Incidence of Gonorrhea and Chlamydia Following HIV Preexposure Prophylaxis among Men Who Have Sex with Men: A Modeling Study

Samuel M. Jenness, PhD[1]
Kevin M. Weiss, MPH[1]
Steven M. Goodreau, PhD[2]
Thomas Gift, PhD[3]
Harrell Chesson, PhD[3]
Karen W. Hoover, MD[4]
Dawn K. Smith, MD[4]
Albert Y. Liu, MD[5]
Patrick S. Sullivan, PhD[1]
Eli S. Rosenberg, PhD[1]

[1] Department of Epidemiology, Emory University, Atlanta, GA
[2] Department of Anthropology, University of Washington, Seattle, WA
[3] Division of STD Prevention, Centers for Disease Control and Prevention, Atlanta, GA
[4] Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA
[5] San Francisco Department of Public Health, San Francisco, CA

Supplementary Technical Appendix

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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 Section 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]

The model algorithms and methods presented here generalize these prior MSM HIV transmission models to investigate emerging biomedical HIV prevention technologies such as oral pre-exposure prophylaxis (PrEP) as part of a collaborative modeling effort (the Coalition for Applied Modeling for Prevention) between Emory University, the University of Washington, the Centers for Disease Control and Prevention, and local health public departments [http://emorycamp.org/].

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.[5]

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-sti.*
- [http://github.com/statnet/stiPrEP] contains the scripts to execute the mathematical models and to run the statistical analyses provided in the manuscript.

2 DYNAMIC NETWORKS OF SEXUAL PARTNERSHIPS

We modeled networks of three interacting types of sexual relations: main partnerships, casual (but persistent) partnerships, and one-time anal intercourse (AI) contacts. We first describe the methods conceptually, including the parameters used to guide the model and their derivation (Section 2.1), and then present the formal statistical modeling methods (Section 2.2). Consistent with our parameter derivations, all relationships are defined as those in which AI is expected to occur at least once.

2.1 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. These 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 and disease status.

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

- The proportion of men 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.

- Variation across men in the numbers of one-time contacts.
- Age mixing within each of the different relational types.
- Prohibitions against partnering for two men who are both exclusively insertive or exclusively receptive.

2.1.1 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*):

	0 Casual	*1 Casual*	*2 Casual*
0 Main	47.1%	16.7%	7.4%
1 Main	22.0%	4.7%	2.1%

2.1.2 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:

	0 Casual	*1 Casual*	*2 Casual*
0 Main	0.065	0.087	0.086
1 Main	0.056	0.055	0.055

2.1.3 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:

Quintile	Value
Lowest quintile	0.000
Second quintile	0.007
Third quintile	0.038
Fourth quintile	0.071
Highest quintile	0.221

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 Section 2.1.2 weighted by the proportions in Section 2.1.1. These reflect the overall expected value across all men for one-time AI acts per time step.

2.1.4 Age Mixing

Respondents also reported on the estimated age of each partner. We model age mixing within a given relational type 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.[1,3,6] For instance, a relationship between a 23-year-old and a 28-year-old would represent $\left|\sqrt{23} - \sqrt{28}\right|$ = 0.496.

	Value
Main partnerships	0.464
Casual partnerships	0.586
One-time contacts	0.544

2.1.5 Mixing by Sexual Role

We assign men a fixed sexual role preference (exclusively insertive, exclusively receptive, or 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 in those partnerships 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. In the absence of longitudinal behavioral data, sexual role preference was assumed to be a fixed trait, rather than a time-varying one, although, for versatile men, the sexual role within each partnership at each simulated time step was stochastic. Unlike interventions such as medical male circumcision,[2] biological PrEP efficacy does not differ by sexual role, nor is PrEP specifically indicated by sexual role, so we would expect that this assumption of a fixed role would not substantially affect the intervention-related results in this model.

	Probability
Exclusively insertive	24.2%
Versatile	43.7%
Exclusively receptive	32.1%

2.1.6 Partnership Durations

We model relational dissolution as a memoryless process with a single parameter per relational type. This implies an exponential distribution for relational durations within each category. 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 were:

	Duration
Main partnerships	407 days
Casual partnerships	166 days

2.2 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,[7] since they persist for multiple time steps. One-time contacts, on the other hand, were modeled using cross-sectional ERGMs.[8] 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 formation 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 Markov chain Monte Carlo (MCMC) methods 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 Section 2.1. 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 parameterized 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 men with 2+ main partners
- $g_{m3}^{+}(y)$ = number of main partnerships for men with 1 casual partner
- $g_{m4}^{+}(y)$ = number of main partnerships for men with 2 casual partners
- $g_{m5}^{+}(y)$ = sum of the absolute difference in the square root of partners' ages across main partnerships
- $g_{m6}^{+}(y)$ = number of main partnerships between men who were both exclusively insertive
- $g_{m7}^{+}(y)$ = number of main partnerships between men who were both exclusively receptive

There are structural zeroes as coefficient constraints for the terms $g_{m2}^{+}(y)$, $g_{m6}^{+}(y)$, $g_{m7}^{+}(y)$. This means that the logit values for their coefficients are set to negative infinity to ensure that no partnerships of these types occur.

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

- $g_{m1}^{-}(y)$ = number of 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 casual partnerships for men with 1 main partner
- $g_{c3}^{+}(y)$ = number of men with 2 casual partners
- $g_{c4}^{+}(y)$ = number of men with 3+ casual partners
- $g_{c5}^{+}(y)$ = sum of the absolute difference in the square root of partners' ages across casual partnerships
- $g_{m6}^{+}(y)$ = number of casual partnerships between men who were both exclusively insertive

- $g^{+}_{m7}(y)$ = number of casual partnerships between men who were both exclusively receptive

There are structural zeroes as coefficient constraints for the terms $g^{+}_{m4}(y)$, $g^{+}_{m6}(y)$, $g^{+}_{m7}(y)$. This means that the logit values for their coefficients are set to negative infinity to ensure that no partnerships of these types occur.

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

- $g^{-}_{c1}(y)$ = number of casual partnerships

One-time contact existence model terms: $g_{o}(y)$ vector:

- $g_{o1}(y)$ = number of one-time contacts
- $g_{o2}(y)$ = total # of one-time contacts for men with 0 main and 1 casual partnership
- $g_{o3}(y)$ = total # of one-time contacts for men with 0 main and 2 casual partnerships
- $g_{o4}(y)$ = total # of one-time contacts for men with 1 main and 0 casual partnerships
- $g_{o5}(y)$ = total # of one-time contacts for men with 1 main and 1 casual partnership
- $g_{o6}(y)$ = total # of one-time contacts for men with 1 main and 2 casual partnerships
- $g_{o7}(y)$ = total # of one-time contacts for men in risk quintile 1
- $g_{o8}(y)$ = total # of one-time contacts for men in risk quintile 2
- $g_{o9}(y)$ = total # of one-time contacts for men in risk quintile 4
- $g_{o10}(y)$ = total # of one-time contacts for men in risk quintile 5
- $g_{o11}(y)$= sum of the absolute difference in the square root of partners' ages across one-time contacts
- $g^{+}_{m12}(y)$ = number of one-time contacts between men who were both exclusively insertive
- $g^{+}_{m13}(y)$ = number of one-time contacts between men who were both exclusively receptive

There are structural zeroes as coefficient constraints for the terms $g^{+}_{m12}(y)$, $g^{+}_{m13}(y)$. This means that the logit values for their coefficients are set to negative infinity to ensure that no partnerships of these types occur.

Our method of converting the statistics laid out in Section 2.1 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 frequencies listed in Section 2.1.5, as well as one-time risk quintiles (20% of the men 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 degree 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 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.[9] During the subsequent model simulation, we use the method of Krivitsky et al.[10] 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.

3 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.

3.1 Disclosure

We model the process by which someone who knows he is HIV-positive discloses this fact to partners of all types. 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; our behavioral estimates in the absence of HIV+ disclosure marginalize over those cases in which men disclose as concordant negative or 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.

Probability of Disclosure of HIV+ Status	**Probability**
to new main partner at outset of relationship	78.7%
to new casual partner at outset of relationship	67.8%
to one-time contact	56.8%
to ongoing partner if diagnosis occurs during relationship	100%

3.2 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. For one-time contacts, the number is set deterministically to 1 for the time step in which it occurs.

AI Acts/Week/Partnership	**Frequency**
Main partnerships	1.54
Casual partnerships	0.96

These rates were calculated based on the two Atlanta studies, derived from questions asking about the number of coital acts per partnership during the recall periods.[10,11] These were then rescaled from the length of the recall period into the weekly rates listed in the table above.

3.3 Condom Use

We conducted logistic regressions to identify the significant predictors of condom use within HIV-discordant relationships (whether diagnosed or not) in our data. Respondents were asked

if they had had unprotected anal sex with each partner during the recall periods.[11,12] Predictors included 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.

Base model coefficients for the nine race/partnership types were defined as logit(P(condom use|anal intercourse):

	Coefficient
Main partnership	-1.325
Casual partnership	-1.046
One-time contact	-1.008

Note that for these, 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 are:

Condition	**Coefficient**
HIV+ diagnosis	0.670
HIV+ status disclosure	0.850

Together, these values, in combination with the frequencies with which AI occurs in all of the different types of situations, imply an overall rate of condom use of approximately 50% across all acts. The rates of condom use were assumed to be stable over the course of a given partnership, but condom usage was stochastic at each time step within that partnership. Differential condom usage rates by partnership type may capture effects of lower condom use that may occur in longer-term partnerships, but subsequent models will extend this model framework to incorporate network-related data to capture temporal trends in condom usage within each type of partnership.

3.4 Sexual Role

Men are assigned an individual sexual role preference (exclusively insertive, exclusively receptive, or versatile) as described in Section 2.1.5. 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 49%, and is derived from the partner-specific role data described in Section 2.1.5. 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.

4 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).

4.1 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.

4.2 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. As noted, we did not explicitly model race within this study, and set all race-specific parameters to averages across stratified estimates. Subsequent models will extend this model framework to explore racial disparities related

to PrEP uptake among 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,[11] 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).[2,13]
- The **CCR5-Δ32 genetic allele** was modeled by assigning a mutation for zero, one, or two chromosomes. Compared to men without a CCR5 mutation, heterozygous men (those with one mutation) were 70% less likely to become infected and homozygous men (those with two mutations) were fully immune from infection.[14,15] The population distribution of CCR5 was differential by race, with 0% of black men and 3.4% of white men expressing as homozygous, and 2.1% of black men and 17.6% of white men expressing as heterozygous.[14] But because race was not explicitly represented in these models, we averaged each set of proportions: 1.7% homozygous and 9.9% heterozygous overall.

4.3 Exits from the Network

All persons exited the network by age 40, either from mortality or 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.[16] The following table shows the probability of mortality per year by age and race.

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 Section 5.

4.4 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.

5 HIV 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. 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. The HIV viral load has a crucial impact on the rates of HIV transmission within serodiscordant couples in the model, and this interaction is detailed in Section 7. The parameters governing these processes are provided in the table below.

Parameter	Value	Reference
Time to peak viremia in acute stage	45 days	Little[37]
Level of peak viremia	6.886 $\log_{10}$	Little[37]
Time from peak viremia to viral set point	45 days	Little,[37] Leynaert[38]
Level of viral set point	4.5 $\log_{10}$	Little[37]
Duration of chronic stage infection (no ART)	3550 days	Buchbinder[39],Katz[40]
Duration of AIDS stage	728 days	Buchbinder[39]
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 Section 6. These transitions are deterministic for all ART-naïve persons.

6 HIV 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.[21]

6.1 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,[11] 6.5% of MSM did not receive HIV testing before age 40. This was calculated based on a survey question about never testing 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.[11,22] This was calculated based on time since last test in the survey, with the assumption that testing was a memoryless process. In this paper, we averaged over the two intervals since we did not explicitly model racial differences in the care

continuum. 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.[23] 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.

6.2 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.[24,25]

Following HIV diagnosis (for the 93.5% of men who ever HIV test before age 40), MSM initiated treatment at a rate of 0.1095 per week. This translates into an average interval between testing and treatment initiation of 9.13 weeks, consistent with empirical data.[22] In the absence of quantitative data, we assumed no gap between treatment entry and ART initiation.

6.3 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.[26] Men on treatment could achieve partial or full suppression. Men who 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.[26] The latter corresponds to an absolute viral load below the standard levels of detection (VL = 50).[27]

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,[24] 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% of young Black MSM who were diagnosed were in care, and 74% of those were on ART, for a combined value of 22% of young Black MSM who were diagnosed being on ART at any time point. Analogous figures for young White MSM were 47%, 84% and 39%. 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.[28] This yielded estimates for the percent of young MSM on ART who are virally suppressed of 62% for Blacks and 68% 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 were:

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

This study averaged over the race-specific parameter estimates because race was not explicitly modeled in this study.

6.4 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.[19] 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 occur 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.

7 HIV 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 section will describe how the overall rate as a function of the intrahost epidemiological profile of each member of a partnership, and behavioral features within the dyad.

7.1 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 Section 2). Dyads were considered active at a specific time step if the terminus of that simulated edge was greater 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 are discordant with respect to HIV status, which was the set of potential partnerships over which a HIV infection may be transmitted at that time step.

7.2 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 Section 2 and 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.

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[39]
		Insertive: 0.003379 base probability when HIV+ partner has 4.5 $\log_{10}$ viral load	Vittinghoff[39]
HIV viral load (VL)	HIV+	Multiplier of 2.45[38, 43]	Wilson[38]
Acute stage	HIV+	Multiplier of 6	Leynaert[44], Bellan[21]
CCR5 status	HIV-	Δ32 homozygote: multiplier of 0	Marmor[41]
		heterozygote: multiplier of 0.3	Marmor[41]
Condom use	Both	Multiplier of 0.25	Varghese[45], Weller[46]
Circumcision status	HIV-, insertive	Multiplier of 0.40	Gray[43]
PrEP status	HIV-	Detailed below	–

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. Four predictors 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), and PrEP status (which we further detail in the following section).

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.

8 STI TRANSMISSION

8.1 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.

8.2 STI Co-Factor Effect on HIV Acquisition Probability

We modeled an increased HIV acquisition risk from a current STI status. Chesson et al.[34] 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.[35] 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.[36] 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.[37] 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.

8.3 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[38–52] with a

wider range of 0.025 to 0.6.[53–60] Estimated per-act transmission risk was generally higher in non-main partnerships when models incorporated or characterized different risk estimates by partnership types.[43] Per-partnership transmission risk estimates ranged widely from 0.09 to 0.7,[50,61–64] and per-day infection probabilities ranged from 0.001571 to 0.154, with higher estimates for casual partnerships relative to main partnerships.[65–68] 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,[39,40,47,52,53,55,66] although some models did estimate that the FTM transmission probability was greater.[38,67]

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,[69] 0.4 for receptive AI,[70] 0.32 for insertive AI,[70] and 0.35 per-partner.[71] 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.[72,73]

8.4 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,[38–42,47,52–54,56,59,62,74–84] with an outer range of 0.1 to 1.[81,85,86] Per-day infection probability estimates ranged from 0.011 to 0.6,[66,76,87] with higher probabilities estimates for non-main partnerships. Per-partnership estimates differed widely, ranging from 0.10 to 0.80.[55,88,89] When FTM transmission was distinguished, the per-act[38–40,52,55,66,74,75,77,81–83,88] and per-partnership[53,89] 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.[47,77,84]

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,[70,71,90–93] 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.

9 STI TESTING AND TREATMENT

9.1 Overview of Model Structure

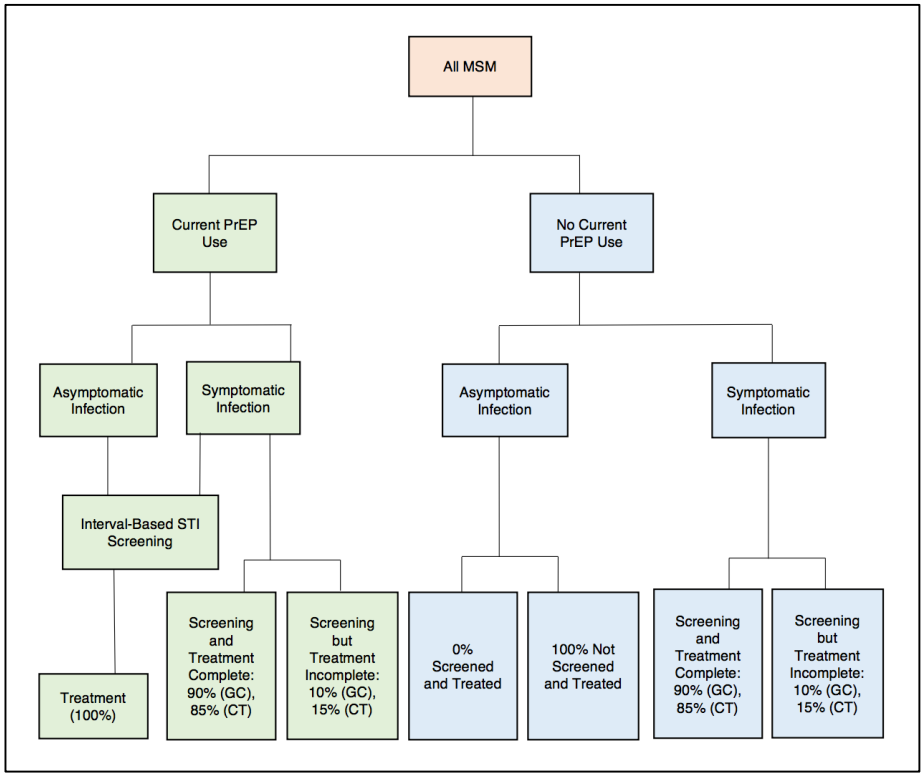
Testing and treatment for NG and CT before the introduction of HIV PrEP and its associated interval-based screening was a function of whether the infection was symptomatic or asymptomatic. Treatment status was assigned stochastically among those with either symptomatic or asymptomatic NG or CT infection 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.[94] The average time on treatment was 2 weeks, with a stochastic recovery process described below.

A flow diagram showing the trajectories of STI testing and treatment off PrEP and on PrEP is shown in Figure S1. 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.[95] 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. In lieu of any consistent data on interval screening rates specific to asymptomatic infection, we assumed no ongoing screening for this infection type outside of PrEP, although we considered some random screening in sensitivity analyses.

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.[96] 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.

Figure S1. Schematic Flow Diagram of STI Testing and Treatment



9.2 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,[38,44,47,49,52,53,56,59,63,64,68,69,74] with an outer range of 0–0.75[42,48,51,97,98] and a sizable cluster of estimates at 0.75.[57,58,66,67,71] Beck et al.[70] 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,[38,44,47–49,52,53,63,64,66–68,74] with a few exceptions where women are estimated to be more symptomatic.[51,59,98] 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.

9.3 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,[38,52,56,59,74,76,82,86,91,92] with a lower quartile of 0.11 to 0.25[42,53,81,97] with a sizable group of estimates between 0.9 to 0.95.[47,66,71,89,99] Beck et al.[70] 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.[38,47,52,53,66,74,81,82,86,89,99] 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.

10 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.

10.1 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,[44,45,48–51,58,64,66,67] but some models have estimates closer to 13–14 days for treated men[56,63,70] or at a higher range between 112–365 days.[47,52,53,70] Models which have not specified whether the infection is symptomatic or asymptomatic have widely divergent estimates ranging from 60 days up to 370 days.[43,46,60,65,71,100,101] Some models specify the length of an infectious stage ranging from 3 weeks in treated infection up to 457 days,[41,74] while Welte et al. estimate the incubation time of CT as 12 days.[50]

For models specifying the duration of an asymptomatic CT infection, estimates tend to cluster between 200–240 days[44,47–50,56,66,67,69] and 433–497 days.[45,58,68,102] Some models estimated 180 days,[51,63] 365 days,[64] or 622 days,[38,52] reflecting a range of uncertainty. Beck et al.[70] 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.[56]

10.2 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,[56,66,70,77,89], generally for treated or care-seeking persons, and others between 105–185 days, including for untreated symptomatic infection.[38,47,52,70] Models which have not specified whether the infection is symptomatic or asymptomatic have widely divergent estimates of duration, ranging from 10–60 days[71,79,80,83–85,103] to 330–365 days[81,100] with estimates also observed at 30-day intervals between 60 days and 200 days.[53,88,92,103] 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[70,78,82] but varied widely between those extremes.[41,74,75,99]

For models specifying the duration of an asymptomatic NG infection, estimates were also bimodal, with clusters at 105–135 days[38,47,52,66] and 180–185 days.[56,89] Beck et al.[70] 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.

11 HIV PRE-EXPOSURE PROPHYLAXIS (PrEP)

PrEP was modeled as daily oral use of combination tenofovir disoproxil fumarate and emtricitabine (trade name: Truvda) among HIV- MSM.[104] Active PrEP use reduces the per-act probability infection for HIV- men based on the level of adherence to PrEP after initiation. In this section, we further describe the methods for modeling PrEP uptake based on the indications for prescription from CDC's guidelines for clinical practice, the role of PrEP uptake and monitoring, variable levels of adherence and its impact on HIV susceptibility, and the calculation of the epidemiological outcomes presented in the main paper.

11.1 PrEP Indications

The indications for PrEP initiation followed the eligibility guidelines for prescription within CDC's recommendations for clinical practice.[96] This paper explicitly models the bio-behavioral components of the PrEP indications for MSM:

1. UAI in monogamous partnerships with a partner not recently tested negative for HIV;
2. UAI outside of a monogamous partnership;
3. AI in a known serodiscordant partnership; and
4. Diagnosis of a bacterial STI.

We modeled PrEP indications based on these four conditions jointly to estimate their individual and combined prevention impact. The CDC guidelines indicate PrEP based on the union of Conditions 1–4. In this paper, risk was measured within a pre-defined "window" period, over which risk behavior accumulates to define any indications. The base window period is 6 months, following the CDC guidelines.

11.2 PrEP Uptake and Monitoring

In our models, diagnostic testing is the gateway through which PrEP is offered. A small percentage of MSM (6.5%) never test before age 40, but the remainder test at regular intervals (approximately yearly before PrEP). MSM are assessed for PrEP indications only at visits in

which their HIV test result is negative. At that time, MSM are considered for PrEP initiation only if the proportion of men on PrEP has not surpassed a threshold coverage fraction, which we vary from 10% to 90% from a default of 40%. Once men initiate PrEP they return to diagnostic testing visits at quarterly intervals. Newly infected men are discontinued on PrEP immediately. On a yearly basis (after 4 quarters of testing after PrEP initiation), their risk behavior is reassessed; if formerly indicated MSM had no behavioral indications in the window period before that reevaluation, their PrEP is discontinued.

11.3 Adherence and Impact on HIV Transmission

Men initiating PrEP were assigned a fixed adherence profile that reflected an average weekly dosage. Adherence parameters were drawn from an open-label demonstration project reweighted by race to account for the small proportion of non-white persons in that study.[105] Our base model assigned 21.1% of men as non-adherent, 7.0% as taking <2 pills/week, 10.0% 2–3 pills/week, and 61.9% at 4+ pills/week. In sensitivity analyses for adherence, we varied the proportion in the highly adherent group from 10% to 90% by proportionally reallocating men into the lower three adherence groups. Use of PrEP resulted in a reduction of the per-act probability of infection correlated with adherence level: 0%, 31%, 81%, and 95%, for the non-adherent to high-adherence groups, respectively, following Grant et al.[104,106]

12 MODEL CALIBRATION AND PARAMETER ESTIMATION

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

12.1 Model Calibration

Starting with a population of 10,000 MSM, HIV infection was initially seeded in 25% of the 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 of 26% from our earlier model.[4] This is a high prevalence, obtained from previous network and incidence studies of Atlanta MSM,[107,108] but this value is consistent with an recent estimated

prevalence rate of 25.4 per 100 MSM in Georgia that harmonized MSM population size estimates with publicly available HIV surveillance data.[109]

Many STI-specific and 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.

Table S1 summarizes the primary STI-related parameters from these models. We used approximate Bayesian computation 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. In Table S1, we provide the posterior values of those parameters, prior distributions (all uniform over the ranges shown), and key references consulted in forming the shape of the priors. Further details on the model calibration are provided in Section 13. Parameter values with a N/A value for the prior were not calibrated and assumed fixed as the posterior mean value shown in the table.

Table S1. Parameter Definitions, Posterior Value, Prior Distributions, and Sources for STI-related Model Parameters

Parameter	Posterior Mean	Priors	Sources
Per-act Transmission Probability			
Rectal Gonorrhea	0.3577	0.30 – 0.60	52,62,92
Urethral Gonorrhea	0.2481	0.20 – 0.50	77,90
Rectal Chlamydia	0.3216	0.30 – 0.60	42
Urethral Chlamydia	0.2130	0.20 – 0.50	40,53,69
Probability of Symptoms Given Infection			
Rectal Gonorrhea	0.0770	0.01 – 0.15	42,53
Urethral Gonorrhea	0.8244	0.60 – 0.95	36,52
Rectal Chlamydia	0.1035	0.01 – 0.15	42,52
Urethral Chlamydia	0.8850	0.60 - 0.95	48,63
Duration of Asymptomatic, Untreated Infection (weeks)			
Gonorrhea	35.1185	26 – 52	42,70
Chlamydia	44.2454	39 – 65	53,56
HIV Acquisition Risk Ratio Multipliers			
Rectal STI Infection	2.7807	2.0 – 3.0	35,36
Urethral STI Infection	1.7324	1.0 – 2.0	37
STI Transmission Risk Ratio Multipliers			
Condom use	0.30	N/A	72,73
Probability of Treatment Given Symptomatic Infection			
Gonorrhea	0.90	N/A	94
Chlamydia	0.85	N/A	94
Duration of Treatment (weeks)			
Gonorrhea	2.00	N/A	110,111
Chlamydia	2.00	N/A	110,111

The targeted NG and CT incidence were based on a recent meta-analysis, which estimated rates in non-PrEP using cohorts of MSM of 4.2 per 100 person-years for NG and 6.6 per 100 person-years for CT.[112] These pooled incidence estimates for non-PrEP using cohorts were drawn from a range of studies on MSM published since 2004: the deferred PrEP intervention group of the open-label PROUD randomized trial in the United Kingdom,[113] a cohort of HIV-positive men attending specialty care clinics in Ontario,[114] a cohort of asymptomatic aging MSM enrolled in the Multicenter AIDS Cohort Study in Washington, D.C.,[115] a randomized trial of a counseling module-based behavioral intervention for MSM in six US cities,[116] a cohort of

HIV-negative Dutch MSM,[117] and Australian MSM presenting at high caseload clinics in Victoria.[118]

We used approximate Bayesian computation with sequential Monte Carlo sampling (ABC-SMC) methods[31,119] 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 posterior distributions for the calibrated parameters are listed in Table S1. 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 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.

13 SUPPLEMENTAL RESULTS

HIV incidence and prevalence would be lower across all scenarios that varied PrEP coverage, risk compensation, and the STI testing interval (Table S2). The factor most strongly associated

with HIV incidence was coverage, with minimal variation across RC and testing intervals given 40% coverage in the reference model. Higher levels of risk compensation increased incidence due to higher biological risk resulting from higher prevalence of current STIs, as well as imperfect efficacy of PrEP in lower-adherence groups. Incidence was slightly higher with longer STI testing intervals for the former reason.

Table S2. HIV Prevalence, Incidence, Hazard Ratios, Percent of Infections Averted (PIA), and Number Needed to Treat (NNT) on PrEP, by PrEP Coverage Level, Behavioral Risk Compensation Level, and STI Screening Interval among Men Who Have Sex with Men in the United States

Model Scenario	*Prevalence (IQR)*	*Incidence(IQR)*	*Hazard Ratio (IQR)*	*PIA (IQR)*	*NNT (IQR)*
Base Model (No PrEP)	25.8 (25.0, 26.8)	3.53 (3.24, 3.78)	-	-	-
PrEP Coverage					
20%	22.1 (21.7, 22.5)	2.54 (2.39, 2.73)	0.72 (0.67, 0.80)	19.6 (15.1, 24.0)	24.9 (23.0, 27.6)
40% (Ref)	19.0 (18.7, 19.4)	1.84 (1.71, 1.98)	0.52 (0.47, 0.59)	34.5 (31.3, 38.1)	27.9 (26.7, 29.2)
60%	16.4 (16.1, 16.7)	1.33 (1.24, 1.43)	0.38 (0.34, 0.42)	47.3 (44.8, 50.0)	30.4 (29.5, 31.0)
80%	14.3 (14.0, 14.5)	0.97 (0.90, 1.04)	0.27 (0.25, 0.30)	57.4 (55.3, 59.4)	32.7 (32.1, 33.4)
Risk Compensation					
0%	18.8 (18.5, 19.1)	1.80 (1.67, 1.90)	0.51 (0.46, 0.55)	35.5 (32.7, 38.8)	26.6 (25.4, 27.4)
20%	18.9 (18.6, 19.2)	1.79 (1.68, 1.93)	0.51 (0.47, 0.56)	35.3 (32.6, 38.5)	27.1 (26.2, 28.3)
40% (Ref)	19.0 (18.7, 19.4)	1.84 (1.71, 1.98)	0.52 (0.47, 0.59)	34.5 (31.3, 38.1)	27.9 (26.7, 29.2)
60%	19.1 (18.8, 19.4)	1.86 (1.73, 1.97)	0.53 (0.48, 0.58)	34.4 (31.1, 37.2)	28.5 (27.2, 29.6)
80%	19.4 (19.0, 19.8)	1.93 (1.79, 2.06)	0.55 (0.49, 0.61)	32.6 (29.3, 36.6)	29.6 (28.2, 31.0)
100%	19.6 (19.3, 20.0)	2.00 (1.88, 2.14)	0.57 (0.53, 0.63)	32.2 (28.6, 35.8)	30.5 (29.2, 31.9)
STI Testing Interval					
3 months	18.8 (18.5, 19.2)	1.80 (1.68, 1.91)	0.51 (0.47, 0.56)	35.7 (32.1, 39.1)	27.1 (26.2, 28.3)
6 months (Ref)	19.0 (18.7, 19.4)	1.84 (1.71, 1.98)	0.52 (0.47, 0.59)	34.5 (31.3, 38.1)	27.9 (26.7, 29.2)
12 months	19.2 (18.9, 19.6)	1.90 (1.78, 2.01)	0.54 (0.49, 0.59)	33.8 (30.1, 37,3)	28.8 (27.6, 30.1)

IQR = interquartile range (25% and 75% percentiles) of the simulation outcomes. Incidence expressed per 100 person-years at risk.

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