Addressing Gaps in HIV Preexposure Prophylaxis Care to Reduce Racial Disparities in HIV Incidence in the United States

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Web Material

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1 WEB APPENDIX 1 (INTRODUCTION)

This supplementary technical appendix describes the mathematical model structure, parameterization, and statistical analysis of the accompanying paper in further detail.

1.1 Model Framework

The mathematical models for HIV transmission dynamics presented in this study are agent-based microsimulation models in which uniquely identifiable sexual partnership dyads were simulated and tracked over time. This partnership structure is represented through the use of separable temporal exponential-family random graph models (STERGMs), described in Web Appendix 2. On top of this dynamic network simulation, the larger epidemic model represents demography (entries, exits, and aging), interhost epidemiology (disease transmission), intrahost epidemiology (disease progression), and clinical epidemiology (disease diagnosis and treatment). Individual attributes related to these processes are stored and updated in discrete time over the course of each epidemic simulation.

The modeling methods presented here depend upon and extend the *EpiModel* software to incorporate HIV-specific epidemiology. The HIV extensions for men who have sex with men (MSM) were originally developed by Goodreau et al. for use in prior modeling studies of MSM in the United States and South America,[1–3] and subsequently used for a model for HIV preexposure prophylaxis (PrEP) among US MSM.[4–7]

1.2 Model Software

The models in this study were programmed in the R and C++ software languages using the *EpiModel* [http://epimodel.org/] software platform for epidemic modeling. *EpiModel* was developed by the authors for simulating complex network-based mathematical models of infectious diseases, with a primary focus on HIV and other sexually transmitted infections (STIs). *EpiModel* depends on *Statnet* [http://statnet.org/], a suite of software in R for the representation, visualization, and statistical analysis of complex network data.[8]

EpiModel allows for a modular expansion of its built-in modeling tools to address novel research questions. For this current research study, we have developed extension modules into an add-on software package to *EpiModel* called *EpiModelHIV*. This open-source software is available for download, along with the scripts used in the execution of these models. The tools and scripts to run these models are contained in two GitHub software repositories:

- [http://github.com/statnet/EpiModelHIV] contains the general extension software package. Installing this using the instructions listed at the repository homepage will also load in *EpiModel* and the other dependencies. We use a branching software architecture such that the version of the software associated with this research project is *prep-race.*
- [http://github.com/EpiModel/PrEPdisparities] contains the scripts to execute the mathematical models and to run the statistical analyses provided in the manuscript.

1.3 Core Model Specifications

With a starting network size of 10,000 MSM aged 18–40, 50% were initialized in each race, a ratio that approximates the distribution for the Atlanta area and provides analytical clarity.[9] Further details on the demography (race and age) are provided in Web Appendix 5. The time unit used throughout the simulations was one week. Thus, all rate-based parameters listed below are to be interpreted as the rate per week and all duration-based estimates are to be interpreted as the duration in weeks, unless otherwise noted.

2 WEB APPENDIX 2 (BEHAVIORAL DATA SOURCES)

The various behavioral modules were parameterized using two studies of HIV/STI disparities in Black and White non-Hispanic MSM, conducted from 2010-2014 in Atlanta, GA. The Involvement Study was a prospective HIV incidence cohort of 803 MSM and the MAN Project was a cross-sectional chain-referral sexual networks study of 314 MSM. Both samples were recruited contemporaneously using venue-time-space sampling, using a modified frame from the 2008 MSM round of the National HIV Behavioral Surveillance system. Study participants completed common self-administered computer-based questionnaire modules that assessed demographics, prevention behaviors, and a detailed dyadic (partnership) section that collected demographic, behavioral, and structural (partnership duration and sequence) data.

We first created a combined ego dataset of Black and White non-Hispanic MSM in Atlanta, ages 18-40 from the baseline visit of Involvement (n=803) and network seed-level respondents from the MAN Project (n=196), for a total of 999 egos. We then created a combined dyadic dataset for partnerships among those egos, which included up to 5 most recent sex partners in the previous 6 months per ego for Involvement or 10 partners in 12 months per ego for MAN Project. Only Black and White non-Hispanic male partners were included, and dyads were limited to those in which AI occurred at least once (at last sex or during the 6- or 12-month interval), resulting in a total of 2,626 dyads. We refer to this as the “combined dyadic dataset” below.

3 WEB APPENDIX 3 (SEXUAL NETWORKS)

We model networks of three interacting types of sexual relations: main partnerships, casual (but persistent) partnerships, and one-time AI contacts. We first describe the methods conceptually, including the parameters used to guide the model and their derivation (Web Appendix 3.1), and then present the formal statistical modeling methods (Web Appendix 3.2). Consistent with our parameter derivations, all relationships are defined as those in which AI is expected to occur at least once.

3.1 Conceptual Representation of Sexual Networks

Our modeling methods aim to preserve certain features of the cross-sectional and dynamic network structure as reported in behavioral studies, while also allowing for mean relational durations to be targeted to those reported for different groups and relational types. Our methods do so all within the context of changing population size (due to births, deaths, arrivals and departures from the population) and changing composition by attributes such as age.

The network features that we aim to preserve are as follows, with the parameters for each described in turn:

- The proportion of men (by race) in any given combination of main and casual partnerships (for example, in 1 main and 0 casual partnerships) at any time point.
- The expected number of one-time contacts per time step had by men in each main-casual combination (by race).
- Variation across men in the numbers of one-time contacts.
- Race mixing within each of the different relational types.
- Age mixing within each of the different relational types, by the races of the two men involved.
- Prohibitions against partnering for two men who are both exclusively insertive or exclusively receptive.

3.1.1 Number of Ongoing Main and Casual Partnerships

Ongoing partnerships (whether main or casual) were defined from the combined dyadic dataset as those in which sex had already occurred more than once, and in which the respondent anticipated having sex again. Within this set, partnerships were defined as main if the respondent indicated that it was someone they “felt committed to above all others” or that they considered the person their “primary sex partner”; if neither of these conditions held, the partner was defined as casual. This yielded the following proportions of men with a given number of main and casual relationships at a point in time (i.e. the expected *momentary degree distribution*) shown in Web Table 1.

Web Table 1. Degree Distribution in Main and Casual Partnerships.

	Black				**White**		
	0 Casual	*1 Casual*	*2 Casual*		*0 Casual*	*1 Casual*	*2 Casual*
0 Main	50.6%	15.1%	5.3%		43.5%	18.4%	9.5%
1 Main	20.7%	6.1%	2.2%		23.3%	3.3%	2.0%

Note that this implies a slightly higher rate of relational concurrency within these two types of relationships for White men (9.5% + 3.3% + 2.0% = 14.8%) than for Black men (5.3% + 6.1% + 2.2% = 13.6%). It also implies a slightly higher proportion of Black men in a main partnership (29.0%) than White men (28.6%), but a higher average number of casual partners for White men (weighted average = 0.447 casual partnerships per person) than Black men (0.362).

3.1.2 Expected Number of One-Time AI Contacts, by Main/Casual Degree

Respondents in the combined dyadic dataset were asked whether they had had sex with each partner once or more than once; the former response led to the contact being defined as one-time. These contacts cannot be analyzed in terms of momentary degree distributions, since none are ongoing at the point of interview, by definition. Instead, we turn the observed frequencies into expected rates of one-time contacts per time step for men under different conditions. One of the sources of heterogeneity in men's propensity for one-time AI contacts is their current relationship status. The expected numbers are given by Web Table 2.

Web Table 2. One-Time AI Contact Rates.

	Black				**White**		
	0 Casual	*1 Casual*	*2 Casual*		*0 Casual*	*1 Casual*	*2 Casual*
0 Main	0.073	0.091	0.080		0.057	0.084	0.091
1 Main	0.055	0.052	0.052		0.057	0.058	0.058

3.1.3 Heterogeneity in the One-Time Contact Rate

In addition to differences by relational status, men also have underlying fixed heterogeneities in their propensity to engage in one-time AI. The distribution of one-time contacts was divided into quintiles, within which the expected values of one-time AI per time step are provided in Web Table 3.

Web Table 3. Heterogeneity in Contact Rates.

Quintile	Black	White
Lowest quintile	0.000	0.000
Second quintile	0.010	0.003
Third quintile	0.039	0.036
Fourth quintile	0.074	0.068
Highest quintile	0.212	0.231

Men are assigned a quintile upon entry into the population, which remains fixed. Any individual man's propensity for AI is determined as a combination of their quintile and their current main/casual partnership counts. Our statistical methods (described below) translate both propensities into conditional log-odds, allowing for their combination. Note that the means of the columns in the quintile table equal the means of the values in Web Appendix 3.1.2 weighted by the proportions in Web Appendix 3.1.1. These reflect the overall expected value across all men within each race for one-time AI acts per time step, which are nearly identical to each other (0.0670 for Black MSM, 0.0676 for White MSM).

3.1.4 Race Mixing

Respondents reported on their perception of the race and ethnicity (Hispanic/non-Hispanic) for each partner. Since this model is limited to young Black and White MSM, we calculated our race mixing proportions based on contacts reported within these two groups. Limiting to these, the self-reports of relations within race are shown in Web Table 4.

Web Table 4. Proportion of Same-Race Partnerships.

	Black	White
Main partnerships	94.8%	91.5%
Casual partnerships	90.2%	85.1%
One-time contacts	90.9%	89.4%

These numbers must balance in our model; that is, the reports by Black men and by White men each imply a specific expected number of cross-race relationships, given the overall numbers of relationships for each group. Although the implied numbers are similar, they are not exactly equal. To reconcile this, we calculated the expected cross-race relationships given each number above and all of the other relational statistics in the model, and took the midpoint of the two values. These equaled 93%, 88%, and 90%, for main, casual and one-time, respectively.

3.1.5 Age Mixing

Respondents also reported on the estimated age of each partner. We model age mixing within a given relational type and race combination using a single parameter for each, the expected mean difference in square root of the ages of men in a relationship, consistent with previous work.[1,3,10] For instance, a relationship between a 23-year-old and a 28-year-old would represent $\left|\sqrt{23} - \sqrt{28}\right|$ = 0.496. These parameters are shown in Web Table 5.

Web Table 5. Mean Difference in Ages by Partnership Type.

	B-B Dyads	**B-W Dyads**	**W-W Dyads**
Main partnerships	0.417	0.454	0.520
Casual partnerships	0.498	0.629	0.632
One-time contacts	0.456	0.585	0.590

3.1.6 Mixing by Sexual Role

We assign men a fixed sexual role preference (exclusively insertive, exclusively receptive, versatile). The model then includes an absolute prohibition, such that two exclusively insertive men cannot partner, nor can two exclusively receptive men. Men's roles at last sex for each of the last 5 (Involvement) or 10 (MAN Project) partners were aggregated; those who had engaged in one role across all of those acts were deemed to be exclusively receptive or insertive, and those who had engaged in at least one act of each were deemed to be versatile. These parameters are shown in Web Table 6.

Web Table 6. Mixing by Sexual Role.

	Black	**White**
Exclusively insertive	24.2%	22.8%
Versatile	43.7%	54.4%
Exclusively receptive	32.1%	22.8%

3.1.7. Partnership Durations

We model relational dissolution as a heterogenous, geometrically distributed process with unique parameters for each relational type and race combination. This distribution for relational durations implies a "memoryless process, which is a common assumption within ordinary differential equation modeling. Although this assumption implies that the rate of dissolution does not depend on the length of the partnership, the overall exponential shape of the dissolution matches reasonably well to empirical data on relational durations. The fit is improved considerably when the partnership types are stratified, as we do here, by multiple attributes, implying a hypergeometric distribution. Our principal stratification here is partnership type, where the key difference between types is the average duration. Once one-time contacts are removed, and longer-duration main partnerships are separated from shorter-term causal partnerships, the hypergeometric distribution fits the empirical data on partnership durations well.

As detailed in previous work,[1] for memoryless processes, the expected age of an extant relationship at any moment in time matches the expected uncensored duration of relationships, given the balancing effects of right-censoring and length bias for this distribution.

To derive our values, we take the median of the observed distribution and then calculate the mean for the exponential distribution with that median. Duration was calculated as the difference between first and last sex date for each dyad the ego reported sex with more than once in the interval. The resulting expected relational durations are provided in Web Table 7.

Web Table 7. Duration of Partnerships by Race Combination.

	B-B Dyads	**B-W Dyads**	**W-W Dyads**
Main partnerships	348 days	372 days	555 days
Casual partnerships	131 days	286 days	144 days

3.2 *Statistical Representation of Sexual Networks*

Exponential-family random graph models (ERGMs) and their dynamic extension separable temporal ERGMs (STERGMs) provide a foundation for statistically principled simulation of local and global network structure given a set of target statistics from empirical data. Main and casual relationships were modeled using STERGMs,[11] since they persist for multiple time steps. One-time contacts, on the other hand, were modeled using cross-sectional ERGMs.[12] Formally, our statistical models for relational dynamics can be represented as five equations for the conditional log odds (logits) of relational formation and persistence at time *t* (for main and casual relationships) or for relational existence at time *t* (for one-time contacts):

$$logit\left(P\left(Y_{ij,t}=1\middle|\, Y_{ij,t-1}=0,\, Y_{ij,t}^{C}\right)\right) = \theta_m^{+\prime}\partial\left(g_m^{+}(y)\right) \qquad \text{Main partnership formation}$$

$$logit\left(P\left(Y_{ij,t}=1\middle|\, Y_{ij,t-1}=0,\, Y_{ij,t}^{C}\right)\right) = \theta_c^{+\prime}\partial\left(g_c^{+}(y)\right) \qquad \text{Casual partnership formation}$$

$$logit\left(P\left(Y_{ij,t}=1\middle|\, Y_{ij,t-1}=1,\, Y_{ij,t}^{C}\right)\right) = \theta_m^{-\prime}\partial\left(g_m^{-}(y)\right) \qquad \text{Main partnership persistence}$$

$$logit\left(P\left(Y_{ij,t}=1\middle|\, Y_{ij,t-1}=1,\, Y_{ij,t}^{C}\right)\right) = \theta_c^{-\prime}\partial\left(g_c^{-}(y)\right) \qquad \text{Casual partnership persistence}$$

$$logit\left(P\left(Y_{ij,t}=1\middle|\, Y_{ij,t}^{C}\right)\right) = \theta_o{}'\partial\left(g_o(y)\right) \qquad \text{One-time contact existence}$$

where:

- $Y_{ij,t}$ = the relational status of persons *i* and *j* at time *t* (1 = in relationship/contact, 0 = not)
- $Y_{ij,t}^{C}$ = the network complement of *i,j* at time *t*, i.e. all relations in the network other than *i,j*
- $g(y)$ = vector of network statistics in each model

- θ = vector of parameters in the model

For $g(y)$ and θ, the superscript distinguishes the formation model (+), persistence model (-) and existence models (neither). The subscript indicates the main (m), casual (c) and one-time (o) models.

The recursive dependence among the relationships renders the model impossible to evaluate using standard techniques; we use MCMC in order to obtain the maximum likelihood estimates for the $\boldsymbol{\theta}$ vectors given the $\boldsymbol{g}(\boldsymbol{y})$ vectors.

Specific model statistics are listed below. Together these sets allow us to retain all of the network features listed in Web Appendix 3.1. it is important to note that, although the statistics are expressed here in terms of number of relationships and enter into the estimation model in this form, the simulation model is then parametrized using the resulting θ coefficients. This means that, as population size and composition changes, it is not the absolute number of relationships of different kinds that will be preserved, but the relative numbers (e.g. the mean number of relationships per person). Similar conversions hold for the other statistics (e.g. the mean age difference per relationship is preserved, not the sum across all relationships).

Main partner formation model statistics: $\mathrm{g}_{\mathrm{m}}^{+}(\mathrm{y})$ vector:

- $g_{m1}^{+}(y)$ = number of main partnerships
- $g_{m2}^{+}(y)$ = number of Black-White main partnerships
- $g_{m3}^{+}(y)$ = number of White-White main partnerships
- $g_{m4}^{+}(y)$ = number of main partnerships for Black men with 1 casual partner
- $g_{m5}^{+}(y)$ = number of main partnerships for Black men with 2 casual partners
- $g_{m6}^{+}(y)$ = number of main partnerships for White men with 1 casual partner
- $g_{m7}^{+}(y)$ = number of main partnerships for White men with 2 casual partners
- $g_{m8}^{+}(y)$ = sum of the absolute difference in the square root of partners' ages across BB main partnerships
- $g_{m9}^{+}(y)$ = sum of the absolute difference in the square root of partners' ages across BW main partnerships
- $g_{m10}^{+}(y)$ = sum of the absolute difference in the square root of partners' ages across WW main partnerships

The main partner formation model also includes three constraints on the sample space: networks are prohibited unless they contain no edges between two men who are both exclusively insertive; no edges between two men who are both exclusively receptive; and no men with more than 1 main partner simultaneously

Main partner persistence model terms: $\mathrm{g}_{\mathrm{m}}^{-}(\mathrm{y})$ vector:

- $g_{m1}^{-}(y)$ = number of main partnerships
- $g_{m2}^{-}(y)$ = number of Black-White main partnerships
- $g_{m3}^{-}(y)$ = number of White-White main partnerships

Casual partner formation model terms: $\mathrm{g}_{\mathrm{c}}^{+}(\mathrm{y})$ vector:

- $g_{c1}^{+}(y)$ = number of casual partnerships
- $g_{c2}^{+}(y)$ = number of Black-White casual partnerships
- $g_{c3}^{+}(y)$ = number of White-White casual partnerships
- $g_{c4}^{+}(y)$ = number of casual partnerships for Black men with 1 main partner
- $g_{c5}^{+}(y)$ = number of casual partnerships for White men with 1 main partner
- $g_{c6}^{+}(y)$ = number of Black men with 2 casual partners
- $g_{c7}^{+}(y)$ = number of White men with 2 casual partners
- $g_{c8}^{+}(y)$ = sum of the absolute difference in the square root of partners' ages across BB casual partnerships
- $g_{c9}^{+}(y)$ = sum of the absolute difference in the square root of partners' ages across BW casual partnerships
- $g_{c10}^{+}(y)$ = sum of the absolute difference in the square root of partners' ages across WW casual partnerships

The casual partner formation model also includes three constraints on the sample space: networks are prohibited unless they contain no edges between two men who are both exclusively insertive; no edges between two men who are both exclusively receptive; and no men with more than 2 casual partners simultaneously

Casual partner persistence model terms: $\mathrm{g}_{\mathrm{c}}^{-}(\mathrm{y})$ vector:

- $g_{c1}^{-}(y)$ = number of casual partnerships
- $g_{c2}^{-}(y)$ = number of Black-White casual partnerships
- $g_{c3}^{-}(y)$ = number of White-White casual partnerships

One-time contact existence model terms: $\mathrm{g}_{\mathrm{o}}(\mathrm{y})$ vector:

- $g_{o1}(y)$ = number of one-time contacts
- $g_{o2}(y)$ = total # of one-time contacts for Black men with 0 main and 1 casual partnership
- $g_{o3}(y)$ = total # of one-time contacts for Black men with 0 main and 2 casual partnerships
- $g_{o4}(y)$ = total # of one-time contacts for Black men with 1 main and 0 casual partnerships
- $g_{o5}(y)$ = total # of one-time contacts for Black men with 1 main and 1 casual partnership
- $g_{o6}(y)$ = total # of one-time contacts for Black men with 1 main and 2 casual partnerships
- $g_{o7}(y)$ = total # of one-time contacts for White men with 0 main and 0 casual partnerships

- $g_{o8}(y)$ = total # of one-time contacts for White men with 0 main and 1 casual partnership
- $g_{o9}(y)$ = total # of one-time contacts for White men with 0 main and 2 casual partnerships
- $g_{o10}(y)$ = total # of one-time contacts for White men with 1 main and 0 casual partnerships
- $g_{o11}(y)$ = total # of one-time contacts for White men with 1 main and 1 casual partnership
- $g_{o12}(y)$ = total # of one-time contacts for White men with 1 main and 2 casual partnerships
- $g_{o13}(y)$ = total # of one-time contacts for Black men in risk quintile 1
- $g_{o14}(y)$ = total # of one-time contacts for Black men in risk quintile 2
- $g_{o15}(y)$ = total # of one-time contacts for Black men in risk quintile 4
- $g_{o16}(y)$ = total # of one-time contacts for Black men in risk quintile 5
- $g_{o17}(y)$ = total # of one-time contacts for White men in risk quintile 1
- $g_{o18}(y)$ = total # of one-time contacts for White men in risk quintile 2
- $g_{o19}(y)$ = total # of one-time contacts for White men in risk quintile 4
- $g_{o20}(y)$ = total # of one-time contacts for White men in risk quintile 5
- $g_{o21}(y)$ = total # of race-homophilous one-time contacts
- $g_{o22}(y)$= sum of the absolute difference in the square root of partners' ages across BB one-time contacts
- $g_{o23}(y)$= sum of the absolute difference in the square root of partners' ages across BW one-time contacts
- $g_{o24}(y)$= sum of the absolute difference in the square root of partners' ages across WW one-time contacts

The one-time existence model also includes two constraints on the sample space: networks are prohibited unless they contain no edges between two men who are both exclusively insertive; and no edges between two men who are both exclusively receptive.

Our method of converting the statistics laid out in Web Appendix 3.1 into our fully specified network models consists of the following steps:

1. Construct a cross-sectional network of 10,000 men with no relationships
2. Assign men sexual roles based on prevalences listed in Web Appendix 3.1.6, as well as one-time risk quintiles (20% of the men in each race per quintile)
3. Calculate the target statistics (i.e., the expected count of each statistic at any given moment in time) associated with the terms in the formation model (for the main and casual partnerships) and in the existence model (for one-time contacts).
4. Assign each node a place-holder main and casual degree (number of on-going partnerships) that is consistent with the race-specific matrices, and store these numbers as a nodal attribute. (Note: this does not actually require individuals to be paired up into the partnerships represented by those degrees).

5. For the main and casual networks, use the mean relational durations by race combination to calculate the parameters of the persistence model, using closed-form solutions, given that the models are dyadic-independent (each relationship's persistence probability is independent of all others).
6. For the main and casual networks, estimate the coefficients for the formation model that represent the maximum likelihood estimates for the expected cross-sectional network structure.
7. For the one-off network, estimate the coefficients for the existence model that represent the maximum likelihood estimates for the expected cross-sectional network structure.

Steps 5-7 occur within the *Statnet* software, and use the ERGM and STERGM methods therein. They are made most efficient by the use of an approximation in Step 6.[13] During the subsequent model simulation, we use the method of Krivitsky et al.[14] to adjust the coefficient for the first term in each model at each time step, in order to preserve the same expected mean degree (relationships per person) over time in the face of changing network size and nodal composition. At all stages of the project, simulated partnership networks were checked to ensure that they indeed retained the expected cross-sectional structure and relational durations throughout the simulations.

4 WEB APPENDIX 4 (BEHAVIOR WITHIN SEXUAL PARTNERSHIPS)

We model four phenomena consecutively within relationships at each time step: HIV+ status disclosure, number of anal sex acts, condom use per sex act, and sexual role per sex act. We model these only within the relationships in our network that are HIV-discordant (whether diagnosed or not), given that only they may lead to potential transmissions.

4.1 Disclosure

We model the process by which someone who knows he is HIV-positive discloses this fact to partners of all types using parameters in Web Table 8. Disclosure affects subsequent decision-making around condom use. We do not explicitly model other forms of serostatus discussion, since our source data do not include these all; our behavioral estimates in the absence of HIV+ disclosure marginalize over those cases in which men disclose as concordant negative and do not discuss at all. Disclosure may occur at the point of a relation commencing (if HIV+ status is already known) or it may occur at the point of diagnosis, in the case of on-going relationships. In the former case, disclosure of HIV+ status was determined from the combined dyadic dataset using the HIV status of the respondent and their response to the question, "Did you and this partner share both of your HIV statuses before you first had sex?" In the latter case, we did not have data and assumed it to be universal.

Web Table 8. HIV Status Disclosure Parameters.

Probability of Disclosure of HIV+ Status	**Black**	**White**
to new main partner at outset of relationship	0.685	0.889
to new casual partner at outset of relationship	0.527	0.828
to one-time contact	0.445	0.691
to ongoing partner if diagnosis occurs during relationship	1.000	1.000

4.2 Number of AI Acts

The number of anal sex acts per week for each ongoing relationship is determined from a Poisson draw, with mean specific to the relational type and race combination of the dyad. For one-time contacts, the number is set deterministically to 1 for the time step in which it occurs. For main and casual partnerships, we used the frequency of AI in those partnerships as a model calibration parameter that was allowed to vary by race. Therefore, there were six parameters in total: main act frequency among black-black partnerships, black-white partnerships, and white-white partnerships; and casual act frequency among black-black partnerships, black-white partnerships, and white-white partnerships. To calibrate the model, we assumed a uniform prior distribution informed by the empirical 95% confidence intervals of the point estimates for each weekly rate. The bounds of the distributions are shown in Web Table 9.

Web Table 9. Priors for AI Acts per Week.

AI Acts/Week/Partnership	**B-B Dyads**	**B-W Dyads**	**W-W Dyads**
Main partnerships	1.01–2.39	1.00–2.08	1.09–1.69
Casual partnerships	0.64–1.52	0.63–1.32	0.69–1.08

After model calibration (statistical details in Web Appendix 12), the point estimates for the posterior distributions that were selected and used for the primary model are shown in Web Table 10.

Web Table 10. Posterior Point Estimates for AI Acts per Week.

AI Acts/Week/Partnership	**B-B Dyads**	**B-W Dyads**	**W-W Dyads**
Main partnerships	2.02	1.54	1.18
Casual partnerships	1.28	0.98	0.75

These rates were calculated based on the two Atlanta studies, derived from questions asking the number of coital acts per partnership during the recall periods.[15,16] These were then rescaled from the length of the recall period into the weekly rates listed in the table above.

4.3 Condom Use

We conducted logistic regression to identify the main predictors of condom use within partnerships in our data. Respondents were asked if they had had unprotected anal sex with each partner during the recall periods. Predictors included the race combination of the men in the relationship, the type of relationship, the HIV diagnosis status of the HIV+ partner (i.e. whether or not he himself knew that he was HIV+), and the disclosure status of the HIV+ partner (whether he had told his partner he was HIV+). Predictors that dropped out of the model included sexual position and perceived monogamy of the partnership.

In contrast to previous models, we added three new features of condom use within this study that impacted the overall simulation of condoms by the target population. First, we also modeled persistent condom use for both causal partnerships and one-time contacts, which depended on empirical data showing no condomless acts over the course of that partnership. The per-act probability of condom use for those two partnership types, therefore, is conditional on being outside the group that always uses condoms. For main partnerships, we assumed no persistent condom use. Second, for all partnership types, we explicitly modeled condom failure or breakage stratified by race. This accounts for the observations that condom failure rates may be 1–4 times higher for black MSM compared to white MSM.[17] Third, similar to AI frequency, we also modeled the probability of condom use and the rates of condom failure as calibration parameters given the sensitivity in reporting condomless sex in behavioral surveys and general uncertainty in measurement of these phenomena.

For persistent condom use, 21.6% always used condoms within casual partnerships and 32.6% always used condoms within one-time contacts. We assumed a correlation in being a persistent condom user across casual and one-time contacts with a correlation coefficient of 50%.

For main partnerships, conditional on having anal intercourse, the probabilities were converted to log odds, with coefficients defined by race/partnership types as logit(P(condom use|anal intercourse). For casual partnerships and one-time contacts, these outcomes were also conditional on not being a consistent condom user, with log odds coefficients also defined by race/partnership types as logit(P(condom use|anal intercourse, non-persistent condom use). For the prior distributions for these 9 coefficients were informed by the empirical 95% confidence intervals around the mean estimates translated into uniform distributions. Those prior distributions, therefore, are shown in Web Table 11.

Web Table 11. Priors for Logistic Model Coefficients for Condom Use.

	B-B Dyads	**B-W Dyads**	**W-W Dyads**
Main partnership	-2.12, -1.03	-1.46, -1.20	-1.46, -0.41
Casual partnership	-1.89, -0.73	-1.19, -0.91	-1.19, -0.02
One-time contact	-1.83, -0.67	-1.13, -0.86	-1.14, 0.05

The final selected point estimates from the posterior distribution after model calibration are provided in Web Table 12.

Web Table 12. Posterior Point Estimates for Logistic Model Coefficients for Condom Use.

	B-B Dyads	**B-W Dyads**	**W-W Dyads**
Main partnership	-1.74	-1.32	-0.68
Casual partnership	-1.48	-1.04	-0.34
One-time contact	-1.44	-0.99	-0.27

Again, the casual/one-time coefficients were conditional on not being a persistent condom user, while the main partnership coefficients were not. Condom failure or misuse translated into a reduction in the per-act efficacy of condoms in the prevention of HIV and STIs, not in the rate of condom use itself. Therefore, we describe this feature in Web Appendix 8 on interhost epidemiology.

For HIV-discordant partnerships, the reference category is the case in which the HIV+ man is undiagnosed, hence the relatively low values of condom use. Modifiers for these logit coefficients for discordant partnerships are shown in Web Table 13.

Web Table 13. Logistic Model Coefficients for Condom Use Modifiers.

Condition	**Coefficient**
HIV+ diagnosis	0.67
HIV+ status disclosure	0.85

Together, these values, in combination with the frequencies with which AI occurs in all of the different types of situations, implies an overall rate of condom use average across all acts of approximately 50%.

4.4 Sexual Role

Men are assigned an individual sexual role preference (exclusively insertive, exclusively receptive, or versatile) as described in Web Appendix 3.1.6. Relationships between two exclusively insertive or two exclusively receptive men are prohibited via the ERGM and STERGM models. Versatile men are further assigned an insertivity preference drawn from a uniform distribution between 0 and 1. When two versatile men are determined to have an AI act, their sexual positions must be determined (all other combinations have only one feasible combination). One option is for men to engage in intra-event versatility (IEV; i.e. both engage in insertive and receptive AI during the act). The probability of this is specific to the race combination of the men (Black-Black = 42%, Black-White = 56%, White-White = 49%), and is derived from the partner-specific role data described in Web Appendix 3.1.6. If IEV does not occur, then each man's probability of being the insertive partner equals his insertivity quotient divided by the sum of the two men's insertivity quotients.

5 WEB APPENDIX 5 (DEMOGRAPHY)

In this model, there are three demographic processes: entries, exits, and aging. Entries and exits are conceptualized as flows to and from the sexually active population of interest: MSM aged 18 to 40 years old. Entry into this population represents the time at which persons become at risk of infection via male-to-male sexual intercourse, and we model these flows as starting at an age after birth (age 18) and ending at an age potentially before death (age 40).

5.1 Entry at Sexual Onset

All persons enter the network at age 18, which was the lower age boundary of our two main source studies. The number of new entries at each time step is based on a fixed rate (3 per 10,000 persons per weekly time step) that keeps the overall network size in a stable state over the time series of the simulations. The model parameter governing this rate was calibrated iteratively in order to generate simulations with a population size at equilibrium, given the inherent variability in population flows related to background mortality, sexual maturation (i.e., reaching the upper age limit of 40), and disease-induced mortality. At each time step, the exact number of men entering the population was simulated by drawing from a Poisson distribution with the rate parameter.

5.2 Initialization of Attributes

Persons entering the population were assigned attributes, some of which remained fixed by definition (e.g., race), others fixed by assumption (e.g., insertive versus receptive sexual role), and yet others allowed to vary over time (e.g., age and disease status). Here we describe three attributes in the first category:

- For **race/ethnicity**, this model was based on a population composition that was 50% black MSM and 50% white MSM. This 1:1 ratio comes close to that for the Atlanta metropolitan area and also provides analytical clarity.
- **Circumcision** status was randomly assigned to incoming men. Based on empirical data from Atlanta MSM,[15] 89.6% of men were circumcised before sexual onset. Circumcision was associated with a 60% reduction in the per-act probability of infection for HIV- males for insertive

anal intercourse only (i.e., circumcision did not lower the *transmission* probability if the HIV+ partner was insertive).[2,18]

- The **CCR5-Δ32 genotype** was modeled by assigning a value of zero, one, or two Δ32 alleles. Compared to men without the Δ32 allele, heterozygous men (those with Δ32 alleles) were 70% less likely to become infected and Δ32 homozygous men (those with two Δ32 alleles) were fully immune from infection.[19,20] The population distribution of genotypes was differential by race, with 0% of black men and 3.4% of white men expressing as Δ32 homozygous, and 2.1% of black men and 17.6% of white men expressing as Δ32 heterozygous.[19]

5.3 Exits from the Network

All persons exited the network by age 40, either from mortality or by reaching the upper age bound of the MSM target population of interest. This upper limit of 40 was modeled deterministically (probability = 1), but other exits due to mortality were modeled stochastically. Mortality included both natural (non-HIV) and disease-induced mortality causes before age 40. Background mortality rates were based on US all-cause mortality rates specific to age and race from the National Vital Statistics life tables.[21] Web Table 14 shows the probability of mortality per year by age and race.

Web Table 14. Mortality Rates by Race and Age Group.

Age	White	Black
18–24	0.00103	0.00159
25–34	0.00133	0.00225
35–39	0.00214	0.00348

Natural mortality was applied to persons within the population at each time step stochastically by drawing from a binomial distribution for each eligible person with a probability parameter corresponding to that person's risk of death tied to his age. Disease-related mortality, in contrast, was modeled based on clinical disease progression, as described in Web Appendix 6.

5.4 Aging

The aging process in the population was linear by time step for all active persons. The unit of time step in these simulations was one week, and therefore, persons were aged in weekly steps between the minimum and maximum ages allow (18 and 40 years old). Evolving age impacted background mortality, age-based mixing in forming new partnerships, and other behavioral features of the epidemic model described below. Persons who exited the network were no longer active and their attributes such as age were no longer updated.

6 WEB APPENDIX 6 (INTRAHOST EPIDEMIOLOGY)

Intrahost epidemiology includes features related to the natural disease progression within HIV+ persons in the absence of clinical intervention. The main component of progression that was explicitly modeled for this study was HIV viral load. In contrast to other modeling studies that model both CD4 and viral load, our study used viral load progression to control both interhost epidemiology (HIV transmission rates) and disease progression eventually leading to mortality.

Following prior approaches,[1,2] we modeled changes in HIV viral load to account for the heighted viremia during acute-stage infection, viral set point during the long chronic stage of infection, and subsequent rise of VL at clinical AIDS towards disease-related mortality. The HIV viral load has a crucial impact on the rates of HIV transmission within serodiscordant pairs in the model, and this interaction is detailed in Section 8. A starting viral load of 0 is assigned to all persons upon infection. From there, the natural viral load curve is fit with the following parameters in Web Table 15.

Web Table 15. HIV Natural History Parameters.

Parameter	Value	Reference
Time to peak viremia in acute stage	45 days	Little[22]
Level of peak viremia	6.886 $\log_{10}$	Little[22]
Time from peak viremia to viral set point	45 days	Little,[22] Leynaert[23]
Level of viral set point	4.5 $\log_{10}$	Little[22]
Duration of chronic stage infection (no ART)	3550 days	Buchbinder,[24] Katz[25]
Duration of AIDS stage	728 days	Buchbinder[24]
Peak viral load during AIDS (at death)	7 $\log_{10}$	Estimated from average duration of AIDS

After infection, it takes 45 days to reach peak viremia, at a level of 6.886 log 10. From peak viremia, it takes another 45 days to reach viral set point, which is set at a level of 4.5 log 10. The total time of acute stage infection is therefore 3 months. The duration of chronic stage infection in the absence of clinical intervention is 3550 days, or 9.7 years. The total duration of pre-AIDS disease from infection is therefore approximately 10 years. At onset of AIDS, HIV viral load rises linearly from 4.5 log 10 to 7 log 10, at which point mortality is assumed to occur. The time spent in the AIDS stage is 728 days, or 2 years. This viral load trajectory is for ART-naïve persons only, and the influence of ART on disease progression is detailed in Web Appendix 7. These transitions are deterministic for all ART-naïve persons.

7 WEB APPENDIX 7 (CLINICAL EPIDEMIOLOGY)

Clinical epidemiological processes refer to all steps along the HIV care continuum after initial infection: diagnosis, linkage to care, treatment initiation and adherence, and HIV viral load suppression. In this model, these clinical features have critical interactions with behavioral features detailed above, as well as impacts on the rates of HIV transmission, detailed below. The features of our model's clinical processes generally follow the steps of the HIV care continuum, in which persons transition across states from infection to diagnosis to medical care linkage and ART initiation to HIV viral suppression.[26]

7.1 HIV Diagnostic Testing

Persons in our models were divided into non-testers (through age 40) and regular interval-based testers. Based on empirical data for Atlanta MSM,[15] 6.5% of MSM did not receive HIV testing before age 40. This was calculated based on a survey about never tested prior to the study, which may overestimate the final proportion who would have never tested before age 40. A fixed individual attribute for HIV treatment trajectories that characterized progression through the care continuum was randomly assigned upon entry into the population, with this group of 6.5% of MSM not accessing HIV testing or other forms of post-diagnostic HIV medical services.

The remaining 93.5% who entered the HIV care continuum HIV tested at regular intervals, with the estimated mean time between tests for HIV-negative persons at 301 days for black MSM and 315 days for white MSM.[15,27] This was calculated based on time since last test in the survey. Diagnostic testing was simulated stochastically using draws from a binomial distribution with probability parameters equal to the reciprocal of this interval. This generated a population-level geometric distribution of times since last test.

We also modeled a 21-day window period after infection during which the tests of the truly HIV+ persons would show as negative to account for the lack of antibody response immediately after infection.[28] HIV+ persons who tested after this window period would be correctly diagnosed with 100% test sensitivity. Individual-level attributes for diagnosis status and time since last HIV test were recorded for all MSM.

7.2 Antiretroviral Therapy (ART) Initiation

Consistent with previous models,[1,2] we simulated the initiation of ART and subsequent clinical outcomes of full or partial HIV viral suppression based on men being in one of three clinical states: never tested, on treatment and partially virally suppressed, and on treatment with full viral suppression. There was insufficient empirical data to represent the patterns and rates at which individual men switch among these three states over the course of their infection, since the clinical ART landscape is constantly evolving. Therefore, we modeled men as being on one of the three fixed treatment trajectories as an individual-level attribute such that our model matched the population-level data on the prevalence of durable HIV viral suppression and treatment-naïve mortality.[29,30]

Following HIV diagnosis (for the 93.5% of men who ever HIV test before age 40), MSM initiated treatment at a rate of 0.924 per week (Black MSM) or 0.1271 (White MSM). This translates into an average interval between testing and treatment initiation of 10.8 weeks (Black MSM) and 7.9 weeks

(White MSM), consistent with empirical data.[27] In the absence of quantitative data, we assumed no gap between treatment entry and ART initiation.

7.3 ART Adherence and Viral Suppression

MSM who initiated ART could cycle on and off treatment, where cycling off treatment resulted in an increase in the VL back up to the assumed set point of 4.5 $\log_{10}$. The slope of changes to VL were calculated such that it took a total of 3 months to transition between the set point and the on-treatment viral loads.[31] Men on treatment could achieve partial or full suppression. Men with partial suppression were assumed to have a $\log_{10}$ viral load of 3.5, compared to 1.5 among those who were fully suppressed.[31] The latter corresponds to an absolute viral load below the standard levels of detection (VL = 50).[32]

The patterns of ART adherence leading to partial and full HIV viral suppression were estimated based on an analysis of HIV care patterns among MSM in the United States,[29] which was required in order to obtain parameters that were specific to young MSM by race. Parameterizing our model used three types of inputs: (1) the proportion of those diagnosed who are on ART; (2) the proportion of those diagnosed who are virally suppressed; (3) the level of durable suppression (proportion on ART who have been suppressed for a year). Our source included recent estimates for (1) by race and by age, but not the interaction of the two. We used a weighted average of their 18–29 and 30–39-year-old data, and assumed that the overall prevalence ratio by race that they observed for each outcome held within this age group as well. This suggested that 30.2% of young Black MSM who were diagnosed were in care, and 74.0% of those were on ART, for a combined value of 22.3% of young Black MSM who were diagnosed being on ART at any time point. Analogous figures for young White MSM were 46.6%, 84.0% and 39.2%. For (3), we used the same method of deriving estimates specific to young Black MSM (47% of those on ART are durably suppressed) and young White MSM (60% for the corresponding figure). For (2), we used figures by race from the same paper; however, similar figures by age were not included. Instead, we adjusted by using the relative rates of retention in care and suppression for young adults (25-44) compared to all respondents from an additional analysis of the care continuum for members of all risk groups (not just MSM-specific) in the US.[33] This yielded estimates for the percent of young MSM on ART who are virally suppressed of 62.4% for Blacks and 67.7% for Whites.

None of these three sets of values entered the model directly as inputs. Parameter (3) was converted into a per-time step probability of falling out of suppression, by using the inverse geometric function to calculate the probability consistent with observed levels of durable suppression after 1 year. Our other two input parameters were the proportion of those initiating ART who achieved full suppression, and the per-time step probability of re-achieving suppression after one had previously fallen out. We simulated our full model iteratively until we identified the unique values of these parameters by race that yielded the values estimated for parameters (1) and (2) above. The resulting set of model inputs are shown in Web Table 16.

Web Table 16. HIV Care Continuum Parameters.

Parameter	Black MSM	White MSM
Proportion of those initiating ART who achieved full suppression	0.614	0.651
Per-time step probability of falling out of suppression	0.0102	0.0071
Per-time step probability of re-achieving suppression	0.00066	0.00291

7.4 Disease Progression and Mortality after ART Initiation

Mortality after ART initiation was modeled based on the cumulative time on and off ART for persons who were fully or partially suppressed. The maximum time between infection and the start of AIDS was 9.7 years.[24] If a person in either the full or partial suppression categories who spent this much time off ART during the course of infection progressed to AIDS. For the partially suppressed, we assumed a maximum time on ART of 15 years, similar to previous models, to account for treatment failure.[1] For this group, the time to AIDS was an additive function of two ratios: (time on treatment / maximum time on treatment) + (time off treatment / maximum time off treatment). AIDS was simulated to begin when the sum of this score exceeded 1. Persons who had ever initiated ART progressed through AIDS at a similar rate as those who were ART-naïve.

8 WEB APPENDIX 8 (INTERHOST EPIDEMIOLOGY)

Interhost epidemiological processes represent the HIV-1 disease transmission within the model. Disease transmission occurs between sexual partners who are active on a given time step. This Web Appendix will describe how the overall rate is calculated as a function of the intrahost epidemiological profile of each member of a partnership, and behavioral features within the dyad.

8.1 Disease-Discordant Dyads

At each time step in the simulation, a list of active dyads was selected based on the current composition of the network. This was called an “edgelist.” Given the three types of partnerships detailed above, the full edgelist was a concatenation of the type-specific sublists. The complete edgelist reflects the work of the STERGM- and ERGM-based network simulations, wherein partnerships formed on the basis of nodal attributes and degree distributions (see Web Appendix 2). Dyads active were considered active at a specific time step if the terminus of that simulated edge was less than or equal to the current time step (right-censored). From the full edgelist, a disease-discordant subset was created by removing those dyads in which both members were HIV- or both were HIV+. This left dyads that were discordant with respect to HIV status, which was the set of potential partnerships over which infection may be transmitted at that time step.

8.2 Per-Act HIV Transmission Probability

Within disease-discordant dyads, HIV transmission was modeled based on a sexual act-by-act basis, in which multiple acts of varying infectiousness could occur within one partnership within a weekly time step. Determination of the number of acts within each discordant dyad for the time step, as well as condom use and role for each of those acts, was described in Web Appendix 3. Transmission by act was then modeled as a stochastic process for each discordant sex act following a binomial distribution with a probability parameter that is a multiplicative function of the following predictors of the HIV- and HIV+ partners within the dyad. The associated parameters are summarized in Web Table 17.

Web Table 17. HIV Transmission Parameters.

Predictor	Partner	Parameters	References
Sexual role (insertive or receptive)	HIV-	*Receptive:* 0.008938 base probability when HIV+ partner has 4.5 $\log_{10}$ viral load	Vittinghoff[34]
		Insertive: 0.003379 base probability when HIV+ partner has 4.5 $\log_{10}$ viral load	Vittinghoff[34]
HIV viral load (VL)	HIV+	Multiplier of $2.45^{(VL - 4.5)}$	Wilson[35]
Acute stage	HIV+	Multiplier of 6	Leynaert,[23] Bellan[36]
CCR5 status	HIV-	Δ32 homozygote: multiplier of 0	Marmor[19]
		heterozygote: multiplier of 0.3	Marmor[19]
Condom use	Both	Multiplier of 0.05	Varghese,[37] Weller[38], Smith[39]
Circumcision status	HIV-, insertive	Multiplier of 0.40	Gray[18]

For each act, the overall transmission probability was determined first with a base probability that was a function of whether the HIV- partner was in the receptive or insertive role, with the former at a 2.6-fold infection risk compared to the latter. The HIV+ partner's viral load modifies this base probability in a non-linear formulation, upwards if the VL was above the VL set point during chronic stage infection in the absence of ART, and downwards if it was below the set point. Following others, we modeled an excess transmission risk in the acute stage of infection above that predicted by the heightened VL during that period. Three covariates of the HIV- partner could reduce the risk of infection: the Δ32 allele on the CCRR5 gene, condom use within the act, circumcision status (only if the HIV- partner was insertive in that act).

For condom use, we updated our previous approach to explicitly represent condom failure that would result in a transmission event. Our previous models used estimates of HIV incidence comparing consistent condom users to occasional or non-condom users, resulting in a condom “efficacy” of 75-80%. However, this efficacy gap of 20-25% is the function of both the biological/physiological gaps in protection given perfect and consistent condom use during anal intercourse as well as the human error resulting in impact use. Such error could represent condom breakage, misapplication, incomplete use during sexual activity, and other related causes.[39] For this model, we assumed a 95% efficacy for the former, and a 15–40% absolute reduction in that efficacy as a function of condom failure to arrive at the previous range of 75–80% total effectiveness. We allowed that condom failure reduction to vary by race, given evidence that black condom failure rates may be 1–4 times higher than white rates.[17] Finally, we included these two parameters in our model calibration given the uncertainty in the rates in this modeled population. We defined the prior distribution based on a uniform ranging from 15% to 40%. The posterior distribution value with the greatest likelihood was 21% for white MSM and 39% for black MSM.

The final transmission rate per partnership per weekly time step was a function of the per-act probability of transmission in each act and the number of acts per time step. The per-act transmission probability could be heterogeneous within a partnership due to various types of acts in each interval: for example, a HIV- man who is versatile in role may have both insertive and receptive intercourse within a single partnership; some acts within a partnership may be protected by condom use while others are condomless. Transmission was simulated for each act within each serodiscordant dyad, based on draws from a binomial distribution with the probability parameter equal to the per-act transmission probabilities detailed above.

9 WEB APPENDIX 9 (STI TRANSMISSION)

9.1 Overview of Model Structure

Directional transmission of NG and CT was modeled between sexual partners who were sexually active during a given time step. At each time step, a list of active dyads (the “edgelist”) was selected based on the current composition of the network. This edgelist concatenated the three types of partnerships included in the network simulations: main, casual, and one-off. Dyads were considered active at a particular time step if the terminus of that simulated edge was greater than or equal to the current time step.

We created a disease-discordant subset of the edgelist for both NG and CT at each time step by removing dyads in which both members had the disease of interest or neither had the disease of interest. This left dyads discordant with respect to both NG and CT infection status, which was the set of potential partnerships in which the infections could be transmitted at that time step.

Site-specific transmission of NG and CT was modeled on a sexual act-by-act basis, in which multiple acts of varying infectiousness could occur within a partnership within a weekly time step. The number of anal sex acts per week for each ongoing relationship was determined from a random draw from a Poisson distribution, with the lambda (event rate) parameter of the distribution specific to the partnership type.[4] For one-time contacts, the number was set deterministically to 1 for the time step in which it occurred.

For site-specific disease transmission to occur, the sexual position of partners within an MSM anal intercourse dyad was considered. For example, receptive AI with a partner infected with a urethral STI was necessary for an individual to become rectally infected. Dual-site and dual-disease infection was possible, such that a man could have had, for example, rectal NG and rectal CT infection, rectal NG and urethral CT, or rectal NG and urethral NG concurrently. We modeled disease transmission by act as a stochastic process for each discordant sex act, which followed a binomial distribution with a probability parameter that was a multiplicative function of the base transmission probability and condom use.

9.2 STI Co-Factor Effect on HIV Acquisition Probability

We modeled an increased HIV acquisition risk from a current STI status. Chesson et al.[40] described this effect for several STIs. Starting with a baseline HIV transmission probability per sex-act of 0.001 (95% CI: 0.0005–0.0015), they estimated a 10-fold (95% CI: 5–15) increase in per-act HIV transmission probability, to 0.014 (95% CI: 0.01–0.05), in the presence of NG infection. For CT infection, they estimated a 5-fold increase (95% CI: 3–15) in per-act HIV transmission probability to 0.0078 (95% CI: 0.003–0.01). Vaughan et al.[41] found that the hazard ratio for existing rectal NG or CT infection on HIV seroconversion was 2.7 (95% CI:1.2–6.4), and Pathela et al.[42] estimated a similar risk ratio for the effect of rectal NG or CT infection on HIV acquisition, which was slightly elevated over estimates not taking site-specific infection into account.[43] Using these estimates, we established a Bayesian prior distribution of 2.00–3.00 for the relative increase in per-act HIV acquisition risk for rectal STI infections, and 1.00–2.00 for urethral STI infections. These estimates incorporate site-specific infection and assume an increased risk associated with rectal infection. After model fitting, the estimated posterior multiplier values for risk of HIV acquisition were 2.7807 for rectal NG and CT, and 1.7324 for urethral NG and CT.

9.3 Chlamydia Transmission Probability

Estimated values of the per-sex-act CT transmission risk in previous STI-only and HIV/STI models have depended on whether the infection was symptomatic, the type of sex act, as well as the role and position of the infected partner. The baseline per-act CT transmission risk for heterosexual encounters has been estimated in multiple models, with the middle 50% of per-act probability estimates describing MTF transmission clustered between 0.09–0.20[44,45,54–58,46–53] with a wider range of 0.025 to 0.6.[59–66] Estimated per-act transmission risk was generally higher in non-main partnerships when models incorporated or characterized different risk estimates by partnership types.[49] Per-partnership transmission risk estimates ranged widely from 0.09 to 0.7,[56,67–70] and per-day infection probabilities ranged from 0.001571 to 0.154, with higher estimates for casual partnerships relative to main partnerships.[71–74] In models where the direction of transmission was reported, the estimated per-act FTM CT transmission probability varied, commonly estimated as 0.5–0.8 times the MTF CT transmission probability,[45,46,53,58,59,61,72] although some models did estimate that the FTM transmission probability was greater.[44,73]

For our model, we focus on the baseline male-to-male CT transmission risk through anal intercourse in STI and HIV/STI models. Fewer models and estimates of this probability exist for MSM than do for heterosexual populations. Estimates of the per-act transmission probability have included 0.1–0.24,[75] 0.4 for receptive AI,[76] 0.32 for insertive AI,[76] and 0.35 per-partner.[77] With greater uncertainty around these parameters, we established a prior distribution of 0.30–0.60 for the per-act rectal CT transmission likelihood, and a distribution of 0.20–0.50 for urethral CT transmission to incorporate site-specific infection. The estimated posterior means were 0.3216 for per sex-act rectal CT transmission probability and 0.2130 for per sex-act urethral CT transmission probability. We also include a multiplier of 0.30 for the effect of condom usage on CT transmission probability to reflect the decreased probability of transmission in protected sex acts, consistent with the literature.[78,79]

9.4 Gonorrhea Transmission Probability

Estimates of the NG transmission risk per sex-act have been diverse in HIV/STI models and STI-only models, depending on the type of sex act as well as the role and position of the infected partner. This baseline per-act risk has been estimated in a number of models, with the middle 50% of estimates of the per-act risk from MTF transmission models located between 0.20 and 0.60,[44,45,65,68,80–87,46,88–90,47,48,53,58–60,62] with an outer range of 0.1 to 1.[87,91,92] Per-day infection probability estimates ranged from 0.011 to 0.6,[72,82,93] with higher probabilities estimates for non-main partnerships. Per-partnership estimates differed widely, ranging from 0.10 to 0.80.[61,94,95] When FTM transmission was distinguished, the per-act[44,45,88,89,94,46,58,61,72,80,81,83,87] and per-partnership[59,95] estimated risk tended to be decreased or halved, compared to the MTF risk, with some exceptions in which the FTM risk was estimated to be greater.[53,83,90]

Compared to CT infection, the baseline transmission probability per sex-act for male-male anal intercourse in STI models has been better characterized for NG infection. Estimates of these risks have ranged widely from 0.02 and 0.8,[76,77,96–99] with greater risks assumed for receptive anal intercourse compared to insertive anal intercourse. To account for the uncertainty in this parameter estimate, we established a prior distribution of 0.30–0.60 for the per-act rectal NG transmission likelihood, and a distribution of 0.20–0.50 for urethral NG transmission to incorporate site-specific infection. Bayesian calibration generated posterior values of 0.3577 for per sex-act rectal NG transmission probability and 0.2481 for per sex-act urethral NG transmission probability. Similar to CT, we also included a multiplier of 0.30 for the effect of condom usage on NG transmission probability to reflect the decreased probability of transmission in protected sex acts.

10 WEB APPENDIX 10 (STI TESTING AND TREATMENT)

10.1 Overview of Model Structure

Testing and treatment for NG and CT before the introduction of HIV PrEP and its associated interval-based screening was a function of whether the infection was symptomatic or asymptomatic. Treatment status was assigned stochastically among those with either symptomatic or asymptomatic NG or CT infection acquired prior to the current time step. Following empirical data, we simulated that 90% of men with NG and 85% of men with CT who have symptomatic infection successfully sought and completed treatment.[100] The average time on treatment was 2 weeks, with a stochastic recovery process described below.

The site of infection influenced the symptomatic status of a given infection, with rectal infections more likely to be asymptomatic and urethral infections more likely to be symptomatic.[101] The symptomatic status of an infection was assigned stochastically from a binomial distribution at the time of infection according to site-specific and infection-specific probability parameters for symptomatic status. We assumed a lower level screening and treatment for asymptomatic infection outside of PrEP (5% to 20%) given the much greater likelihood that those asymptomatic infections would prompt testing events independent of routine, planned STI screening.

After the introduction of PrEP in the intervention model scenarios, we simulated STI screening among MSM by the recommended CDC clinical practice guidelines for PrEP.[102] Men were screened for STIs every 6 months after PrEP initiation, and sensitivity analyses varied this screening interval from 1–12 months. We varied the fraction of STI-screened PrEP users who received effective treatment from 0% to 100% in another sensitivity analysis. While we did not explicitly model treatment failure for those treated for STIs, this parameter may serve as a potential representation. While on PrEP, men were assumed to continue the symptoms-based treatment for their STIs at the same frequency as before PrEP.

10.2 Chlamydia Symptoms

The asymptomatic nature of some CT infections can have an impact on the risk of transmission, as well as the dynamics of spread in a population. These estimates have varied widely for CT. For men, the middle 50% of estimates of the proportion of infections that are symptomatic from STI or HIV/STI models has ranged from 0.3–0.5,[44,50,74,75,80,53,55,58,59,62,65,69,70] with an outer range of 0–0.75[48,54,57,103,104] and a sizable cluster of estimates at 0.75.[63,64,72,73,77] Beck et al.[76] differentiated between the probability of symptoms of urethral and rectal CT infections in MSM, estimating a 4-fold increase in the likelihood of symptoms (0.58 versus 0.14) at the urethral site. The proportion symptomatic in males tends to be increased 1.5–3 fold over the same proportion in women,[44,50,73,74,80,53–55,58,59,69,70,72] with a few exceptions where women are estimated to be more symptomatic.[57,65,104] Given the uncertainty surrounding this estimate, we established a prior distribution for calibration of 0.01–0.15 for the probability that a rectal CT infection would be symptomatic, and a distribution of 0.60–0.95 for the probability that a urethral CT infection would be symptomatic to incorporate site-specific infection. The estimated posterior values were 0.1035 for the probability of symptomatic rectal CT, and a probability of 0.8850 for symptomatic urethral CT.

10.3 Gonorrhea Symptoms

NG infections can also be present with or without symptoms, and estimates of the proportion of infections that are symptomatic have been varied. The middle 50% of estimates of this proportion from STI or HIV/STI models for men has ranged from 0.35–0.88,[44,58,62,65,80,82,88,92,97,98] with a lower quartile of 0.11 to 0.25[48,59,87,103] with a sizable group of estimates between 0.9 to 0.95.[53,72,77,95,105] Beck et al.[76] differentiated between the probability of symptoms of urethral and rectal NG infections in MSM, estimating a nearly 6-fold increase in the likelihood of symptoms (0.90 versus 0.16) at the urethral site. The proportion symptomatic in males tends to be increased 1.5–3 fold over the same proportion in women for NG.[44,53,105,58,59,72,80,87,88,92,95] With less certainty about these parameters, we established a prior distribution of 0.01–0.15 for the probability that a rectal NG infection would be symptomatic, and a distribution of 0.60–0.95 for the probability that a urethral NG infection. The resulting posterior values were 0.0770 for the probability of symptomatic rectal NG, and 0.8244 for the probability of symptomatic urethral NG. As with CT, these reflect an increased likelihood of symptomatic urethral infection, which could be due to easier detection at a urethral site.

11 WEB APPENDIX 11 (STI RECOVERY)

We modeled recovery from a NG or CT infection according to whether men were treated for their infection. Recovery from infection back to susceptibility can occur through natural clearance of each infection or through effective antibiotic treatment. Recovery from untreated NG or CT infection was simulated as a stochastic process among those whose infection, whether symptomatic or asymptomatic, had been present for a duration of time greater than the natural history of asymptomatic infection, a calibrated parameter. The probability of recovery per time-step for symptomatic and asymptomatic untreated infection was the reciprocal of the duration of infection. Recovery from treated NG or CT infection was a stochastic process based on draws from a binomial distribution among those who treated for their infection, occurring with a per-time-step probability equal to the reciprocal of the duration of the length of treatment. Upon recovery, individuals were immediately susceptible to reinfection.

11.1 Duration of Chlamydia Infection

Estimates of the duration of CT infection have varied broadly depending on whether the infection was symptomatic. STI and HIV/STI models have generally estimated the duration of symptomatic CT infection in men primarily as 30–35 days,[50,51,54–57,64,70,72,73] but some models have estimates closer to 13–14 days for treated men[62,69,76] or at a higher range between 112–365 days.[53,58,59,76] Models which have not specified whether the infection is symptomatic or asymptomatic have widely divergent estimates ranging from 60 days up to 370 days.[49,52,66,71,77,106,107] Some models specify the length of an infectious stage ranging from 3 weeks in treated infection up to 457 days,[47,80] while Welte et al. estimate the incubation time of CT as 12 days.[56]

For models specifying the duration of an asymptomatic CT infection, estimates tend to cluster between 200–240 days[50,53–56,62,72,73,75] and 433–497 days.[51,64,74,108] Some models estimated 180 days,[57,69] 365 days,[70] or 622 days,[44,58] reflecting a range of uncertainty. Beck et al.[76] have estimated 240 days for urethral infection and 497 days for rectal infection. Given this uncertainty, we established a prior distribution of 39–65 weeks for the duration of asymptomatic rectal or urethral CT infection. These resulted in posterior values of 44.25 weeks for the duration of asymptomatic CT infection.[62]

11.2 Duration of Gonorrhea Infection

Estimates of NG duration have also varied widely depending on whether the infection was symptomatic. STI and HIV/STI models have modeled the duration of symptomatic NG infection as bimodal, with some estimates as low as 12–13 days,[62,72,76,83,95], generally for treated or care-seeking persons, and others between 105–185 days, including for untreated symptomatic infection.[44,53,58,76] Models which have not specified whether the infection is symptomatic or asymptomatic have widely divergent estimates of duration, ranging from 10–60 days[77,85,86,89–91,109] to 330–365 days[87,106] with estimates also observed at 30-day intervals between 60 days and 200 days.[59,94,98,109] Estimates of the duration of the infectious stage of NG ranged from 14 days in treated individuals[6] to 180–185 days in untreated individuals[76,84,88] but varied widely between those extremes.[47,80,81,105]

For models specifying the duration of an asymptomatic NG infection, estimates were also bimodal, with clusters at 105–135 days[44,53,58,72] and 180–185 days.[62,95] Beck et al.[76] have estimated 240 days for urethral infection and 300 days for rectal infection. Given this uncertainty, we established a prior distribution of 26–52 weeks for the duration of both asymptomatic rectal and asymptomatic urethral NG infection. The estimated posterior means were 35.12 weeks for the duration of asymptomatic rectal and urethral NG infection.

12 WEB APPENDIX 12 (MODEL CALIBRATION AND ANALYSIS)

This Web Appendix describes the methods for executing the simulations and conducting the data analysis on the outcomes in further detail.

12.1 Calibration Methods

Starting with a population of 10,000 MSM, HIV infection was initially seeded in 13.2% of the white MSM population and 43.4% of the black MSM population, urethral NG and CT in 1.5% of the population, and rectal NG and CT in 1.5% of the population. A set of burn-in simulations was then used to allow the natural dynamics of HIV and STI transmission, demography, and other population features to evolve over time. The goal of the burn-in simulation was to arrive at a network of MSM that was independent of the initial conditions resulting from the seeding. This also established a population composition with behavioral and biological features calibrated to match external targets for HIV prevalence and STI incidence.[4]

Many HIV/STI models of disease transmission have been parameterized using populations both in the United States and internationally. These models have differed in type, including deterministic compartmental models, stochastic models, and agent-based transmission models. They have also differed by the populations explicitly modeled, whether MSM only, heterosexual men and women only, or a combination of both populations. Given the variation in parameter values from population to population, we use and evaluate information and estimates from models of male-to-female (MTF), female-to-male (FTM), and male-to-male disease transmission to establish our parameters and prior distributions. These include calibrated estimates from published mathematical models, findings from natural history studies that have been parameters in those models, and estimates where other information is not available.

We used Bayesian approaches to define model parameters with uncertain values, construct prior distributions for those parameters, and fit the model to HIV/STI prevalence and incidence data to estimate the posterior distributions of those parameter values.

We used approximate Bayesian computation with sequential Monte Carlo sampling (ABC-SMC) methods[36,110] to calibrate behavioral parameters in which there was measurement uncertainty in order to match the simulated HIV prevalence and STI incidence at the end of the burn-in simulations to the targeted HIV prevalence and STI incidence. The details of ABC depend on the specific algorithm used, but in this case, ABC-SMC proceeded as follows.

For each candidate parameter, θ, to be estimated, we:

1. Sampled a candidate θ^i from a prior distribution $\pi(\theta)$
2. Simulated the epidemic model with candidate value, θ^i.
3. Tested if a distance statistic, d (e.g., the difference between observed HIV prevalence and model simulated prevalence) was greater than a tolerance threshold, ϵ.
    a. If $d > \epsilon$ then discard
    b. If $d < \epsilon$ then add the candidate θ^i to the posterior distribution of θ.
4. Sample the next sequential candidate, θ^{i+1}, either independently from $\pi(\theta)$ (if 3a) or from θ^i plus a perturbation kernel with a weight based on the current posterior distribution (if 3b).

For the ABC algorithms to calibrate to the observed HIV prevalence and STI incidence, a total of 500 simulations were required for 50 years of calendar time each. The target statistics were matched during this burn-in model and also during the no-PrEP base model featured in the main manuscript.

12.2 Calibration Outcomes

Model calibration performed as expected for mean HIV prevalence by race compared to the target statistics, with average HIV prevalence among Black MSM of 43.1% (compared to the 43.4% target statistic) and 13.1% among White MSM (compared to the 13.2% target statistic). By race-specific model calibration, therefore, the calibration was successful.

As a method of externally validating the model, we also compared simulated HIV prevalence from the calibrated burn-in model to HIV prevalence by the interaction of race and age group. Although the model was not calibrated to this interaction, the external validity of the model is improved with this type of out-of-model fit. The summary statistics of the simulated data compared to the empirical estimates from the target population from Sullivan et al. are shown in Web Table 18 below.[111]

Web Table 18. HIV Care Continuum Parameters.

	Black MSM Prevalence		**White MSM Prevalence**	
	Empirical (95% CI)	*Simulated*	*Empirical (95% CI)*	*Simulated*
Age Group				
18–19	7.4% (2.1%, 23.4%)	2.9%	6.3% (1.1%, 28.3%)	0.9%
20–24	33.9% (27.0%, 41.7%)	30.4%	5.5% (2.4%, 12.2%)	5.6%
25–29	45.2% (37.2%, 53.6%)	47.4%	14.3% (8.9%, 22.2%)	12.8%
30–39	60.0% (51.2%, 68.2%)	66.1%	15.7% (10.3%, 23.2%)	19.9%

As shown in Web Table 18, the simulated prevalence was within the 95% confidence intervals for 7 out of the eight target statistics. This provides strong evidence of model validity for reproducing the HIV transmission dynamics across race and age in this target population. The one target statistic in which the simulated prevalence fell outside the 95% confidence intervals of the empirical data was White MSM aged 18–19, where the simulated prevalence was less than 1% and the empirical prevalence was 6.3%, with a lower bound of the confidence interval of 1.1%. This suggests that the transmission dynamics particularly in this age and race combination may not be well represented by the model, with one example being the initialization of incoming 18-year-olds as uninfected. Future model interactions will explore this assumption in greater detail. However, because the model was able to produce HIV prevalence by race and age for the remaining 7 target statistics, the overall model has been sufficiently validated for these current purposes of the study.

12.3 Intervention Simulations

The intervention scenarios are described fully within the main paper. For each scenario, we simulated the model scenario 250 times for 10 calendar years each. Data from each simulation were merged, and a complete 250-simulation data file was retained for each scenario. All burn-in and intervention simulations were conducted on the Hyak high-performance computing platform at the University of Washington.

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