Impact of CDC's HIV Preexposure Prophylaxis Guidelines among MSM in the United States

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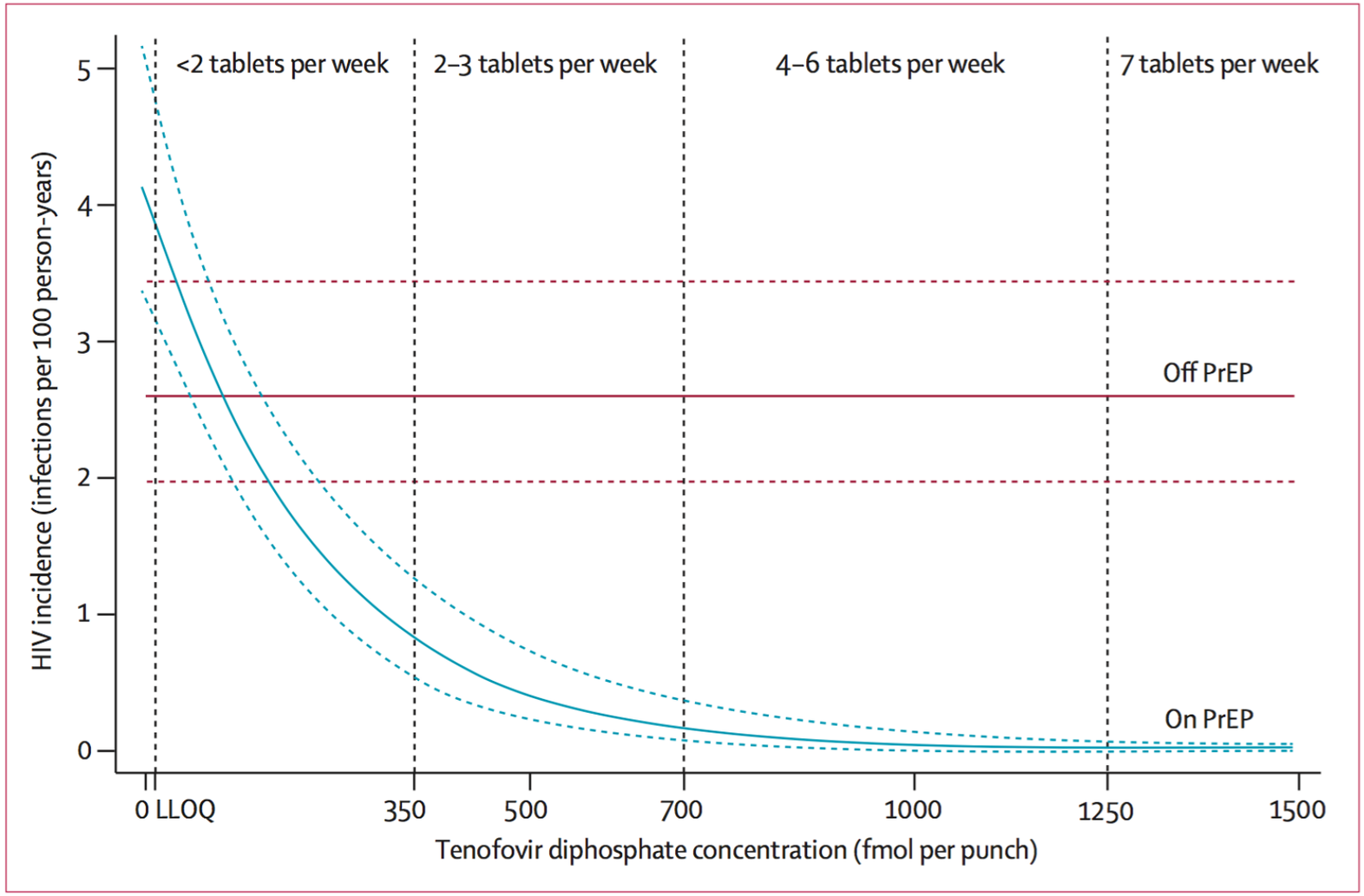
HIV Preexposure Prophylaxis

- Anti-retroviral treatment provided to HIV-uninfected persons
- Decreases biological risk of infection when HIV-infected partner has uncontrolled viral replication
- Men who have sex with men (MSM) in the US are a high-priority population for PrEP
- 5% to 10% of MSM with indications currently using it

PrEP is More Effective When Adherence is Better

- Efficacy of daily oral PrEP established in several RCTs
  - iPrex trial among MSM and TG women: 44% incidence reduction in intent-to-treat analyses
- Secondary iPrEx analyses suggest non-linear dose-response effect



Grant, 2014, Lancet Infect Dis

Adherence is Better When Effectiveness is Known

Original Investigation

Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services

Albert Y. Liu, MD, MPH; Stephanie E. Cohen, MD, MPH; Eric Vittinghoff, PhD; Peter L. Anderson, PharmD;
Susanne Doblecki-Lewis, MD; Oliver Bacon, MD, MPH; Wairimu Chege, MD, MPH; Brian S. Postle, BS;
Tim Matheson, PhD; K. Rivet Amico, PhD; Teri Liegler, PhD; M. Keith Rawlings, MD; Nikole Trainor, MPH;
Robert Wilder Blue, MSW; Yannine Estrada, PhD; Me
Daniel J. Feaster, PhD; Robert Grant, MD, MPH; Susa
Susan Buchbinder, MD; Michael A. Kolber, PhD, MD

Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study

Robert M Grant, Peter L Anderson, Vanessa McMahan, Albert Liu, K Rivet Amico, Megha Mehrotra, Sybil Hosek, Carlos Mosquera, Martin Casapia, Orlando Montoya, Susan Buchbinder, Valdilea G Veloso, Kenneth Mayer, Suwat Chariyalertsak, Linda-Gail Bekker, Esper G Kallas, Mauro Schechter,
he iPrEx study team

Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial

Sheena McCormack, David T Dunn*, Monica Desai, David I Dolling, Mitzy Gafos, Richard Gilson, Ann K Sullivan, Amanda Cl*
Gabriel Schembri, Nicola Mackie, Christine Bowman, Charles J Lacey, Vanessa Apea, Michael Brady, Julie Fox, Stephen Taylor,
Saye H Khoo, James Rooney, Anthony Nardone, Martin Fisher, Alan McOwan, Andrew N Phillips, Anne M Johnson, Brian Gaz

No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting

Jonathan E. Volk,[1] Julia L. Marcus,[2] Tony Phengrasamy,[1] Derek Blechinger,[1] Dong Phuong Nguyen,[1] Stephen Follansbee,[1] and C. Bradley Hare[1]

CDC PrEP Guidelines for Clinical Practice

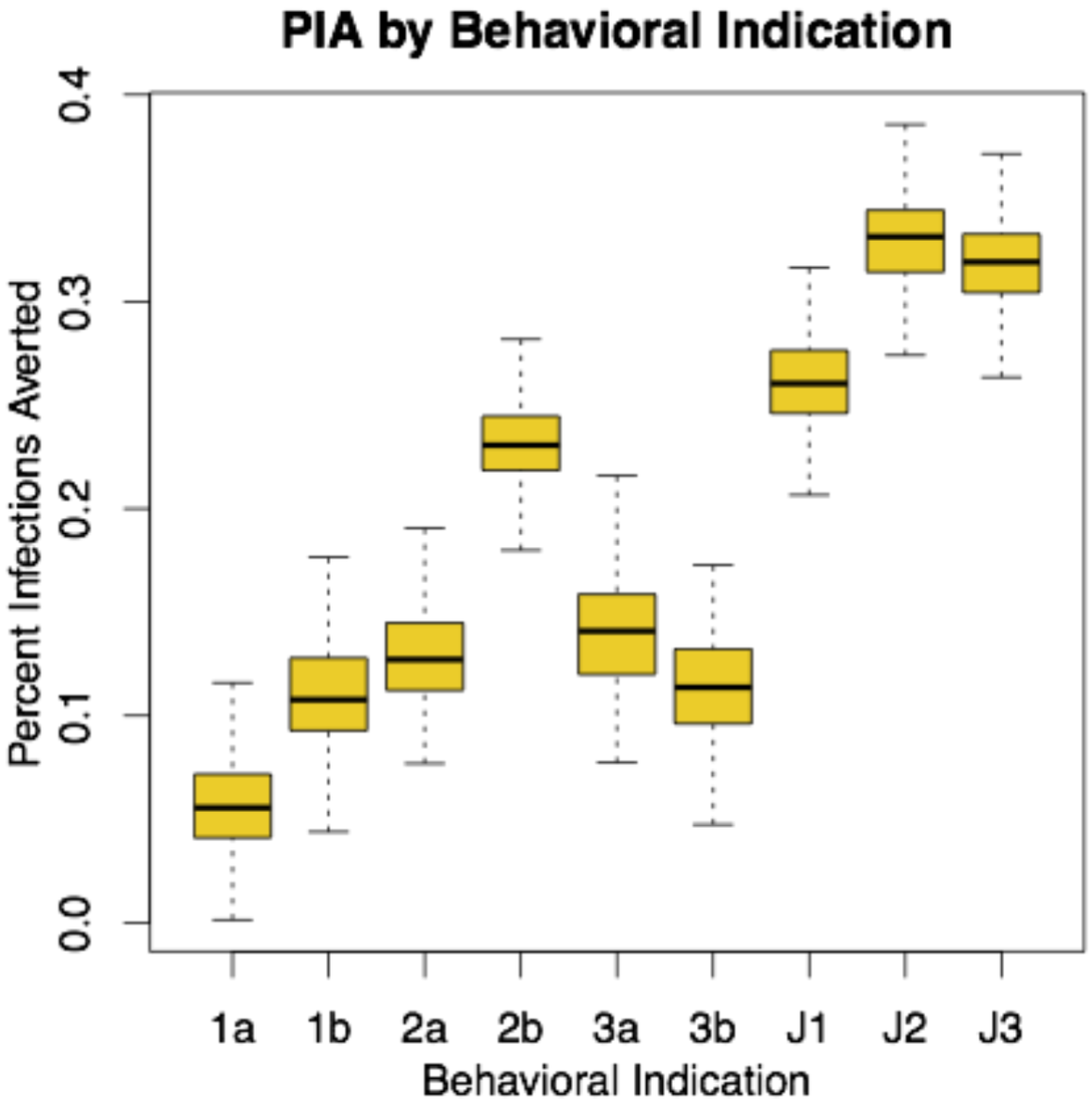
- US PHS/CDC released clinical practice guidelines indicating PrEP for those at “substantial risk” in 2014
- For MSM, prescription indications were:
  - Unprotected anal intercourse (UAI) in monogamous partnership with person not recently tested for HIV
  - UAI outside of a monogamous partnership
  - AI (including with condoms) in a known serodiscordant partnership
  - Any non-HIV STI diagnosis
- Clinicians recommended to screen for conditions in past 6 months, reevaluate risk every 12 months

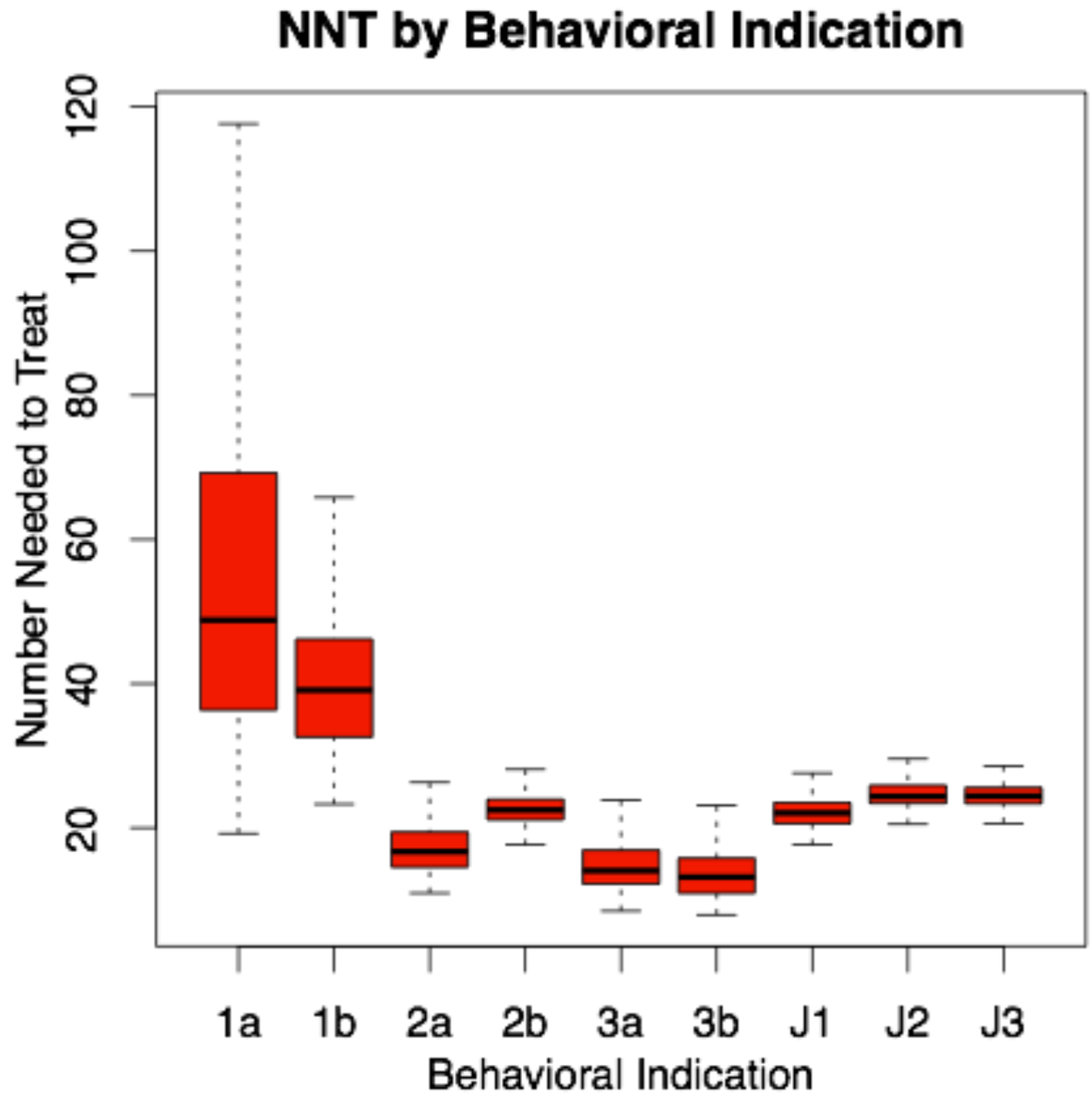
Model Example

Jenness SM, Goodreau SM, Rosenberg E, Beylerian EN, Hoover KW, Smith DK, Sullivan PS. Impact of CDC's HIV Pre-Exposure Prophylaxis Guidelines among MSM in the United States. *Journal of Infectious Diseases*. 2016; 214(12): 1800–1807.

Results by CDC Guideline Indication

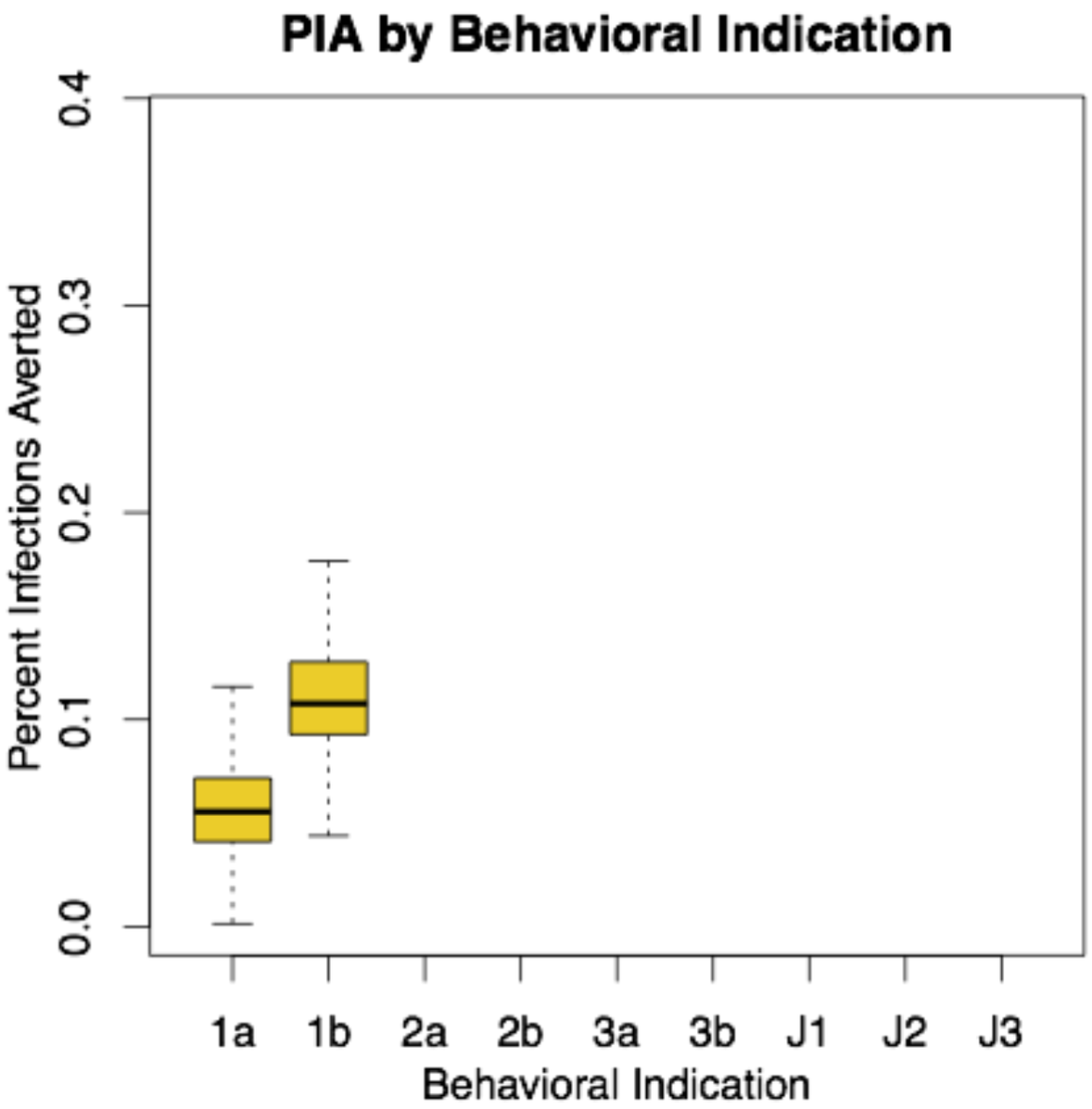
Effectiveness and efficacy across indications

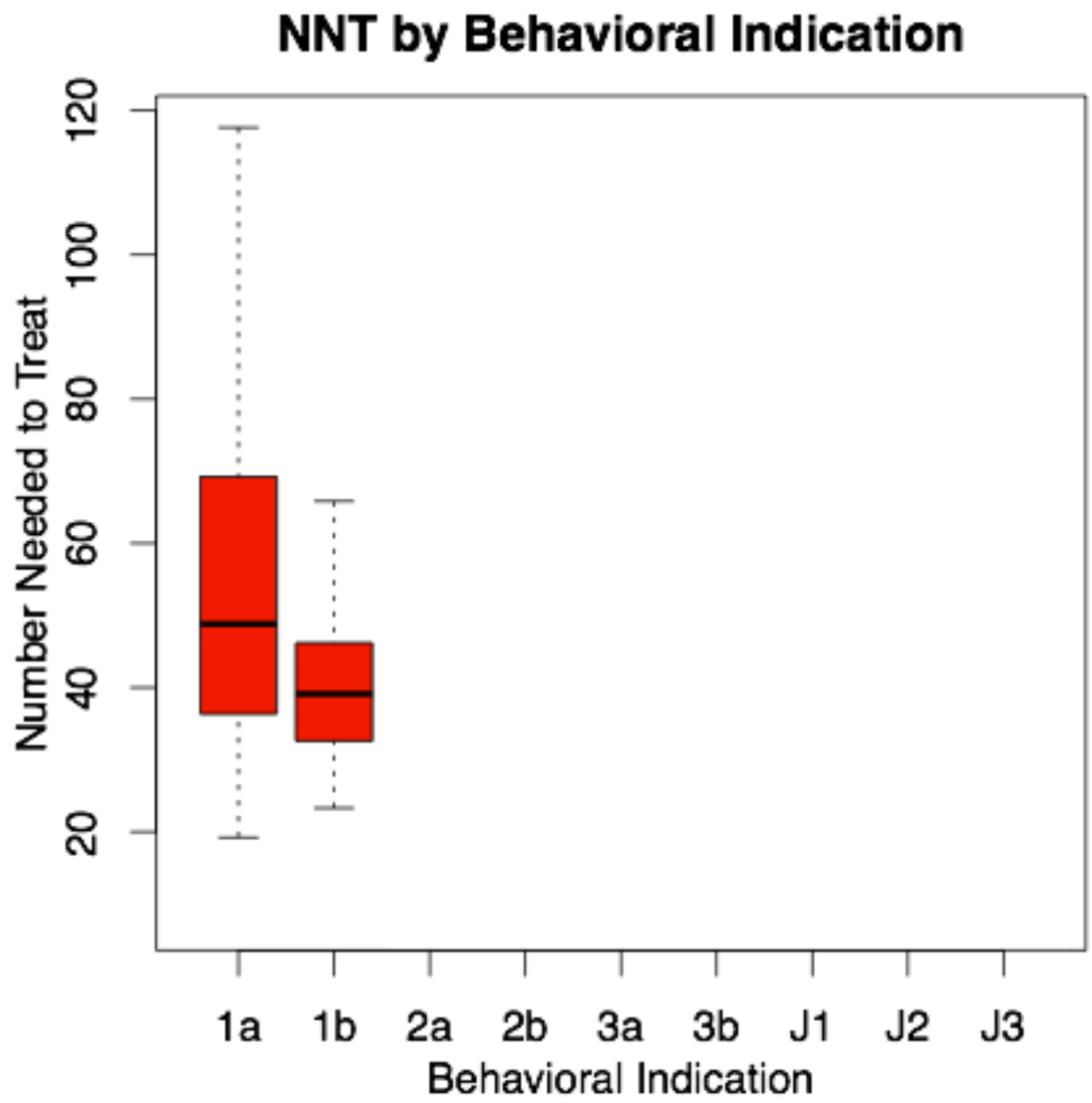




Results by CDC Guideline Indication

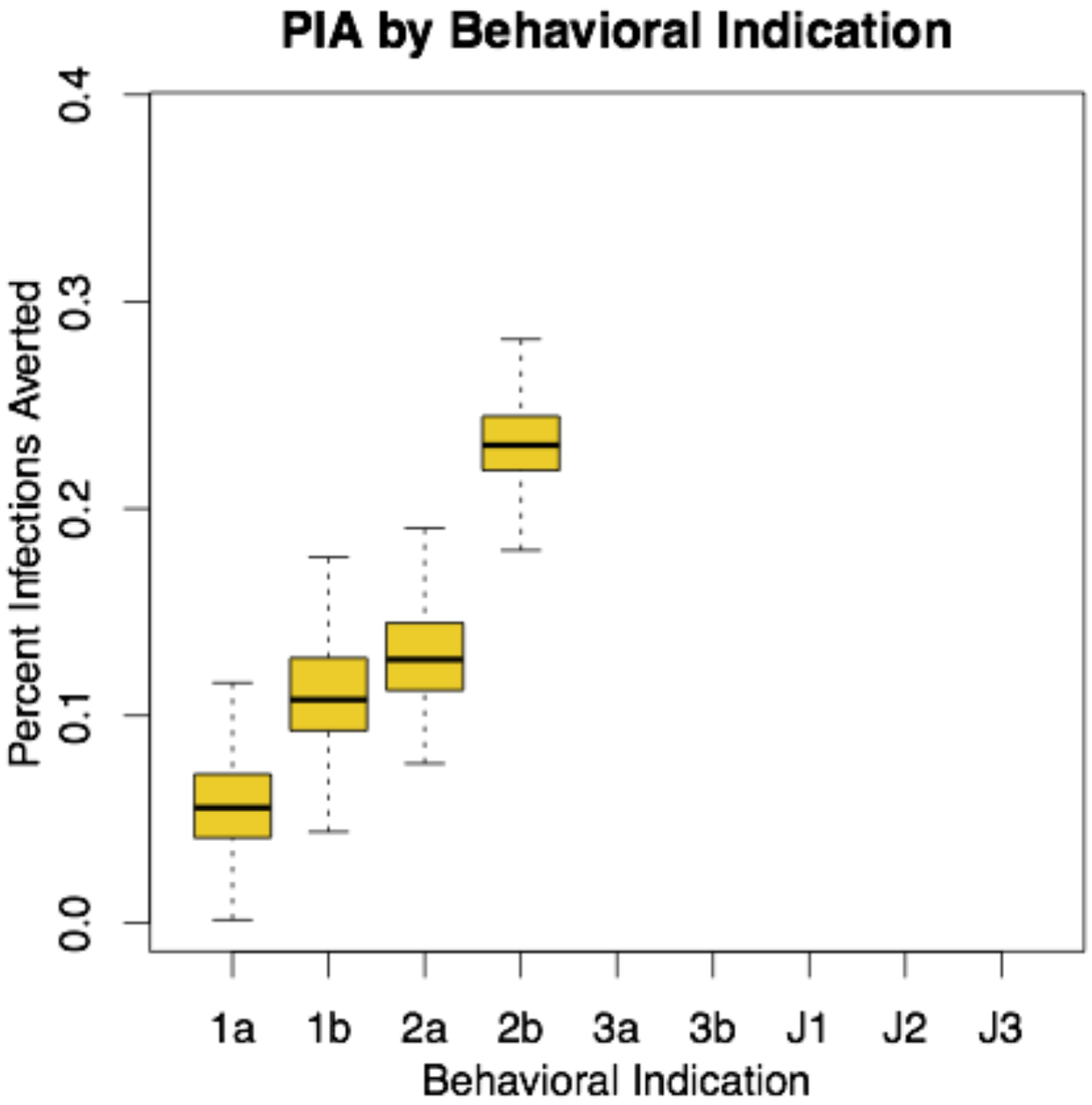
UAI with HIV status-unknown monogamous partner

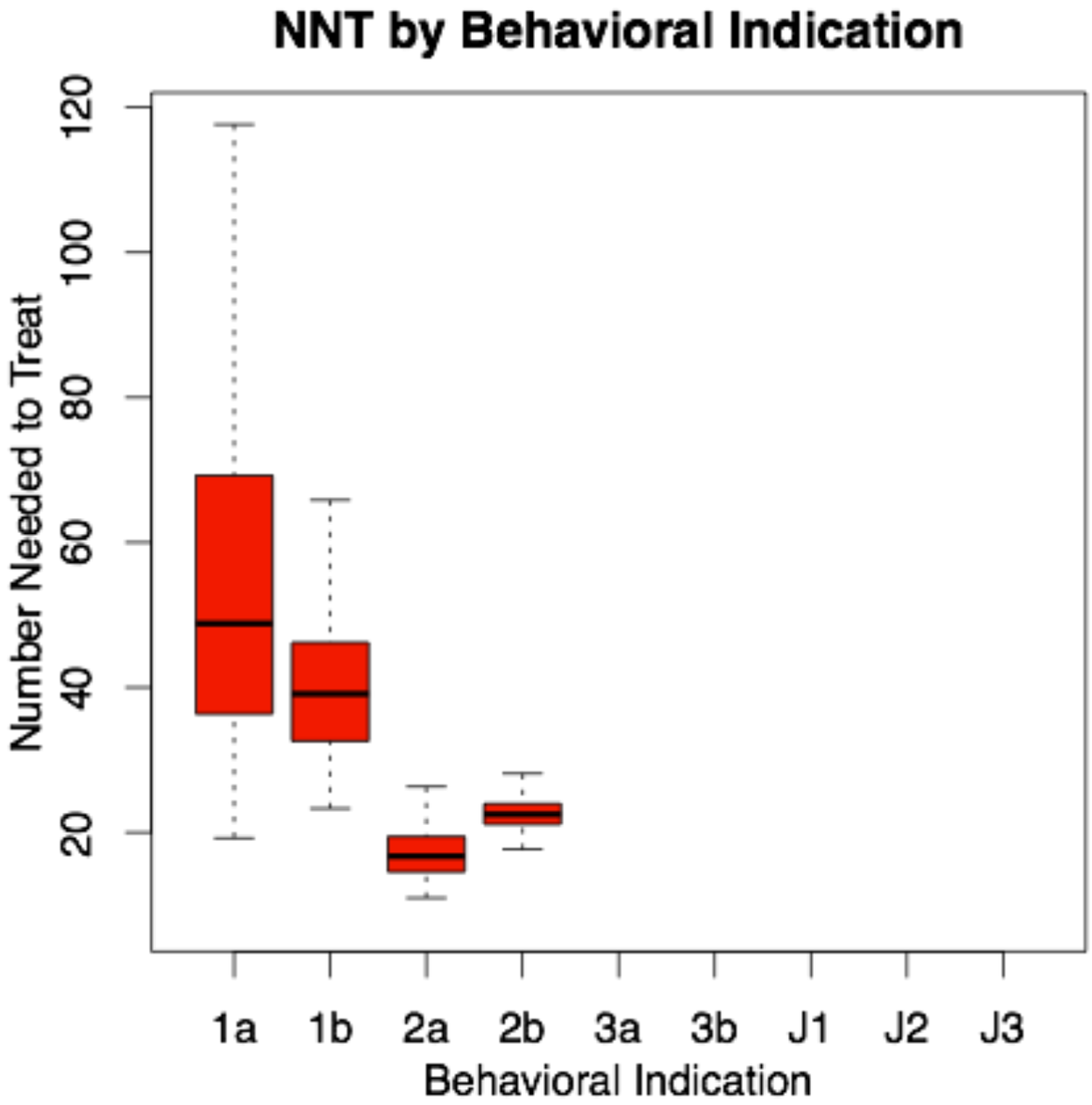




Results by CDC Guideline Indication

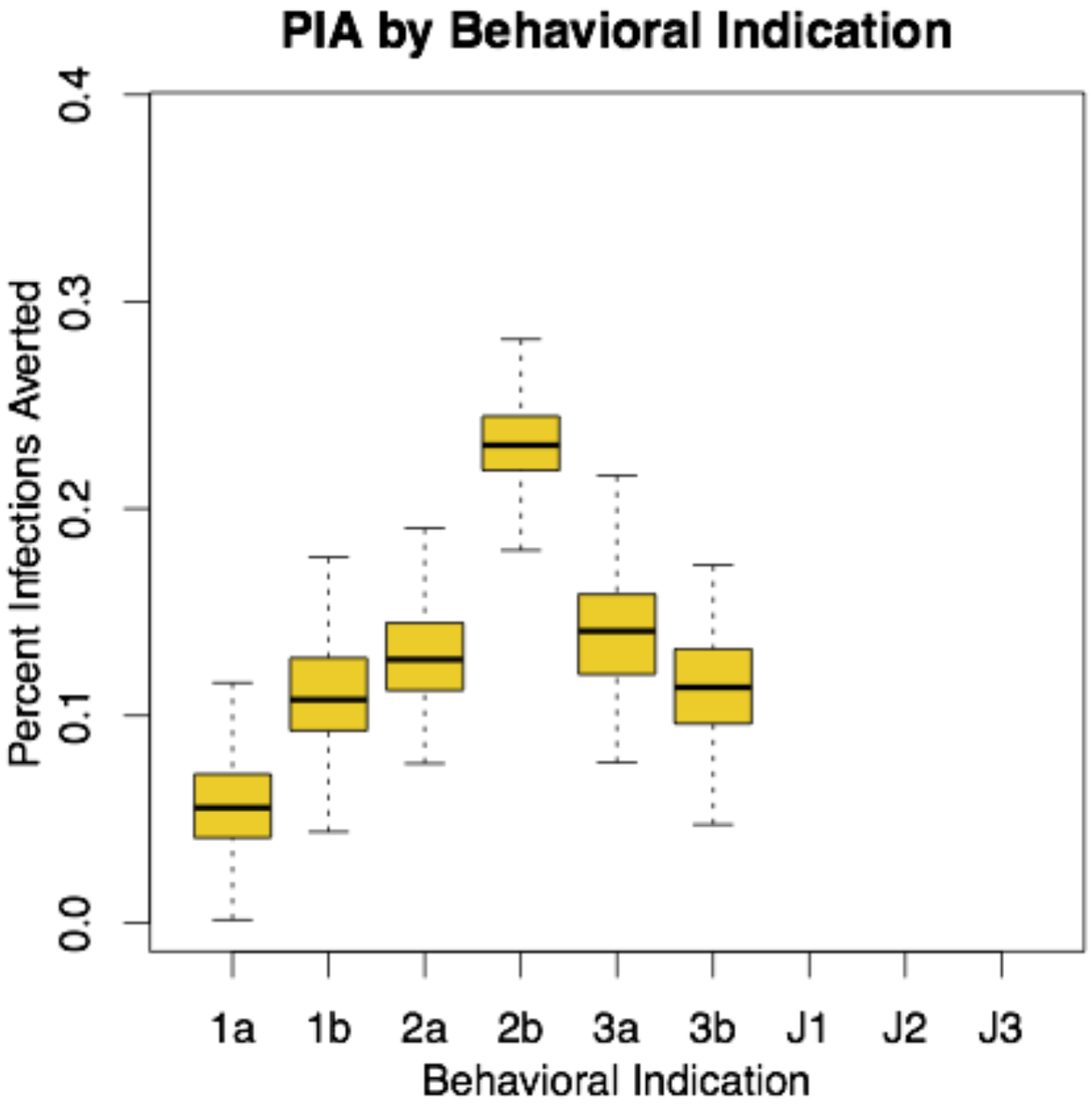
UAI outside of monogamous partnership

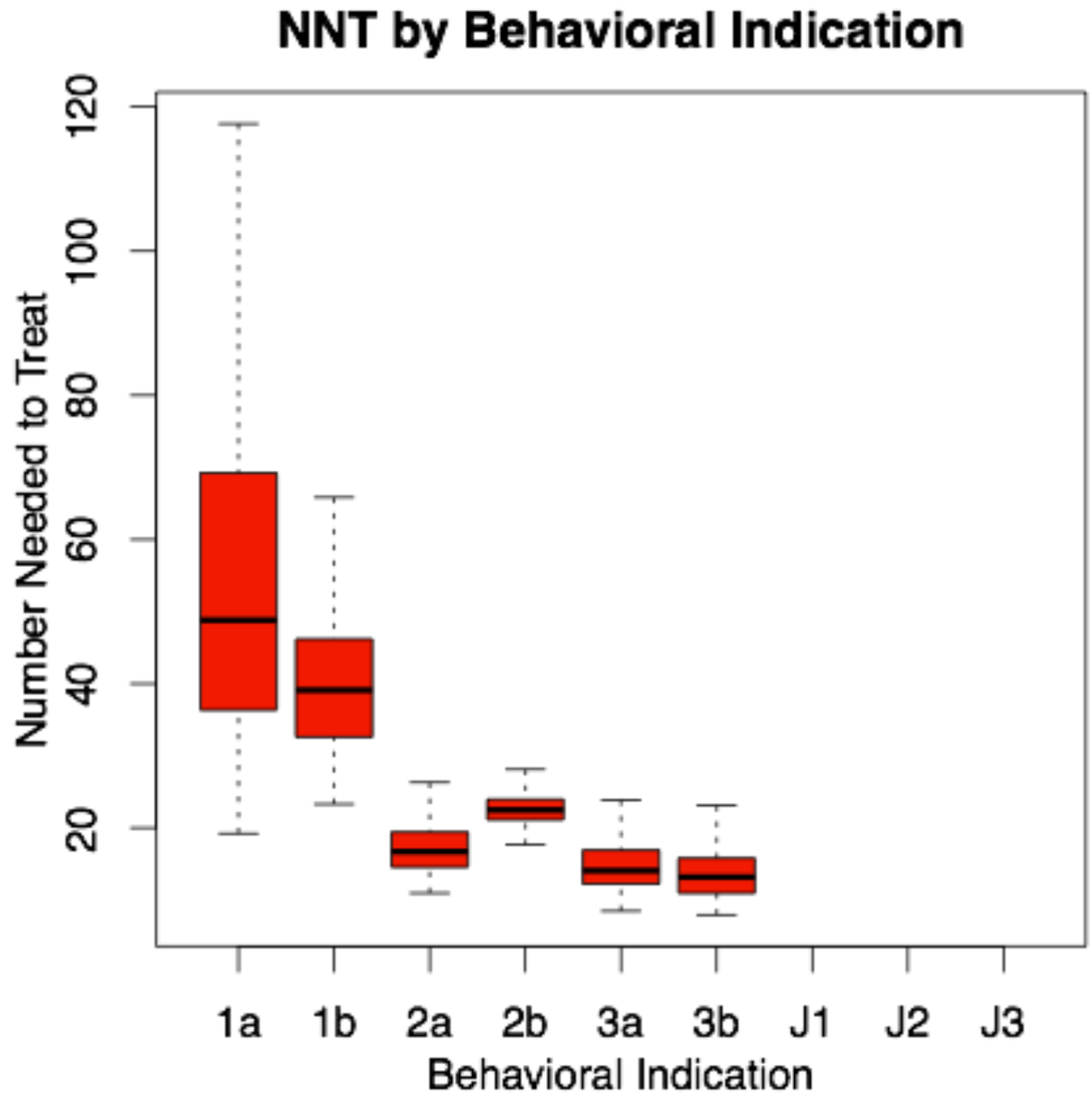




Results by CDC Guideline Indication

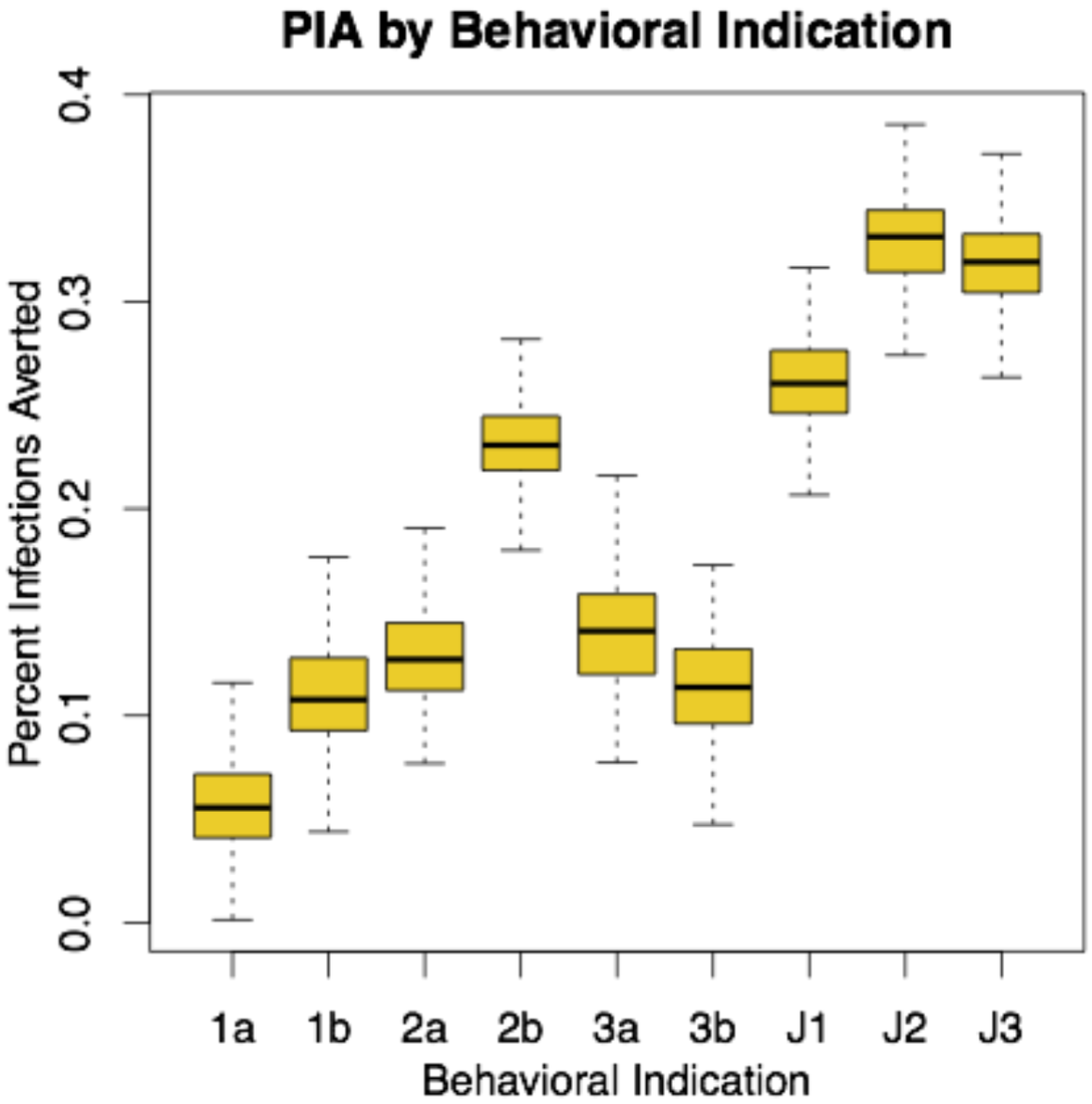
AI in known-serodiscordant partnership

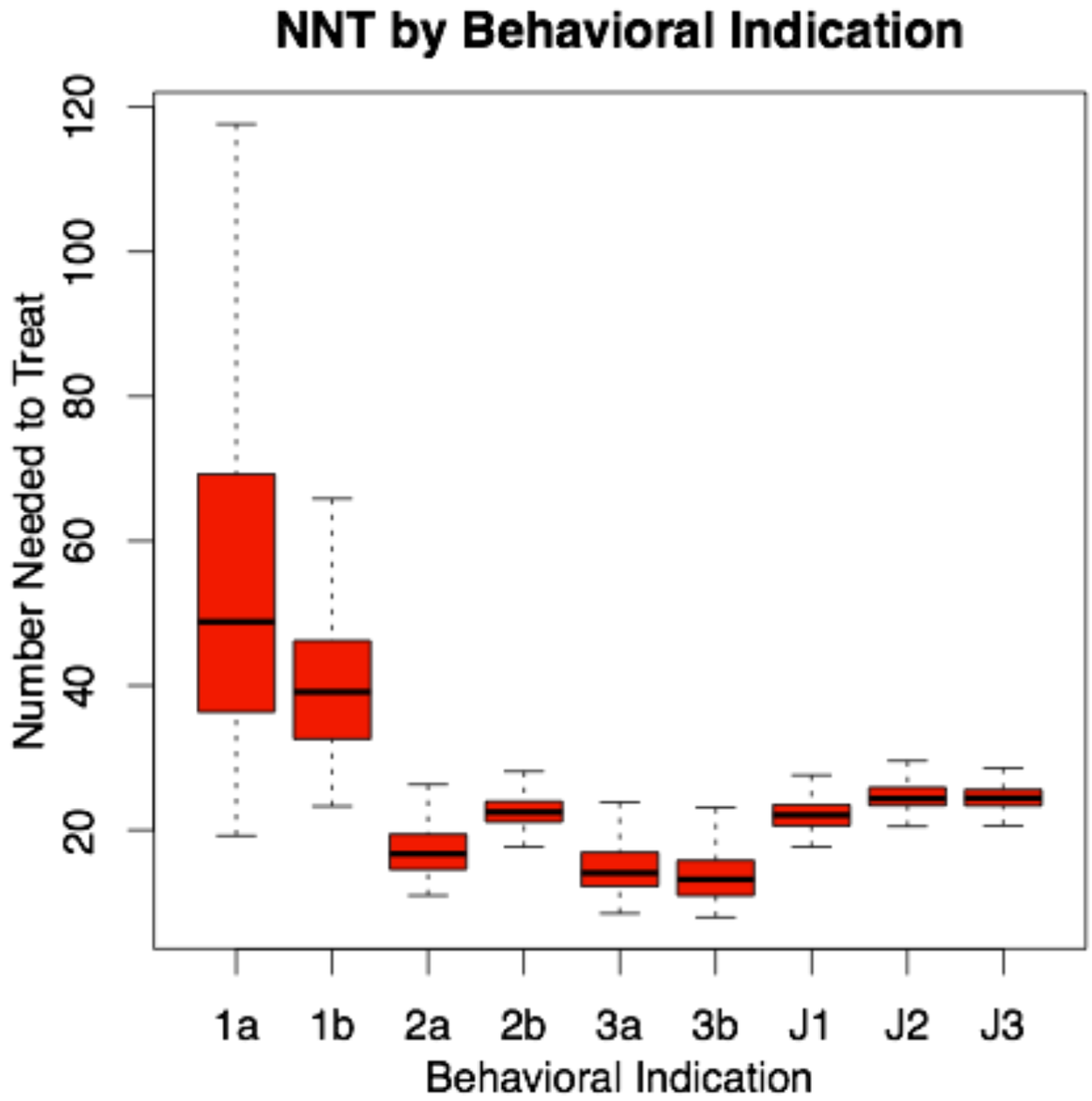




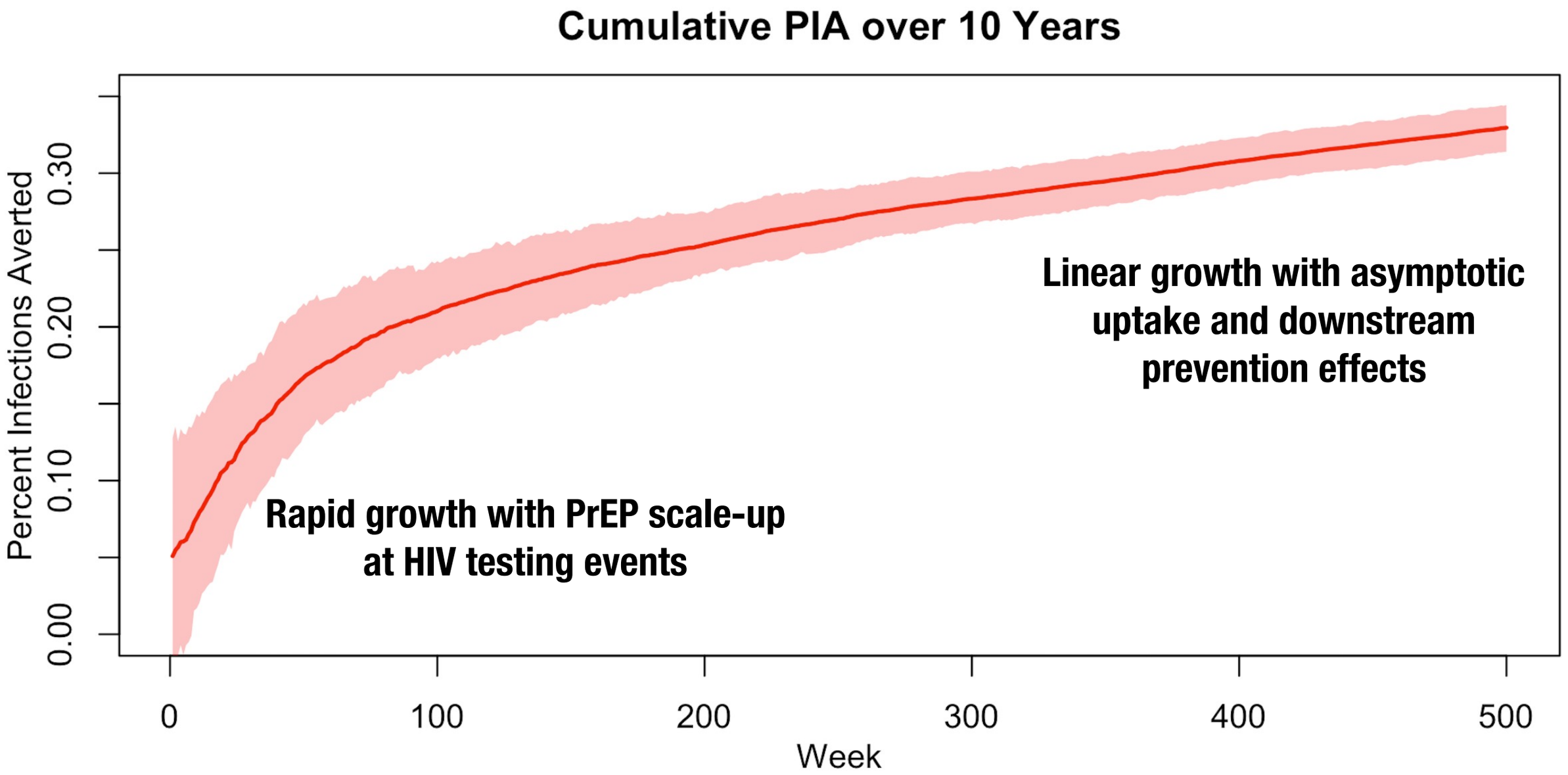
Results by CDC Guideline Indication

Joint scenarios = interpretations of CDC guidelines





Percent of Infections Averted in Joint Scenario



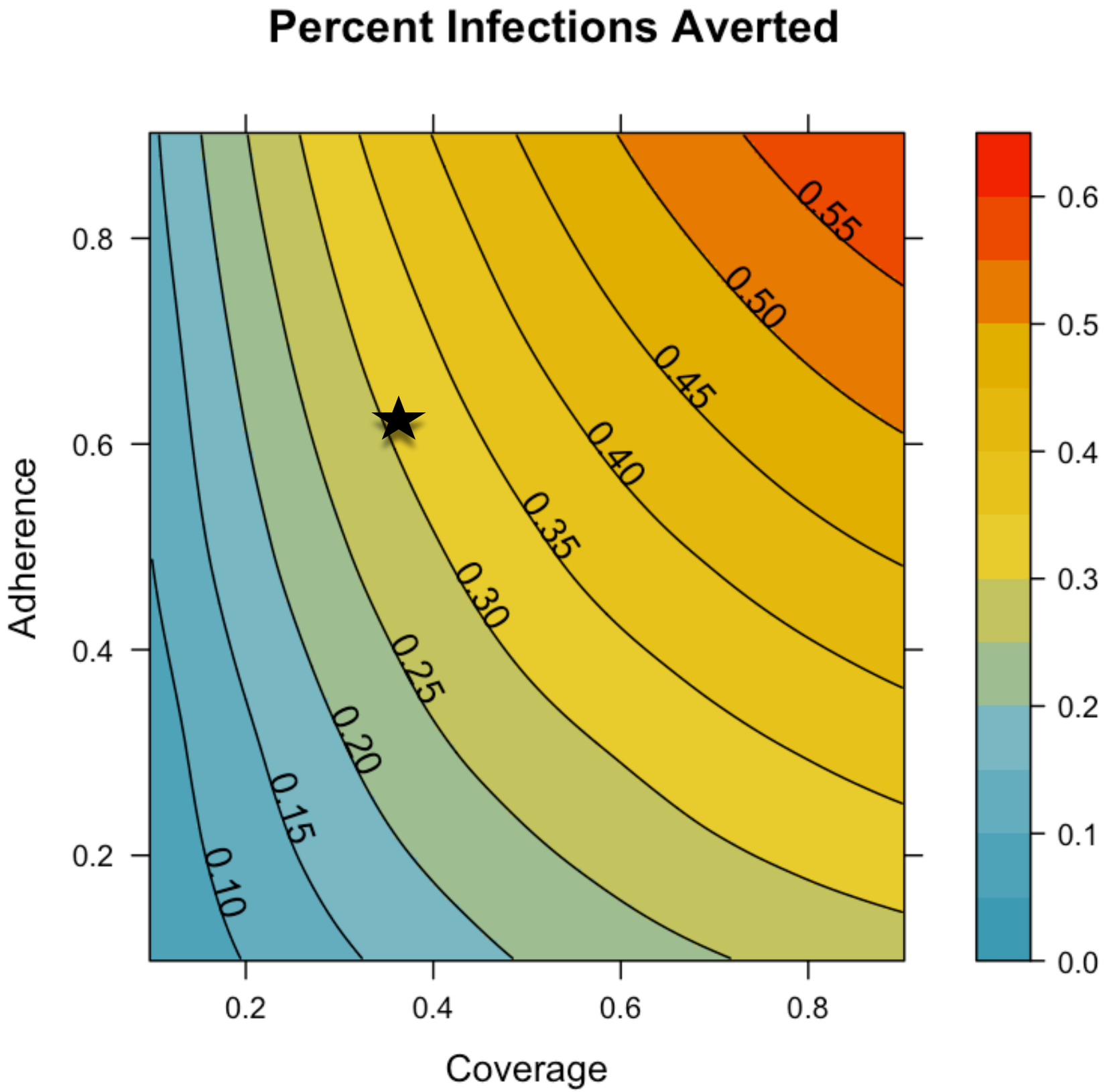
Interaction of Adherence and Coverage

Adherence

% of MSM who were highly adherent (4+ pills / week)

Coverage

% of CDC-indicated MSM who initiate PrEP



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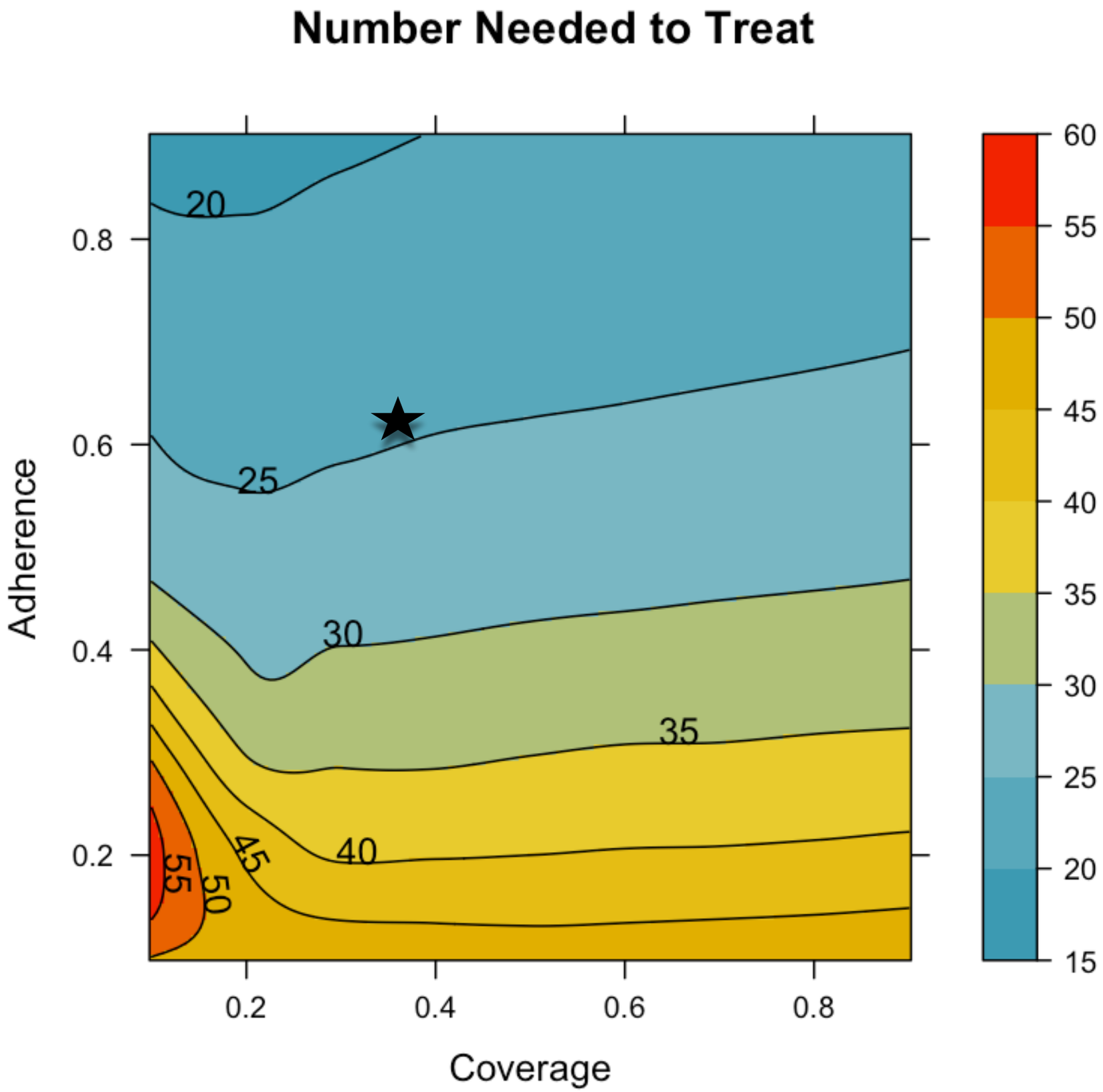
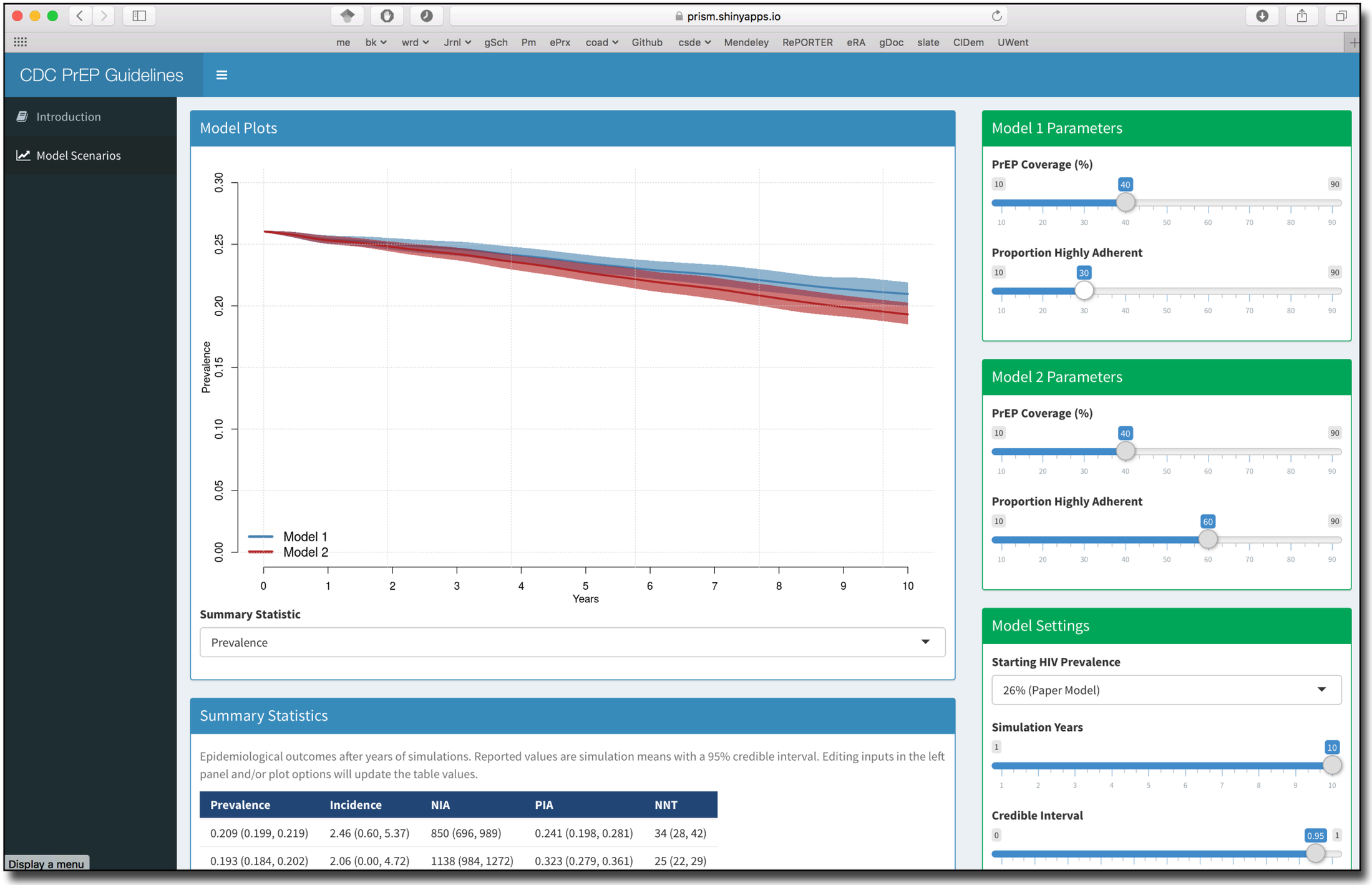


Web-Based Modeling Tool for Public Health Practice

http://prism.shinyapps.io/cdc-prep-guidelines/



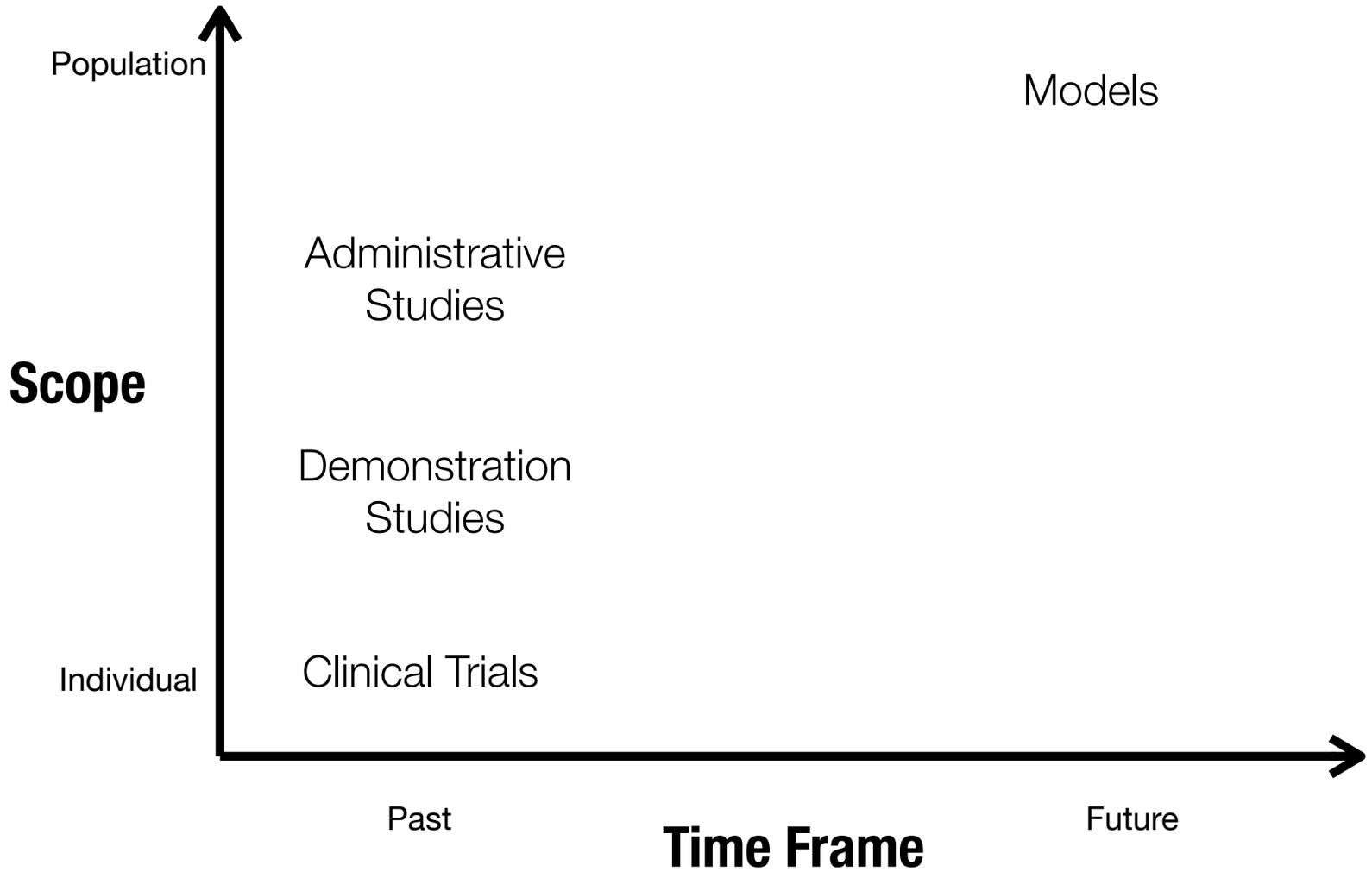
Why did we use a mathematical/mechanistic model?

What makes this a network model?

Why did we use a network model?

How did we use EpiModel to do this?

Why Model?



Models

Clinical trials **establish** efficacy at **individual** level

Models **predict** effectiveness (and other things) at **population** level

Models also allow studying **unmeasurable outcomes** and empirically **infeasible counterfactuals**

Study Aims

- Model HIV transmission dynamics among MSM in the US after implementation of PrEP according to CDC guidelines
  - Use a robust mathematical framework to represent complex MSM bio-behavioral population evolution

- **Quantify reduction in HIV incidence associated with:**
  - **Individual behavioral criteria in the guidelines, separately and jointly**
  - **Varying levels of PrEP coverage, adherence**

Why did we use a mathematical/mechanistic model?

What makes this a network model?

Why did we use a network model?

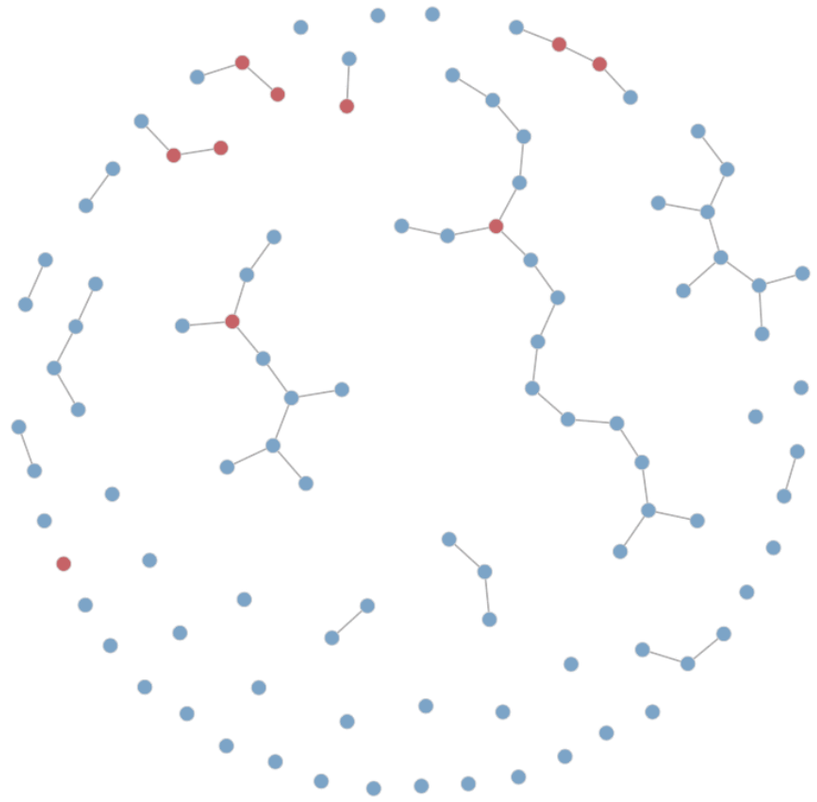
How did we use EpiModel to do this?

Methods Overview

- Stochastic network-based mathematical model
- Model parameters based on robust, partnership-based HIV incidence studies of MSM in Atlanta and national-level data on clinical care engagement
- Epidemiological, demographic, and intervention modules designed in EpiModel software (www.epimodel.org)
- Simulates open population of MSM, aged 18 to 40, in the US over a 10-year time span

HIV Transmission over Dynamic Sexual Networks

- Temporal exponential random graph models (ERGMs) define partnership formation and dissolution
  - Sexual network types: main, casual, one-off
  - Men form partnerships according to model terms based on numbers of each partner type, mixing or race and age, sexual role segregation



- HIV epidemiology
  - Natural history (disease stages, continuous VL, HIV-related mortality)
  - ART initiation and adherence
  - HIV transmission dynamics within serodiscordant partnerships
- Demographic processes

Why did we use a mathematical/mechanistic model?

What makes this a network model?

Why did we use a network model?

How did we use EpiModel to do this?

Linking Behavior to Biomedical Prevention

- US PHS/CDC released clinical practice guidelines indicating PrEP for those at “substantial risk” in 2014
- **For MSM, prescription indications were:**
  - **Unprotected anal intercourse (UAI) in monogamous partnership with person not recently tested for HIV**
  - **UAI outside of a monogamous partnership**
  - **AI (including with condoms) in a known serodiscordant partnership**
  - Any non-HIV STI diagnosis
- **Clinicians recommended to screen for conditions in past 6 months, reevaluate risk every 12 months**

Representing Complexities in PrEP

- Initiation
  - HIV-uninfected men encounter diagnostic HIV testing
  - Risk assessment for PrEP over past 6-month window based on CDC behavioral indications
  - Indicated men start PrEP if the % of already initiated men is less than a fixed coverage threshold (40% in base models)
- Adherence
  - Men assigned a fixed adherence profile following PrEP demonstration project data (62% high, 10% moderate, 7% low, and 21% null adherence)
  - Adherence translates into a 95%, 81%, 31%, and 0% reduction in transmission risk
  - Men discontinued from PrEP if, at yearly follow-up visit, no longer behavioral indications

Why did we use a mathematical/mechanistic model?

What makes this a network model?

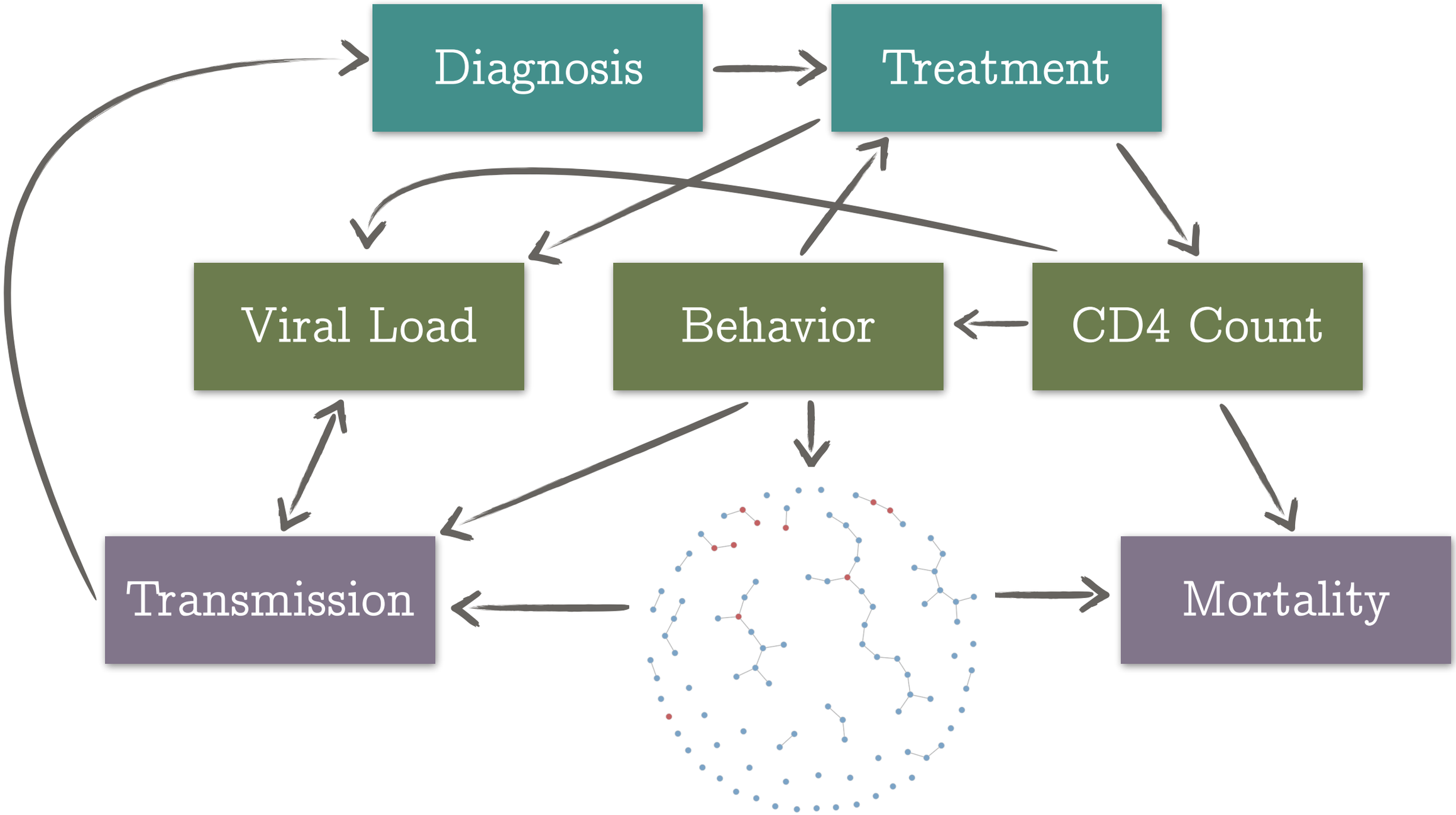
Why did we use a network model?

How did we use EpiModel to do this?

EpiModel is Modular

- Most of this week (Mon to Thurs)
  - We will focus on generic epidemics (SI/SIS/SIR) in basic population structures
  - While learning the theory and math of modeling dynamic networks
  - The “out of the box” models in EpiModel are not intended to address complex research questions
- Then on Friday (and thereafter)
  - We teach you about how to translate your modeling questions to EpiModel code
  - This involves adding and replacing modules within EpiModel
  - This is exactly what we do in our modeling research

Translating Concept to Code



This Modular Framework Does Two Things

- Allows you to easily add in any processes of interest into the ID system, and use the base EpiModel tools (estimation, simulation, analysis, plotting)

- It enforces you (the user) to *think* modularly: building a complex system in small, interconnected building blocks

- This allows for efficient expansion once you have a solid codebase

Extension #1: Risk Compensation

PLOS | ONE

RESEARCH ARTICLE

Individual HIV Risk versus Population Impact of Risk Compensation after HIV Preexposure Prophylaxis Initiation among Men Who Have Sex with Men

Samuel M. Jenness[1]*, Akshay Sharma[1], Steven M. Goodreau[2], Eli S. Rosenberg[1], Kevin M. Weiss[1], Karen W. Hoover[3], Dawn K. Smith[3], Patrick Sullivan[1,4]

1 Department of Epidemiology, Emory University, Atlanta, Georgia, United States of America, **2** Department of Anthropology, University of Washington, Seattle, Washington, United States of America, **3** Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, **4** Department of Global Health, Emory University, Atlanta, Georgia, United States of America

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OPEN ACCESS

Citation: Jenness SM, Sharma A, Goodreau SM, Rosenberg ES, Weiss KM, Hoover KW, et al. (2017) Individual HIV Risk versus Population Impact of Risk Compensation after HIV Preexposure Prophylaxis Initiation among Men Who Have Sex with Men. PLoS ONE 12(1): e0169484. doi:10.1371/journal.pone.0169484

Editor: Garrett Prestage, University of New South Wales, AUSTRALIA

Received: September 6, 2016

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Published: January 6, 2017

Data Availability Statement: All software code and relevant data for simulating the models contained in this study are stored on Github at: http://github.com/statnet/EpiModelHIV and http://github.com/statnet/HIV-Risk-Comp.

Funding: This work was supported by Centers for Disease Control [grant: U38 PS004646], the National Institutes of Health [R21 HD075662], the Center for AIDS Research at Emory [grant: P30 AI050409] and the University of Washington

Abstract

Objectives

Risk compensation (RC) could reduce or offset the biological prevention benefits of HIV pre-exposure prophylaxis (PrEP) among those at substantial risk of infection, including men who have sex with men (MSM). We investigated the potential extent and causal mechanisms through which RC could impact HIV transmission at the population and individual levels.

Methods

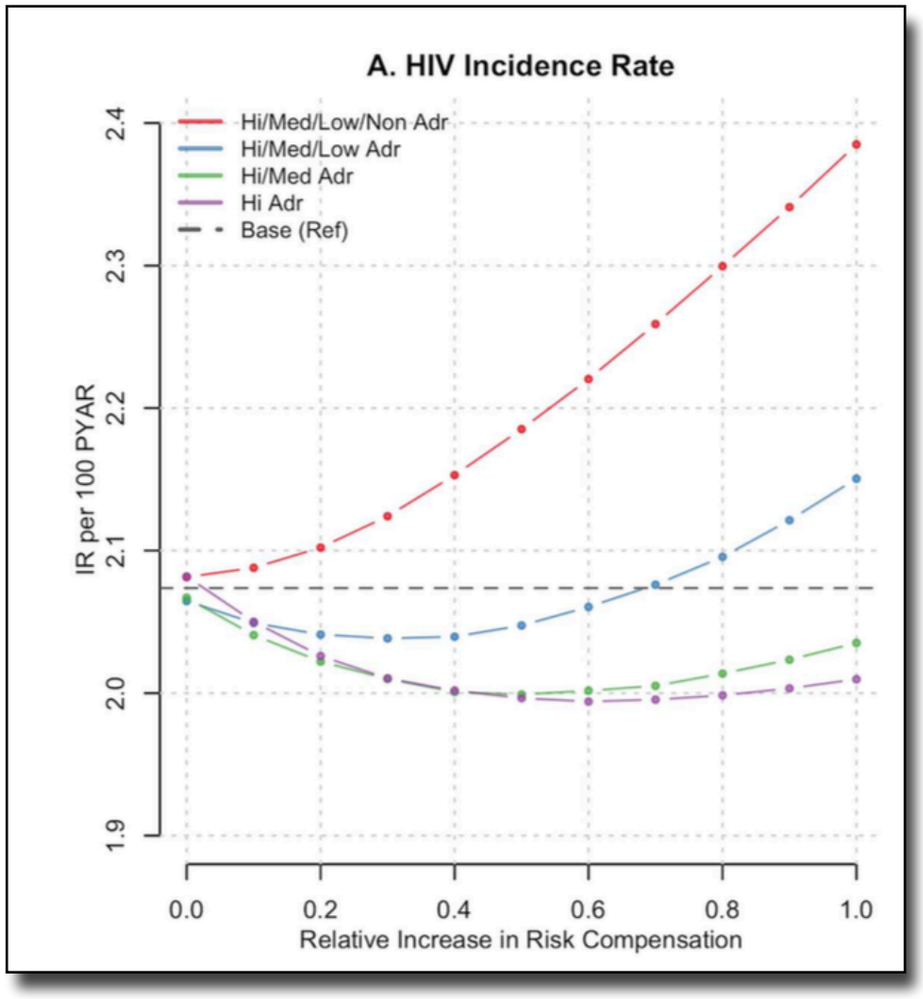
Using a stochastic network-based mathematical model of HIV transmission dynamics among MSM in the United States, we simulated RC as a reduction in the probability of condom use after initiating PrEP, with heterogeneity by PrEP adherence profiles and partnership type in which RC occurred. Outcomes were changes to population-level HIV incidence and individual-level acquisition risk.

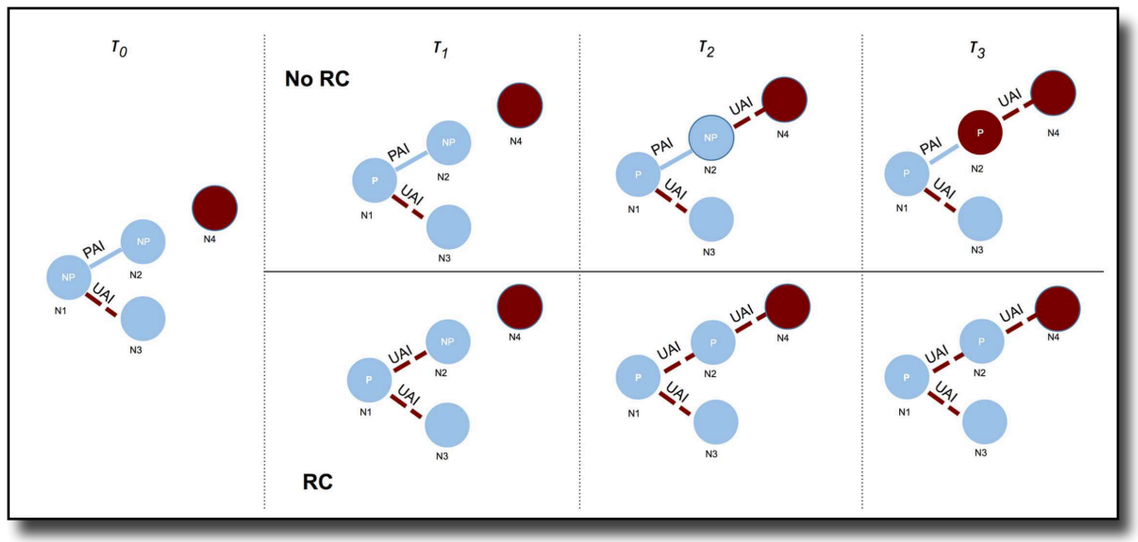
Results

When RC was limited to MSM highly/moderately adherent to PrEP, 100% RC (full replacement of condoms) resulted in a 2% relative decline in incidence compared to no RC, but an 8% relative increase in infection risk for MSM on PrEP. This resulted from confounding by indication: RC increased the number of MSM indicated for PrEP as a function of more condomless anal intercourse among men otherwise not indicated for PrEP; this led to an increased PrEP uptake and subsequent decline in incidence.

Conclusions

RC is unlikely to decrease the prevention impact of PrEP, and in some cases RC may be counterintuitively beneficial at the population level. This depended on PrEP uptake scaling





Extension #2: HIV PrEP and Bacterial STI Incidence

Clinical Infectious Diseases

MAJOR ARTICLE

Incidence of Gonorrhea and Chlamydia Following Human Immunodeficiency Virus Preexposure Prophylaxis Among Men Who Have Sex With Men: A Modeling Study

Samuel M. Jenness,[1] Kevin M. Weiss,[1] Steven M. Goodreau,[2] Thomas Gift,[3] Harrell Chesson,[3] Karen W. Hoover,[4] Dawn K. Smith,[4] Albert Y. Liu,[5] Patrick S. Sullivan,[1] and Eli S. Rosenberg[1]

[1]Department of Epidemiology, Emory University, Atlanta, Georgia; [2]Department of Anthropology, University of Washington, Seattle; [3]Division of STD Prevention, and [4]Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; and [5]San Francisco Department of Public Health, California

Background. Preexposure prophylaxis (PrEP) is highly effective for preventing human immunodeficiency virus (HIV) infection, but risk compensation (RC) in men who have sex with men (MSM) raises concerns about increased sexually transmitted infections (STIs). The Center for Disease Control and Prevention's (CDC's) PrEP guidelines recommend biannual STI screening, which may reduce incidence by treating STIs that would otherwise remain undiagnosed. We investigated these two counteracting phenomena.

Methods. With a network-based mathematical model of HIV, *Neisseria gonorrhoeae* (NG), and *Chlamydia trachomatis* (CT) transmission dynamics among MSM in the United States, we simulated PrEP uptake following the prescription indications and HIV/STI screening recommendations in the CDC guidelines. Scenarios varied PrEP coverage (the proportion of MSM indicated for PrEP who received it), RC (a reduction in the per-act probability of condom use), and the STI screening interval.

Results. In our reference scenario (40% coverage, 40% RC), 42% of NG and 40% of CT infections would be averted over the next decade. A doubling of RC would still result in net STI prevention relative to no PrEP. STIs declined because PrEP-related STI screening resulted in a 17% and 16% absolute increase in the treatment of asymptomatic and rectal STIs, respectively. Screening and timely treatment at quarterly vs biannual intervals would reduce STI incidence an additional 50%.

Conclusions. Implementation of the CDC PrEP guidelines while scaling up PrEP coverage could result in a significant decline in STI incidence among MSM. Our study highlights the design of PrEP not only as antiretroviral medication but as combination HIV/STI prevention incorporating STI screening.

Keywords. *Neisseria gonorrhoeae*; *Chlamydia trachomatis*; men who have sex with men; preexposure prophylaxis; mathematical model.

Preexposure prophylaxis (PrEP) can reduce the risk of human immunodeficiency virus (HIV) infection by more than 95% among men who have sex with men (MSM) when taken consistently [1]. Adherence to PrEP has been strong in open-label studies, including a clinical cohort in California in which no incident HIV infections were observed among active PrEP users [2]. However, 50% of men on PrEP in that cohort were diagnosed with a sexually transmitted infection (STI) within 12 months of starting medication. High levels of STI incidence were also observed in the PrEP Demo Project, where the overall STI incidence rate was 90 per 100 person-years [3]. A recent metaanalysis compared the STI incidence among MSM in PrEP cohorts to MSM in non-PrEP cohorts, estimating that incidence among PrEP users was 33.3 per 100 person-years at risk (PYAR) higher for *Neisseria gonorrhoeae* (NG) and 31.4 per 100 PYAR higher for *Chlamydia trachomatis* (CT) [4]. There are at least 3 noncausal explanations for these excess rates: increased STI detection (if STIs were more frequently screened for in the PrEP cohorts), selection bias (if the PrEP cohorts recruited higher-risk samples of MSM), and secular trends (STI incidence has increased over time, and the PrEP cohorts included more recent samples).

The primary causal mechanism by which PrEP use could lead to higher STI incidence would be behavioral risk compensation (RC); MSM who initiate PrEP may reduce their use of other disease prevention strategies [5]. Estimates of whether RC occurs among MSM on PrEP, and by how much, have been mixed. The PrEP Demo Project saw no increase in condomless anal intercourse (AI) [3], consistent with the iPrEx trial [6], whereas 41% of PrEP users in the California clinic-based

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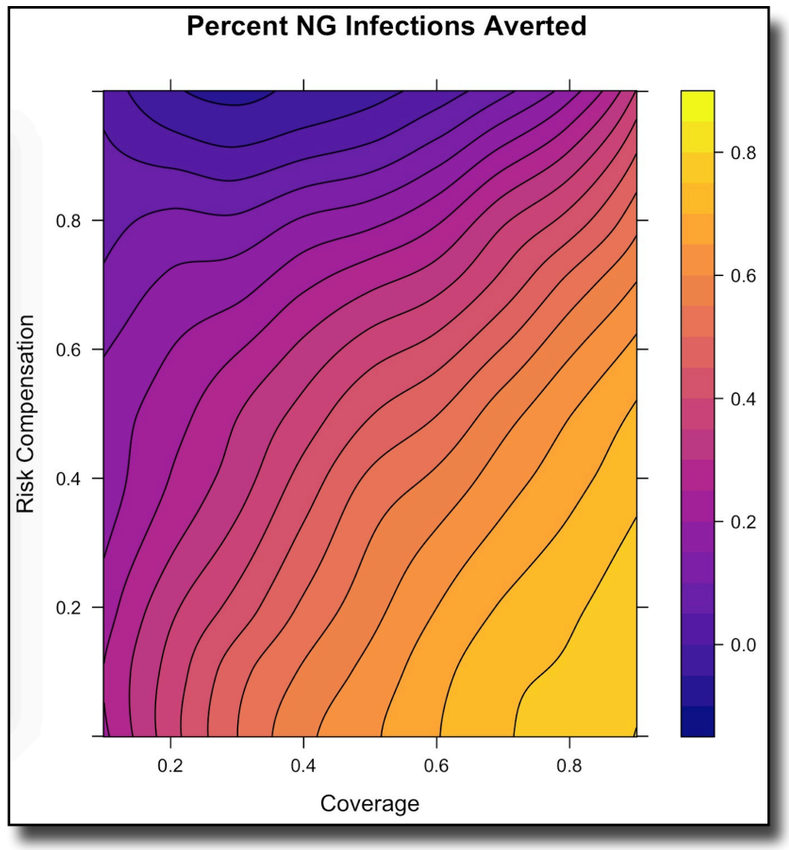
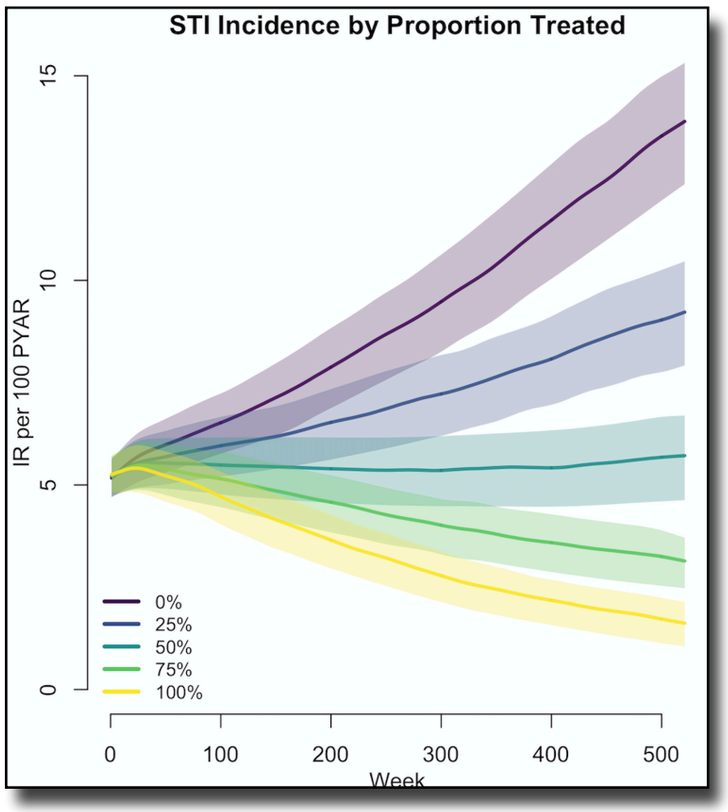
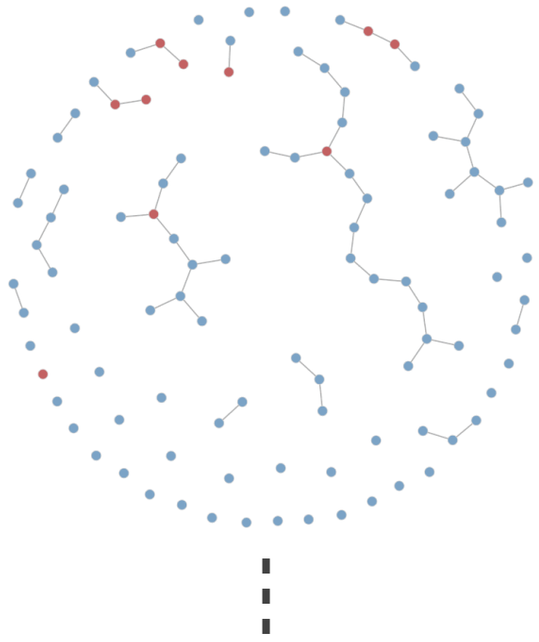
DOI: 10.1093/cid/cix439





Monday to Thursday



Susceptible → Infected → Recovered

Fixed

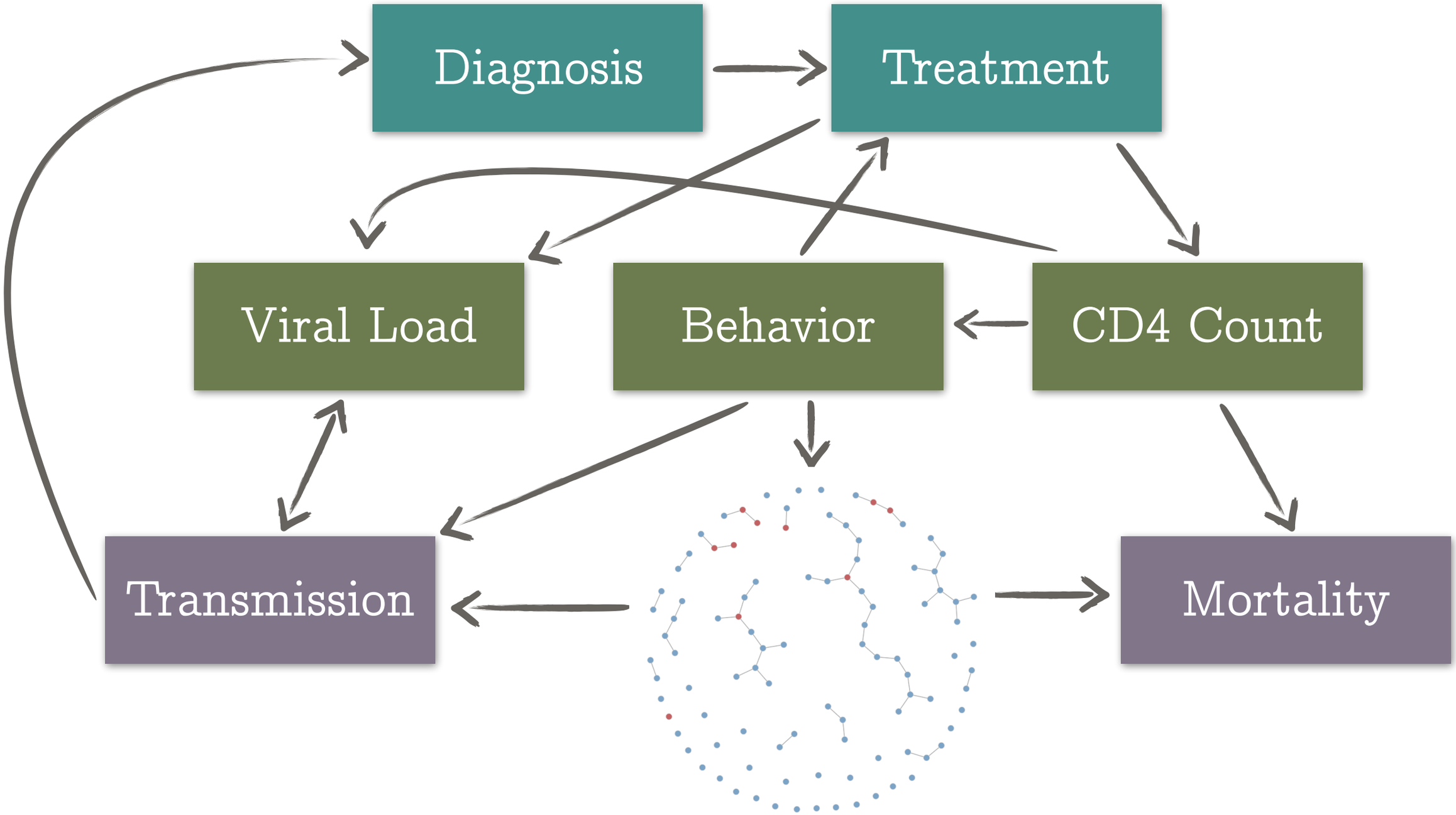
Structure of states and flows

Modifiable

Epidemic parameters

Dynamic network structure

Friday


Diagnosis
Treatment
Viral Load
Behavior
CD4 Count
Transmission
Mortality

After the Course

```
sti_recov <- function(dat, at) {

  # Parameters
  rgc.dur.asympt <- dat$param$rgc.dur.asympt
  ugc.dur.asympt <- dat$param$ugc.dur.asympt
  gc.dur.tx <- dat$param$gc.dur.tx
  gc.dur.ntx <- dat$param$gc.dur.ntx

  rct.dur.asympt <- dat$param$rct.dur.asympt
  uct.dur.asympt <- dat$param$uct.dur.asympt
  ct.dur.tx <- dat$param$ct.dur.tx
  ct.dur.ntx <- dat$param$ct.dur.ntx


  # GC recovery
  idsRGC_asympt <- which(dat$attr$rGC == 1 & dat$attr$rGC.infTime < at &
                           dat$attr$rGC.sympt == 0)
  idsUGC_asympt <- which(dat$attr$uGC == 1 & dat$attr$uGC.infTime < at &
                           dat$attr$uGC.sympt == 0)
  idsRGC_tx <- which(dat$attr$rGC == 1 & dat$attr$rGC.infTime < at &
                       dat$attr$rGC.sympt == 1 & dat$attr$rGC.tx == 1)
  idsUGC_tx <- which(dat$attr$uGC == 1 & dat$attr$uGC.infTime < at &
                       dat$attr$uGC.sympt == 1 & dat$attr$uGC.tx == 1)
  idsRGC_ntx <- which(dat$attr$rGC == 1 & dat$attr$rGC.infTime < at &
                        dat$attr$rGC.sympt == 1 & dat$attr$rGC.tx == 0)
  idsUGC_ntx <- which(dat$attr$uGC == 1 & dat$attr$uGC.infTime < at &
                        dat$attr$uGC.sympt == 1 & dat$attr$uGC.tx == 0)

  recovRGC_asympt <- idsRGC_asympt[which(rbinom(length(idsRGC_asympt), 1,
                                                1/rgc.dur.asympt) == 1)]
  recovUGC_asympt <- idsUGC_asympt[which(rbinom(length(idsUGC_asympt), 1,
                                                1/ugc.dur.asympt) == 1)]

  recovRGC_tx <- idsRGC_tx[which(rbinom(length(idsRGC_tx), 1,
                                        1/gc.dur.tx) == 1)]
  recovUGC_tx <- idsUGC_tx[which(rbinom(length(idsUGC_tx), 1,
                                        1/gc.dur.tx) == 1)]

  if (!is.null(gc.dur.ntx)) {
    recovRGC_ntx <- idsRGC_ntx[which(rbinom(length(idsRGC_ntx), 1,
                                            1/gc.dur.ntx) == 1)]
    recovUGC_ntx <- idsUGC_ntx[which(rbinom(length(idsUGC_ntx), 1,
                                            1/gc.dur.ntx) == 1)]
  } else {
    recovRGC_ntx <- idsRGC_ntx[which(rbinom(length(idsRGC_ntx), 1,
                                            1/rgc.dur.asympt) == 1)]
    recovUGC_ntx <- idsUGC_ntx[which(rbinom(length(idsUGC_ntx), 1,
                                            1/ugc.dur.asympt) == 1)]
  }

  recovRGC <- c(recovRGC_asympt, recovRGC_tx, recovRGC_ntx)
  recovUGC <- c(recovUGC_asympt, recovUGC_tx, recovUGC_ntx)

  dat$attr$rGC[recovRGC] <- 0
  dat$attr$rGC.sympt[recovRGC] <- NA
  dat$attr$rGC.infTime[recovRGC] <- NA
  dat$attr$rGC.tx[recovRGC] <- NA

  dat$attr$uGC[recovUGC] <- 0
  dat$attr$uGC.sympt[recovUGC] <- NA
  dat$attr$uGC.infTime[recovUGC] <- NA
  dat$attr$uGC.tx[recovUGC] <- NA

  dat$attr$GC.cease[c(recovRGC, recovUGC)] <- NA

  # CT recovery
  idsRCT_asympt <- which(dat$attr$rCT == 1 & dat$attr$rCT.infTime < at &
                           dat$attr$rCT.sympt == 0)
  idsUCT_asympt <- which(dat$attr$uCT == 1 & dat$attr$uCT.infTime < at &
                           dat$attr$uCT.sympt == 0)
  idsRCT_tx <- which(dat$attr$rCT == 1 & dat$attr$rCT.infTime < at &
                       dat$attr$rCT.sympt == 1 & dat$attr$rCT.tx == 1)
  idsUCT_tx <- which(dat$attr$uCT == 1 & dat$attr$uCT.infTime < at &
                       dat$attr$uCT.sympt == 1 & dat$attr$uCT.tx == 1)
  idsRCT_ntx <- which(dat$attr$rCT == 1 & dat$attr$rCT.infTime < at &
                        dat$attr$rCT.sympt == 1 & dat$attr$rCT.tx == 0)
  idsUCT_ntx <- which(dat$attr$uCT == 1 & dat$attr$uCT.infTime < at &
                        dat$attr$uCT.sympt == 1 & dat$attr$uCT.tx == 0)

  recovRCT_asympt <- idsRCT_asympt[which(rbinom(length(idsRCT_asympt),
                                                1, 1/rct.dur.asympt) == 1)]
  recovUCT_asympt <- idsUCT_asympt[which(rbinom(length(idsUCT_asympt),
                                                1, 1/uct.dur.asympt) == 1)]

  recovRCT_tx <- idsRCT_tx[which(rbinom(length(idsRCT_tx),
                                        1, 1/ct.dur.tx) == 1)]
  recovUCT_tx <- idsUCT_tx[which(rbinom(length(idsUCT_tx),
                                        1, 1/ct.dur.tx) == 1)]

  if (!is.null(ct.dur.ntx)) {
    recovRCT_ntx <- idsRCT_ntx[which(rbinom(length(idsRCT_ntx),
                                            1, 1/ct.dur.ntx) == 1)]
    recovUCT_ntx <- idsUCT_ntx[which(rbinom(length(idsUCT_ntx),
                                            1, 1/ct.dur.ntx) == 1)]
  } else {
    recovRCT_ntx <- idsRCT_ntx[which(rbinom(length(idsRCT_ntx),
                                            1, 1/rct.dur.asympt) == 1)]
    recovUCT_ntx <- idsUCT_ntx[which(rbinom(length(idsUCT_ntx),
                                            1, 1/uct.dur.asympt) == 1)]
  }
```