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

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• 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

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


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

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

- Age
- Race
- Education
- Gender identity
- Sexual orientation
- Incarceration
- Employment
- Economic stability
- Insurance
- Housing
- Violence/Trauma
- Mental health
- Sexual risk
- Substance use
- Disrupted sexual networks
- Disrupted ART/PrEP care
- Reduced ART/PrEP adherence
- HIV transmission

Key:
- Time-fixed covariates
- Distal/structural
- Intermediate/psychosocial
- Proximal/hio-behavioral
- Outcomes
- Time-varying
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

<table>
<thead>
<tr>
<th>Agents</th>
<th>Agent-Agent interactions</th>
<th>Environments</th>
<th>Agent-environment interactions</th>
</tr>
</thead>
</table>
| • 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

Basic notation: Agents

• At each time step $t$ ($t = 1, ..., T$), each agent $i$ ($i = 1, ..., N$) has a set of $m$ ($m = 1, ..., M$) internal traits that can be described by the matrix $S^t$

\[
S^t = \begin{bmatrix}
S_{1,1}^t & S_{1,2}^t & \cdots & S_{1,M}^t \\
S_{2,1}^t & S_{2,2}^t & \cdots & S_{2,M}^t \\
\vdots & \vdots & \vdots & \vdots \\
S_{N,1}^t & S_{N,2}^t & \cdots & S_{N,M}^t 
\end{bmatrix}
\]

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

• Analogously, agents can be placed in $p$ ($p = 1, ..., P$) environments where $E^t$ represents an environmental state matrix

Agent-agent interactions

• At each time step $t$ ($t = 1, \ldots, T$) each agent $i$ interacts with a subset of the population $\{1, \ldots, i-1, i+1, \ldots, N\}$
  • Described by agent-agent interaction matrix $K^t$ where each element $k^t_{i,j}$ indicates whether agent $i$ interacts with agent $j$ during timestep $t$ where $i$ and $j = 1, \ldots, N$
  • 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 $Z$ for updating of agent traits, agent-agent interactions, and movement between or interaction with environments
  • Rules $Z$ are defined by functions

• At each time step: update the model based on previous values and pre-defined rules $Z$
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 ([\( Z, S^T_A, K^T_A, E^T_A \)]) vs. Scenario B ([\( Z, S^T_B, K^T_B, E^T_B \)])

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

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

CJI

Disrupted sexual networks

Disrupted ART/PrEP care

Higher partner turnover, more sex partners, concurrency

Reduced ART/PrEP adherence

HIV transmission
• Age existing agents by 1 time step
• Remove existing agents due to death (natural and infection-related)

• Partnership formation and dissolution
• Condom use

• Update viral load in HIV-infected agents
• Update CD4 counts in HIV-infected agents (both parameters depend on ART status)

• HIV-infected agents initiate ART
• HIV uninfected agents can initiate PrEP

• 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

• Agents cycle in and out of jail
• Impacts existing partnerships and ART/PrEP engagement
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

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

<table>
<thead>
<tr>
<th>Population</th>
<th>HIV incidence per 100 person-years</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Individuals</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever incarcerated</td>
<td>5.72</td>
<td>5.52 – 5.92</td>
</tr>
<tr>
<td>Never incarcerated</td>
<td>4.73</td>
<td>4.65 – 4.83</td>
</tr>
<tr>
<td><em>Partners of individuals with CJI</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Incarceration Partners</td>
<td>6.83</td>
<td>6.31 – 7.40</td>
</tr>
<tr>
<td>Post-Release Partners</td>
<td><strong>12.14</strong></td>
<td><strong>11.4 – 13.0</strong></td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th></th>
<th>Post-Release Partners</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence per 100 person-years (95% CI)</td>
<td>Incidence per 100 person-years (95% CI)</td>
</tr>
<tr>
<td>Intervention: Targeted and sustained care</td>
<td>5.80 (5.40, 6.28)</td>
<td>3.81 (3.74, 3.89)</td>
</tr>
<tr>
<td>Standard: No change in care</td>
<td>9.90 (9.27, 10.50)</td>
<td>4.70 (4.59, 4.82)</td>
</tr>
<tr>
<td>Incidence rate ratio</td>
<td>0.59 (0.53, 0.65)</td>
<td>0.86 (0.84-0.89)</td>
</tr>
<tr>
<td>Incidence rate difference</td>
<td>-4.10 (-4.85, -3.35)</td>
<td>-0.89 (-1.02, -0.76)</td>
</tr>
</tbody>
</table>
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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Citations: Agent-based modeling, G-computation, and causal inference


Citations: Agent-based modeling, G-computation, and causal inference continued


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


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


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

Tutorials on agent-based modeling:


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
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

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