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ABSTRACT

Pre-exposure prophylaxis (PrEP) for HIV prevention may not only benefit the individual 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, GA. Components (subsets of agents connected through partnerships in a sexual network, but not sharing sexual partnerships any other agents) were first randomized to an intervention coverage level or control, then within intervention components, eligible agents were randomized to PrEP. We estimated direct and disseminated (indirect) effects using randomization-based estimators and reported corresponding 95% simulation intervals (SI) across scenarios ranging from 10% to 90% coverage in the intervention components. A population of 11,245 agents was simulated for two years, with an average of 1,551 components identified. Comparing agents randomized to PrEP in 70% coverage components to control agents, there was an 15% disseminated risk reduction in HIV incidence (95% SI = 0.65, 1.05). Individuals not on PrEP may receive a protective benefit by being in a sexual network with higher PrEP coverage. Agent-based models are useful to evaluate possible direct and disseminated effects of HIV prevention modalities in sexual networks.

INTRODUCTION

Once daily pre-exposure prophylaxis (PrEP) is a single tablet containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) that is effective for preventing HIV transmission among men who have sex with men (MSM) (1, 2). Despite strong evidence of its effectiveness (3, 4), access to PrEP among MSM remains low, particularly among MSM in the Southern United States who experience among the highest incidence and prevalence burdens of HIV infection among all groups in the United States (5-7).

Traditional randomized clinical trials assessing the effect of PrEP use on HIV incidence only consider the direct (individual) effect of reducing HIV incidence among individuals who use PrEP. However, PrEP for HIV prevention may not only benefit the individual user, but also their sexual risk contacts (8). In preventing HIV acquisition among an individual who uses PrEP, the possibility of secondary transmission to this individual's other 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 users, as well as the impact of the intervention on individuals who did not use the intervention themselves, but were connected to users.

In causal inference methodology, a fundamental assumption of much work is the **s**table **u**nit **t**reatment **v**alue **a**ssumption (SUTVA) (12), which includes an assumption of no dissemination, or interference, between individuals. An assumption of no dissemination requires that the potential outcomes of one individual be unaffected by the treatment or

intervention assignment of other individuals. Both effects are readily identifiable in two-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 control) and then at an individual level (i.e., individuals are assigned to receive an intervention or not 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, GA, USA (16, 17), to emulate a two-stage randomized clinical trial (18), which may be considered unfeasible or currently unethical to implement in this population, as PrEP is currently FDA-approved for HIV prevention and often used as an active control in studies of 'next generation' HIV prevention modalities (19). We selected the city of Atlanta, GA 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 aim to evaluate the magnitude and direction of possible disseminated effects of PrEP use among MSM in Atlanta, GA.

METHODS

Model Setting

We adapted a previously published model of PrEP uptake and HIV transmission among MSM in Atlanta and complete details about this model can be found in (14). We

employed a discrete-time, stochastic, agent-based model to simulate a two-stage randomized trial of PrEP for HIV prevention in a population of MSM (aged 18-65 years) in Atlanta, GA, USA and followed agents for two years from 2015 to 2017 (14, 22). Each agent in the model was assigned characteristics related to demographic, behavioral, HIV status, and clinical status. The simulated agent population was 51% 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 substances, 32% had a preferred receptive sexual role, and 24% had a preferred insertive sexual role. Among white non-Hispanic agents, we assumed that the median age was 35 years, 49% were using 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 based on empirical estimates from the study setting. Several parameter values (e.g., those governing initial HIV prevalence and treatment) were stratified by race (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 two-stage randomized trials. Because this ABM was simulating a randomized trial with a short duration of follow-up, agents and their characteristics were generated in a base population and no new agents were allowed to enter the population. Python (version 2.7.12) was used for coding, testing and performing sensitivity analyses of this model and R (Version 3.5.1) was used to analyze the model output. Additional information regarding parameter values, key model assumptions, and data sources are included in the Supplemental Appendix.

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 that are all connected through at least one partnership and not connected to any other agents in the network. After two-stage randomization, where components were first randomized to an intervention allocation strategy, then within each component, agents were randomized according to that strategy, annual number of partners and number of sex acts were assumed to follow stochastic distributions with parameters based on the literature (20, 25). At discrete time-steps (measured in months since randomization) over the two 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 (26, 27). These partnerships at enrollment were used to determine network components of size 2 to 100 agents.

HIV Transmission, Treatment and Progression

Detailed HIV transmission, treatment, and disease progression processes and parameters have been described in detail previously (14, 15). At each monthly interval, agents had a certain number of sex acts with their partners. The probability of condom use was lower if the agent used 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 non-zero probability of HIV transmission (per-act probability for condomless receptive anal intercourse was 1.38% and insertive was 0.11%) (28). This probability varied depending upon the following factors: if the HIV-negative agent was randomized to PrEP; among HIV-negative agents randomized to PrEP, their adherence to PrEP; and among HIV-infected agents, knowledge of their HIV status, HIV treatment, and if they achieved viral suppression after initiation of HIV treatment.

Impact of Substance Use on Agent Behavior

We included an agent class characterized by substance use, which was defined at model initialization and remained stable for the duration of the study. The prevalence of substance use, defined as any drug use, was set to 30% among African Americans and 48.5% among whites (20, 23). In the model, 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 (29). In addition, we assumed that 20% of substance using agents mix with other substance using agents.

Oral Pre-Exposure Prophylaxis (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 two-year duration of the trial. For the two-year duration of this simulated trial, all agents were retained in the study and no agents died. At enrollment in the trial, agents were classified as optimally adherent to PrEP (defined as 4 or more doses per week), or were sub-optimally adherent (defined as 2 to 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 (30). Agents on ART were less likely to progress to AIDS than other HIV-infected agents. This was achieved through a scalar reduction in profession probability, with the reduction dependent on ART adherence (31, 32).

Simulated Trial Design

The current study simulated a two-stage randomized trial (Figure 2). In the first stage, network components were randomized 1:1 to either receive a certain PrEP coverage (referred to as "intervention components) or no PrEP coverage (referred to as "control components) (18, 33). 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 one or more partnerships and ages 18 to 65 years old at enrollment. PrEP coverage was assigned at baseline. We assumed that agents assigned to PrEP take at minimum two or more doses per week with adherence pattern remained stable for the duration of follow-up. We assumed that PrEP adherence did not change PrEP coverage following an intention-to-treat approach 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 consider the following scenarios: PrEP coverage level (in each component) of 10% to 90%, in increments of 10%.

At the baseline visit of the trial, agents who were randomized to PrEP initiated their intervention and all agents, regardless of HIV status, were followed for two years to ascertain their HIV status. We assumed no drop out (i.e., 100% retention on PrEP over the two years of follow-up). We also assumed over the two years that the probability of death

is zero, which may be reasonable given the age range of agents and 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 only, but does not extend to other agents outside their component. We also 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 (34). We also make the usual assumptions required for causal inference (exchangeability, consistency, and positivity) (35). Due to randomization at both the component- and agent-level, marginal exchangeability holds: Components randomized to the intervention will be, on average, comparable to components randomized to the control. Furthermore, 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 non-zero probability of exposure within each level of the covariates (36, 37). We assumed an independent Bernoulli allocation strategy for intervention assignment within each intervention component (13).

In our simulated trial, the sexual risk component sizes vary, so we employed estimators that account for varying component size (38). Assume there are I components and each of the component has n_i individuals indexed by $j = 1,2,\ldots,n_i$ and $\sum_{i=1}^{I} n_i = N$. Let Y_{ij}, A_{ij} represent an observed outcome and intervention assignment status of 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. Let $A(n)$ be the set of vectors of all possible exposure allocations of length n. 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 three possible combinations of the following potential outcomes: $Y_{ij}(1,1), Y_{ij}(1,0), Y_{ij}(0,0)$. By (causal) consistency (39-41), the observed outcome is a function of the intervention assignment and potential outcomes; that is, $Y_{ij}^{obs} = C_i A_{ij} Y_{ij}(1,1) + C_i\big(1 - A_{ij}\big)Y_{ij}(1,0) + (1 - C_i)Y_{ij}(0,0)$. Let $T_{ca} = \{(i,j)\text{: } C_i = c \; and \; A_{ij} = a\}$ 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 two types of estimands: component-weighted estimands that assign equal weight to components, regardless of the number of individuals in each component; and agent-weighted estimands that assign equal weight to agents, regardless of the distribution across components. The *direct* (i.e., individual) effect measures the additional benefit of being on PrEP beyond being in an intervention component with a fixed PrEP coverage level (Figure 1) and is defined as

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

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

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

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

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

The *overall* effect marginalizes over the agent exposure and compares intervention to control components; that is,

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

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

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

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

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

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

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

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 a two-stage randomized design (12).

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 component PrEP coverage level among the intervention group, separately for agents on PrEP and agents not on PrEP. These parameters were computed using nonparametric estimators, as described above, along with 95% simulation intervals (i.e., credible intervals) given the stochastic framework of these models (i.e., middle 95% of simulated output) (42). Comparisons were made between the intervention agents and control agents within each simulated trial and across trials comparing various intervention coverage levels.

Sensitivity Analyses

Because we are evaluating disseminated effects, the results may depend 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 performed one-way sensitivity analyses to evaluate the impact of modifying adherence to PrEP and maximum PrEP efficacy to prevent HIV (see Supplemental Appendix). Specifically, 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. We also performed a sensitivity analysis excluding the substance use agent class.

RESULTS

There were 11,245 agents in the simulated population, followed from 2015 to 2017 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% to 50%) at enrollment. Although our model considered a range of intervention coverage levels (Table 1), we focused the discussion of results on two simulated trial designs that provide insights into two strategies: (1) intervention components with lower (30%) PrEP coverage and (2) intervention components with higher (70%) PrEP coverage.

We first report 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 to 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 estimated 8% risk reduction (RR = 0.92, 95% SI: 0.79, 1.06). The estimated composite (combined direct and disseminated) effect was an estimated 83% risk reduction (RR = 0.17, 95% CI: 0.11, 0.22). Comparing agents within intervention components to those within control components, marginalizing over individual-level PrEP use, there was an estimated 30% reduction in the overall risk (RR = 0.70, 95% SI: 0.60, 0.80).

We then report 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

to 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 to 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 components (RR = 0.15, 95% SI = 0.11, 0.20). Comparing agents within intervention components to those within control components, there was an estimated 65% reduction in the overall effect (RR = 0.35, 95% SI: 0.28, 0.42).

Figure 3 displays the estimated direct and disseminated risk difference and risk ratio effects on cumulative incidence of HIV as a function of component PrEP coverage with 95% simulation intervals. As the intervention coverage increases in a component, the estimated direct effect is attenuated towards 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 increased in magnitude on both the difference and ratio scale.

We performed one-way sensitivity analyses to assess the impact of our model parameterization on the results, specifically cumulative HIV incidence over two years. In Table S8 and S9 (see Supplemental Appendix), we display the HIV prevalence and cumulative incidence at the end of two years of follow-up after randomization based on a simulated trial with 30% 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 (RD = -0.02 and RR = 0.65) and 70% coverage trials (RD = -0.03 and RR = 0.24) (Table S4 to S7). The linear trends of the effects on the difference scale across increasing coverage levels were more visually apparent (Figure S2 to S3). We also displayed the estimated effects across the one-way sensitivity analysis (Tables S10 and S11, Figures S4 to S7). The estimated effects were typically attenuated towards the null on the difference scale and away from the null on the ratio scale.

DISCUSSION

We employed an ABM to simulate an idealized two-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 not randomized to PrEP, but who shared a sexual risk network component with agents randomized to PrEP (with up to a 15% reduction in cumulative HIV incidence at coverage level 70%). We found that increasing PrEP coverage levels in a component strengthens the disseminated effect on reducing HIV incidence among those who were not randomized to the intervention; however, increasing PrEP coverage also possibly weakens the direct effect among those who were randomized to the intervention 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 is 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 considering related risk factors, such as substance use.

Many evaluations of the efficacy and effectiveness of PrEP focus on overall effect without consideration of the sexual risk network in which these individuals are embedded (43). Many of these studies are individually-randomized designs and often lack inference regarding the influence of others 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, it will likely not be generalizable from one study to the next or to any scaled-up population, unless these features remain constant (44). In this ABM, 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. As it would be unethical and likely unfeasible to conduct a two-stage randomized trial in this population, this ABM-based approach provides insights about the direction and magnitude of these various effects. Furthermore, we can run numerous simulated trials with different coverage PrEP levels to better understand the impact on population-level HIV incidence. To the best of our knowledge, this is the first paper to assess causal disseminated effects in the context of an ABM and 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 two 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 interference or the stratified interference assumptions. Future methods work is needed to develop appropriate methods for interference structures that change over time. Randomized trials, as well as two-stage randomized trials, are subject to Hawthorne effects, and may not actually represent the patient experience in medical care. Unfortunately, there are no two-staged randomized trials of PrEP to compare and contrast our model results; however, further comparisons to 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 will evaluate possible effect modification by component-level characteristics, such as HIV prevalence, racial distribution, and substance use prevalence, and this information can be used to better allocate resources. We will also 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 levels, we will triangulate this approach with a *g*-formula approach in the context of dissemination (45, 46). Future work could also compare different counterfactual definitions in agent-based models, including simulating potential outcomes at the component level. Individuals not on PrEP may benefit by being in a sexual network with higher PrEP coverage levels.

ABMs are useful to evaluate potential direct and disseminated effects of HIV prevention modalities in complex sexual networks among men who have sex with men. Employment of these models can provide more timely information about the most impactful ways to increase PrEP access, particularly among those underserved in the Southern United States.

Tables and Figures

Table 1. Cumulative incidence of HIV over two years of follow-up after two-stage randomization among agents within PrEP intervention and control components with 95% simulation intervals (SI) in an agent-based model representing among men who have sex with men Atlanta, Georgia, 2015-2017 (n = 11,245)

	Agents on PrEP			*Agents Not on PrEP*			*Control Agents*		
Component PrEP Coverage Level,%	*Total Persons*	*HIV+*	*Cumulative Incidence*	*Total Persons*	*HIV+*	*Cumulative Incidence*	*Total Persons*	*HIV+*	*Cumulative Incidence*
10	396.94	17.4	0.044	3098.96	711.5	0.230	4095.03	894.3	0.137
20	771.12	32.27	0.042	3113.59	612.65	0.197	4091.70	895.05	0.138
30	1163.53	44.3	0.038	3109.28	519.21	0.167	4100.73	897.47	0.138
40	1572.93	59.07	0.038	3115.15	432.86	0.139	4096.74	893.14	0.137
50	1967.04	68.08	0.035	3106.68	339.58	0.109	4093.03	885.55	0.136
60	2395.52	77.5	0.032	3117.22	257.92	0.083	4083.12	884.76	0.136
70	2806.26	84.92	0.030	3141.71	183.82	0.059	4065.79	871.33	0.135
80	3177.9	91.83	0.029	3139.32	120.57	0.038	4037.26	874.74	0.136
90	3612.07	97.8	0.027	3146.35	50.31	0.013	4031.51	871.25	0.136

Table 2. Effects of PrEP on cumulative incidence of HIV over two years of follow-up after two-stage randomization among agents within PrEP intervention and control components with 95% simulation intervals (SI) in an agent-based model representing men who have sex with men, Atlanta, Georgia, 2015-2017 (n = 11,245)[1]

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

[1] RD = Risk Difference; RR = Risk Ratio.

Figure 1: Types of causal effects in the context of dissemination (or interference) in two-stage randomized designs of a pre-exposure prophylaxis (PrEP) intervention in an agent-based model representing men who have sex with men, Atlanta, Georgia, 2015-2017 (17).

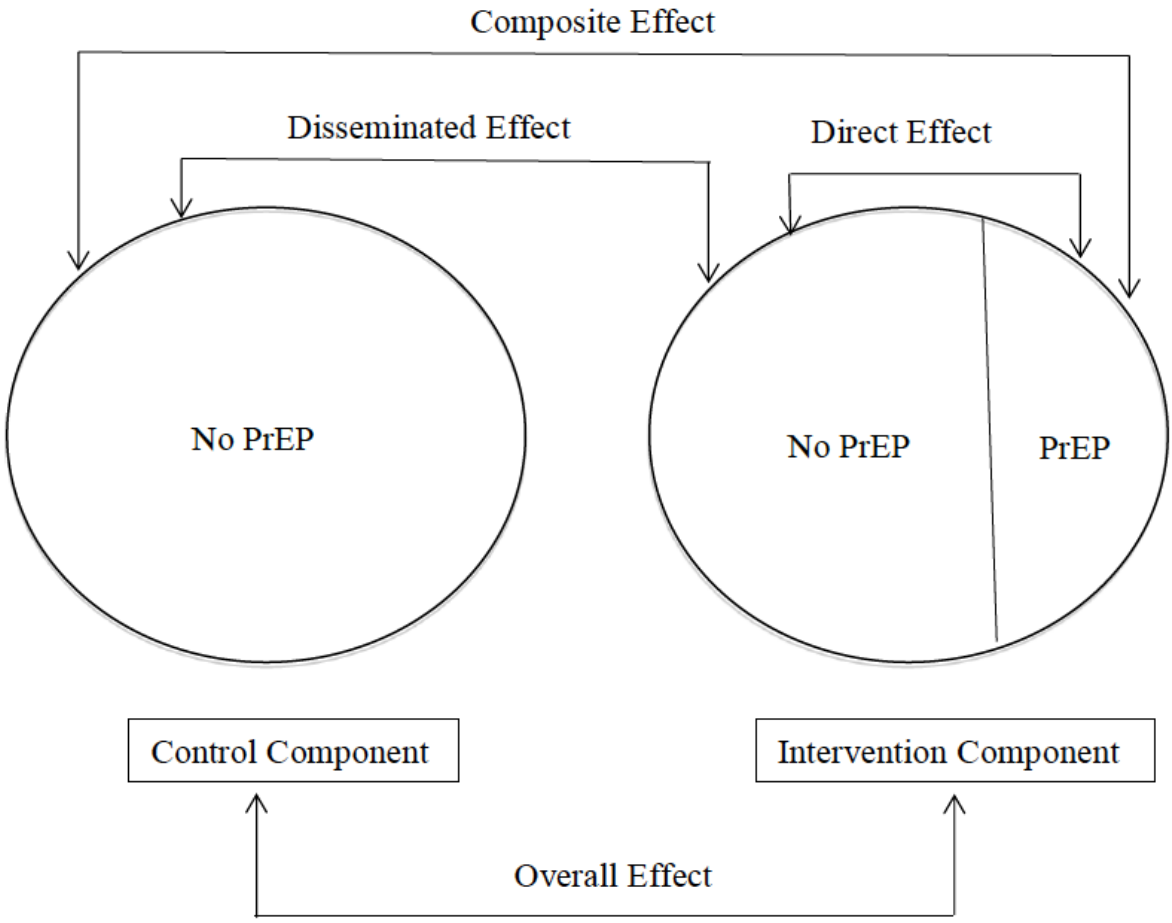


Figure 2: Two-stage randomized design to evaluate PrEP for HIV prevention in a population of MSM. Trial 1 corresponds to a PrEP allocation strategy with 33% coverage in intervention components. Trial 2 corresponds to a PrEP allocation strategy with 66% coverage in intervention components.

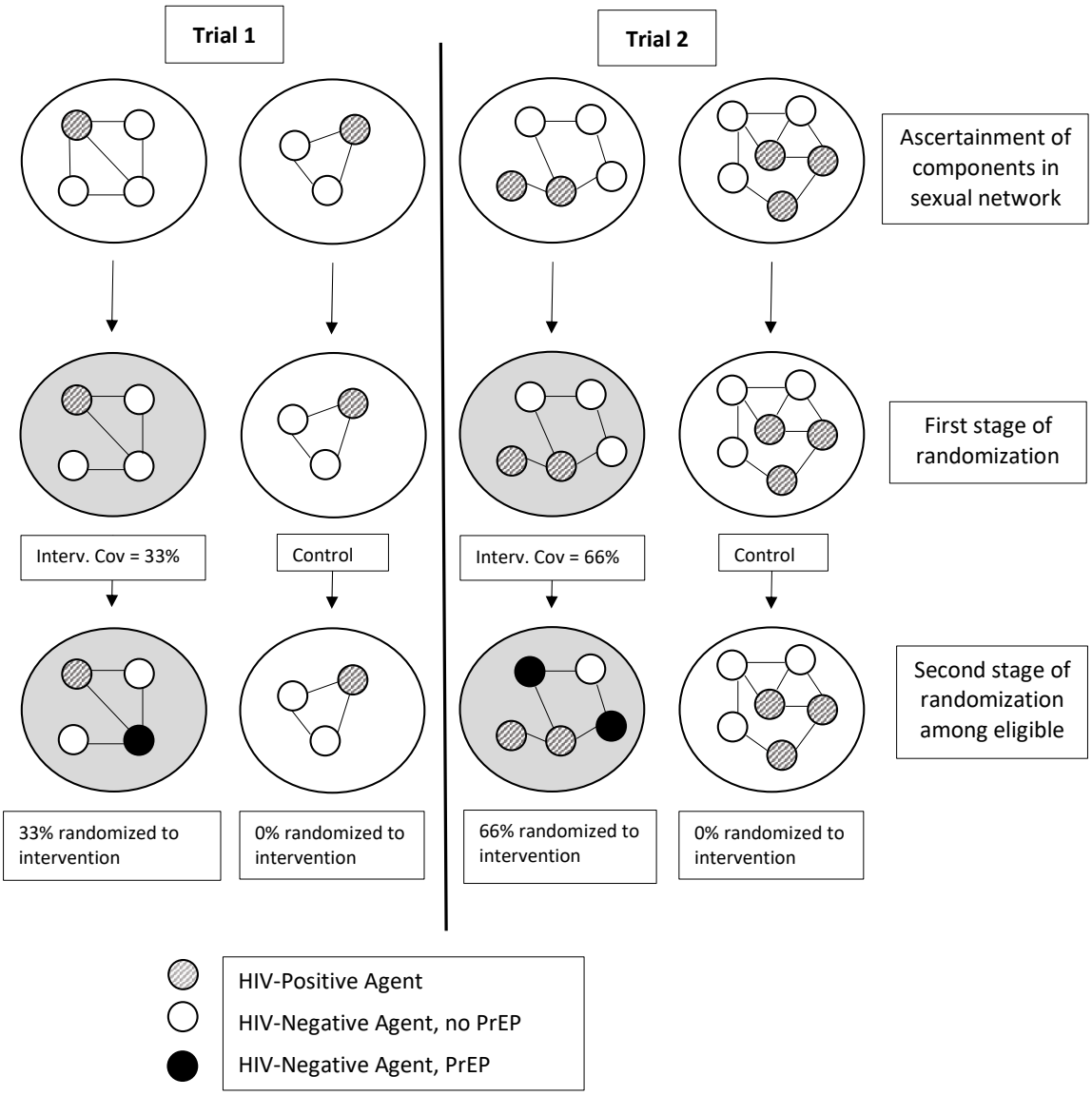
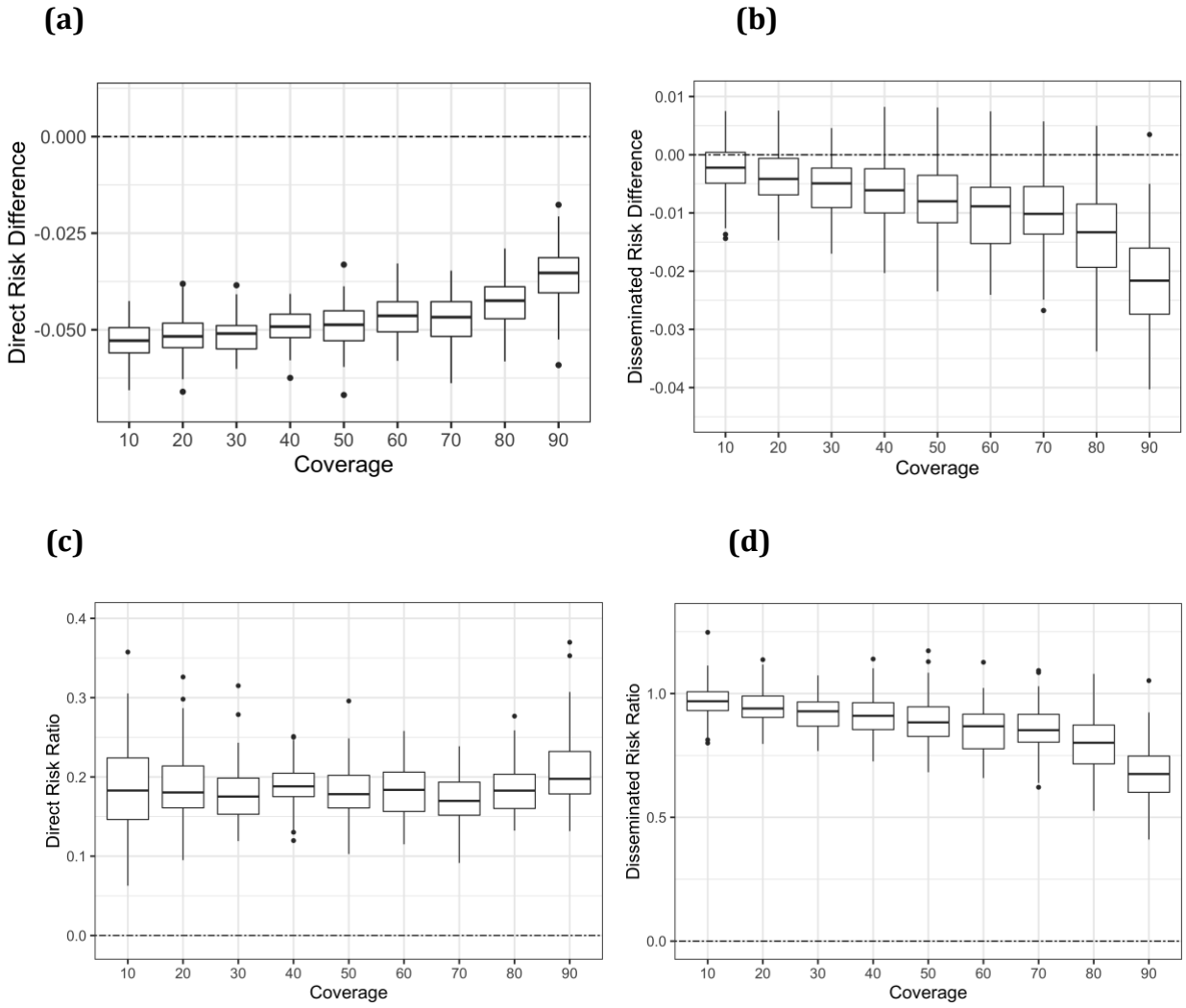


Figure 3. Estimated **(a)** direct risk difference effects **(b)** disseminated risk difference effects **(c)** direct risk ratio effects **(d)** disseminated risk ratio effects of PrEP on cumulative incidence of HIV as a function of component PrEP coverage with 95% simulation intervals in two-stage randomized designs of a pre-exposure prophylaxis (PrEP) intervention in an agent-based model representing men who have sex with men, Atlanta, Georgia, 2015-2017



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