rakai *Retrospective Couples* Cohort



Rakai *Retrospective Couples* Cohort

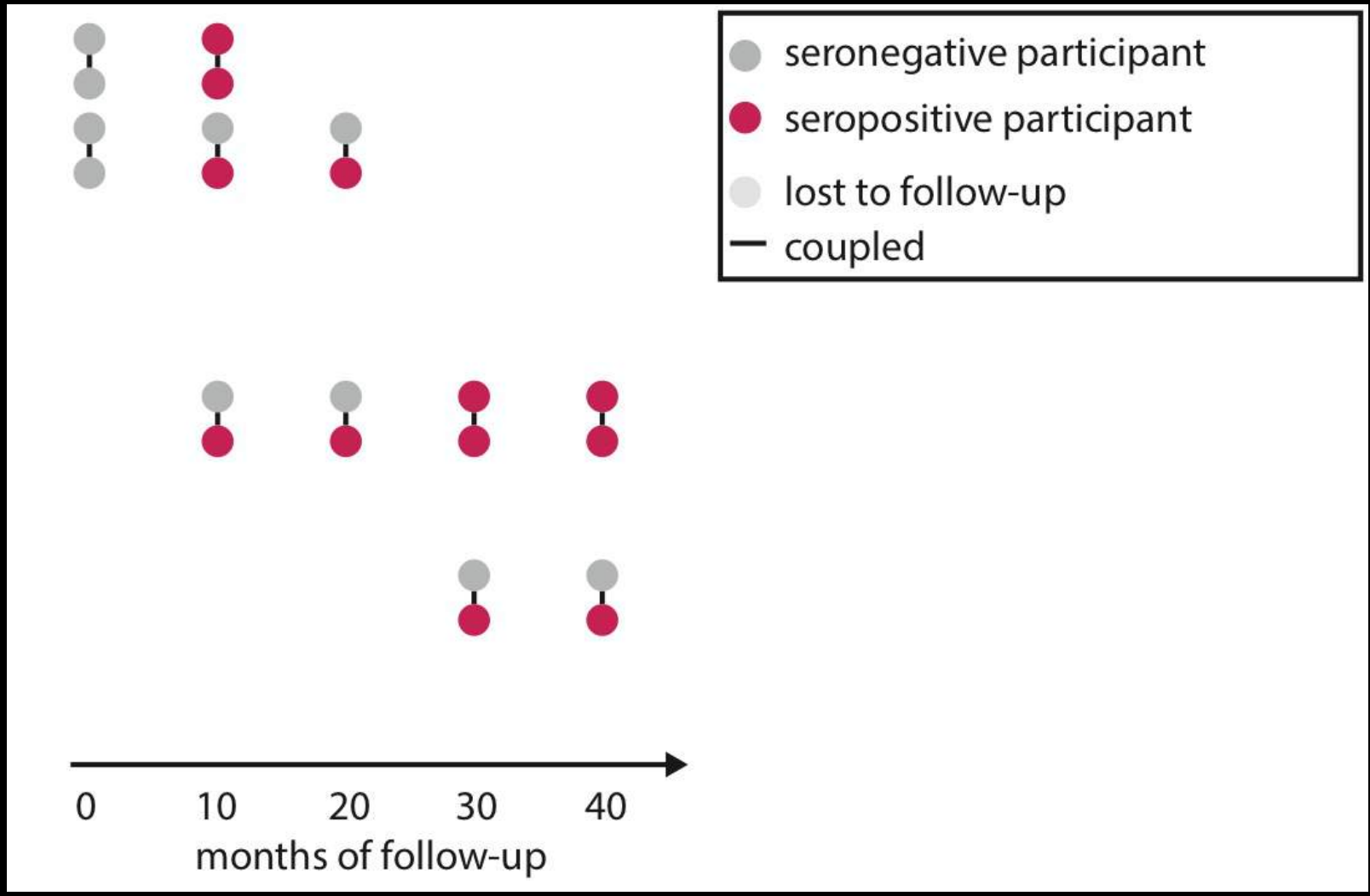


Rakai *Retrospective Couples* Cohort

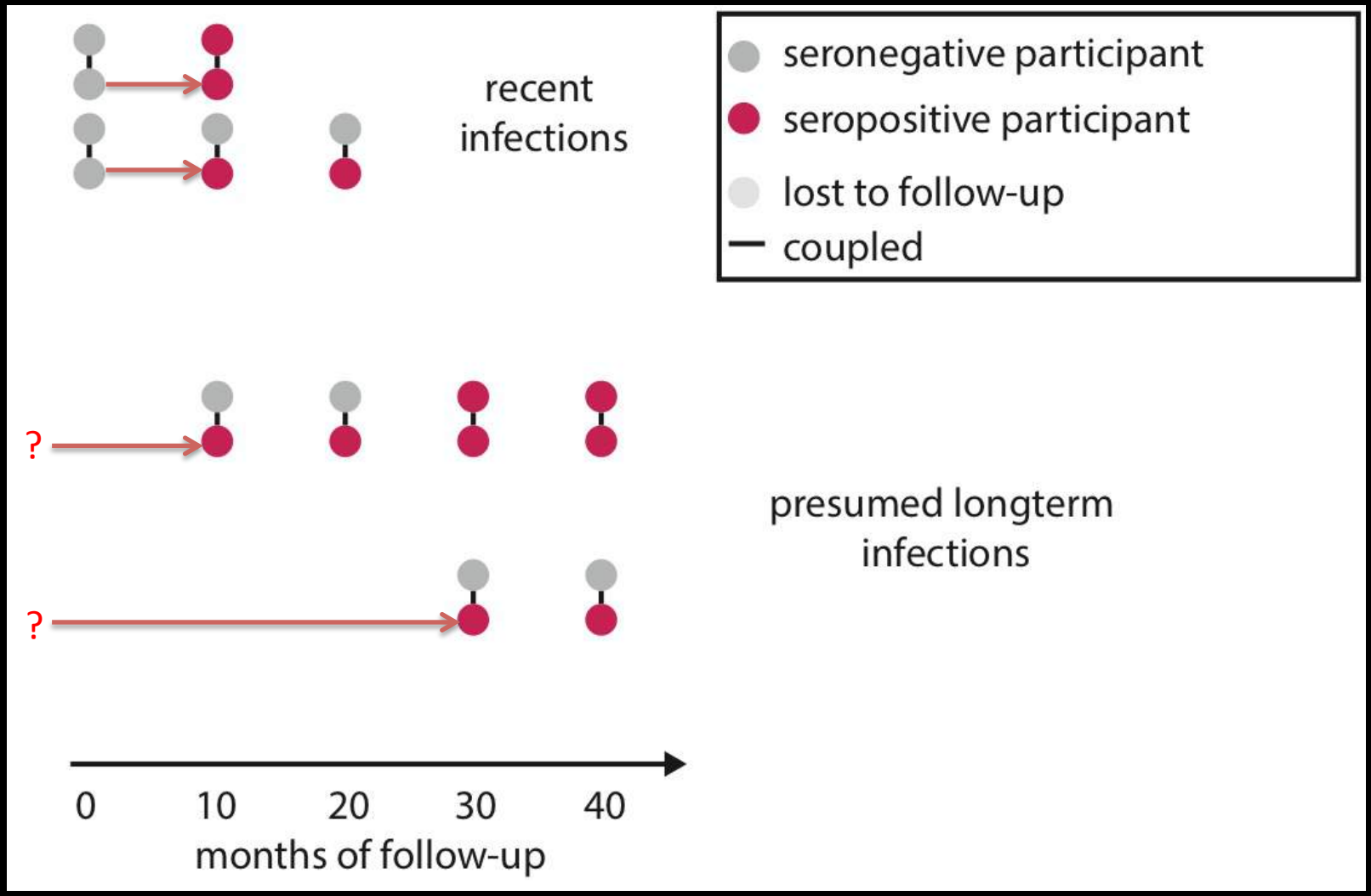


Analyze couples observed serodiscordant once and then followed up

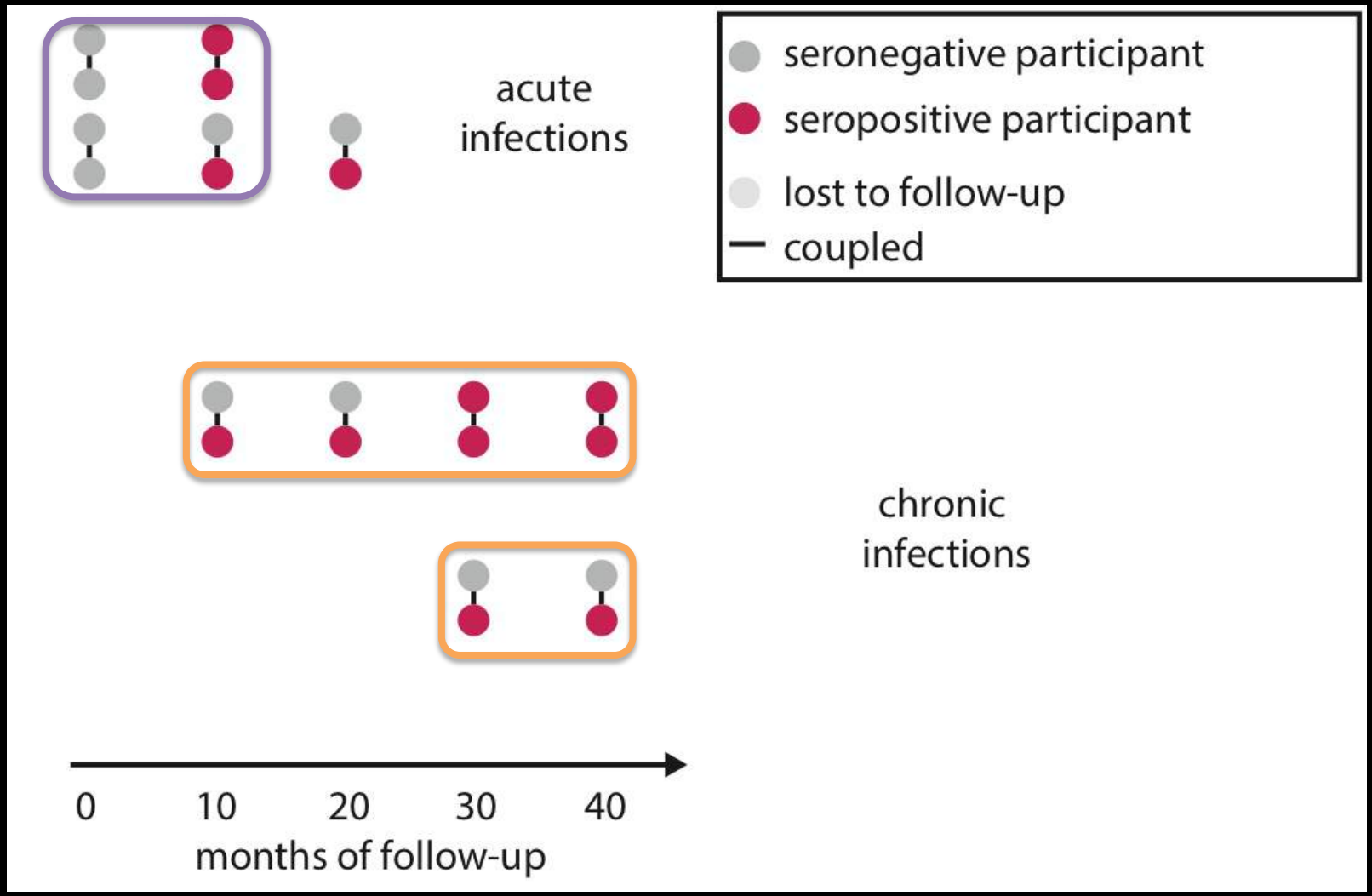
Rakai *Retrospective Couples* Cohort



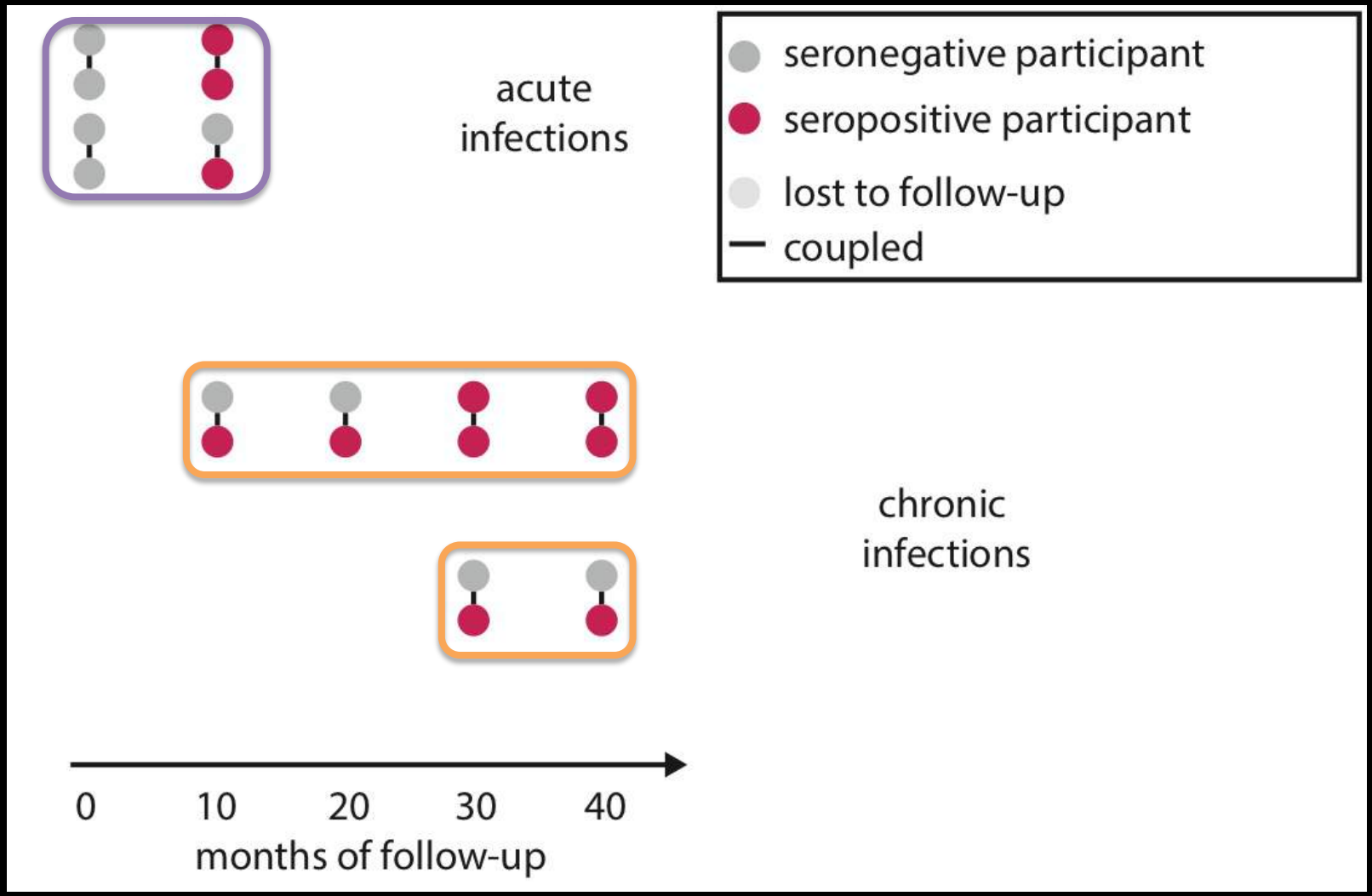
Rakai *Retrospective Couples* Cohort



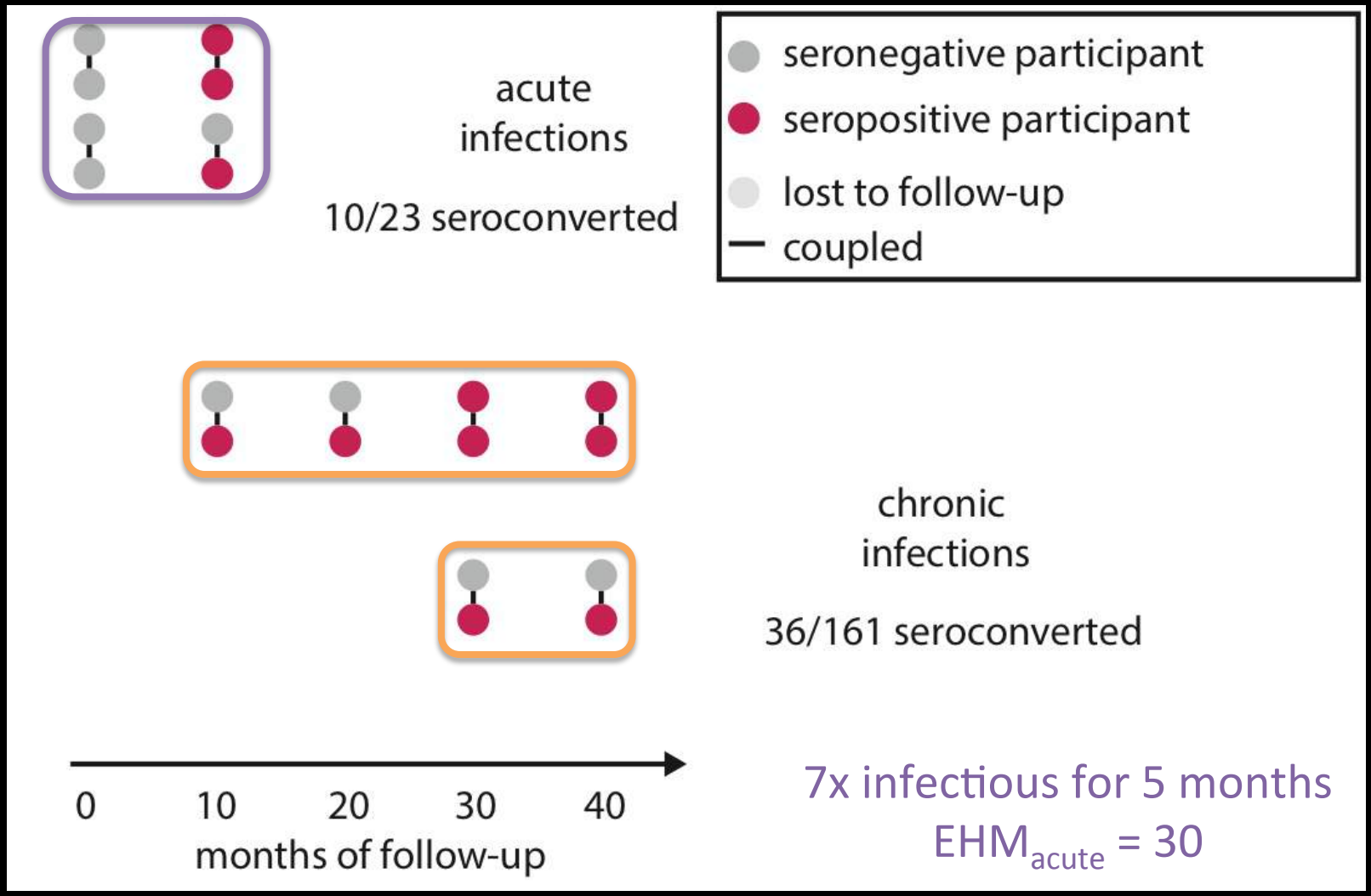
Rakai *Retrospective Couples* Cohort



Rakai *Retrospective Couples* Cohort

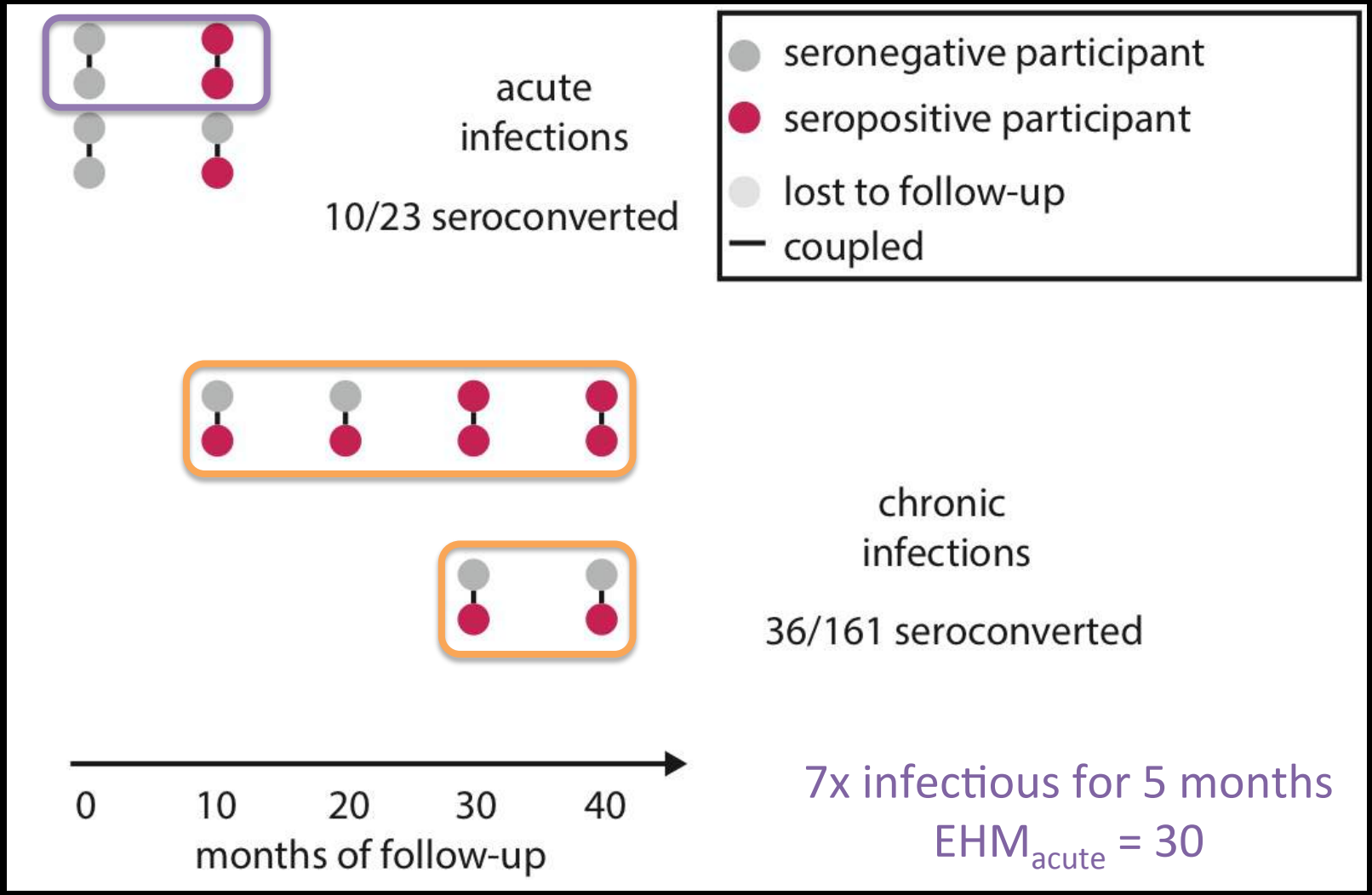


Rakai *Retrospective Couples* Cohort



Rakai *Retrospective Couples* Cohort

Suggestive of HIGH acute infectivity



7x infectious for 5 months

$EHM_{acute} = 30$

Why re-analyze these data?

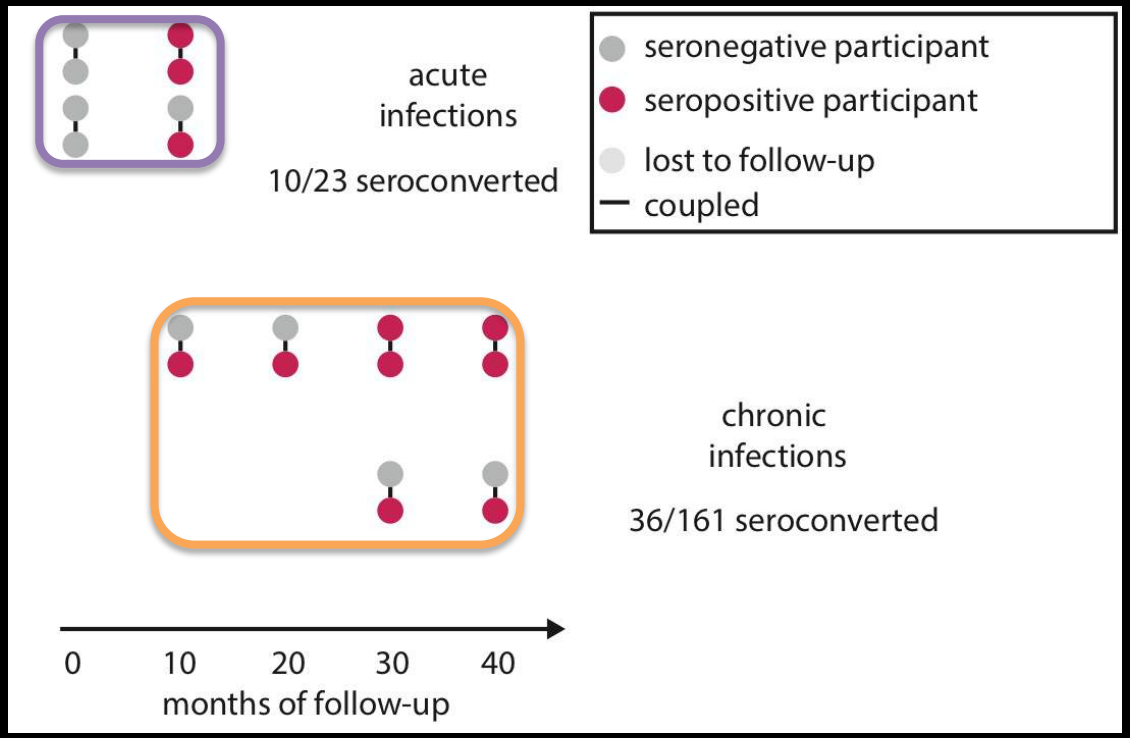
Heterogeneity in Transmission Rates

- 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

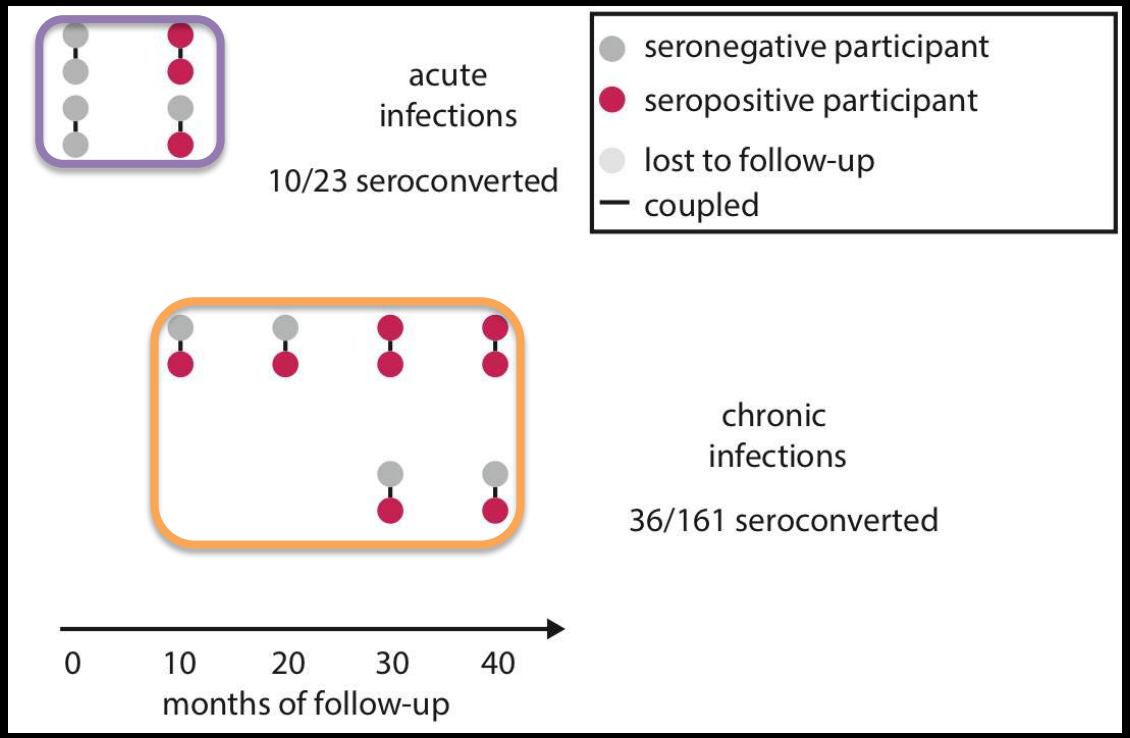
Persistently serodiscordant.
Selected to be low risk



Bias 1: Unmodeled Heterogeneity

Average risk
acutely infected partners

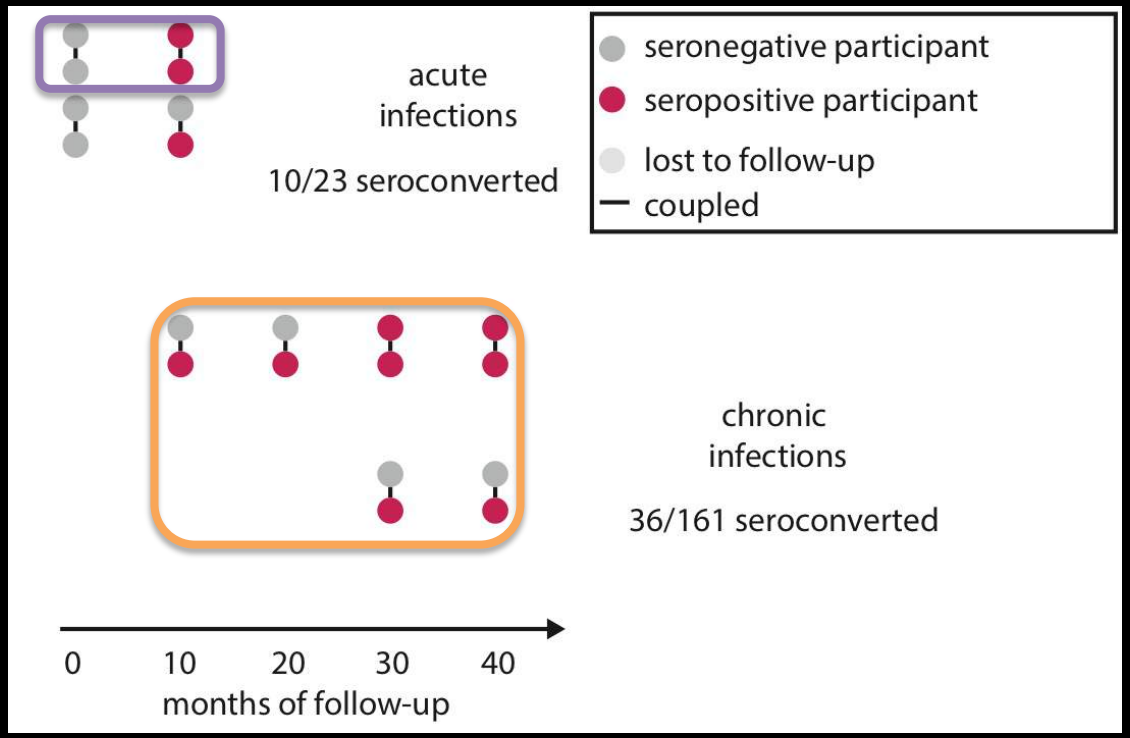
Low risk
chronically infected partners



Unmodeled heterogeneity might bias EHM_{acute} upwards

Bias 2: Inclusion Criteria

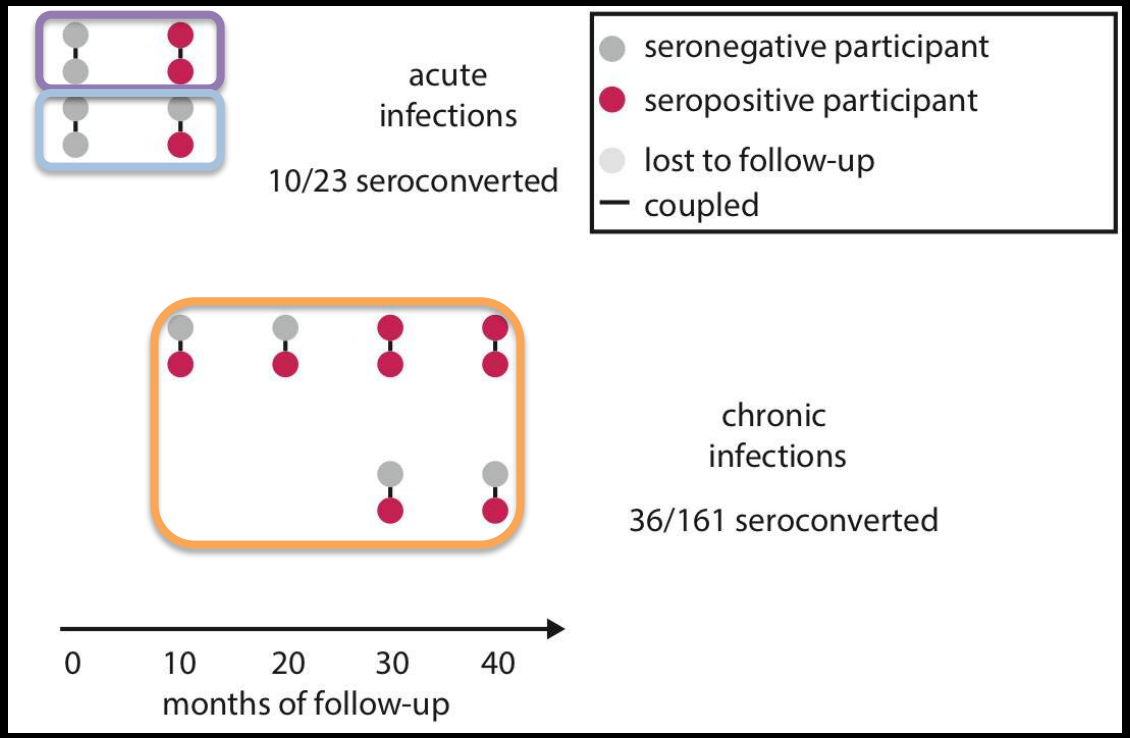
HIGH acute infectivity



Bias 2: Inclusion Criteria

HIGH acute infectivity

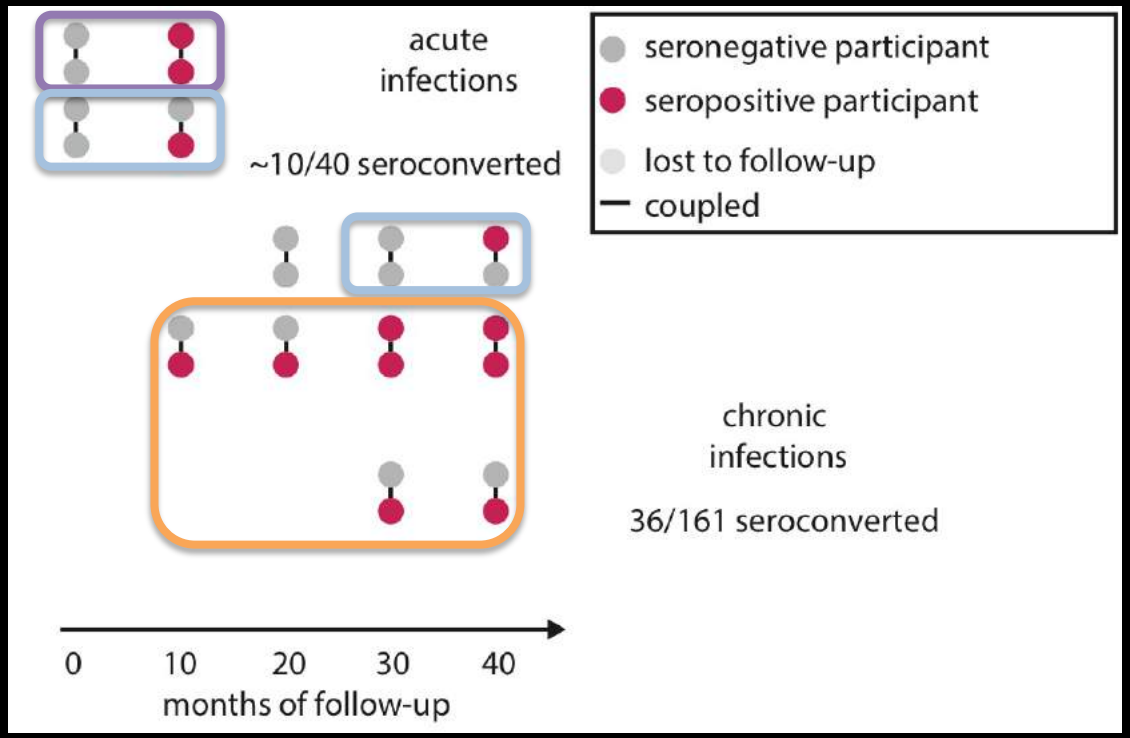
LOW acute infectivity



Bias 2: Inclusion Criteria

HIGH acute infectivity

LOW acute infectivity

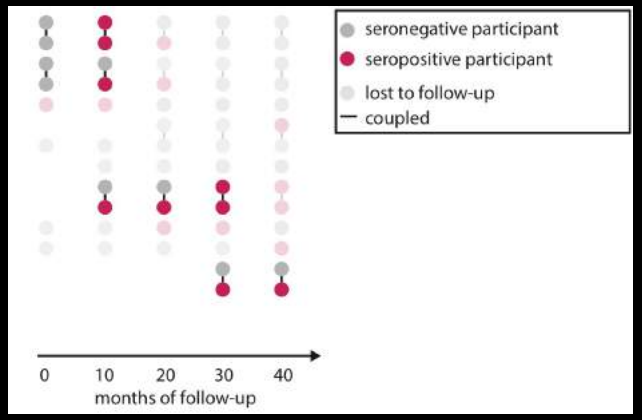


Accidentally excluded
~17 couples suggestive of low infectivity

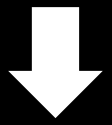
Simulating Rakai Transmission & Observation

Input EHM_{acute}

1. Simulate transmission
2. Replicate Rakai study design

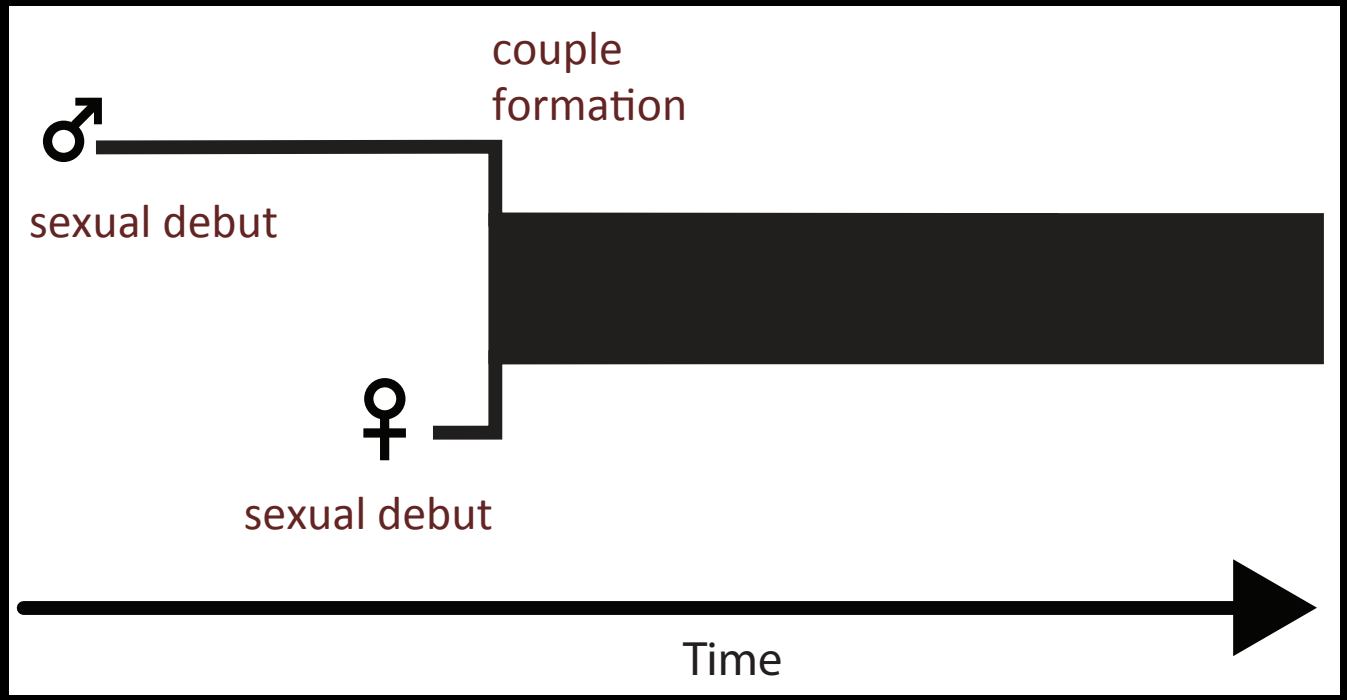


3. Apply published analyses to simulated data.



Estimated EHM_{acute}

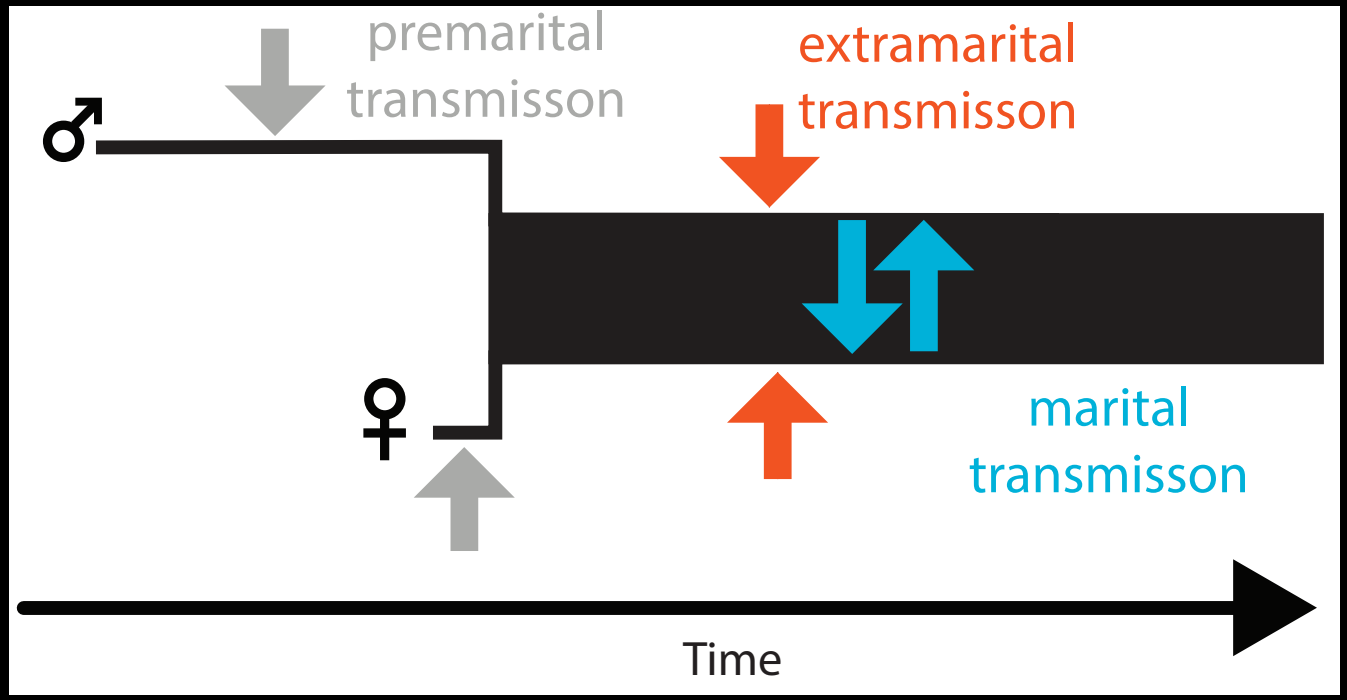
Couple Transmission Model



example relationship history

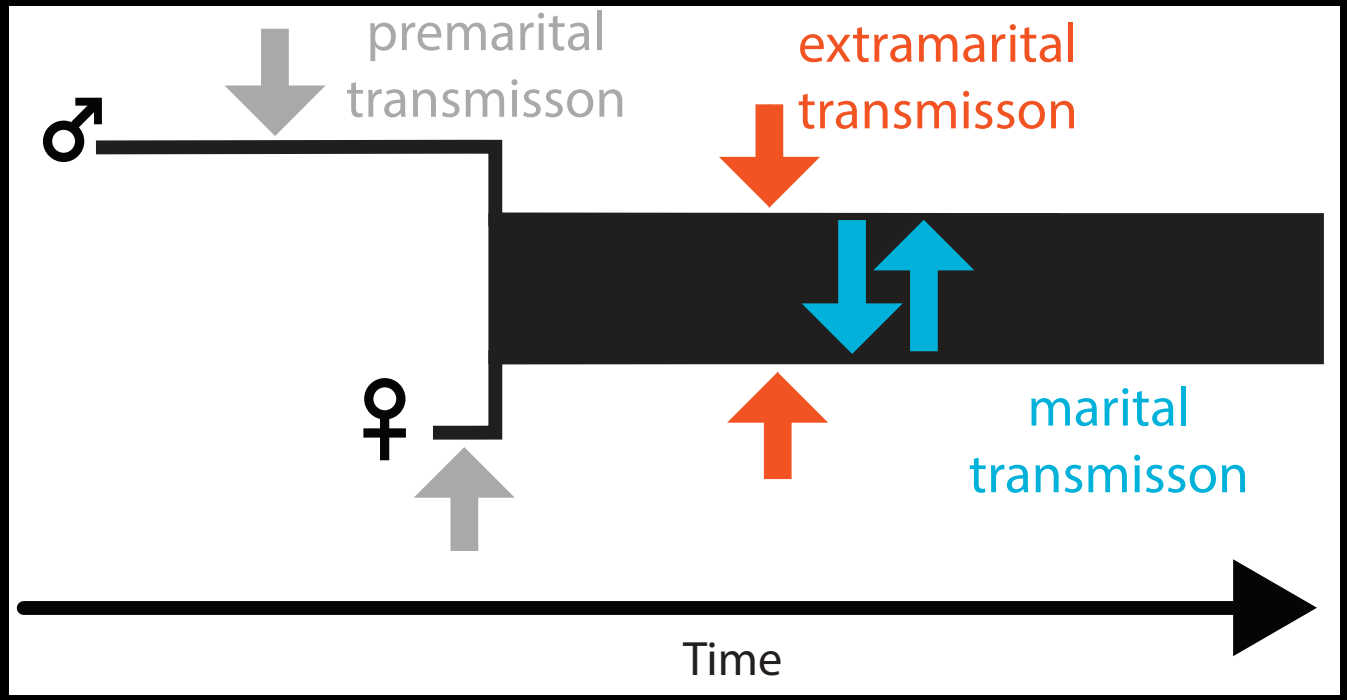
Bellan et al. (2013). *Lancet*.

Couple Transmission Model

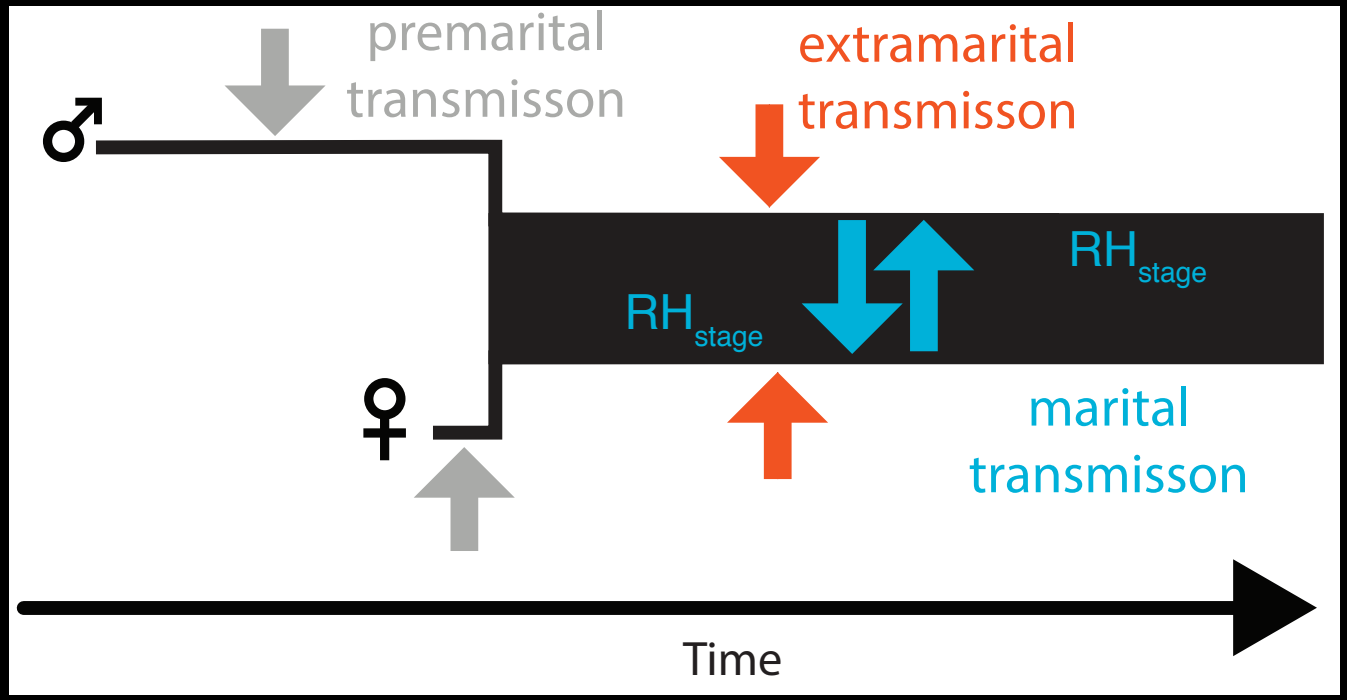


Bellan et al. (2013). *Lancet*.

Couple Transmission Model

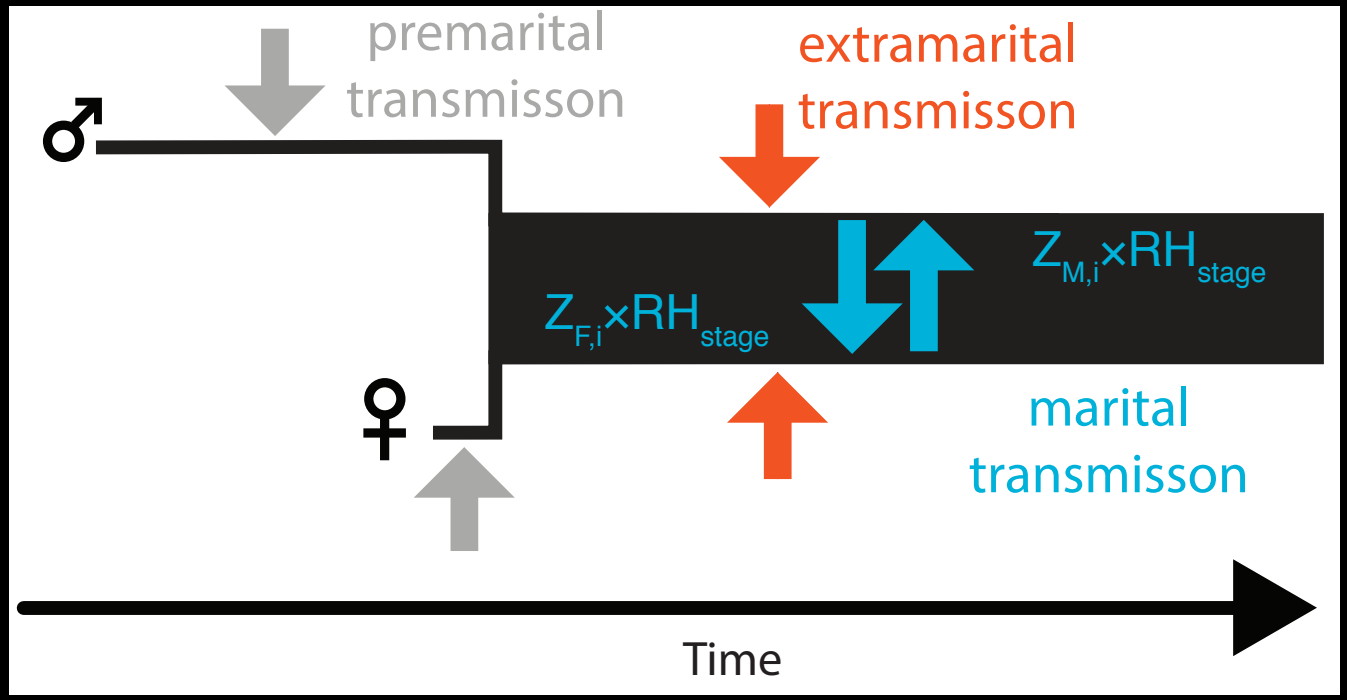


Couple Transmission Model

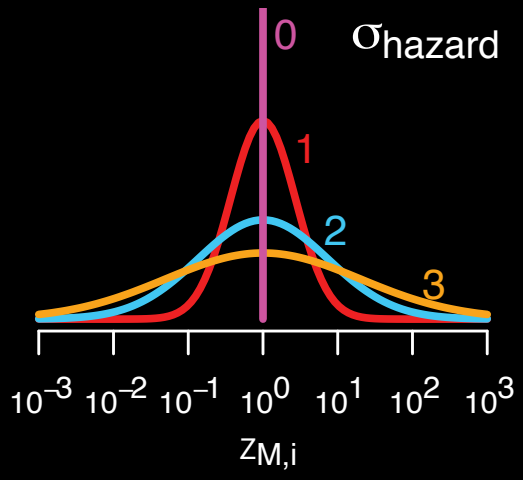


relative hazard (RH) varies by HIV stage

Couple Transmission Model

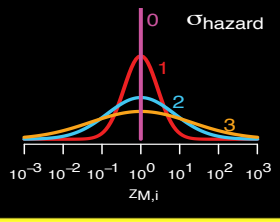


Heterogeneity



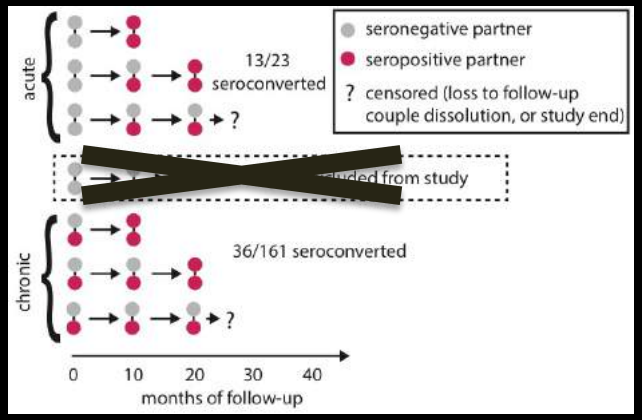
Simulating Rakai Transmission & Observation

Inputs



1. Simulate transmission in couples cohort ← process-centric
2. Replicate Rakai study design

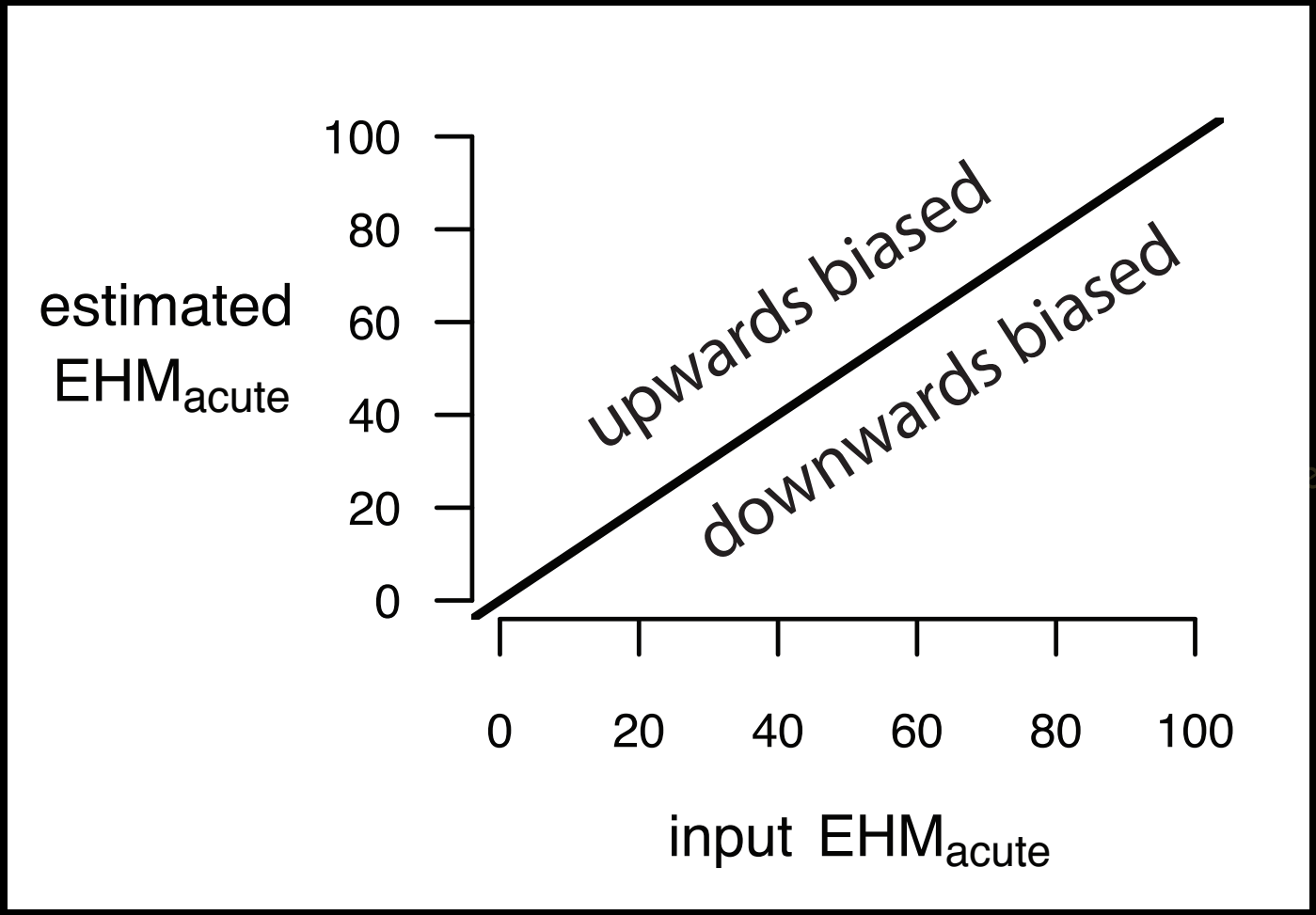
data-centric →



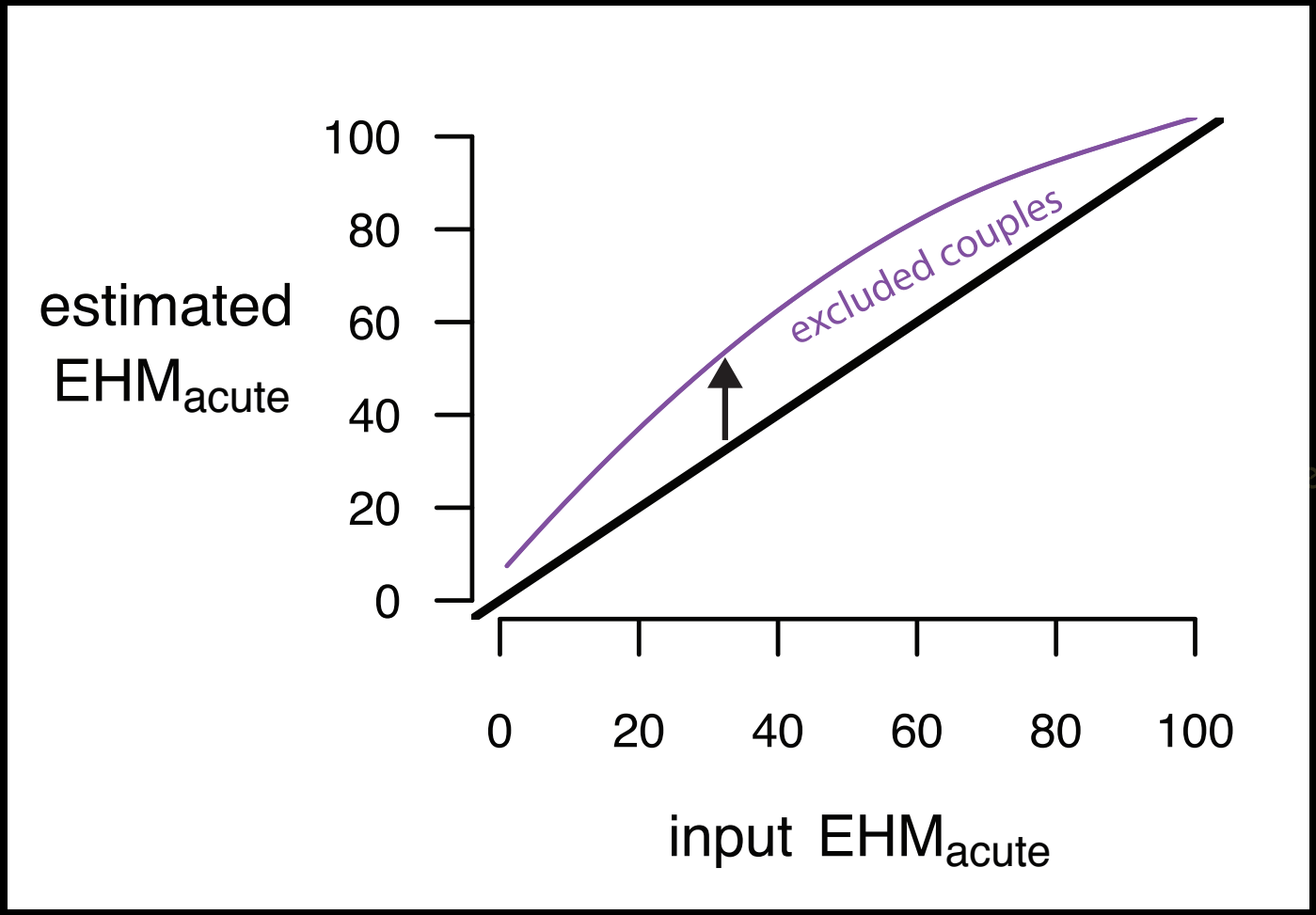
3. Apply published analyses to simulated data.

Estimated EHM_{acute}

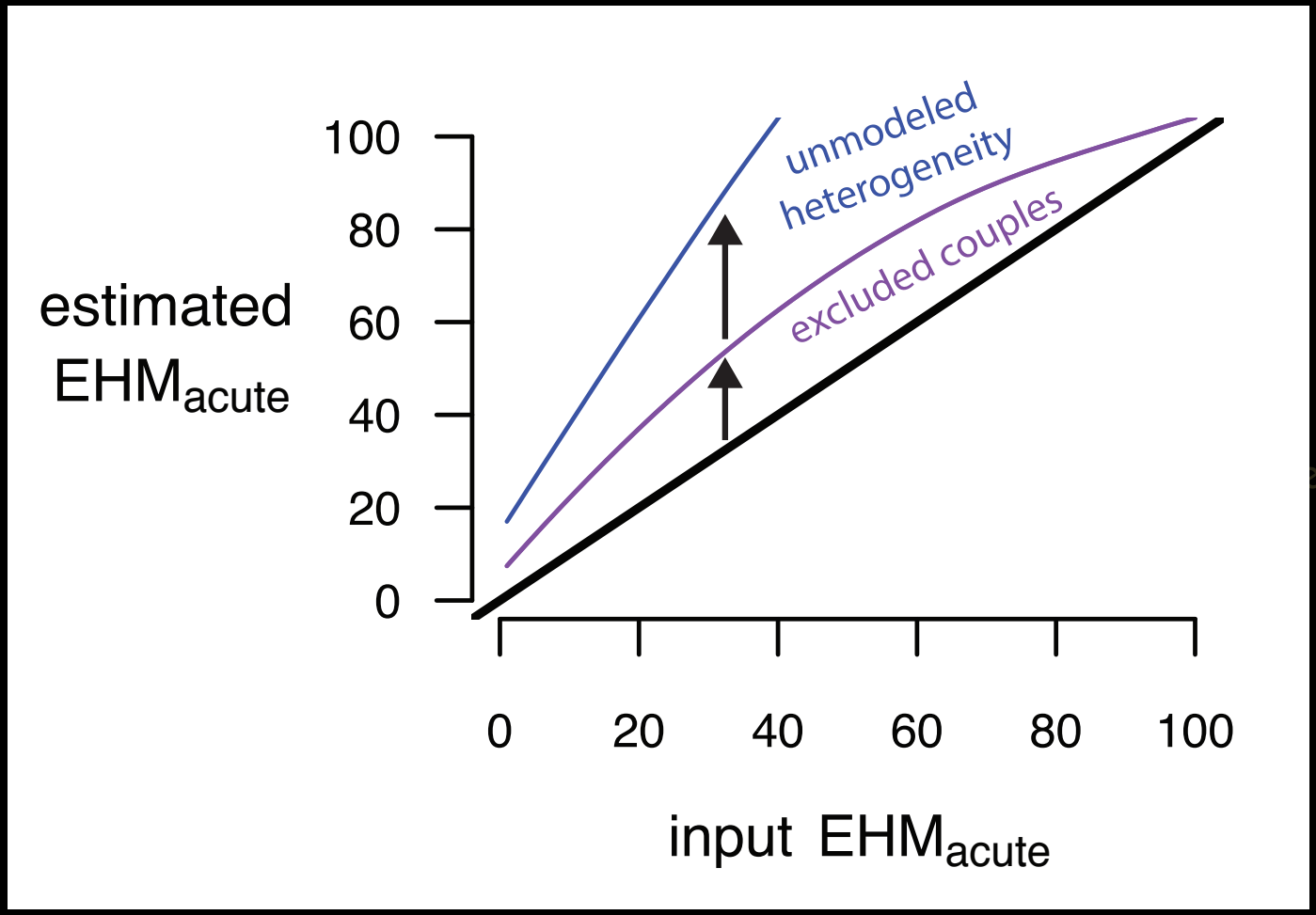
Bias Analysis



Bias Analysis



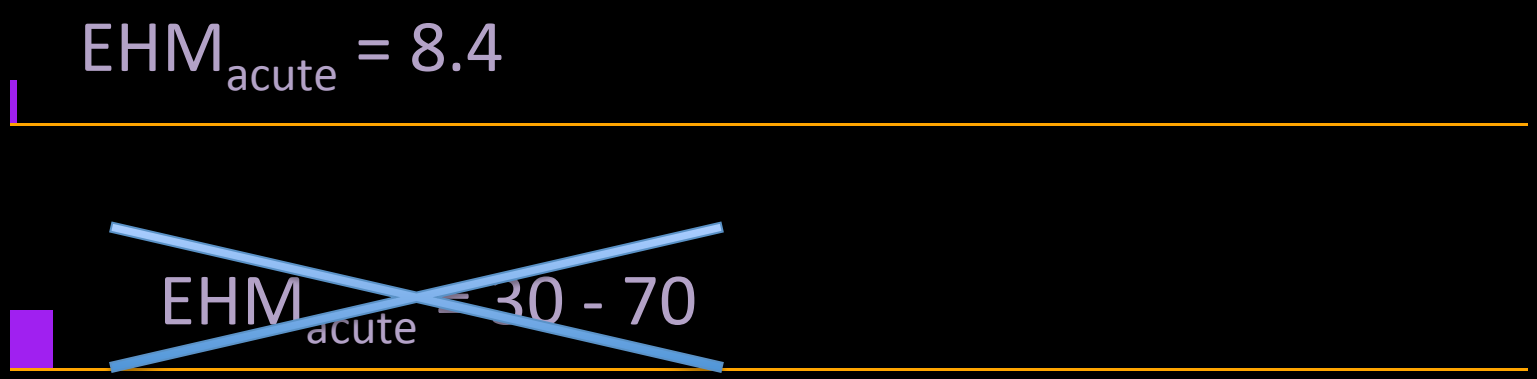
Bias Analysis



Bias-Adjusted Estimates (ABC-SMC)

Estimation

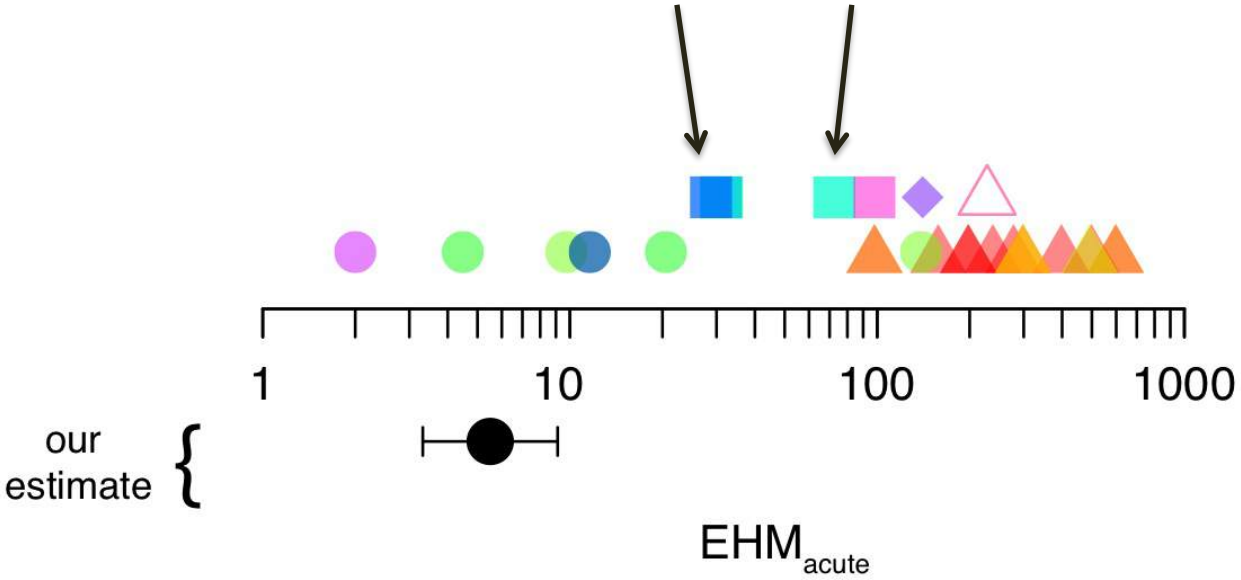
What inputs consistent with Rakai data?



Variation in EHM_{acute} Estimates

Most commonly cited estimates

EHM_{acute} = 35 and 71



(1) Jacquez et al. 1994
(2) Pinkerton and Abramson 1996
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(4) Kretzschmar & Dietz 1998
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(15) Rasmussen et al. 2014

based on
epidemic curve
viral load
Rakai
Rakai & epidemic curve
phylogenetics

Variation in EHM_{acute} Estimates

Most commonly cited estimates

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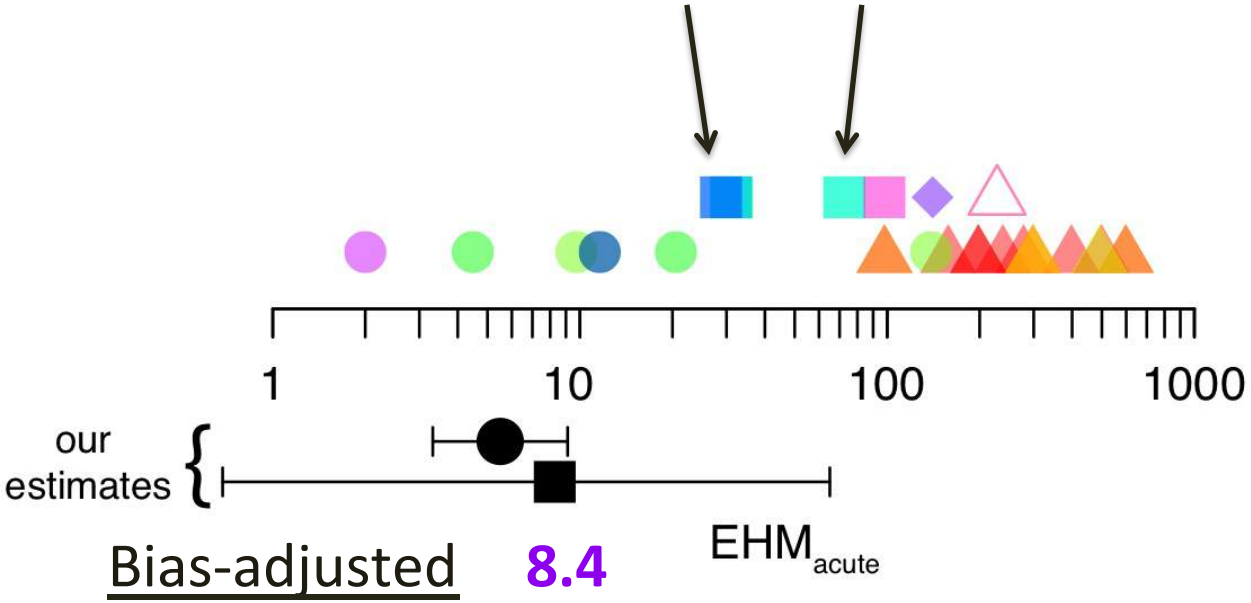

Bias-adjusted **8.4**

- (1) Jacquez et al. 1994
- (2) Pinkerton and Abramson 1996
- (3) Koopman et al. 1997
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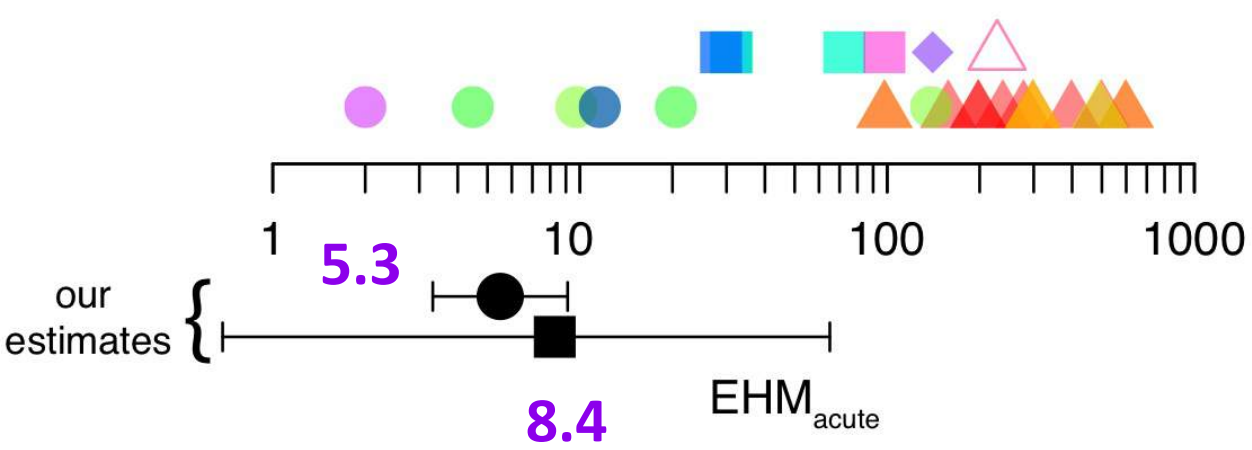
based on

- epidemic curve
- viral load
- Rakai
- Rakai & epidemic curve
- phylogenetics

Variation in EHM_{acute} Estimates

Viral load & Rakai estimates reconciled by adjusting for biases.



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based on

- epidemic curve
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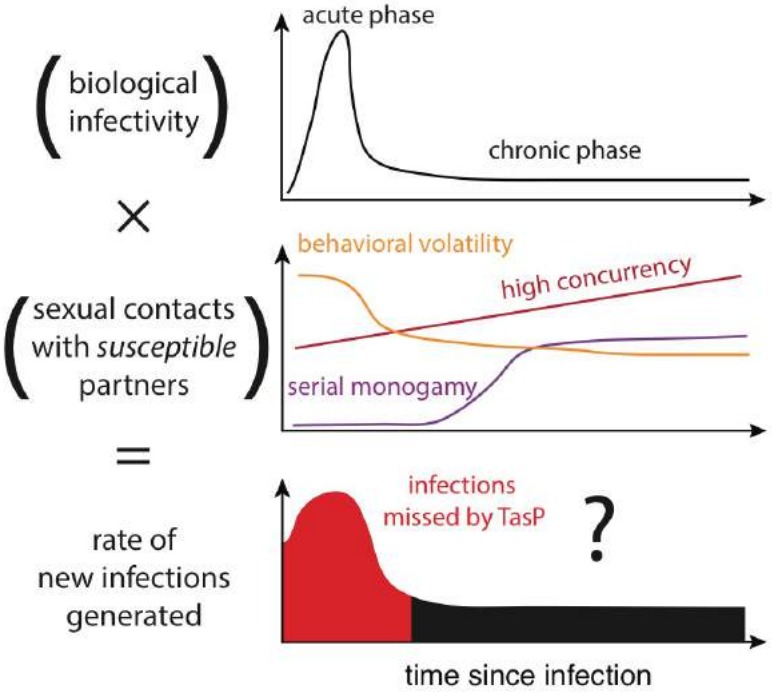
- phylogenetics

Early proportion of transmission AF_{early}?



- (1) Jacquez et al. 1994
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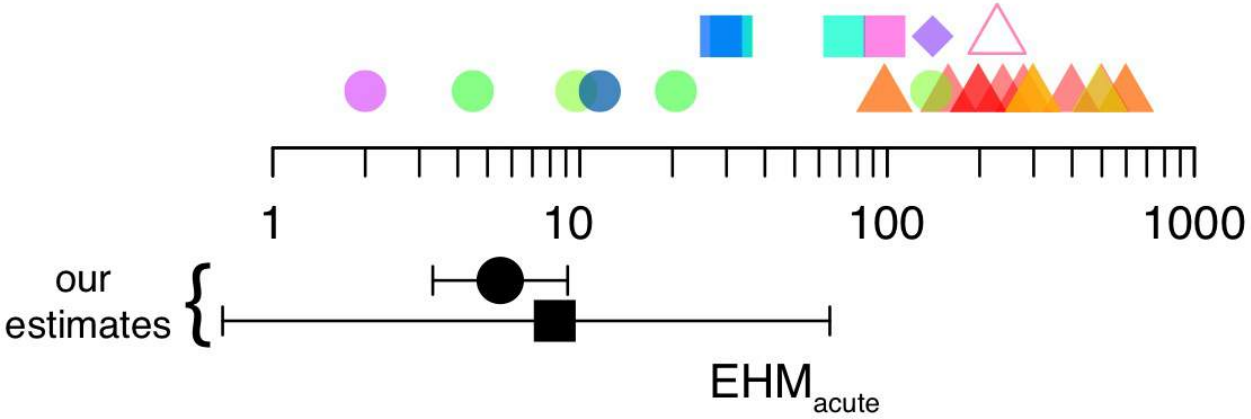
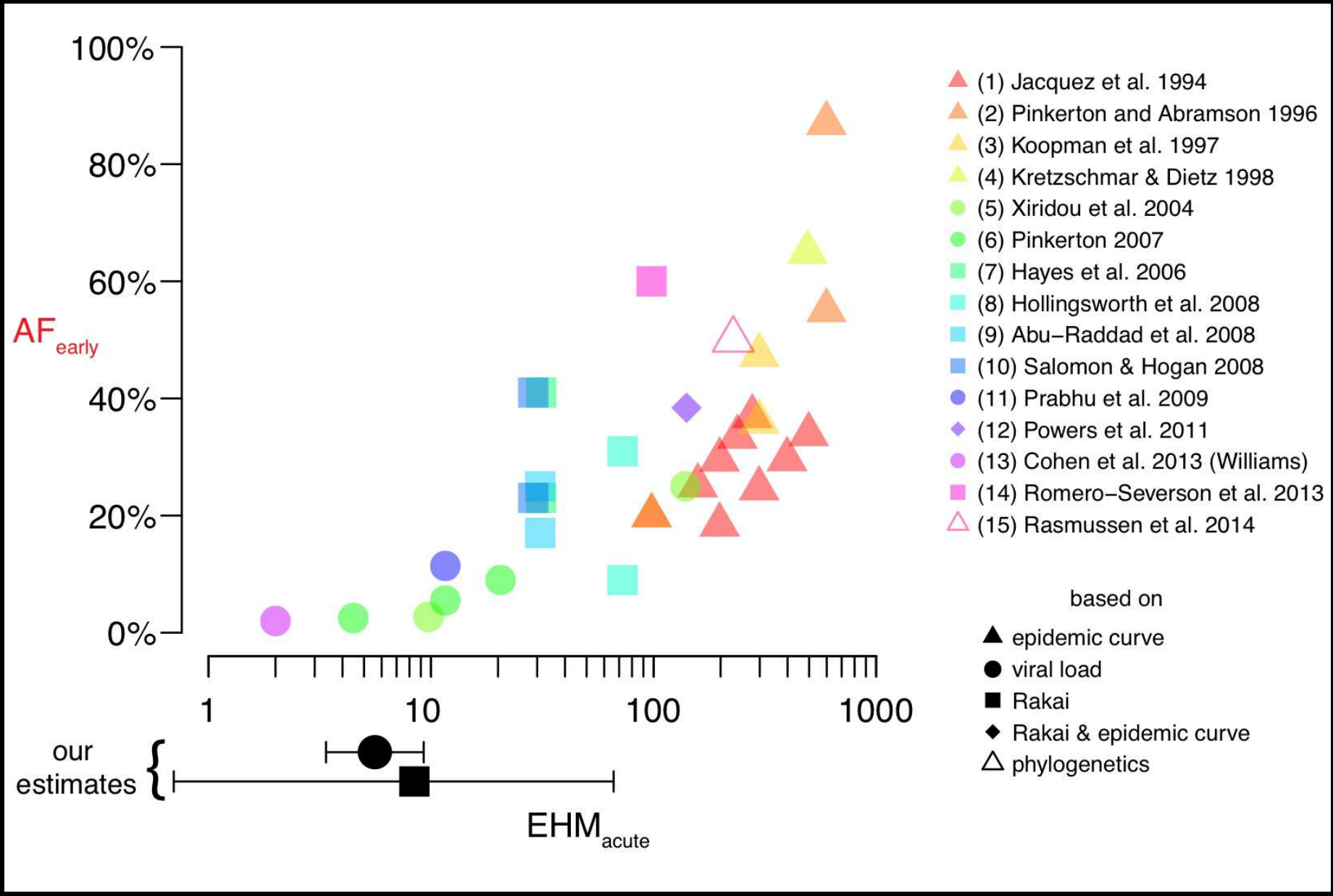


based on

- epidemic curve
- viral load
- Rakai
- Rakai & epidemic curve
- phylogenetics

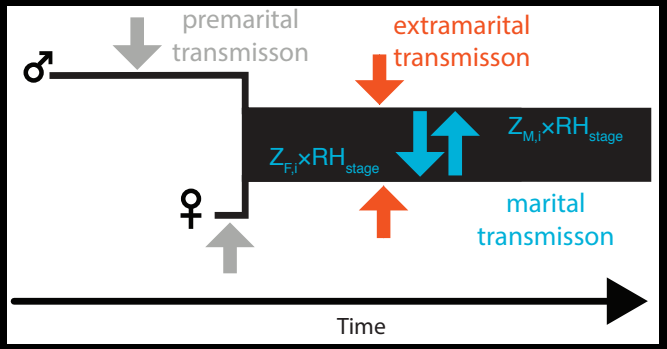
What about AF_{early}?



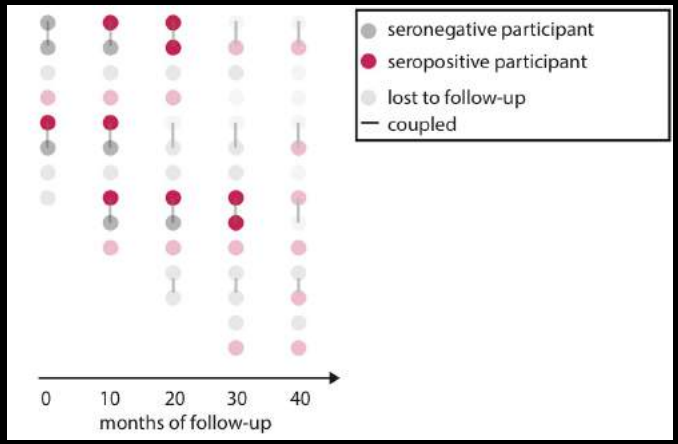
Conclusions

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

process-centric



data-centric



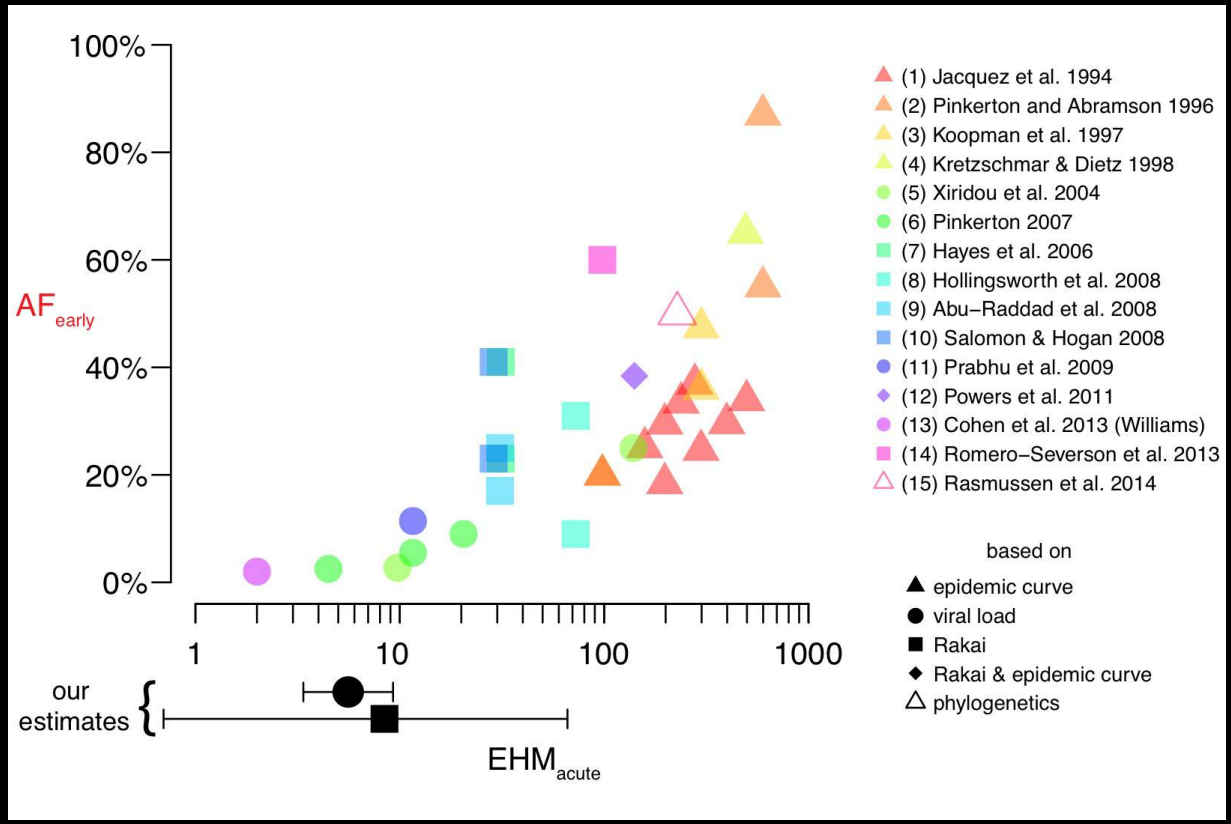
Bellan et al. 2015. *PLOS Medicine*.

Why publish?

- Communication (advance science & policy)
- Career
- Peer Review

How do modeling projects differ?

- Do not always collect empirical data
- Rely more heavily on literature

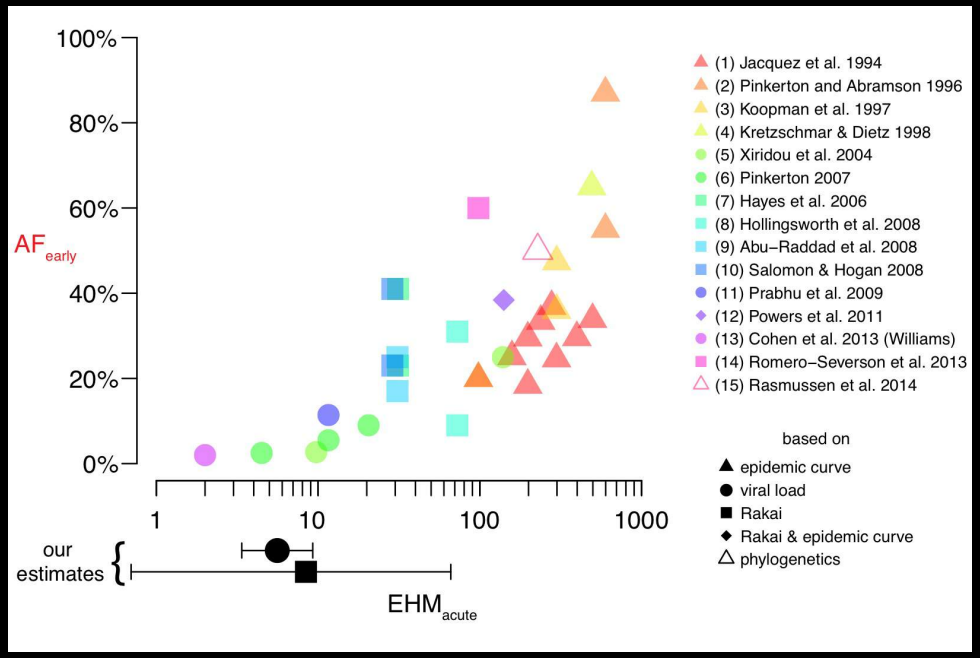


Development of Study Concept

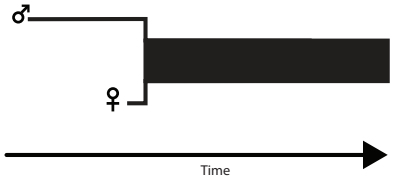
- What is your question?
  How infectious is acute phase of HIV?
- Why is it interesting?
  Affects effectiveness of TasP
- Who is interested?
  HIV epidemiologists, policy makers
- Can it be narrowed down to a question about specific quantitative relationships?
  ~~Hazard ratio acute vs chronic~~
  EHM_{acute} estimated from available data

Review of Literature & Available Data

- Who has tried to answer this before and how did they do it?
- What are these studies short-comings?
- Find useful parameter estimates or data sets



The DHS Program
Demographic and Health Surveys



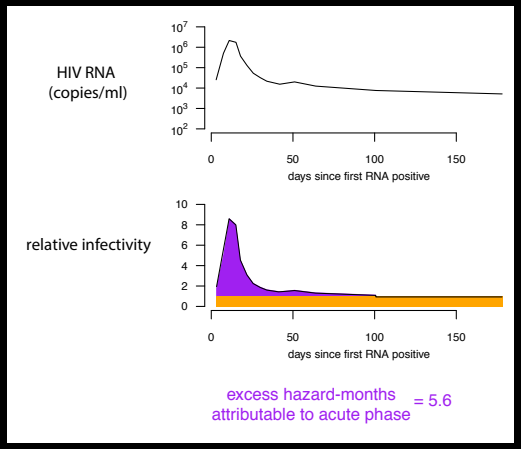
Construction of Modeling Framework

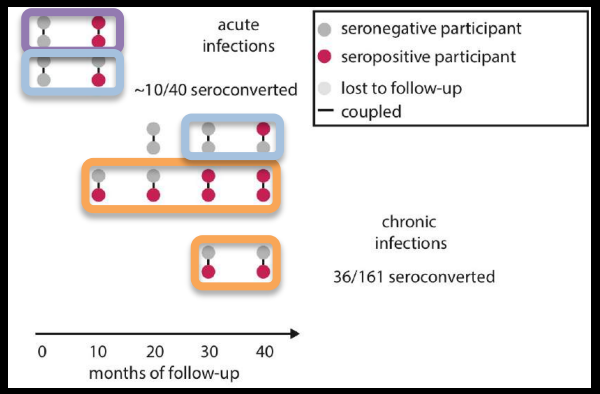
- Drawbacks of previous studies to mitigate
  - EHM_{acute}
  - heterogeneity/study design
  - simulation for validation

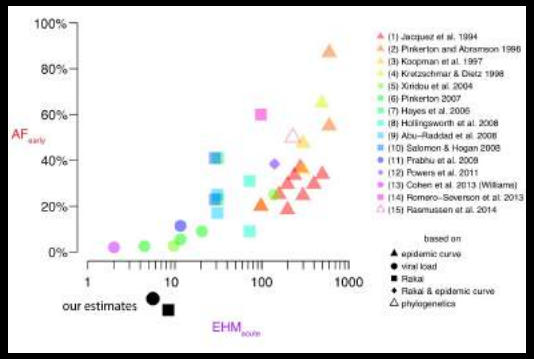
- modeling elements necessary for question
  - couple-centric
  - stochastic
  - monthly time step
  - heterogeneity, study design, variable infectivity

Writing the Model & Producing Output

- What are the 1-3 graphical outputs that will display the answer(s) to my question?







- Coding & debugging & commenting
- Simulation to verify methods & debug
- Write your methods at this stage!

Model Validation & Robustness

- Sensitivity/Elasticity analyses
- Model Validation (out-of-sample predictions)
- Comparison to alternative models

Choose the Journal

- Journal scope statement (on their website)

  "general interest on biomedical, environmental, social and political determinants of health… emphasizes work that advances clinical practice, health policy or pathophysiological understanding to benefit health"

- Audience

  epidemiologists, clinicians, policymakers, modelers

- How mathematical will your article be?

  slightly, most math in appendix (23 pgs, 9 figures, data)

- Text, figure, table limits

Write-Up of Results, Intro/Discussion

- State assumptions clearly

S5 Table. Assumptions made by previous analyses of the Rakai retrospective cohort that are relaxed in our re-analysis.

Study	Assumption	Bias in EHM_{acute}	Correction
Wawer et al. 2005	All infections and deaths occur exactly at the midpoint of the cohort interval in which they were observed.	Slight downward	We relax this assumption (as does Hollingsworth et al.) by including a latent (unobserved) variable for infection time.
Wawer et al. 2005 Hollingsworth et al. 2008	Incident, prevalent and late couples are *different types* of couples and real couples do *not* switch between these categories.	Slight downward	We relax this assumption by modeling in such a way that each of these categories simply represents that the cohort study only *observed* each couple in one of their disease phase categories.
Wawer et al. 2005 Hollingsworth et al. 2008	Couples were sampled in an unbiased manner.	Substantial upward	In reality, couples providing strong evidence for lower acute phase infectivity were more likely to be excluded from the Rakai cohort based on exclusion criteria of couples lost to follow-up. We relaxed this assumption by explicitly including the study inclusion criteria in our model.
Wawer et al. 2005 Hollingsworth et al. 2008	Transmission rates into couples and between serodiscordant partners are the same (i.e. homogenous) for all couples.	Substantial upward	We relaxed this assumption by allowing each individual to have a risk deviate that affects their risk of acquiring HIV; risk deviates were sampled from lognormal distributions with standard deviations estimated by fitting our couples transmission model to the data.

Submission

- Cover letter:

  If journal isn't mathematical,
  state clearly why approach is appropriate!

Revisions

- Expect reviewers to question assumptions
  - Helps you choose additional sensitivity analyses
- Expect some reviewers to not understand methods
  - Helps improve clarity

Revisions

Please also keep in mind the general medical audience of PLOS Medicine; the paper needs to be understandable by individuals who are not expert modellers in the field.

We have made several changes to the manuscript to make it more understandable to the general reader:

- We have moved the technical explanation of the couples transmission model to the appendix, and only highlight the two main points necessary to understand our results: (1) changing hazard by disease stage, (2) heterogeneity in risk between couples.
- Replaced the technical description of the simulation model with a schematic diagram in Figure 3.

Revisions

"We believe that the reviewer misinterpreted XXXX because we were not clear enough. We have clarified this by XXXX."

Acknowledgements

- Juliet Pulliam, Meyers Lab at UT Austin
- International Clinics on Infectious Disease Dynamics and Data (ICI3D)

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NSERC
CRSNG

Title: Reassessment of HIV-1 Acute Phase Infectivity

Attribution:

Bellan SE, Dushoff J, Galvani AP, Meyers LA (2015) Reassessment of HIV-1 Acute Phase Infectivity: Accounting for Heterogeneity and Study Design with Simulated Cohorts. PLOS Med: 1–28. doi:10.1086/429411.

Code: https://github.com/sbellan61/AcuteRetroSim

For further information or slides in Microsoft Powerpoint please contact Steven Bellan (steve.bellan@uga.edu).