**SUPPLEMENTAL APPENDIX**

This supplemental appendix contains information on model structure, parameterization, processes for the agent-based model described in “Projecting the Impact of Equity-Based Implementation of Pre-Exposure Prophylaxis on Racial Disparities in HIV Incidence Among Men Who Have Sex with Men”

The structure of this supplemental file is based on the ‘overview, design concepts, and details’ (ODD) document protocol for describing agent-based models.1 All information presented is in line with the Strengthening the Reporting of Empirical Simulation Studies (STRESS-ABS) guidelines.2

**OVERVIEW**

**Purpose**

The Treatment of Infectious Transmission in Agent-Based Networks (TITAN) model was designed with the purpose of representing infectious disease transmission dynamics in micro-epidemics within the United States and evaluating the impact of combination HIV prevention and treatment strategies on trajectories in HIV incidence and prevalence within these settings.3

**Entities, State Variables, and Scales**

The model included only one type of entity: agents. Agents were characterized by several discrete state variables. All agents were characterized by age, sex, gender, race/ethnicity, sexual orientation, and HIV infection status. Agents with HIV infection were further characterized by their diagnosis status, their use of antiretroviral treatment, and their achievement of viral suppression. Agents without HIV infection were further characterized by their use of PrEP and their associated adherence to daily pill-taking. All discrete state variables, with the exception of sex, gender, race/ethnicity, and sexual orientation, were considered to be dynamic and could be updated as time progressed. In the model, time was represented as a series of discrete time-steps each corresponding to one calendar month.

**Process Overview and Scheduling**

Each agent formed one or more sexual partnerships with other agents. After these partnerships were formed, agents interacted with their respective partners through anal intercourse. At this time, HIV transmission could occur through these interactions in serodiscordant dyads. If a transmission event occurred, an agent’s HIV status was updated. At the end of the partnering and interaction routines, agents could be tested for HIV infection and enter care if diagnosed. If diagnosed, agents could initiate antiretroviral treatment and achieve viral suppression. Agents who had been diagnosed with HIV infection at a previous time-step could also discontinue or re-initiate antiretroviral treatment at this time. Once this testing and treatment routine was completed, agents could die and be replaced by a new agent. After all the processes have been completed, a number of key statistics were calculated for each time-step, such as the number of new HIV infections and number of newly diagnosed HIV infections.

**DESIGN CONCEPTS**

Per the ODD document protocol,1 we present a brief overview of the basic principles of the model and the relevant design concepts (emergence, interaction, and stochasticity).

**Basic Principles**

The TITAN model was designed as a stylized model of infectious disease transmission dynamics through contact networks, allowing for the representation of multiple modes of transmission (e.g., transmission via sexual and injection-related contact) among multiple key subpopulations (e.g., men who have sex with men, people who inject drugs, heterosexual women) within localized micro-epidemics in the United States.

**Emergence**

In the model, HIV incidence was an emergent phenomenon arising from the interactions of agents and their engagement with any number of HIV prevention and treatment services (e.g., treatment as prevention, pre-exposure prophylaxis, syringe services programs) over the course of the simulation.

**Interaction**

Agents interacted within sexual networks. Social networks were not simulated in the model, nor were interactions between agents and their environments. That is, agents did not explicitly alter their behavior based on system-level properties (e.g., identification of an HIV outbreak in the community). Agents could enter partnerships with other agents and, within those partnerships, engage in acts that pose a risk for HIV transmission (e.g., condomless anal intercourse).

**Stochasticity**

In creating the base population at model initialization, agents’ baseline demographic and behavioral characteristics were assigned through a stochastic process. The assignment of a target number of sex acts per month also reproduced a discrete distribution for sexual frequency preferences in the population, but the actual distribution represented a series of “compromises” between agents within partnerships. HIV transmission was also a stochastic process based on the per-act risk of HIV transmission associated with a specific behavior, the number of risk acts engaged in within a given dyad, and the engagement with HIV prevention and treatment services among members of the dyad.

**DETAILS**

**Initialization**

The percentage of men aged 18 years and older who have had sexual contact with another man in each of the thirty counties included in the Atlanta–Sandy Springs–Roswell MSA was drawn from an estimate in the literature. Grey and colleagues (2016) used data from the American Community Survey to calculate a weight for each county in the United States based on its relative proportion of households that were headed by a male who lived with a male partner compared with the overall proportion among counties at the same level of urbanicity.4 These weights were then used to adjust urbanicity-stratified estimates of the percentage of adult men who had sex with a man in the past year derived from the National Health and Nutrition Examination Survey by Oster and colleagues (2015) for each county.5 These percentages were applied to estimates of the adult male population as reported in the Centers for Disease Control and Prevention’s Wide-Ranging Online Database for Epidemiologic Research (WONDER) for each county to yield the total number of MSM in the Atlanta–Sandy Springs–Roswell MSA (*n* = 65,890).

Based on the population estimates provided in WONDER,6 it is assumed that 26.5% of all MSM aged 18 years and older in the region are Black/African American and White MSM between 18 and 39 years old, corresponding to 17,440 MSM (38.9% Black/African American; 61.1% White).

The model was initialized in a virtual population consisting of 17,440 agents who represented all Black/African American and White MSM between 18 and 39 years old residing in the Atlanta–Sandy Springs–Roswell MSA. For each model iteration, the base population was created stochastically to generate the desired racial distributions and race-specific prevalence of HIV infection in the population, in addition to behavioral and clinical state variables that were assigned to each agent.

**Population Demography**

The model simulated a population of virtual agents representing Black/African American and White MSM aged 18 to 39 years old in the Atlanta–Sandy Springs–Roswell MSA. Agents exited the model in a deterministic fashion upon exceeding the age of 40 years old or through a stochastic process according to mortality rates that varied by race.6 Agents who died or otherwise exited the population were replaced by agents without HIV infection with characteristics drawn from these initial distributions.

Mortality Rates

Race-specific mortality rates were implemented based on statistics for Black/African American and White men in the Atlanta–Sandy Springs–Roswell MSA as provided in WONDER by the National Center for Health Statistics.6 Because the population denominators used for these estimates use mid-year population size estimates, they should represent reasonable estimates of person-time, assuming linear changes in the population throughout a given year.7 The mortality rate was 1.67 deaths per 1,000 persons for Black/African American MSM and 1.49 deaths per 1,000 persons for White MSM.6

These base age-specific mortality rates were scaled based on HIV status. HIV-uninfected agents and HIV-infected agents with viral suppression were assumed to have the same underlying age-specific mortality rates based on studies that have shown either similar life expectancy or comparable mortality rates among HIV-infected agents with good clinical outcomes and timely initiation of antiretroviral treatment.8 Age-specific mortality rates among HIV-infected agents without viral suppression were three times higher than those among their HIV-uninfected peers based on recent research comparing age-standardized mortality rates among HIV-infected agents and their HIV-uninfected counterparts.9 It was assumed that age-specific mortality rates among agents with stage 3 disease were ten-times higher than their HIV-uninfected counterparts, based on research comparing mortality rates among HIV-infected agents with CD4 counts of less than 200 cells/mm3 relative to their HIV-uninfected peers.10

**Network Formation and Interactions**

At initialization, the injection and sexual networks were formed within the population. Each agent was assigned a target number of sexual partners, as well as a target number of sex acts per month (see “Number of Sexual Partners” and “Number of Sex Acts” below). The construction of the network occurred through an iterative process in which the routines proceeds sequentially through the network set of *N* agents, matching each agent in need of a partner to others in need of a partner. During a particular time-step, agents determine their need for a partner and, if indicated, seek out and pair with other searching agents. A list of 100 partner-seeking agents that are able to mix with a given index agent is enumerated and one of these agents is selected at random based on parameters governing assortative mixing. This process is part of a negative binomial searching process in which partners are drawn from the population until each agent has achieved the necessary number of partners for the current time-step. The negative binomial model assumes that all agents have a fixed rate of sexual partner acquisition but does not require that this rate be homogenous within the population.11 The process of sexual partnering is represented as a sequential search with parameters *n*, *r*, and *p*: over *n* trials, partners are acquired with a given probability *p* until the search is stopped when *r* suitable partners are found.11 This model was selected based on previous work suggesting it has the best overall fit to producing degree distributions in sexual networks compared to other processes.11 Partner selection is governed by the race of the index agent. The probability of selecting a same-race sexual partner is 76.5% for Black/African American MSM and 72.2% for White MSM.12

At their formation, each partnership is assigned a duration based a distribution derived from reports in the Men’s Atlanta Networks (MAN) Project, a cross-sectional assessment of racial differences in the networks of Black/African American and White MSM aged 18 to 39 years old residing in the Atlanta–Sandy Springs–Roswell MSA.12 In the MAN Project, 45.6% of relationships were between 1 and 3 months in duration, 30.0% of relationships were between 4 and 12 months in duration, and 24.5% of relationships were between 13 and 24 months in duration.12 This distribution was not stratified by race. The formation and dissolution of partnerships creates a dynamic network in the model.

Number of Sexual Partners

At model initialization, a value is drawn from a negative binomial distribution representing the range of total numbers of male sexual partners per twelve-month period. This distribution was informed by reports in InvolveMENt, a longitudinal cohort formed to understand sources of racial disparities in HIV incidence among Black/African American and White MSM aged 18 to 39 years old in the Atlanta–Sandy Springs–Roswell MSA. The median number of sexual partners was 5 partners (IQR: 3–10) for Black/African American MSM and 7 partners (IQR: 4–15) for White MSM.13 The value drawn from this distribution represents the mean value for an agent-specific Poisson distribution governing the agent’s target number of sexual partners per year. At the beginning of each year, agents draw a new target number from their agent-specific distribution. This process allows for each agent to exhibit particular proclivities with regard to partner acquisition patterns from year-to-year without holding this behavior constant over time. These values represent targets and the actual number of partners may be above or below these values.

Number of Sex Acts

At initialization, each agent is assigned a target number of sex acts per partner per month.14 Upon formation of a partnership, these two values are averaged, resulting in a single value that becomes the mean of a Poisson distribution. At each time-step, a value is drawn from this distribution to determine the number of sex acts. Each of these sex acts is subject to a probability of condom use (68.8% for Black/African American MSM and 52.8% for White MSM).15 Condom-protected sexual acts are assumed to carry a negligible risk of HIV transmission and were not explicitly simulated to increase efficiency as the model progressed.

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| --- | --- |
| **Number of Sex Acts** | **Percentage** |
| 1 to 2 sex acts per month | 24.4% |
| 3 to 4 sex acts per month | 49.3% |
| 5 to 12 sex acts per month | 12.3% |
| 13 to 20 sex acts per month | 14.0% |

**HIV Transmission and Treatment**

Initialization

HIV prevalence at initialization was informed by InvolveMENt. At their enrollment visits, all participants in InvolveMENt were screened with a rapid HIV testing and additional serum specimens were collected by venipuncture for further confirmatory testing to arrive at prevalence estimates stratified by race. The initial prevalence of HIV infection was 43.4% for Black/African American MSM and 13.2% for White MSM.16

Transmission

A binomial distribution is used to model the process of HIV transmission, where the number of trials (*n*) is the number of condomless sex acts and the probability of success (*p*) is the probability of HIV transmission associated with a particular behavior. Parameters governing the per-act probability of HIV transmission are informed by a systematic review by Patel and colleagues (2014).17 The probability of HIV acquisition is 138 per 10,000 exposures for agents engaging in condomless anal intercourse as the receptive partner and 11 per 10,000 exposures for agents engaging engaged in condomless anal intercourse as the insertive partner.17 In the absence of additional prevention interventions, an agent’s risk of HIV acquisition in a given time-step is dependent on the number of risk acts and whether the partner with HIV infection is experiencing the acute stage of infection, using antiretroviral treatment, or has achieved viral suppression.17

Diagnosis and Treatment

Following diagnosis, agents are able to initiate antiretroviral treatment use and achieve viral suppression.18 Use of antiretroviral treatment and achievement of viral suppression decrease the risk of transmission. In dyads where the partner living with HIV infection is using antiretroviral treatment but has not achieved viral suppression, the base per-act probabilities of HIV infection are decreased by 19%.19 Agents who have achieved viral suppression are assumed to have no risk of onward transmission to their partners.19 The proportions of MSM in each stage of the continuum of care were held constant across all simulations.

|  |  |  |
| --- | --- | --- |
| **Care Continuum Stage** | **Black/African American** | **White** |
| Diagnosis | 65.5% | 81.8% |
| Antiretroviral Treatment | 43.1% | 48.8% |
| Viral Suppression | 35.2% | 43.2% |

All agents who initiated antiretroviral treatment were subject to a probability of discontinuation. In the absence of information on continuity of antiretroviral treatment use in the target population, parameter values governing this behavior are drawn from national estimates from the National HIV Surveillance System. As of 2015, 70.6% of Black/African American MSM with diagnosed HIV infection and 77.3% of White MSM with diagnosed HIV infection were believed to have received any HIV-related medical care (defined as one or more CD4 or viral load tests performed in 2014).20 Further, it was estimated that 53.6% of Black/African American MSM with diagnosed HIV infection and 59.4% of White MSM with diagnosed HIV infection received continuous HIV-related medical care (defined as two or more CD4 or viral load tests performed at least three months apart during 2014).20 Based on these data, it is assumed that 75.9% of Black/African American MSM and 76.9% of White MSM will maintain continuous antiretroviral treatment use in a given year, with a monthly probability of discontinuation of 2.0% and 1.9%, respectively.20

At model initialization, a set proportion of agents who have not been diagnosed with HIV infection are assumed to have ever been tested (89.2% of Black/African American MSM and 94.2% of White MSM).16 Agents who have ever been tested can seek out testing for HIV infection at any point during a given iteration. There are no limits on how many times an agent can test in a given year, but input parameters assume that a certain percentage of agents will test at least once per year. It is assumed that 66.3% of Black/African American MSM and 73.6% of White MSM will test at least once in a given year.16

Disease Progression

Following seroconversion, agents experience a period of increased infectiousness, corresponding to the acute stage of HIV infection. This stage is assumed to last two months.17 During this stage, the base per-act probabilities of HIV infection are increased by a factor of 7.25.17

Following this period, agents enter a chronic stage of HIV infection. At model initialization, it was assumed that 51.7% of Black/African American MSM and 53.1% of White MSM living with HIV infection had AIDS based on surveillance estimates for the state of Georgia reported by the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) of the Centers for Disease Control and Prevention. All HIV-infected agents were subsequently subject to a monthly probability of progression to AIDS dependent on their utilization of antiretroviral treatment and achievement of viral suppression. Among HIV-infected agents who did not use antiretroviral treatment, this probability was 0.0029. This probability decreases to 0.0021 among agents who used antiretroviral treatment but did not achieved viral suppression and to 0.0009 among agents who achieved viral suppression. These probabilities are estimated based on rates of clinical progression in a cohort of HIV-infected agents in Switzerland in an analysis that aimed to estimate the effectiveness of treatment in preventing AIDS.21

**Pre-Exposure Prophylaxis**

The number of available prescriptions is determined based on the desired population coverage. Agents are eligible for PrEP if they (a) are in an ongoing relationship with an agent living with diagnosed HIV infection or (b) have two or more ongoing relationships and engage in condomless anal intercourse.22

The impact of PrEP use on the probability of HIV infection is dependent on adherence. The efficacy associated with each level of adherence is derived from the STRAND trial, an open-label trial that aimed to established benchmarks for serum drug concentrations through directly observed dosing.23 In comparing those concentrations to those observed among agents in the iPrEx trial, Anderson and colleagues (2012) concluded that the risk of HIV infection declined by 76% for agents who took two doses per week, 96% for agents who took four doses per week, and 99% for agents who took seven doses per week.23 In the model, the per-act probability of HIV infection is reduced by 76% among agents in the model who take two to three pills per week and by 96% among agents who take four or more pills per week.

In the absence of information on adherence to daily pill-taking in the target population, parameter values governing this behavior are drawn from an open-label demonstration project that examined the feasibility of integrating PrEP with municipal- and community-based sexual health services in three cities in the United States.24 Among MSM who initiated PrEP, 56.8% of Black/African American MSM and 91.1% of White MSM had serum drug concentrations consistent with taking four or more doses per week.24

All agents who initiate PrEP are subject to a probability of discontinuation each month post-initiation. This probability is informed by data from the PrEP clinic operated by the Fulton County Board of Health.25 Between October 2015 and March 2017, 174 MSM initiated PrEP use.25 Few MSM continued to use PrEP beyond six months after initiation, but White MSM were more likely to be retained in PrEP care than Black/African American MSM at all time-points.25 In the model, White MSM who used PrEP were subject to monthly probability of discontinuation of 9.3% and Black/African American MSM who used PrEP were subject to a monthly probability of discontinuation of 9.5%.

**Model Calibration**

Given that population-level trends emerge from characteristics and behaviors specified at the agent level, the recreation of specified epidemic behaviors provides some level of confidence that the model was able to represent essential components of the system (Figure 1). The primary calibration targets were successful recreation of the observed race-specified incidence rates from InvolveMENt (6.5 per 100 person-years for Black/African American MSM and 1.7 per 100-person-years for White MSM).13

Model calibration was conducted using Latin hypercube sampling, a method developed to sample from and search a multidimensional parameter space.26 For each set of parameter values, the model was run and a statistic reflecting how closely the set recreated the empirical calibration targets was calculated. Parameter sets that did not provide adequate fit to these calibration targets were discarded to narrow the ranges from which values for input parameters could be sampled. Given that nearly all parameter values are drawn from well-characterized studies involving the target population, parameters with those most uncertainty or those drawn from other studies were the focus of calibration efforts. In particular, a set of scaling factors were applied to the parameter governing the number of sex acts per month, where the mean target number of sex acts per month was reduced from 5.45 to 2.45 (scaled by a factor of 0.45), the per-month probability of being diagnosed following infection, where the probability was reduced from 66.3% to 20.0% among Black/African American MSM and from 81.8% to 24.5% among White MSM (scaled by a factor of 0.3); and the per-month probability of initiating antiretroviral treatment upon diagnosis, where this probability was reduced from 43.1% to 8.6% among Black/African American MSM and from 48.8% to 9.8% among White MSM (scaled by a factor of 0.2). These scaling factor values were used to first create stable portions of agents in each stage of the care continuum for the duration of the model run and then to calibrate HIV incidence in line with the race-specific calibration targets.

**Sensitivity Analyses**

The results of the main analyses were robust to improvements in the continuum of care (Supplemental Figure 1). The model predicted a rate ratio of 3.78 (95% SI: 3.43, 4.16) and a rate difference of 3.69 (95% SI: 3.37, 4.04) in a scenario without PrEP implementation where the UNAIDS ‘90-90-90’ targets have been achieved and maintained compared to the status quo scenario without PrEP provision. In a scenario where the UNAIDS ‘90-90-90’ targets have been achieved and maintained and there are ten agents using PrEP for each newly diagnosed agent in both racial groups, the rate ratio decreased by 51.5% to 1.83 (95% SI: 1.65–2.07) and the rate difference decreased by 78.3% to 0.80 (95% SI: 0.64–0.97). In a comparable scenario where the continuum of care is maintained at the status quo, the rate ratio decreased by 51.1% to 1.87 (95% SI: 1.70–2.08) and the rate difference decreased by 77.3% to 1.02 (95% SI: 0.82–1.25).

The results of the main analyses were sensitive to improvements in adherence to daily pill-taking among Black/African American MSM who used PrEP (Supplemental Figure 2). Across all model scenarios, the relative change in the rate ratio and rate difference was larger when Black/African American MSM were as likely to achieve optimal adherence as White MSM. For example, in a scenario where ten agents used PrEP for every new HIV infection, the rate ratio decreased by 58.1% to 1.60 (95% SI: 1.43–1.76) and the rate difference decreased by 84.7% to 0.69 (95% SI: 0.52–0.86). In a comparable scenario with the observed differences in adherence to daily pill-taking, the rate ratio decreased by 51.1% to 1.87 (95% SI: 1.70–2.08) and the rate difference decreased by 77.3% to 1.02 (955 SI: 0.82–1.25).

The results of the main analyses were robust to improvements in retention in care among Black/African American MSM who used PrEP (Supplemental Figure 3). Across all model scenarios, the relative change in the rate ratio and rate difference were similar when Black/African American MSM were as likely to achieve optimal adherence as White MSM. For example, in a scenario where ten agents used PrEP for every new HIV infection, the rate ratio decreased by 50.9% to 1.87 (95% SI: 1.69–2.07) and the rate difference decreased by 77.2% to 1.03 (95% SI: 0.84–1.22). In a comparable scenario with the observed differences in retention in care, the rate ratio decreased by 51.1% to 1.87 (95% SI: 1.70–2.08) and the rate difference decreased by 77.3% to 1.02 (955 SI: 0.82–1.25).

**Technical Details**

Python (Version 3.7.2), an open-source programming language, was used for model coding, testing, and calibration. The simulations were run on Oscar, the primary research computing cluster located at the Brown University Center for Computation and Visualization. Oscar operates on the CentOS 6.7 Linux operating system and utilizes the Simple Linux Utility for Resource Management (SLURM) workload manager. The simulations were processed using Intel Xeon E5540 processors (2.53 gigahertz) operating with eight cores at 14.84 teraflops and 12 gigabytes of double date rate type III (DDR3) memory. Each model scenario was run for 1,000 unique iterations. All model output was processed in R (Version 3.5.3).

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**Supplemental Figure 1.** Changes in the incidence rate ratio and incidence rate difference in main analyses where the observed continuum of care is maintained versus sensitivity analyses where the United Nations Joint Programme on HIV/AIDS ‘90-90-90’ targets are achieved and maintained



**Supplemental Figure 2**. Changes in the incidence rate ratio and incidence rate difference in main analyses where the observed disparities in adherence to daily pill-taking among men who have sex with men who use pre-exposure prophylaxis are maintained versus sensitivity analyses where these disparities in adherence to daily pill-taking are eliminated

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**Supplemental Figure 3.** Changes in the incidence rate ratio and incidence rate difference in main analyses where the observed disparities in adherence to daily pill-taking among men who have sex with men who use pre-exposure prophylaxis are maintained versus sensitivity analyses where these disparities in adherence to daily pill-taking are eliminated

