Study Design, Methods, and Modeling in Networks to Inform HIV Interventions and Policy in Marginalized Populations

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ABSTRACT

The Networks and Causal Inference for Public Health Research (NCIPHER) Lab at the University of Rhode Island (URI) was established in 2018, with an initial pilot project supported by Advance Rhode Island Clinical Translational Research (RI-CTR), to develop methodological and computational approaches for evaluating interventions in real-world settings where individuals are connected in ways that impact their health. Leveraging bioinformatics and high-performance computing resources through Advance RI-CTR, we integrate empirical and simulation methods to estimate causal intervention effects (i.e., change in an outcome caused by a specific intervention) beyond treated individuals, including spillover through social and healthcare networks and clusters. Our work demonstrates that accounting for spillover improves understanding of the effectiveness of HIV and opioid use disorder (OUD) interventions. In the Transmission Reduction Intervention Project Athens, Greece, participants not exposed themselves to community alerts about HIV risk, with 50% of their immediate contacts exposed, reported three fewer unsafe injection behaviors (per 100 participants), compared to those who had 20% of their contacts exposed (95% CI: –7, 0). We also found 26 fewer reports (per 100 persons) at six months under individual treatment with medication for opioid use disorder with 60% of other individuals in the network treated, compared to no treatment with 20% of others treated (95% CI: -38, –13). Understanding effects in networks can improve translation from intervention delivery to population-level impact, supporting evidence-based policy.

KEYWORDS: Agent-based models; HIV/AIDS; interference; spillover; marginalized populations; substance use

BACKGROUND

Many public health interventions aimed at addressing the syndemics of HIV and overdoses likely not only affect the treated, but also others in the treated individuals' networks. This is known as *spillover*, a systematic, often unintended treatment effect on individuals who were not treated themselves. This is especially important for the marginalized and stigmatized populations with lower access and uptake of health interventions who are disproportionately impacted by these syndemics.[1] There are large disparities in healthcare and outcomes of individuals living with HIV, including men who have sex with men (MSM), and people who inject drugs (PWID).[2-4] Measuring and quantifying spillover can improve disease outcomes by expanding the reach of interventions beyond traditional research and clinical settings, informing intervention policy development, and mitigating infectious diseases.[5,6]

Studying causal mechanisms allows us to understand the processes by which HIV-related outcomes occur.[7] Causal mechanisms include biological, behavioral, or social processes through which an intervention affects health outcomes. Causal inference quantifies what would happen under different interventions and determines whether observed differences in health outcomes are caused by specific interventions. Readers may be familiar with confounding bias, in which a third variable distorts the relationship between an exposure and outcome, and we aim to isolate the effect of an exposure by removing confounding either by design or analysis. Causal inference using a potential outcomes framework can assess causal effects from both randomized and observational study data. In the setting of no interference/spillover, each individual's (potential) outcome is indexed by their own exposure; however, with spillover, each person's outcome is indexed by their own exposure and the exposure of others.[6] Heuristically, we can estimate spillover by comparing outcomes among individuals with similar characteristics and exposure histories but differing exposure patterns among their contacts.[6] By summarizing contacts' treatments through exposure mapping (e.g., the number or proportion treated in the group) and appropriately weighting or modeling the data, we can assess how modifying the intervention for network contacts changes the average outcomes, even for untreated individuals.

Although spillover has been traditionally studied for therapies like vaccines, other interventions may cause meaningful spillover, such as treatment as prevention (TasP) and pre-exposure prophylaxis (PrEP) for HIV, medication for opioid use disorder (MOUD), and naloxone for opioid overdose rescue. Standard evaluation methods may underestimate the benefits of these interventions by overlooking these effects, so we must account for them in the design, analysis, and modeling of public interventions. For example, PrEP

provides a 90% reduction in HIV acquisition in randomized trials among participants with high medication adherence.[8] However, if we evaluate the exposure as receipt of PrEP on preventing HIV acquisition only among treated individuals, we will miss the additional spillover benefit due to a reduction in onward transmission to their partners and possibly partners' partners. The Networks and Causal Inference for Public Health Research (NCIPHER) lab (co-Directors: Buchanan and Katenka) seeks to understand how interventions affect groups of people impacted by these syndemics, rather than individuals, recognizing that people are socially connected in complex and meaningful ways that can be leveraged to improve public health.

Marginalized populations continue to face a disproportionately high burden of HIV, including PWID and MSM. In 2022, the Centers for Disease Control and Prevention found that PWID accounted for 10% of all people living with HIV in the US.[9] PWID face HIV-transmission risk due to sexual and injection-related behaviors and often have limited access to harm reduction services, further constrained by stigma, incarceration, housing instability, and socioeconomic challenges.[10-12] In the PWID population, the majority inject unregulated opioids, and many of those individuals are also diagnosed with HIV.[13,14] Although three FDA-approved medications, including buprenorphine, methadone, and naltrexone, are available for treating OUD, major treatment gaps persist, with fewer than 20% of individuals with OUD receiving MOUD in 2022.[14-21] Because PWID are members of social, drug-use, and sexual networks,[22] increased MOUD uptake may protect both treated individuals and their contacts, including via medication sharing or the diffusion of harm-reduction information,[6,23-30] and reducing HIV injection-related risk behaviors of others in the network.[16-22,31]

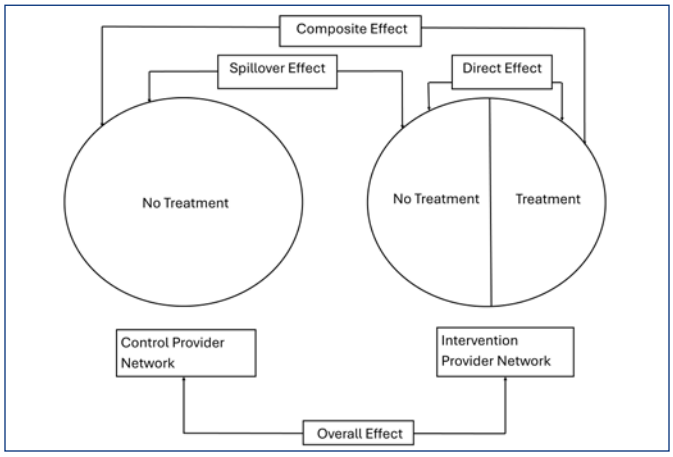
Young Black MSM (BMSM) face substantial barriers to optimal use of HIV-prevention modalities, including PrEP, due to factors such as misinformation, mistrust, and co-occurring substance use disorders that elevate HIV-transmission risk.[32-36] Between 2008 and 2014, HIV incidence increased among young BMSM in the United States while declining in other groups.[37] Network-based interventions show promise for addressing these disparities.[3,38-40] For example, The Transmission Reduction Intervention Project (TRIP) in Athens, Greece, and Chicago, IL, successfully used network recruitment to identify recently infected individuals and link them to care,[41,42] and PrEP Chicago demonstrated that peer-based network interventions can increase PrEP uptake among young BMSM.[36,43] Yet, how to most efficiently leverage networks to maximize spillover effects of peer-change agents, treatment as prevention (TasP), and PrEP remains unclear. Because many traditional trials and cohorts ignore underlying network structure, they risk bias from network dependence.[44] Developing methods to account for this dependence and statistically valid approaches to appropriately assess spillover are therefore essential for a wide range of study designs and research questions.

REVIEW OF ADVANCE RI-CTR SUPPORT

The NCIPHER lab was launched with support from an initial pilot project by the Advance Rhode Island Clinical Translational Research (RI-CTR) in 2018 that improved statistical methodology for quantifying spillover (disseminated) effects using administrative health claims databases. In this pilot project and subsequent federally funded research, our team has leveraged bioinformatics and computing resources from the Advance RI-CTR service cores. We have also gained access to important health databases to advance our research and impact, including the Rhode Island All-Payer Claims Database and the National COVID Cohort Collaborative. Through the Advance RI-CTR network, NICPHER lab members at URI access the service cores, which offer consultative services from experienced investigators skilled in key areas such as epidemiologic methods and qualitative research.

Our work in the Advance RI-CTR pilot project provided new insights into how interventions may be leveraged to more effectively and efficiently advance OUD prevention and treatment among patients receiving medical care across the United States. Patients are part of provider-based networks (based on medical claims data) and may exert social influence on others' treatment behaviors through shared clinical environments, overlapping provider relationships, and geographic proximity. These dynamics have the potential to shape collective norms surrounding opioid use and OUD treatment. In this framework, patients who are prescribed MOUD are considered index patients, and individuals who are not prescribed MOUD, but who share a provider-based network with an index patient, are defined as network members [(**Figure 1**]. The *individual* (direct) effect refers to the impact of MOUD on the index patients themselves, while the *spillover* (indirect or disseminated) effect represents the impact of these treatments on network members who share a connection (in this case, the same healthcare provider) with an index patient.[45]

Figure 1. Schematic diagram of the subsets of data used for each estimator (direct, spillover, composite and overall) based on a format provided in.[59] A provider network is a group of patients who share the same provider for their medication for opioid use disorder claims.



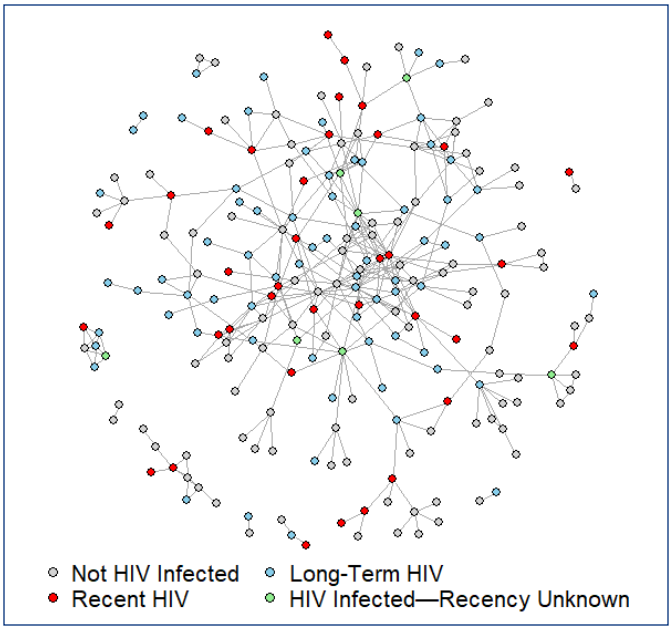
PUBLICATIONS AND FINDINGS

We summarized the primary findings from the Advance RI-CTR pilot project and subsequent key findings during the National Institute on Drug Abuse (NIDA) Avenir Award. NIDA's Avenir Awards focus on innovation and potentially transformative research from early-stage investigators, and our award was the first given nationally to a biostatistician. We examined the impact of timely initiation of buprenorphine/naloxone following an OUD diagnosis in a large cohort of insured adults using Optum's Clinformatics® Data Mart from 2010 to 2018 (n=8,388).[46] Prior to assessing spillover, we quantified the health outcomes and healthcare costs associated with timely MOUD initiation. We classified patients who started treatment within 30 days of diagnosis as early initiators and compared them to late initiators (those initiating later within one year). We employed generalized linear models to compare outcomes between groups, adjusting for baseline covariates and using multiple imputation to address missing data. After adjustment for baseline covariates, early initiation was associated with a 42% lower rate of opioid overdose (adjusted rate ratio [aRR] = 0.58, 95% CI: 0.52–0.64), a 51% lower rate of opioid overdose–related emergency department visits (aRR = 0.49, 95% CI: 0.44–0.55), and a 31% reduction in total healthcare costs (adjusted cost ratio = 0.69, 95% CI: 0.66–0.72) during the year after diagnosis compared with late initiation. Early initiation was associated with lower overdose risk, fewer ED visits, and lower healthcare costs among insured adults with OUD.

We proposed a novel application of causal inference methods for spillover in retrospective studies using administrative claims data, which can be employed to emulate a target trial when randomized trial data is not available. Extending this framework to an idealized two-stage randomized trial, an evaluation of direct and spillover effects within provider-based networks is possible. We developed an approach to build a provider network among individuals based on their primary MOUD providers using MOUD prescription claims and National Provider Identifiers, then assessed the proportion of patients in a provider network who were prescribed MOUD (i.e., coverage). Using generalized estimating equations with covariate adjustment, we constructed estimators for both individual and disseminated effects tailored to retrospective observational study designs in claims data. There were 2,273 patients in 722 provider networks, and 64% had a MOUD prescription.[45] We found modest evidence of direct and spillover effects in this setting. For the estimated spillover effect, we would expect 3 fewer overdoses per 100 people (95% CI: –5, –1) in untreated patients within high-coverage clusters compared to within low-coverage clusters. The direct effect was protective with an estimated 3 fewer cases per 100 people (95% CI: –6, –0) receiving treatment (vs no treatment) within 33% coverage clusters.

From 2018 to 2023, our team worked on the Avenir project funded by the NIDA. We evaluated the spillover of interventions and treatments using both secondary data analyses of existing datasets and simulation approaches, requiring the development of novel study designs and inferential and modeling methods in networks. We developed and implemented a novel methodology to evaluate spillover among networks of people who use drugs. Our work was largely motivated by TRIP in Athens, Greece, which successfully recruited and intervened in this population by identifying and engaging injection and sexual networks of recently-infected PWID through contact tracing [**Figure 2**]. We developed and evaluated approaches to quantify spillover in a network-based study with a non-randomized intervention.[47] These methods were used to evaluate spillover of HIV interventions, including community alerts, MOUD, and antiretroviral treatment (ART). Most estimates of the risk differences for community alerts reduced HIV-risk behavior, including spillover from sexual and drug use partners.[47] We estimated spillover effects of the alert intervention coverage on risk behavior, with 3 fewer reports per 100 participants under 50% versus 20% coverage (95% CI: –7, 0). We also employed causal inference methods to evaluate the spillover effects of MOUD and ART on subsequent HIV-risk behaviors with the spillover set defined by network communities or neighbors. Although the magnitude of these effects was sometimes sensitive to the community detection method, we found significant and protective effects of MOUD on HIV-risk behaviors and the estimated total effect was more robust to the community detection method used to define the interference set. For example, we expect 26 fewer reports

Figure 2. The TRIP network by HIV status. This network originally consisted of 10 connected components, and a community detection algorithm was used to further divide it into 20 components.[49] Individuals (nodes) are shaded by their HIV-infection status at baseline.



per 100 persons (95% CI = –38, –13) at the 6-month visit under MOUD in communities with 60% coverage, compared to under no MOUD in communities with 20% coverage.[31] However, our team did not observe any significant spillover effects of ART in TRIP Athens.[48]

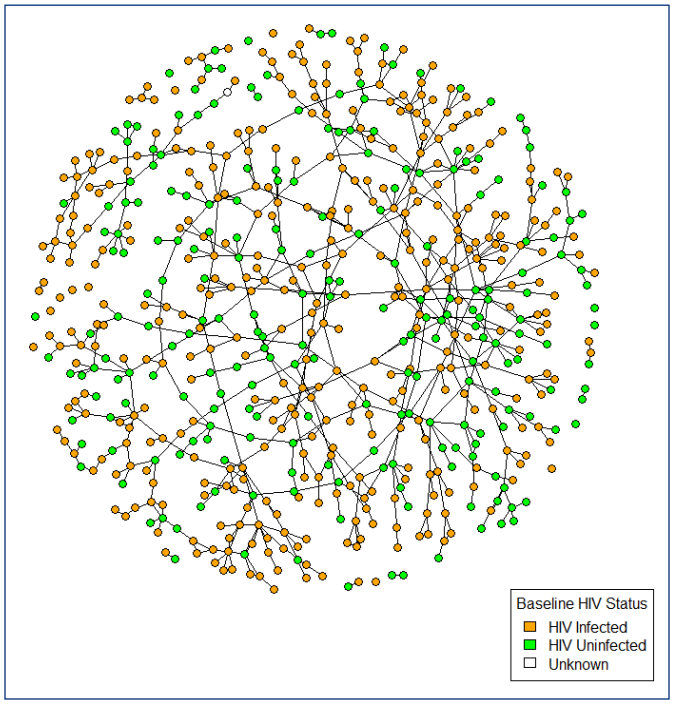
We developed an agent-based model (ABMs; computational models to study the impact of the individual's actions on the disease processes in the population) using a novel trial emulation framework to quantify spillover effects of pre-exposure prophylaxis (PrEP) among a sexual network of MSM in Atlanta, GA.[50-52] The estimated composite (total: direct and spillover) effect was an 85% reduction in the cumulative incidence of HIV, comparing agents on PrEP within intervention components to agents within control components (RR = 0.15, 95% SI = 0.11, 0.20).[50] As coverage levels increased, the spillover effect of PrEP was larger in magnitude, while the direct effect attenuated towards the null. Other publicly available resources included R programs to implement the new methodology for networks through Github[53] and a curated TRIP Athens data set.[54]

Significance and Future Work

Our current R01 project funded by NIDA will develop and apply new methods to evaluate HIV interventions using both secondary data analyses and simulation approaches. This project will inform intervention-coverage levels considering spillover and will be used to determine the types of individuals who could benefit the most from interventions with spillover. This project will provide new insights into spillover in the following network studies of MSM in Chicago, Illinois: uConnect [**Figure 3**], PrEP Chicago, and the Neighborhood and Networks Cohort Study.[4,36,55] We developed new methods to quantify spillover in a network setting with a variance estimator that better accounts for the network structure. We now need new approaches to address missing data and network dependence when assessing spillover, ensuring valid analyses in the more realistic data settings. We will develop a framework using agent-based models to evaluate the spillover of PrEP change agent interventions and PrEP delivery focused on those with substance use. Our team is also advancing methods for more flexible estimation approaches in networks that rely less on strong modeling assumptions, including targeted learning.[56] Targeted learning first learns patterns in the data, then adjusts those estimates to quantify a specific causal effect.[57,58] These methods make minimal and realistic assumptions about data distributions and are therefore a critical improvement for generating meaningful knowledge from real-world data.

Our research will provide new insights into spillover to reduce the spread and morbidity of HIV and other infectious diseases, often complicated by a high burden of substance use in marginalized populations. Estimated spillover effects in public health are modest at times, but can have a substantial population-level impact across connected individuals.

Figure 3. The uConnect study network with respondent-driven sample (RDS), social and sex partner ties, by baseline HIV status. Entity resolution was conducted to identify unobserved ties and individuals appearing in the network multiple times.[55] Individuals (nodes) are shaded by their baseline HIV-infection status.



Accounting for spillover is needed for valid inference to avoid bias and spillover remains largely unknown in many settings, especially in HIV prevention and treatment, where networks play a major role in disease transmission yet are often unmeasured. These advancements in methods and study design resources can be used to design and evaluate interventions for reducing HIV- risk behavior, increasing engagement in HIV-prevention measures, and strengthening HIV treatment among marginalized populations. These methods will also be applicable to studies of other infectious diseases, including sexually transmitted infections, hepatitis C, tuberculosis, and SARS-CoV-2, and are an important contribution to intervention research methodology. Although network structures may differ across contexts, the methods developed in our motivating settings may apply to a wide range of network types. Collectively, these findings illustrate how network causal inference methods can improve translation from intervention development to community impact, supporting evidence-based policy and demonstrating the translational value of Advance RI-CTR-supported infrastructure.

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