Understanding socio-structural drivers of HIV transmission using epidemiology and systems science

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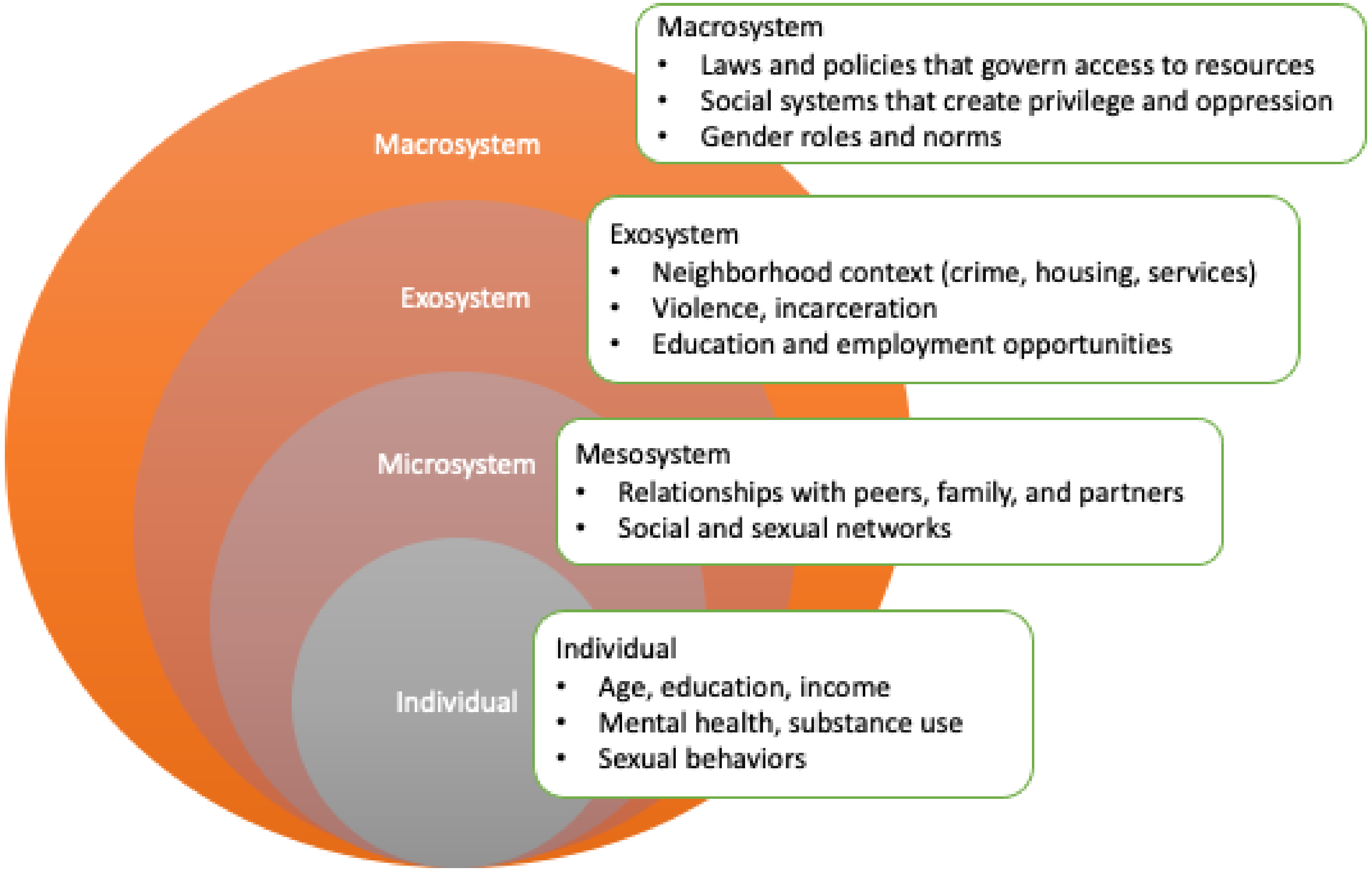
Outline

- Introduction
- HIV in Chicago
- Brief overview of agent-based modeling (ABM)
- ABM and counterfactual frameworks
- Example: ABM to understand the impact of criminal justice involvement on HIV transmission
- Future research and next steps

Introduction

- Socio-structural & contextual influences
  - Dyad-level factors
  - Network influences, environmental context
  - Social determinants of health (SDOH)

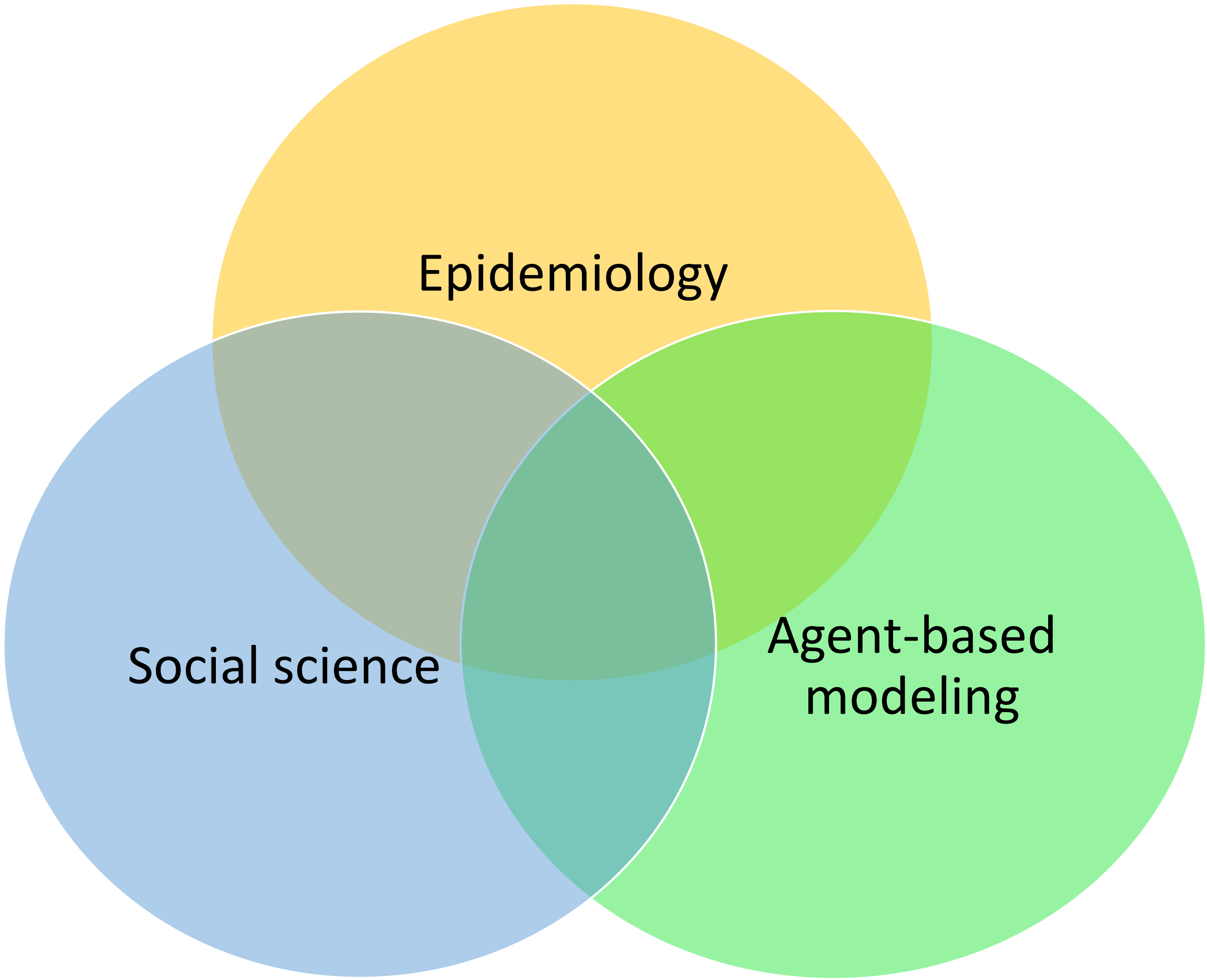
- Populations disproportionately affected by HIV/STIs



Adapted from Ecological Systems Theory. Source: Bronfenbrenner, U. (1979). *The Ecology of Human Development: Experiments by Nature and Design*. Cambridge, MA: Harvard University Press.

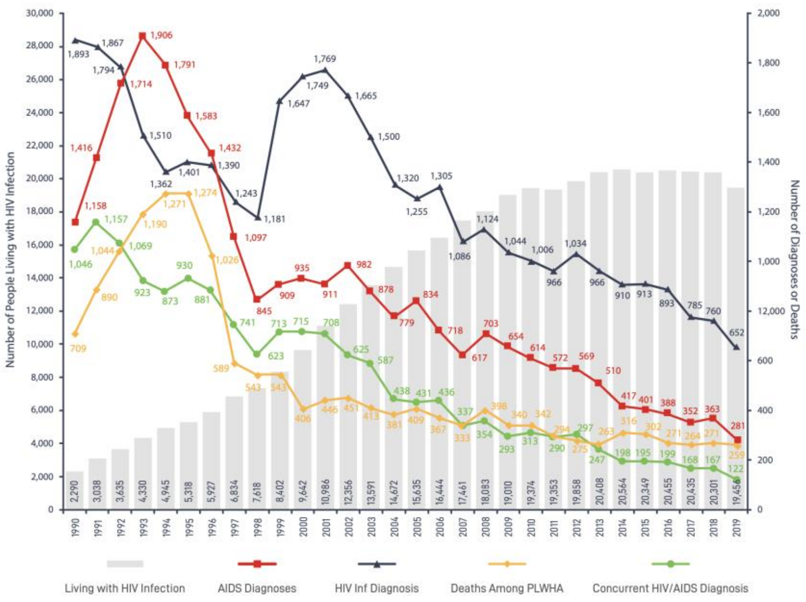
Research Methods

- Epidemiology
  - Observational research, interventions
  - Causal inference
- Social sciences
  - Conceptual frameworks
  - Social determinants of health
- Systems science & agent-based modeling
  - Useful for studying complex systems
  - Epidemiologic analyses provide input parameters for agent-based models



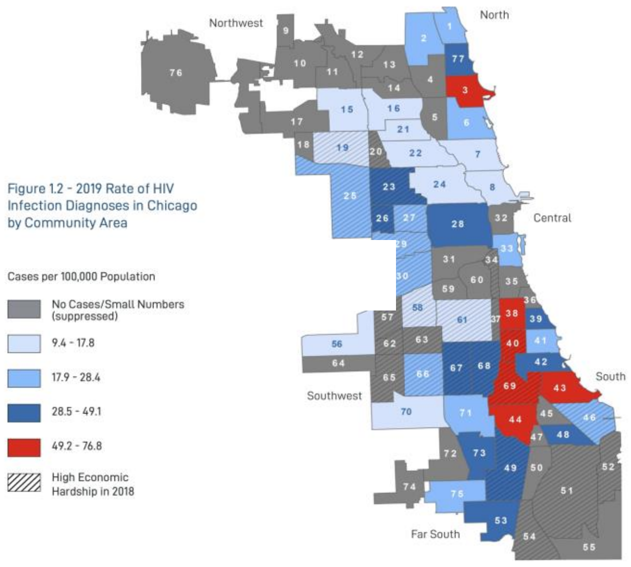
HIV in Chicago

Trends in HIV/AIDS Infections, Diagnoses, and Deaths, Chicago, 1990-2019

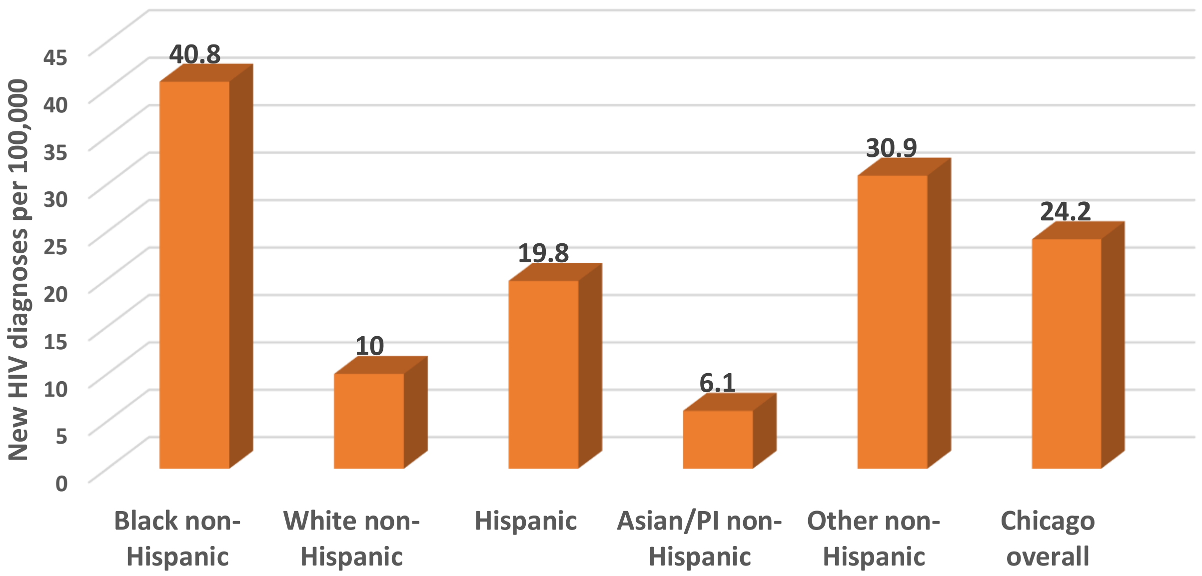


Source: Chicago Department of Public Health. HIV/STI Surveillance Report, 2019. Chicago, IL: City of Chicago; December 2020.

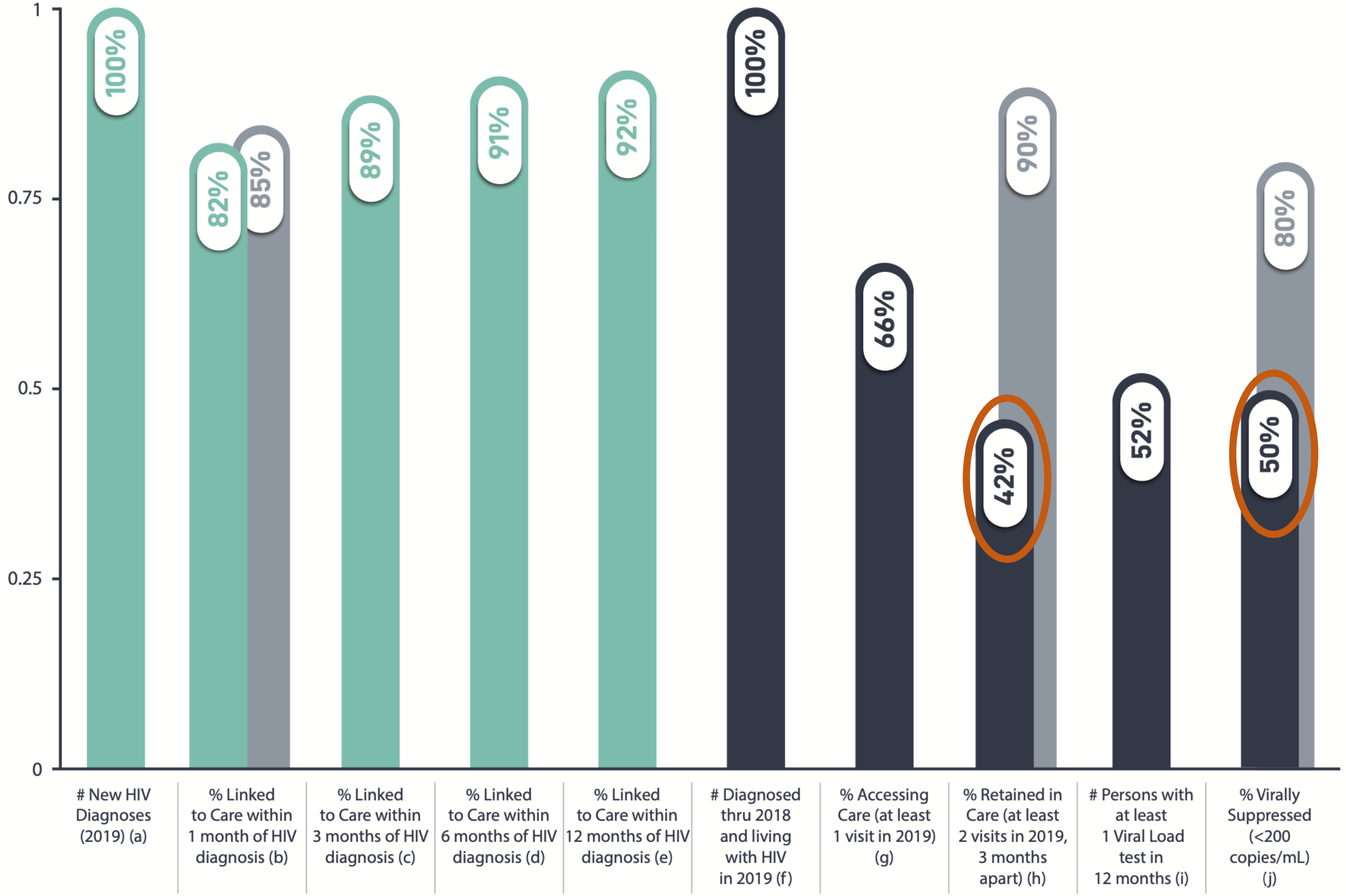
HIV Infection Rates by Chicago Community Area, 2019



New HIV diagnoses per 100,000, Chicago, 2019



HIV Continuum of Care Among Persons Aged ≥13 Years, Chicago, 2019



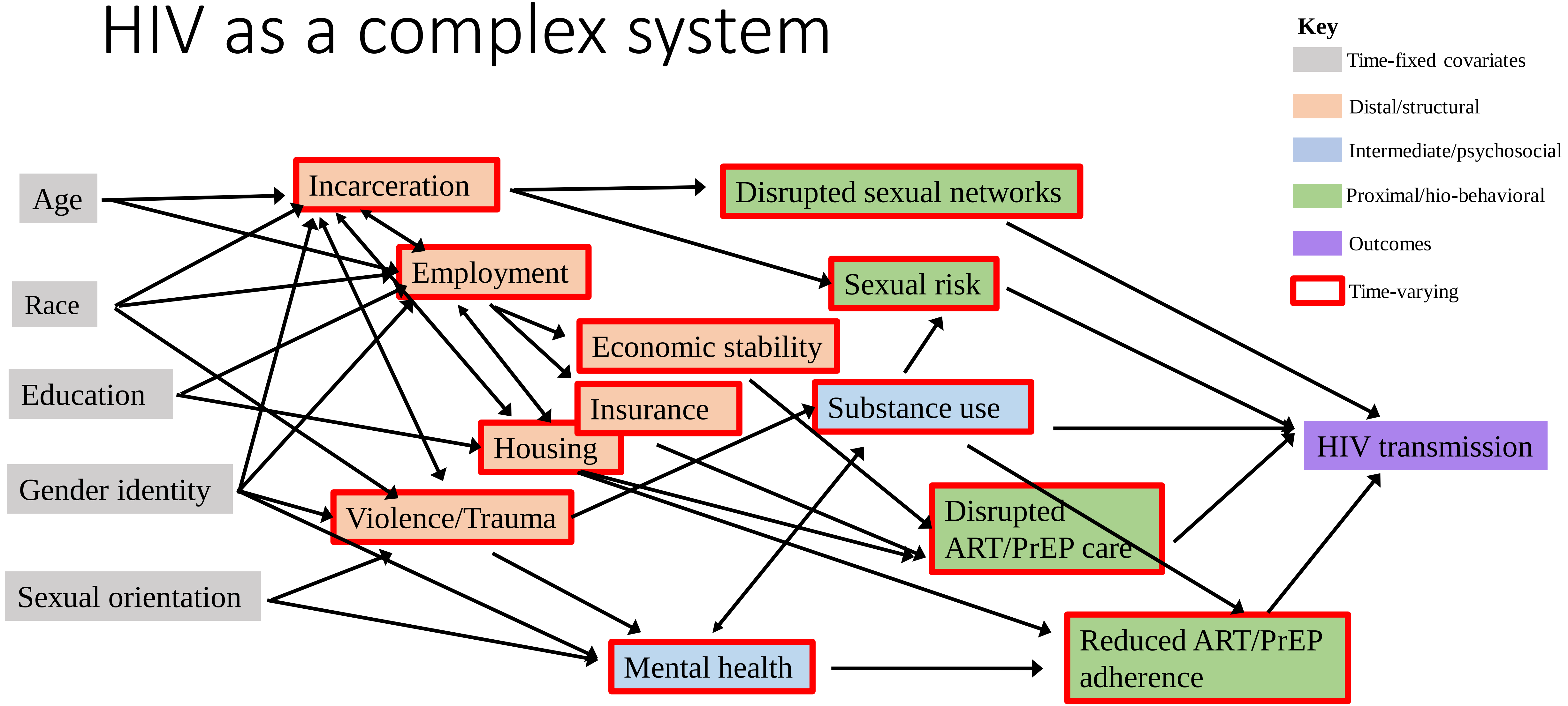
Source: Chicago Department of Public Health. HIV/STI Surveillance Report, 2019. Chicago, IL: City of Chicago; December 2020.

HIV Elimination goals

- Interventions will need to focus on communities with complex and co-occurring socio-structural barriers to engagement in HIV prevention and care

- Much previous research focused on behavior change at the individual level (sexual risk, substance use), but there is a recognized need to focus on more distal influences on HIV transmission
  - E.g., Housing, employment, incarceration

HIV as a complex system



Existing evidence and knowledge gaps

Evidence

- Associations of SDOH with HIV transmission related factors across multiple observational studies
  - Sexual behaviors
  - Substance use, mental health
  - Engagement in care, viral suppression, PrEP uptake

Gaps

- Many cross-sectional studies
- Focused on single factors or pathways
- Lacked statistical power or sufficient confounder control; causal associations cannot be inferred
- Effect size magnitude varies widely due to differences in study populations, design, timeframe, confounder control

Limitations of traditional study designs for understanding complex systems

- Logistical
  - Long duration of follow up required to observe effects
  - Very resource intensive to follow people longitudinally
  - Settings may not be conducive to traditional research designs (e.g., criminal justice settings)

- Ethical
  - Not always feasible or possible to randomize people
  - High participant burden/burnout

Statistical challenges

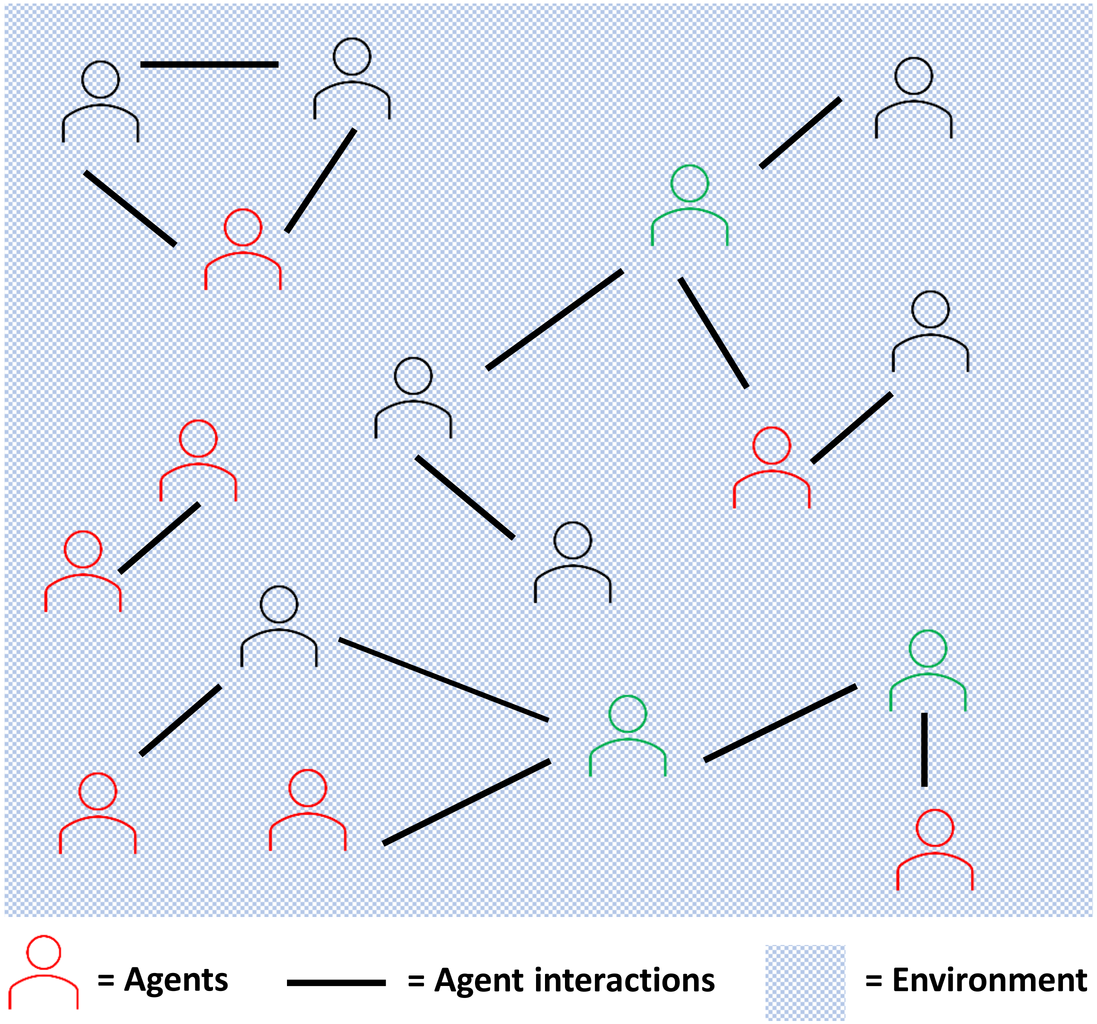
- Standard regression models typically assume relationships between exposures and outcomes are unidirectional, linear, and time-constant and exposures are independent
  - Not well suited to relationships characterized by causal interdependence, non-linearity (e.g., thresholds), feedback loops (magnified or dampening effects), and interference (one person's exposure influences the outcomes of others)
  - Many traditional causal inference frameworks assume these are absent (e.g., unidirectionality, no interference, etc.)
- For rare outcomes (e.g., HIV), very large sample sizes required for sufficient power

Limitations of randomized controlled trials (RCTs) for evaluating complex interventions

- RCTs – useful for isolating a single intervention effect or component, generally while holding other factors and contexts constant
- Systems science approaches are better suited to studying complex interventions
  - Questions that couldn’t be answered with simpler designs or models

Agent-Based Models (ABMs)

- Computer simulation approach to modeling the dynamics of complex systems
- Models represent social systems composed of agents that interact with and influence each other
- Observe system-level consequences of agent behaviors and interactions
- Effects of interventions can be simulated under various assumptions in a virtual environment



Agent-based model components

Agents	Agent-Agent interactions	Environments	Agent-environment interactions

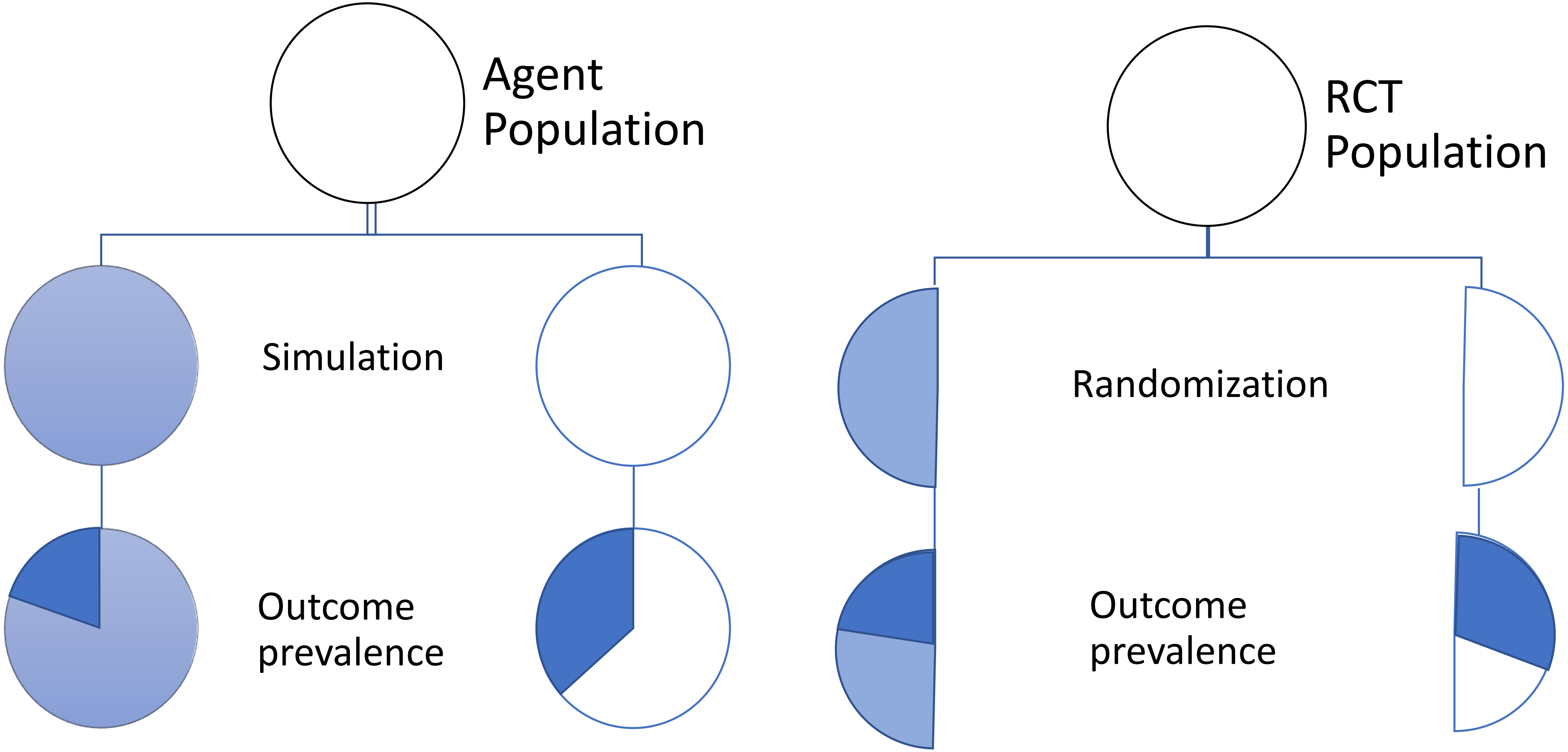
• Attributes (age, sex, race, employment, housing)
  • Static or dynamic
• Behaviors
  • Based on current information & past history
	• Information exchange
	• Disease transmission
	• Contend for resources
		• Social or sexual networks
		• Physical, social, neighborhood environments
			• Take in information on environment
			• Shape environment

Uses of agent-based modeling in epidemiology

- Understand mechanisms by which exposures (e.g., SDOH) impact population level health outcomes
  - Can show how patterns at the population level arise from exposures that might not be evident in a single study
  - Conduct counterfactual experiments to evaluate hypotheses that may not be possible with standard statistical models

- Evaluate potential interventions
  - Mechanisms by which interventions work
  - How interventions can be most efficiently focused (identify subgroups)
  - Optimal combination/sequence of interventions

ABM and counterfactual frameworks



Adapted from Marshall BD, Galea S. Formalizing the role of agent-based modeling in causal inference and epidemiology. Am J Epidemiol. 2015 Jan 15;181(2):92-9.

Basic notation: Agents

- At each time step t ($t = 1, \ldots, T$), each agent i ($i = 1, \ldots, N$) has a set of m ($m = 1, \ldots, M$) internal traits that can be described by the matrix $\mathbf{S}^{\mathrm{t}}$

$$\mathbf{S}^{\mathrm{t}} = \begin{bmatrix} s_{1,1}^{t} & s_{1,2}^{t} & \cdots & s_{1,M}^{t} \\ s_{2,1}^{t} & s_{2,2}^{t} & \cdots & s_{2,M}^{t} \\ \vdots & \vdots & \vdots & \vdots \\ s_{N,1}^{t} & s_{N,2}^{t} & \cdots & s_{N,M}^{t} \end{bmatrix}$$

- Traits:
  - Continuous, nominal, dichotomous
  - Can represent sociodemographics, exposures, behavioral proclivity, etc.

- Analogously, agents can be placed in p ($p = 1, \ldots, P$) environments where $\mathbf{E}^{\mathrm{t}}$ represents an environmental state matrix

Example from Marshall BD, Galea S. Formalizing the role of agent-based modeling in causal inference and epidemiology. Am J Epidemiol. 2015 Jan 15;181(2):92-9.

Agent-agent interactions

- At each time step t ($t = 1, …., T$) each agent i interacts with a subset of the population $\{1, …, i - 1, i + 1, …, N\}$
    - Described by agent-agent interaction matrix $\mathbf{K}^t$ where each element $k_{i,j}^t$ indicates whether agent *i* interacts with agent *j* during timestep *t* where i *and* $j = 1, …., N$
    - Can be symmetric or asymmetric (information or disease transmission can flow one way or bidirectionally)

Steps

- Initialize ABM by populating agent trait matrix, environmental state matrix, and interaction matrix with values from pre-defined probability distributions and functions

- Define set of rules $\mathbf{Z}$ for updating of agent traits, agent-agent interactions, and movement between or interaction with environments
  - Rules $\mathbf{Z}$ are defined by functions

- At each time step: update the model based on previous values and pre-defined rules $\mathbf{Z}$

Steps

- Monte Carlo simulations to obtain outcomes (e.g., disease incidence, prevalence, mortality) from runs r ($r = 1, \ldots, R$) at time T for counterfactual scenarios of interest:
  - Scenario A ($[\mathbf{Z}, \mathbf{S}_A^T, \mathbf{K}_A^T, \mathbf{E}_A^T]$) vs. Scenario B ($[\mathbf{Z}, \mathbf{S}_B^T, \mathbf{K}_B^T, \mathbf{E}_B^T]$)

- Compute point estimates from scenario A vs. scenario B by averaging across runs for each outcome of interest

$$\hat{\mu}_{o,A}^{T,R} = \frac{\sum_{r=1}^{R} y_{r,o,A}^{T}}{R} \text{ vs. } \hat{\mu}_{o,B}^{T,R} = \frac{\sum_{r=1}^{R} y_{r,o,B}^{T}}{R}$$

Example: Agent-based modeling to study the impact of criminal justice involvement (CJI) on HIV transmission among young Black sexual and gender minorities (SGM)

R01DA033934 (Fujimoto, Harawa, & Schneider, PIs)

R21MH128116 (Hotton, PI)

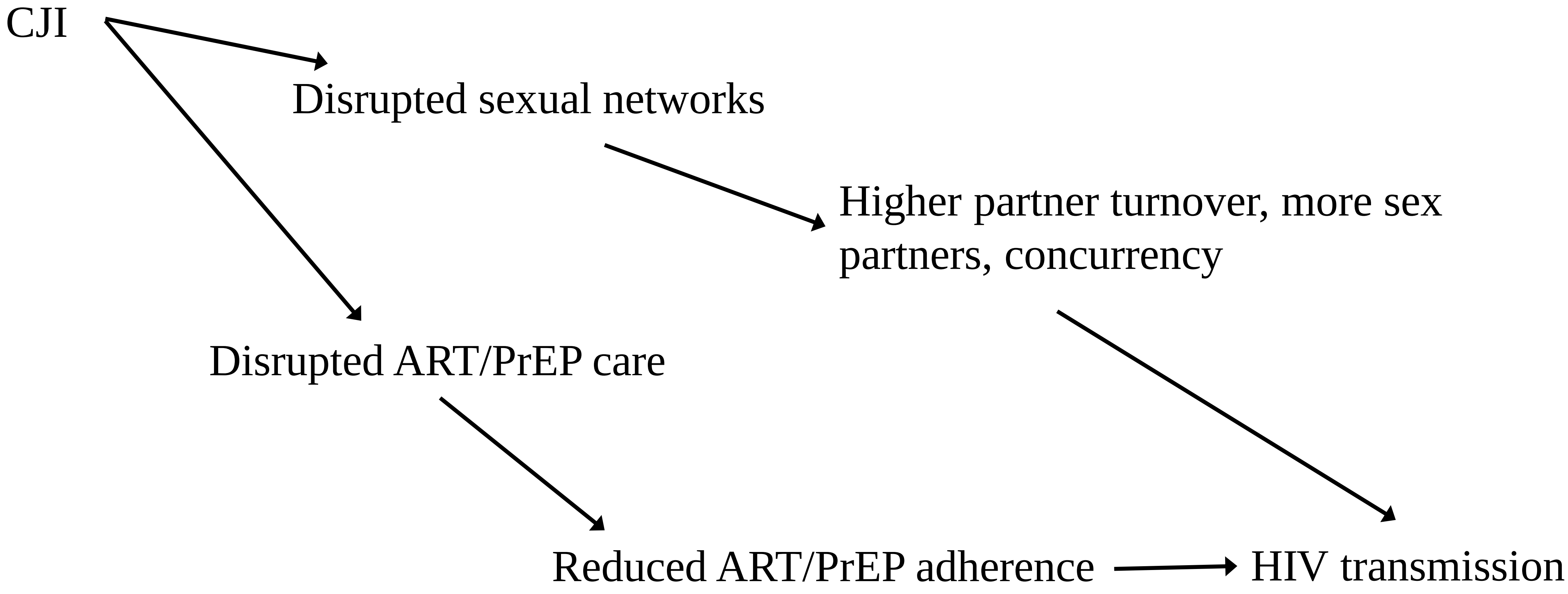
Intersection of HIV and criminal justice involvement

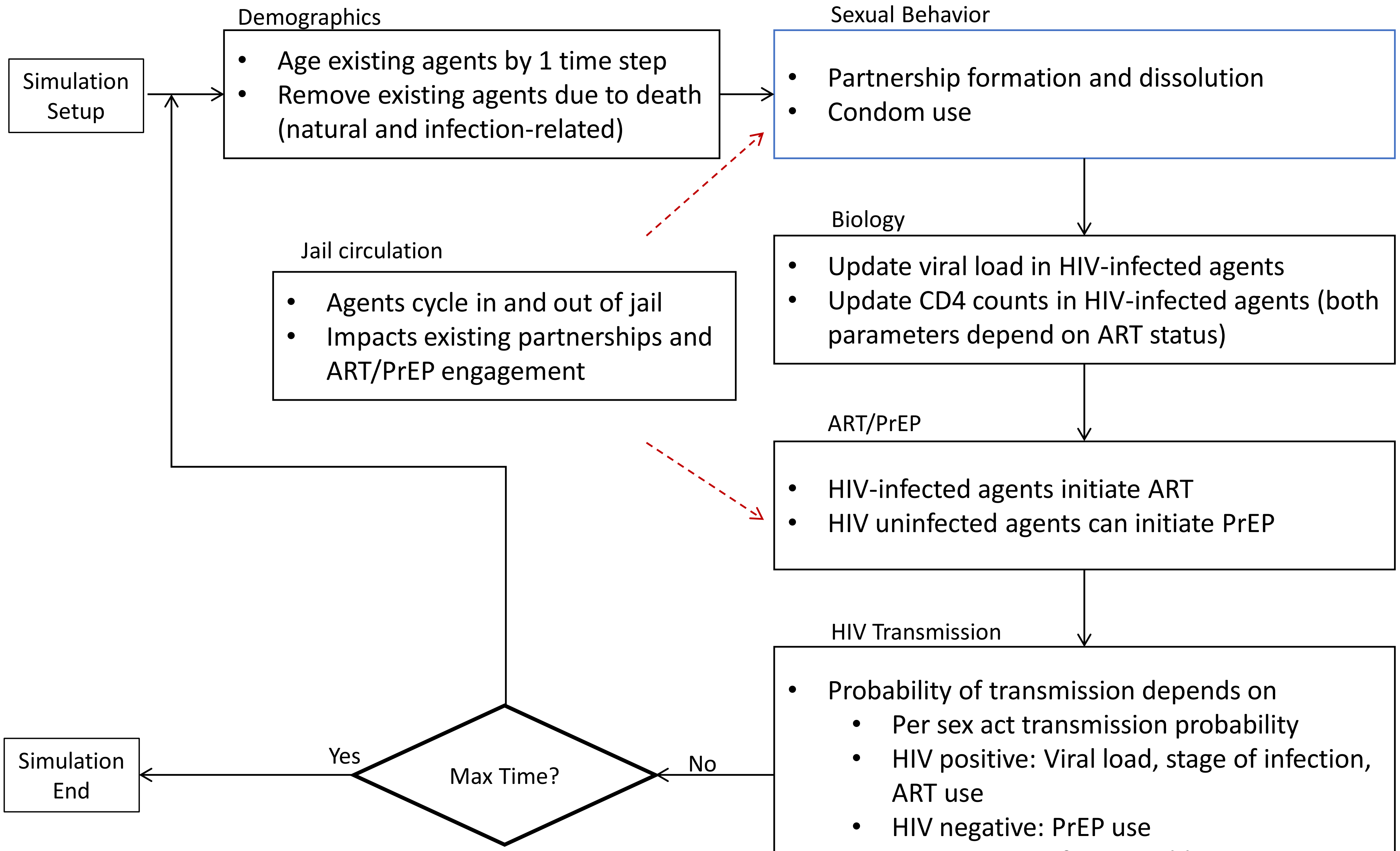
- Black SGM are disproportionately impacted by HIV and criminal justice involvement
  - Frequent cycling between communities and criminal justice settings

- CJI can impact:
  - Employment and housing opportunities
  - Access to medical care
  - Social and sexual network stability

- Agent-based models can be used to:
  - Provide insights to understand how CJI impacts HIV transmission
  - Evaluate interventions for criminal justice involved individuals and their networks

Hypothesized mechanisms by which justice involvement impacts HIV transmission




Simulation Setup
Demographics
Age existing agents by 1 time step
Remove existing agents due to death (natural and infection-related)
Sexual Behavior
Partnership formation and dissolution
Condom use
Jail circulation
Agents cycle in and out of jail
Impacts existing partnerships and ART/PrEP engagement
Biology
Update viral load in HIV-infected agents
Update CD4 counts in HIV-infected agents (both parameters depend on ART status)
ART/PrEP
HIV-infected agents initiate ART
HIV uninfected agents can initiate PrEP
HIV Transmission
Probability of transmission depends on
Per sex act transmission probability
HIV positive: Viral load, stage of infection, ART use
HIV negative: PrEP use
Circumcision of susceptible partners
Max Time?
Yes
No
Simulation End

Model population and data sources

- Model population: 10,000 agents representing Black SGM ages 18-34 in the city of Chicago
- Data sources: Local cohort studies, clinical data, and public health surveillance
- Outcomes: HIV incidence and prevalence (average annualized estimates computed over 10 years)
- Calibration: local HIV incidence and prevalence estimates (CDPH surveillance and local studies), incarceration incidence and prevalence
- Model components: Developed with Repast HPC ABM toolkit using C++
- Network formation and dissolution dynamics modeled with exponential random graph models using the *statnet* suite of packages in R

Khanna et al. A modeling framework to inform preexposure prophylaxis initiation and retention scale-up in the context of 'Getting to Zero' initiatives. AIDS 2019, 33(12): 1911-1922.

Experiments

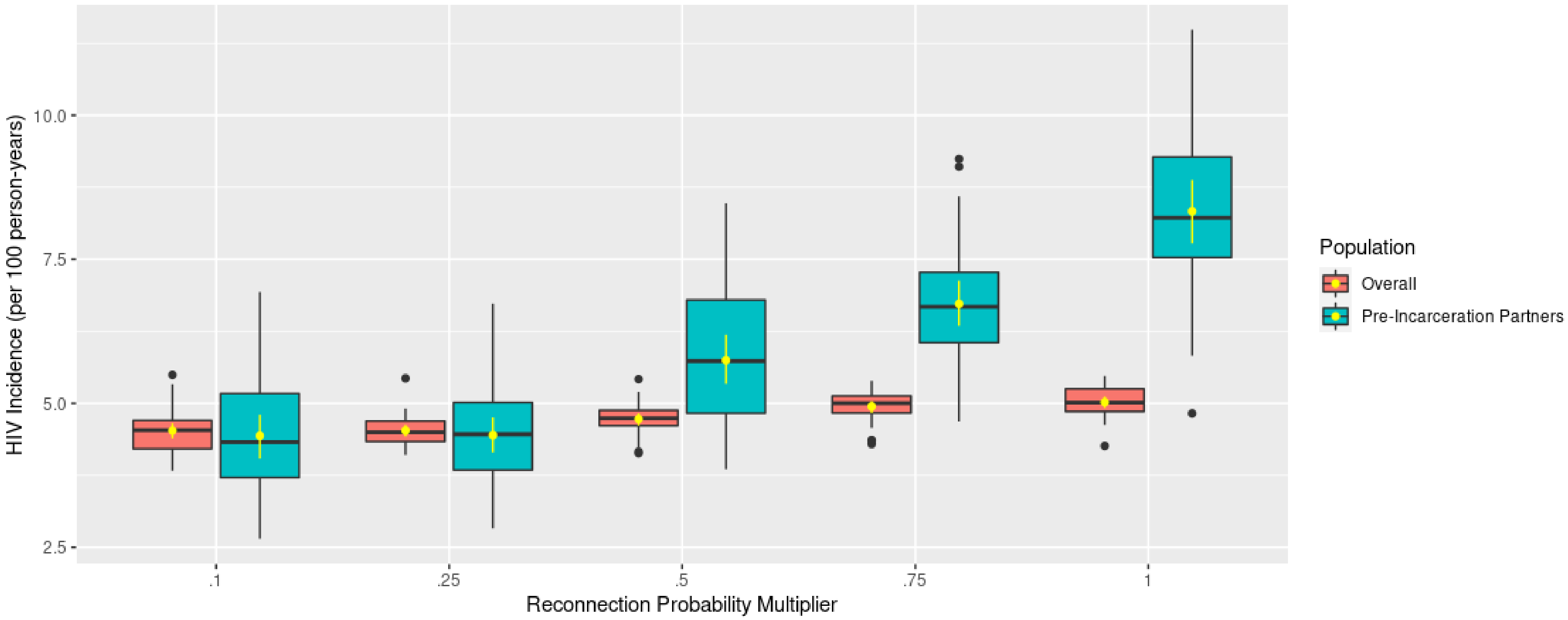
- Quantify the impact of criminal justice involvement:
  - Population level HIV incidence
  - HIV incidence among justice involved individuals and their networks
- Evaluate interventions to reduce the impact of justice involvement on HIV transmission in different sub-populations
  - Examples:
    - Reduce post-release disruption in HIV/PrEP care (e.g., interventions to facilitate care engagement by reducing insurance, housing, or employment barriers)
    - Focused or enhanced PrEP and ART interventions for justice involved individuals and their networks
- Each scenario was repeated across 30 runs to incorporate stochasticity and outcomes were averaged across runs

Annual HIV incidence by subpopulation

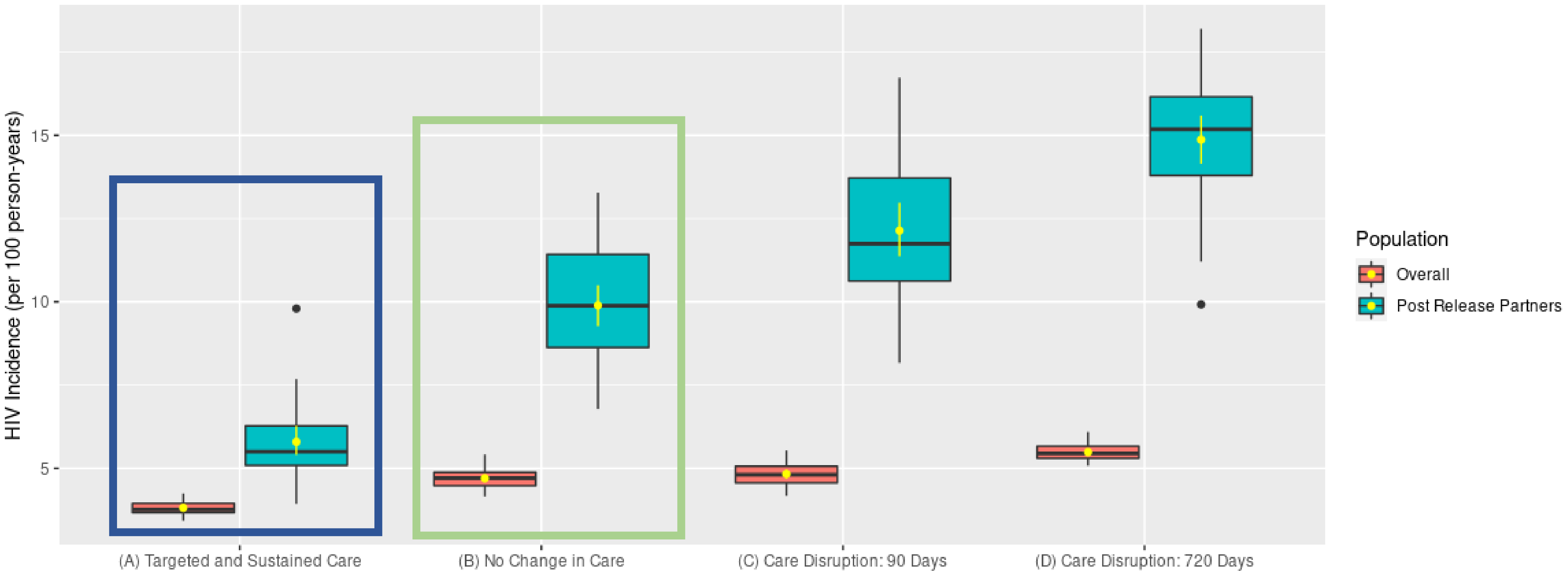
Population	**HIV incidence per 100 person-years**	**95% CI***
Individuals		
Ever incarcerated	5.72	5.52 – 5.92
Never incarcerated	4.73	4.65 – 4.83
Partners of individuals with CJI		
Pre-Incarceration Partners	6.83	6.31 – 7.40
Post-Release Partners	12.14	11.4 – 13.0

*Confidence intervals obtained via bootstrapping

HIV incidence by probability of partner reconnection after release from jail



HIV incidence under various levels of post-release care disruption and intervention



Average HIV incidence under different care disruption scenarios

	Post-Release Partners Incidence per 100 person-years (95% CI)	Overall Incidence per 100 person-years (95% CI)
Intervention: Targeted and sustained care	5.80 (5.40, 6.28)	3.81 (3.74, 3.89)
Standard: No change in care	9.90 (9.27, 10.50)	4.70 (4.59, 4.82)
Incidence rate ratio	0.59 (0.53, 0.65)	0.86 (0.84-0.89)
Incidence rate difference	-4.10 (-4.85, -3.35)	-0.89 (-1.02, -0.76)

Summary

- Identified a subgroup who could benefit from targeted PrEP interventions (partners of those recently released from jail) which may have been hard to identify using observational research designs
  - Can give ideas about where to target limited public health resources

- Suggests need for interventions to increase ART and viral suppression among HIV-positive individuals with CJI *and* increase PrEP/ART use in their networks

- Next steps
  - Evaluate impact of interventions to distribute PrEP to networks of released individuals
  - Explicitly model interventions to reduce post-release disruption in care by reducing insurance, housing, or employment barriers and recidivism
  - Combinations of interventions applied simultaneously or sequentially

Limitations & open questions

- Estimates used as input parameters for agent-based models are often uncertain or potentially biased – need for sensitivity analysis
  - Model results may be dependent on parameter inputs for which the true magnitude of effect is often unknown
  - Transportability – estimates of effect from one population may not generalize to another

- Can provide a range of effect estimates as priors and use computational techniques to refine estimates – ongoing work in this area
  - Large-scale sensitivity analyses and model exploration with high-performance computing
  - Identify variables that have the most impact on model (system) behavior

Extensions and ongoing work

- Ongoing work: extend existing model to incorporate additional social determinants of health (housing, employment) and evaluate their impact
  - Increase the granularity of the synthetic population in order to represent HIV transmission with sufficient realism to examine more nuanced research questions
- Develop formal methods for evaluating assumptions needed for valid inference with agent-based modeling
  - Counterfactual frameworks and high-dimensional sensitivity analyses to assess the impact of varying causal or mechanistic assumptions
  - Quantify the impact of incomplete or imprecise empirical data

- G-computation
  - Methods to estimate the causal effect of a time-varying exposure in the presence of time-varying confounders affected by the exposure; also applies to settings with feedback loops
  - Extensions can address interference (auto g-computation)
  - May complement agent-based modeling to triangulate information if adequate longitudinal data are available
  - Can provide causal effects estimates as starting parameters for agent-based models to be refined using computational approaches within the ABM

Collaborators and funding

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Technical resources and documentation

Repast for High performance computing:

Homepage: https://repast.github.io/repast_hpc.html

Repast documentation, including Repast4Py (Python implementation) and lots of tutorials: https://repast.github.io/docs.html

Collier N, North M. Parallel agent-based simulation with Repast for High Performance Computing. *SIMULATION.* 2013;89(10):1215-1235.

Estreme-scale Model Exploration with Swift: https://emews.github.io/

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EpiModel (R package for mathematical models of infectious disease): https://www.epimodel.org/

Tutorials on agent-based modeling:

C M Macal (2016) Everything you need to know about agent-based modelling and simulation, Journal of Simulation, 10:2, 144-156, DOI: 10.1057/jos.2016.7

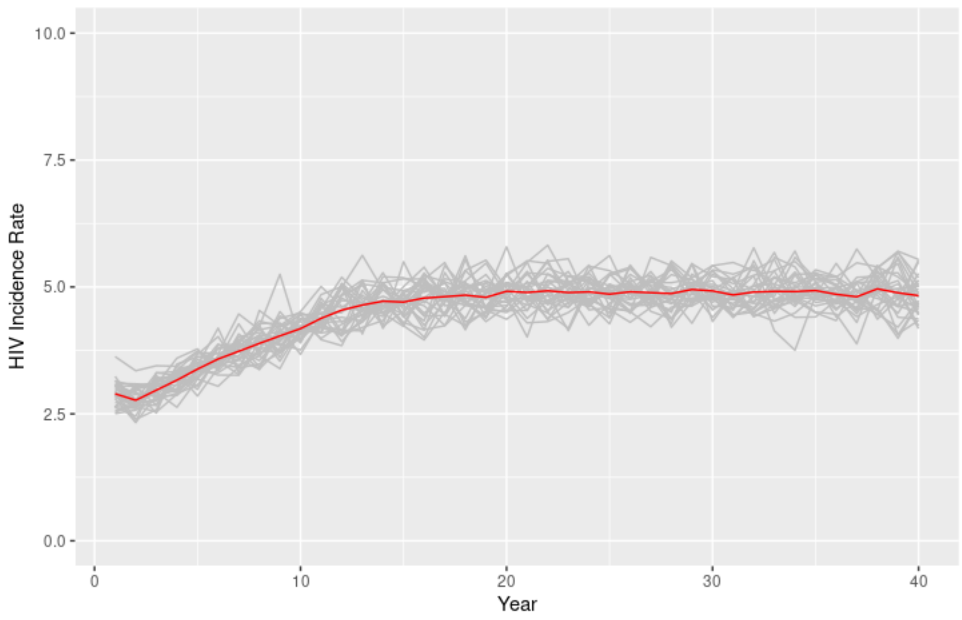
Macal & North: Introductory tutorial on agent-based modeling and simulation: http://simulation.su/uploads/files/default/2014-macal-north.pdf

Extra slides

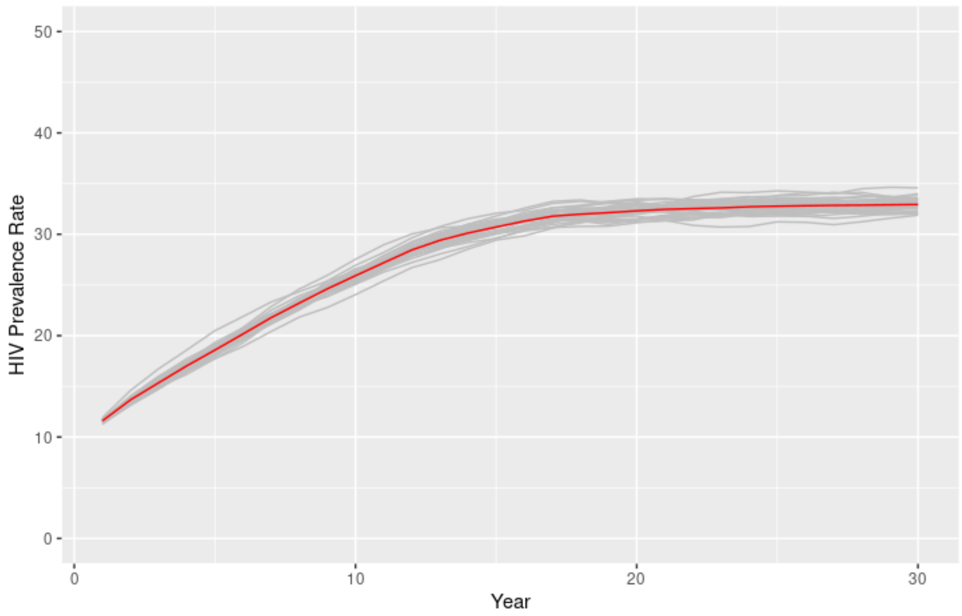
Model calibration

- Initial set of 270 calibration runs
- Calibration targets: annual HIV incidence (5-7%), HIV & incarceration prevalence
  - Examined differences by age and prior incarceration
- Tested a range of scenarios using empirical estimates from local data as inputs
  - Probability & duration of incarceration
  - PrEP & ART care continuum disruption
  - Network tie retention probabilities
- Refined estimates after initial examination of model output
- Selected the set of parameters that produced outputs consistent with empirical calibration targets for further experimentation

HIV incidence

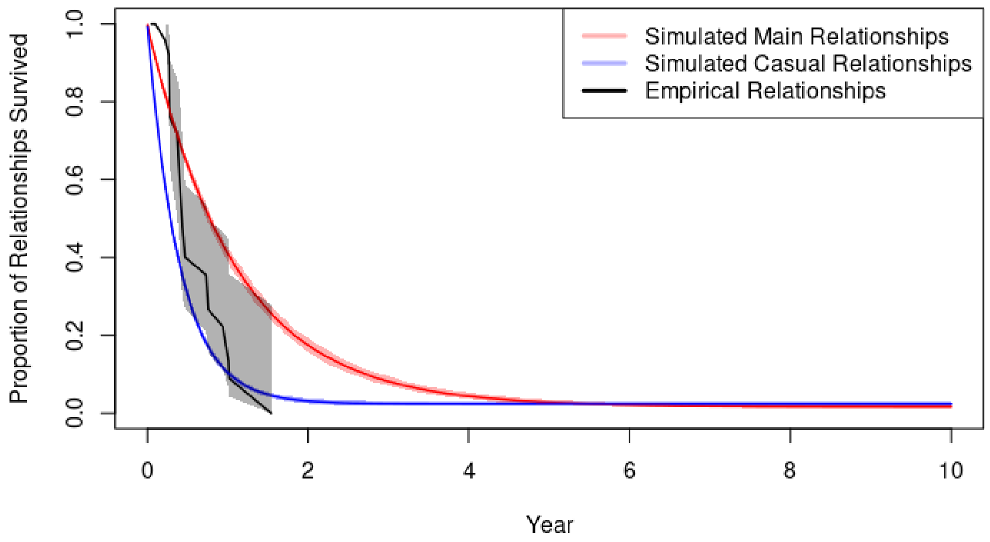


HIV prevalence



Network tie retention

- When agents go to jail existing network ties are broken with a probability of reconnecting after release
- Determine the status quo survival rate of relationship ties over time using the existing ABM with no incarceration processes implemented
- Apply multiplier to represent the impact of incarceration on probability of reconnecting ties after release
    - Results in a shift in the status quo distribution
        - Multiplier = 1: no impact on tie retention
        - Multiplier < 1: probabilities of retained ties less than the status quo



Local data sources

Source	Year	Description	Parameter categories
UConnect (R01DA033875)	2013-2015	Cohort study of Black MSM & transwomen ages 16-29, RDS recruitment (n=618)	Sociodemographics, networks, substance use, risk/prevention behavior, HIV/STI prevalence Chicago
National HIV Behavioral Surveillance (NHBS)	June-December 2017 (MSM cycle V)	Time location venue sampling of White, Black, Hispanic/Latino MSM (transwomen not eligible) of all ages (n ~ 500)	Sociodemographics, substance use, risk/prevention behavior, HIV prevalence, PrEP & ART use, partner by partner characteristics/sex behaviors for up to 3 partners
CDPH HIV surveillance	Ongoing	HIV surveillance records	HIV incidence and prevalence, retention in care, viral suppression
US Census Bureau	Ongoing	Demographics of Chicago population	Age-specific mortality rates, population growth rates, population size overall and by subgroup

Agent-based models for evaluating adaptive interventions

- Adaptive interventions modify intervention or intervention components based on participants' initial response
- ABM can provide insights about the potential impact of adaptive interventions
  - Observe predicted patient trajectories to inform and adjust dose or other intervention components
  - Adjustments to service-level factors, such as provider training
- Can model dynamic, time-varying processes, multicomponent interventions

Agent-based models for implementation science research

- What-if scenarios can be used to evaluate questions at a conceptual level at the beginning of the implementation process even if empirical data are limited
  - Rerun models under different implementation strategies or policy scenarios
  - Can identify barriers and strengths early in the implementation process
- Incorporate behavioral rules at the individual level and organizational-level interactions
- Individual interventions; combinations of interventions applied simultaneously or sequentially; multi-level interventions; cost-benefit analysis