Practice of Epidemiology

Disseminated Effects in Agent-Based Models: A Potential Outcomes Framework and Application to Inform Preexposure Prophylaxis Coverage Levels for HIV Prevention

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Preexposure prophylaxis (PrEP) for prevention of human immunodeficiency virus (HIV) infection may benefit not only the person who uses it but also their uninfected sexual risk contacts. We developed an agent-based model using a novel trial emulation approach to quantify disseminated effects of PrEP use among men who have sex with men in Atlanta, Georgia, from 2015 to 2017. Model components (subsets of agents connected through partnerships in a sexual network but not sharing partnerships with any other agents) were first randomized to an intervention coverage level or the control group; then, within intervention components, eligible agents were randomized to receive or not receive PrEP. We calculated direct and disseminated (indirect) effects using randomization-based estimators and report corresponding 95% simulation intervals across scenarios ranging from 10% coverage in the intervention components to 90% coverage. A population of 11,245 agents was simulated, with an average of 1,551 components identified. When comparing agents randomized to no PrEP in 70% coverage components with control agents, there was a 15% disseminated risk reduction in HIV incidence (risk ratio = 0.85, 95% simulation interval: 0.65, 1.05). Persons not on PrEP may receive a protective benefit by being in a sexual network with higher PrEP coverage. Agent-based models are useful for evaluating possible direct and disseminated effects of HIV prevention modalities in sexual networks.

agent-based models; HIV; HIV prevention; interference/dissemination; men who have sex with men; preexposure prophylaxis

Abbreviations: ABM, agent-based model; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, preexposure prophylaxis; RR, risk ratio; SI, simulation interval.

Once-daily preexposure prophylaxis (PrEP) is administered as a single tablet containing tenofovir disoproxil fumarate and emtricitabine and is effective for preventing transmission of human immunodeficiency virus (HIV) among men who have sex with men (MSM) (1, 2). Despite strong evidence of effectiveness (3, 4), access to PrEP among MSM remains low, particularly in the southern United States, where MSM have some of the highest incidence and prevalence burdens of HIV infection of all US subpopulations (5–7).

Traditional randomized clinical trials assessing the effect of PrEP on HIV incidence have considered only the direct

(individual) effect of reducing HIV incidence among persons who use PrEP. However, PrEP for HIV prevention may benefit not only the individual user but also their sexual risk contacts (8). In preventing HIV acquisition in a person who uses PrEP, the possibility of secondary transmission to their HIV-uninfected sexual risk contacts and possibly their partners' partners is also eliminated (9). This feature (common to other prophylactic therapies such as vaccines) is referred to as spillover, dissemination, or interference (10, 11). Estimators of the maximal attainable benefit of an intervention like PrEP, referred to as its composite (total) effect, should account for both the impact of the intervention on its

Figure 1. Types of causal effects in the context of dissemination (or interference) in 2-stage randomized design of a preexposure prophylaxis (PrEP) intervention in an agent-based model representing men who have sex with men, Atlanta, Georgia, 2015–2017 (18).

users and the impact of the intervention on persons who did not use the intervention themselves but were connected to users.

In causal inference, a fundamental assumption of much work is the stable unit treatment value assumption (12), which includes an assumption of no dissemination, or interference, between individuals. An assumption of no dissemination requires that the potential outcomes for one individual be unaffected by the intervention assignment of other individuals. These effects are readily identifiable in 2-stage randomized trials (Figure 1) (10, 13), where randomization first occurs at a group level (i.e., groups of connected individuals are randomly assigned to an intervention allocation strategy or the control group) and then at an individual level (i.e., individuals are assigned to receive or not receive an intervention according to their group allocation strategy) (Figure 2). The disseminated (indirect) effect of the intervention is defined as the effect of being in an intervention group and randomized to not receive an intervention versus being in a control group.

We adapted a previously published agent-based model (ABM) (14, 15) simulating HIV transmission in a hypothetical population of MSM in Atlanta, Georgia (16, 17) to emulate a 2-stage randomized clinical trial (18), which may be considered unfeasible or unethical to implement in this population, because PrEP is currently approved by the Food and Drug Administration for HIV prevention and is often used as an active control in studies of “next-generation” HIV prevention modalities (19). We selected the city of Atlanta as a case study because of the high HIV incidence and prevalence among MSM in this setting (20). Access to PrEP could be improved in this population, and benchmarks for coverage could be used to inform and expedite efforts to end the HIV epidemic in the southeastern United States (21). We aimed to evaluate the magnitude and direction of possible disseminated effects of PrEP use among MSM in Atlanta.

METHODS

Model setting

We adapted a previously published model of PrEP uptake and HIV transmission among MSM in Atlanta; complete details about this model can be found elsewhere (14). We employed a discrete-time, stochastic ABM to simulate a 2-stage randomized trial of PrEP for HIV prevention in a population of Atlanta MSM aged 18–65 years and followed agents for 2 years, from 2015 to 2017 (14, 22). Each agent in the model was assigned characteristics related to demographic factors, behavioral factors, HIV status, and clinical status. The simulated agent population was 52% African-American. Aligning with empirical estimates (20, 23, 24), we assumed that, among African-American agents, the median age was 32 years, 30% were using any substances, 32% had a preferred receptive sexual role, and 24% had a preferred insertive sexual role. Any substance use was defined as self-reported use of cannabis, cocaine, amphetamines, methamphetamines, inhalant nitrites, heroin/opioids, or benzodiazepines in the past 12 months (23). Among non-Hispanic White agents, we assumed that the median age was 35 years, 49% were using illegal substances, 23% had a preferred receptive sexual role, and 23% had a preferred insertive sexual role. Whenever possible, each individual agent’s behaviors and characteristics were parameterized on the basis of empirical estimates from the study setting. Values for several parameters (e.g., those governing initial HIV prevalence and treatment) were stratified by race/ethnicity (14), reflecting the substantial racial/ethnic disparities in HIV incidence and prevalence in this setting (20).

The model simulated a dynamic population with 1,000 total simulations per scenario, where the scenarios corresponded to a series of 2-stage randomized trials. Because this ABM was simulating a randomized trial with a short duration of follow-up, agents and their characteristics were

Figure 2. Two-stage randomized design used to evaluate preexposure prophylaxis (PrEP) for prevention of human immunodeficiency virus (HIV) infection in a simulated population of men who had sex with men, Atlanta, Georgia, 2015–2017. Trial 1 corresponds to a PrEP allocation strategy with 33% coverage in intervention components. Trial 2 corresponds to a PrEP allocation strategy with 66% coverage in intervention components.

generated in a base population and no new agents were allowed to enter the population. Python software, version 2.7.12 (25), along with the NumPy (26) and NetworkX (27) packages, was used for coding, testing, and performing sensitivity analyses of this model, and R software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) (28), along with ggplot2 (29), was used to analyze the model output and produce figures.

Additional information regarding parameter values, key model assumptions, data sources, and HIV prevalence results are included in Web Appendices 1–8 (available at <https://doi.org/10.1093/aje/kwaa239>) and Web Tables 1–3.

Sexual networking and components

Prior to “enrollment” (i.e., model initialization) in the hypothetical trial, agents formed sexual partnerships to create a sexual network of many distinct components. A sexual network component was defined as a subset of the agents in a network who are all connected through at least 1 partnership and are not connected to any other agents in the network. After 2-stage randomization, where first components were randomized to an intervention allocation strategy and then, within each component, agents were randomized according to that strategy, annual numbers of partners and numbers of

sex acts were assumed to follow stochastic distributions with parameters based on the literature (20, 30). At discrete time points (measured in months since randomization) over the 2 years of follow-up, relationships were not dissolved and new relationships were not formed, but rather sexual networks were assumed to be static, as ascertained prior to enrollment in the trial. This is akin to a randomized trial design, where often the sexual networks are ascertained only once at the start of the study (31, 32). These partnerships at enrollment were used to determine network components of size 2–100 agents.

HIV transmission, treatment, and progression

Detailed HIV transmission, treatment, and disease progression processes and parameters have been described previously (14, 15). At each monthly interval, agents engaged in a certain number of sex acts with their partners. The probability of condom use was lower if the agent used any substances and also decreased as a function of the number of prior contacts with a given partner. In the absence of any biomedical intervention (PrEP or treatment as prevention, known as TasP), any condomless sex act in a serodiscordant partnership had a nonzero probability of HIV transmission (the per-act probability was 1.38% for condomless receptive anal intercourse and 0.11% for condomless insertive anal intercourse) (33). This probability of HIV transmission varied depending upon the following factors: whether the HIV-negative agent was randomized to receive PrEP; adherence to PrEP among HIV-negative agents randomized to receive PrEP; and, among HIV-infected agents, knowledge of their HIV status, HIV treatment, and whether they achieved viral suppression after initiation of HIV treatment.

Impact of substance use on agent behavior

We included an agent class characterized by any substance use, which was defined at model initialization and remained stable for the duration of the study. The prevalence of substance use was set to 30% among African Americans and 49% among Whites (20, 23). Substance use influenced PrEP adherence, condomless sex, and assortative mixing in sexual partner selection. Agents who were defined as substance users had a 35% lower probability of achieving optimal adherence to PrEP (8) and a 20% higher probability of engaging in condomless sex (34). We assumed that 20% of substance-using agents mixed with other substance-using agents.

Oral PrEP use and HIV treatment

After enrollment in the hypothetical trial, eligible agents who were randomized to the PrEP intervention were assumed to continue to receive PrEP for the 2-year duration of the trial. For the 2-year duration, all agents were retained in the study and no agents died. At enrollment in the trial, agents were classified as either optimally adherent to PrEP (defined as 4 or more doses per week) or suboptimally

adherent (defined as 2–4 doses per week). Those with optimal adherence had a 96% reduction in the per-act probability of HIV acquisition, while those with partial adherence had only a 76% reduction (35). Agents on antiretroviral therapy were less likely to progress to acquired immunodeficiency syndrome than other HIV-infected agents. This was achieved through a scalar reduction in progression probability, with the reduction being dependent on antiretroviral therapy adherence (36, 37).

Simulated trial design

The current study simulated a 2-stage randomized trial (Figure 2). In the first stage, network components were randomized 1:1 to receive either a certain level of PrEP coverage (referred to as “intervention” components) or no PrEP coverage (referred to as “control” components) (18, 38). PrEP coverage level was defined as the proportion of eligible agents receiving PrEP in a component, where eligible agents were defined as those who were HIV-negative with 1 or more partnerships and aged 18–65 years at enrollment. PrEP coverage was assigned at baseline. We assumed that agents assigned to PrEP took a minimum of 2 or more doses per week, with adherence patterns that remained stable for the duration of follow-up. Following an intention-to-treat approach, we assumed that PrEP adherence did not change PrEP coverage and that PrEP coverage generally remained stable during follow-up. HIV-negative agents in each intervention component were randomized to PrEP according to the assigned coverage level. We considered PrEP coverage levels (in each component) of 10%–90%, in increments of 10% corresponding to each scenario.

At the baseline visit, agents who were randomized to receipt of PrEP initiated their intervention, and all agents, regardless of HIV status, were followed for 2 years to ascertain their HIV status. We assumed no dropout (i.e., 100% retention on PrEP over the 2 years of follow-up). We also assumed that the probability of death over the 2 years was 0, which may have been reasonable given the age range of the agents and the short duration of follow-up.

Causal inference methods for evaluation of dissemination using ABMs

Several assumptions are needed to identify causal effects in the presence of dissemination. We assumed *partial interference* (13)—that is, the intervention assignment affects the outcomes of other agents in the same component but does not extend to other agents outside their component. We assumed *stratified interference*, in which an agent’s potential outcome is dependent only on their own intervention assignment and the proportion of those randomized to the intervention in their component (39). We also made the usual assumptions required for causal inference (exchangeability, consistency, and positivity) (40). Because of randomization at both the component level and the agent level, marginal exchangeability holds: Components randomized to the intervention will be, on average, comparable to components randomized to the control. Within each component, agents randomized to

the intervention will be, on average, comparable to agents randomized to the control. Positivity means that there is a nonzero probability of exposure within each level of the covariates (41, 42). We assumed an independent Bernoulli allocation strategy for intervention assignment within each intervention component (13).

In our simulated trial, the sexual risk component sizes varied, so we employed estimators that account for varying component size (43). Assume that there are I components and each of the components has n_i individuals indexed by $j = 1, 2, \dots, n_i$ and $\sum_{i=1}^I n_i = N$. Let Y_{ij} , A_{ij} represent an observed outcome and intervention assignment status of the j th agent in component i . In addition, C_i denotes the intervention assignment strategy at the component level that corresponds to intervention coverage denoted by α , where $C_i = 1$ if the intervention allocation strategy was α and $C_i = 0$ otherwise. We consider the potential outcome for agent j in component i as $Y_{ij}(C_i = c, A_{ij} = a)$. Because we have a “pure control group,” there are 3 possible combinations of the following potential outcomes: $Y_{ij}(1, 1)$, $Y_{ij}(1, 0)$, and $Y_{ij}(0, 0)$. By (causal) consistency (44–46), the observed outcome is a function of the intervention assignment and potential outcomes; that is, $Y_{ij}^{\text{obs}} = C_i A_{ij} Y_{ij}(1, 1) + C_i (1 - A_{ij}) Y_{ij}(1, 0) + (1 - C_i) Y_{ij}(0, 0)$. Let $T_{ca} = \{(i, j): C_i = c \text{ and } A_{ij} = a\}$ to denote the set of components and agents who are assigned to $C_i = c$ and $A_{ij} = a$.

In the setting with varying component sizes, there are 2 types of estimands: 1) component-weighted estimands that assign equal weight to components, regardless of the number of individuals in each component, and 2) agent-weighted estimands that assign equal weight to agents, regardless of the distribution across components (43). The *direct effect* (DE) (i.e., individual effect) measures the additional benefit of being randomized to PrEP beyond being in an intervention component with a fixed PrEP coverage level (Figure 1) and is defined as

$$DE = \sum_{i=1}^I w_i^* \sum_{j=1}^{n_i} [Y_{ij}(1, 1) - Y_{ij}(1, 0)].$$

The *disseminated effect* (i.e., indirect effect (IE)) compares agents who were not randomized to PrEP themselves in an intervention component with those who were in a control component and is defined as

$$IE = \sum_{i=1}^I w_i^* \sum_{j=1}^{n_i} [Y_{ij}(1, 0) - Y_{ij}(0, 0)].$$

The *composite effect* (i.e., total effect (TE)) is the combined direct and disseminated effects and is defined as

$$TE = \sum_{i=1}^I w_i^* \sum_{j=1}^{n_i} [Y_{ij}(1, 1) - Y_{ij}(0, 0)].$$

The *overall effect* (OE) marginalizes over the agent-level exposure and compares intervention components with

control components; that is,

$$OE = \sum_{i=1}^I w_i^* \sum_{j=1}^{n_i} [Y_{ij}(1, \cdot) - Y_{ij}(0, \cdot)],$$

where $w_i^* = \frac{1}{I n_i}$ corresponds to component-weighted estimands and $w_i^* = \frac{1}{N}$ corresponds to agent-weighted estimands.

To quantify these estimands, we employed 2-stage inverse probability weights $w_i^{(0)}$, $w_i^{(10)}$, and $w_i^{(11)}$ as $w_i^{(11)} = \frac{1}{\Pr(C_i=1) \Pr(A_{ij}=1|C_i=1)}$, $w_i^{(10)} = \frac{1}{\Pr(C_i=1) \Pr(A_{ij}=0|C_i=1)}$, and $w_i^{(0)} = \frac{1}{\Pr(C_i=0)}$, respectively. Define $w_i^{(c)} = \frac{1}{\Pr(C_i=c)}$. The weighted direct, disseminated, composite, and overall effect estimators are, respectively,

$$\widehat{DE} = \sum_{(i,j) \in T_{11}} w_i^* w_i^{(11)} Y_{ij}^{\text{obs}}(1, 1) - \sum_{(i,j) \in T_{10}} w_i^* w_i^{(10)} Y_{ij}^{\text{obs}}(1, 0),$$

$$\widehat{IE} = \sum_{(i,j) \in T_{10}} w_i^* w_i^{(10)} Y_{ij}^{\text{obs}}(1, 0) - \sum_{(i,j) \in T_{00}} w_i^* w_i^{(0)} Y_{ij}^{\text{obs}}(0, 0),$$

$$\widehat{TE} = \sum_{(i,j) \in T_{11}} w_i^* w_i^{(11)} Y_{ij}^{\text{obs}}(1, 1) - \sum_{(i,j) \in T_{00}} w_i^* w_i^{(0)} Y_{ij}^{\text{obs}}(0, 0),$$

and

$$\widehat{OE} = \sum_{(i,j) \in T_1} w_i^* w_i^{(1)} Y_{ij}^{\text{obs}}(1, \cdot) - \sum_{(i,j) \in T_0} w_i^* w_i^{(0)} Y_{ij}^{\text{obs}}(0, \cdot).$$

For example, the estimator of the disseminated effect is the weighted average of the outcomes among agents assigned to no PrEP in intervention components minus the weighted average of the outcomes among agents in control components (Figure 1). These estimators are unbiased in an empirical or simulation study with a 2-stage randomized design with a single allocation strategy and a “pure control group” (43, 47).

Outcome measures

The primary outcome measure was cumulative HIV incidence over 24 months after randomization in the simulated trial. We examined the estimated HIV incidence for each trial scenario corresponding to different PrEP coverage levels, separately for agents on PrEP and agents not on PrEP. These parameters were computed using nonparametric estimators, as described above, and estimates were averaged across all simulations, along with 95% simulation intervals (i.e., credible intervals) given the stochastic framework of these models (i.e., middle 95% of simulated output) (48). Comparisons were made between the intervention agents and control agents within each simulated trial and across trials comparing various intervention coverage levels.

Sensitivity analyses

We performed a sensitivity analysis excluding the substance-use agent class (Web Appendix 9, Web Tables 4–7). Because we were evaluating disseminated effects, the results may have depended on not only the efficacy of PrEP but also the number and probability of sexual partnerships, as well as the size of the components. We also performed 1-way sensitivity analyses to evaluate the impact of modifying adherence to PrEP and maximum PrEP efficacy to prevent HIV infection (Web Appendix 10, Web Tables 8–11). We assessed the following: probability of partnership, baseline number of sexual acts, adherence to PrEP, efficacy of PrEP for suboptimal adherence, and maximum component size.

RESULTS

There were 11,245 agents in the simulated population, with an average of 1,551 components identified in each iteration of the model. At enrollment in the entire simulated trial with 70% PrEP coverage, the HIV point prevalence was 29% (95% simulation interval (SI) = 27, 30). The majority of components (48%) had low HIV prevalence (<5%), while 26% had higher HIV prevalence (45%–50%) at enrollment. Although our model considered a range of intervention coverage levels (Table 1), we focused the discussion of results on 2 simulated trial designs that provide insights into 2 strategies: 1) intervention components with lower (30%) PrEP coverage and 2) intervention components with higher (70%) PrEP coverage.

We first calculated the average results from simulated trials with 30% coverage in the intervention components (Table 2). Within intervention components, there was an estimated 82% direct risk reduction in cumulative HIV incidence among agents on PrEP compared with agents not on PrEP (risk ratio (RR) = 0.18, 95% SI: 0.13, 0.24). Comparing agents not on PrEP within intervention components to agents within control components, the estimated disseminated effect was an 8% risk reduction (RR = 0.92, 95% SI: 0.79, 1.06). The estimated composite effect (combined direct and disseminated effects) was an 83% risk reduction (RR = 0.17, 95% SI: 0.11, 0.22). Comparing agents within intervention components to those within control components, marginalizing over agent-level PrEP use, there was an estimated 30% reduction in the overall risk (RR = 0.70, 95% SI: 0.60, 0.80).

We then calculated the average results from simulated trials with 70% coverage in the intervention components (Table 2). The estimated direct effect was an 83% reduction (RR = 0.17, 95% SI = 0.13, 0.23) in cumulative HIV incidence among agents on PrEP compared with agents not on PrEP within intervention components. The estimated disseminated effect was a 15% reduction (RR = 0.85, 95% SI = 0.65, 1.05) in cumulative HIV incidence, which means that agents not on PrEP in the intervention group had lower cumulative HIV incidence, as compared with control agents. The estimated composite effect was an 85% reduction in the cumulative incidence of HIV, comparing agents on PrEP within intervention components to agents within control

Table 1. Cumulative Incidence of Human Immunodeficiency Virus Infection Over 2 Years of Follow-up After 2-Stage Randomization Among Agents Within Preexposure Prophylaxis Intervention and Control Components in an Agent-Based Model Representing Men Who Have Sex With Men ($n = 11,245$), Atlanta, Georgia, 2015–2017

Component Coverage Level, %	Intervention Agents on PrEP			Intervention Agents Not on PrEP			Control Agents		
	Total No. of Agents	No. HIV+	Cumulative Incidence ^a	Total No. of Agents	No. HIV+	Cumulative Incidence ^a	Total No. of Agents	No. HIV+	Cumulative Incidence ^a
10	396.94	17.40	0.044	3,098.96	711.50	0.230	6,506.18	894.30	0.137
20	771.12	32.27	0.042	3,113.59	612.65	0.197	6,495.83	895.05	0.138
30	1,163.53	44.30	0.038	3,109.28	519.21	0.167	6,512.94	897.47	0.138
40	1,572.93	59.07	0.038	3,115.15	432.86	0.139	6,499.15	893.14	0.137
50	1,967.04	68.08	0.035	3,106.68	339.58	0.109	6,499.86	885.55	0.136
60	2,395.52	77.50	0.032	3,117.22	257.92	0.083	6,488.80	884.76	0.136
70	2,806.26	84.92	0.030	3,141.71	183.82	0.059	6,471.65	871.33	0.135
80	3,177.90	91.83	0.029	3,139.32	120.57	0.038	6,436.72	874.74	0.136
90	3,612.07	97.80	0.027	3,146.35	50.31	0.016	6,428.61	871.25	0.136

Abbreviations: HIV+, human immunodeficiency virus–positive; PrEP, preexposure prophylaxis.
^a Cumulative incidence is presented as a proportion (number HIV+/total number).

Table 2. Estimated Effects of Preexposure Prophylaxis on Cumulative Incidence of Human Immunodeficiency Virus Infection Over 2 Years of Follow-up After 2-Stage Randomization Among Agents Within Preexposure Prophylaxis Intervention and Control Components in an Agent-Based Model Representing Men Who Have Sex With Men ($n = 11,245$), Atlanta, Georgia, 2015–2017

PrEP Coverage and Effect	RD	95% SI	RR	95% SI
30% coverage				
Direct	−0.05	−0.06, −0.04	0.18	0.13, 0.24
Disseminated	−0.01	−0.01, 0.00	0.92	0.79, 1.06
Composite	−0.06	−0.06, −0.05	0.17	0.11, 0.22
Overall	−0.02	−0.03, −0.01	0.70	0.60, 0.80
70% coverage				
Direct	−0.05	−0.06, −0.04	0.17	0.13, 0.23
Disseminated	−0.01	−0.02, 0.00	0.85	0.65, 1.05
Composite	−0.06	−0.06, −0.05	0.15	0.11, 0.20
Overall	−0.04	−0.05, −0.04	0.35	0.28, 0.42

Abbreviations: PrEP, preexposure prophylaxis; RD, risk difference; RR, risk ratio; SI, simulation interval.

components (RR = 0.15, 95% SI = 0.11, 0.20). Web Figure 1 displays a contour plot for the estimated composite effect risk difference across a range of coverage value contrasts of PrEP allocation strategies. Comparing intervention components with control components, there was an estimated 65% reduction in the overall effect (RR = 0.35, 95% SI: 0.28, 0.42).

Figure 3 displays box plots of the estimated direct and disseminated risk difference and risk ratio effects on cumulative incidence of HIV as a function of component PrEP coverage. As the intervention coverage increases in a component, the estimated direct effect is attenuated toward the null, although this trend is more apparent on the difference scale. On the other hand, when the intervention coverage is increased in a component, the estimated disseminated effect increases in magnitude on both the difference and ratio scales.

We performed 1-way sensitivity analyses to assess the impact of our model parameterization on the results, specifically cumulative HIV incidence over 2 years. In Web Tables 8 and 9, we display the HIV prevalence and cumulative incidence at the end of 2 years of follow-up after randomization based on simulated trials with 30% coverage and 70% coverage, respectively. The number of incident HIV infections among agents in the base case was typically between the estimates for the scenarios with the parameters either half or double the base case, except for annual sexual partnerships. In a sensitivity analysis excluding the substance-use agent class, the disseminated effect was stronger for 30% coverage trials (risk difference = −0.02 and RR = 0.65) and 70% coverage trials (risk difference = −0.03 and RR = 0.24) (Web Tables 4–7). The linear trends of the effects on the difference scale across increasing coverage levels were more visually apparent (Web Figures 2 and 3). We also calculated the estimated effects across the 1-way sensitivity analysis (Web Tables 10 and 11, Web Figures 4–7). The

estimated effects were typically attenuated toward the null on the difference scale and away from the null on the ratio scale.

DISCUSSION

We employed an ABM to simulate an idealized 2-stage randomized trial to evaluate the direct and disseminated effects of PrEP among MSM in Atlanta (14). We observed disseminated effects of PrEP among those who were randomized to not receive PrEP themselves but shared a sexual risk network component with agents randomized to use PrEP (with up to a 15% reduction in cumulative HIV incidence at a coverage level of 70%). We found that increasing PrEP coverage levels in a component strengthens the disseminated effect on reducing HIV incidence among persons who were not randomized to the intervention; however, increasing PrEP coverage also possibly weakens the direct effect among those who were randomized to receive the intervention, which was observed on the difference scale only. In other words, the individual benefit of receiving PrEP depends on the coverage of PrEP in an individual's network: the higher the proportion of one's sexual partners on PrEP, the smaller the absolute direct, *additional* individual benefit of therapy beyond being in an intervention component. This type of simulation study can help to inform PrEP coverage levels needed to reduce HIV incidence below a targeted threshold, while considering the complex sexual risk networks in which MSMs are embedded, as well as related risk factors such as substance use.

Many evaluations of the efficacy and effectiveness of PrEP focus on the overall effect without consideration of the sexual risk networks in which these persons are embedded (49). Many of these studies have individually randomized designs and often lack inference regarding the influence

Figure 3. Estimated effects of preexposure prophylaxis (PrEP) on the cumulative incidence of human immunodeficiency virus infection as a function of component PrEP coverage in a 2-stage randomized simulated trial of a PrEP intervention in an agent-based model representing men who have sex with men, Atlanta, Georgia, 2015–2017. A) Direct risk difference effects; B) disseminated risk difference effects; C) direct risk ratio effects; D) disseminated risk ratio effects. Lines within boxes, median values; box borders, interquartile ranges (75th and 25th percentiles); bars, 90th and 10th percentiles; points, outliers. Dashed lines represent the null value, which is out of range in panel C.

of other people in the sexual network component or study cluster. Overall effects depend on spurious features of the study design, including the size of the components and PrEP coverage in each component. Therefore, this effect will probably not be generalizable from one study to the next or to any scaled-up population, unless these features remain constant (50). We observed many scenarios contrasting adjacent coverage levels for which the overall effect estimate was closer to the null while the composite effect demonstrated a more protective effect, highlighting the importance of considering the suite of disseminated and direct effects when dissemination may be present.

There are several strengths to this approach. Because it would be unethical and probably unfeasible to conduct a 2-stage randomized trial in this population, this ABM-based approach provides insights about the direction and magnitude of these various effects. Furthermore, we can conduct numerous simulated trials with different PrEP coverage levels to better understand the impact on population-level HIV incidence. To the best of our knowledge, this

is the first study to have assessed causal disseminated effects in the context of an ABM, and it offers additional insight on how to leverage causal inference methodology to improve the inference gleaned from simulation-based techniques.

This particular agent-based modeling approach has several limitations. We made strong assumptions, such as static sexual networks and 100% retention in care during the 2 years of study follow-up. Assuming static components in the sexual networks does not accurately reflect the underlying true sexual network; however, if we allow the sexual networks to vary over time, there could be a violation of the partial or stratified interference assumptions. Future methodological work is needed to develop appropriate methods for interference structures that change over time. Randomized trials, as well as 2-stage randomized trials, are subject to Hawthorne effects and may not actually represent the patient's experience in medical care. Unfortunately, there are no 2-stage randomized trials of PrEP with which to compare and contrast our model results; however,

further comparisons with trial-based estimates of HIV prevalence and incidence could help to improve the model to simulate more realistic scenarios that emulate a real-world trial.

In future work, we plan to evaluate possible effect modification by component-level characteristics, such as HIV prevalence, racial/ethnic distribution, and substance-use prevalence, and this information can be used to better allocate resources. We will extend our approach for other study design settings, including cluster-randomized trials and observational cohort studies. When the design requires adjustment for confounding at either the agent and/or component level, we will triangulate this approach with a g-formula approach in the context of dissemination (51, 52). Future work could also include comparing different counterfactual definitions in ABMs, including simulating potential outcomes at the component level.

Persons not on PrEP may benefit by being in a sexual network with higher PrEP coverage levels. ABMs are useful for evaluating potential direct and disseminated effects of HIV prevention modalities in complex sexual networks among MSM. Employment of these models can provide more timely information about the most impactful ways to increase PrEP access, particularly among underserved individuals in the southern United States.

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