Impact of the Centers for Disease Control's HIV Pre-Exposure Prophylaxis Guidelines for Men Who Have Sex with Men in the United States

Samuel M. Jenness, PhD MPH[1] Steven M. Goodreau, PhD[2] Eli Rosenberg, PhD[1]
Emily N. Beylerian, MS[3] Karen W. Hoover, MD MPH[4]
Dawn K. Smith, MD, MS, MPH[4] Patrick Sullivan, DVM PHD[1,5]

[1] Department of Epidemiology, Emory University, Atlanta, GA
[2] Department of Anthropology, University of Washington, Seattle, WA
[3] Center for Studies in Demography and Ecology, University of Washington, Seattle, WA
[4] Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA
[5] Department of Global Health, Emory University, Atlanta, GA

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 3. 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 in a research project investigating the causes and consequences of racial disparities in HIV incidence among young MSM in the US (results forthcoming).

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.[4]

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

Simulations were performed on the Hyak high-performance computing (HPC) system at the University of Washington. This 11,000-core HPC allowed execution of multiple simulations in parallel to reduce the overall computation time. Instructions for adapting the simulation scripts within the repositories above to run on smaller scale systems are provided within the repository help documentation.

2 EMPIRICAL DATA

The behavioral modules within the larger epidemic model were parameterized using two studies of HIV/STI disparities in black and white non-Hispanic MSM, conducted from 2010–2014 in Atlanta, Georgia. The **Involvement Study** was a prospective HIV incidence cohort of 803 MSM and the **MAN Project** was a cross-sectional chain-referral sexual network study of 314 MSM. Both samples were recruited contemporaneously using venue-time-space sampling, using a modified frame from the 2008 cycle 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. Then a combined dyadic dataset was created 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.

Due to the broad focus of this modeling paper, we did not explicitly model race/ethnicity in either the input parameters or as output statistics. Future models that explore racial disparities in HIV incidence attributable to scale-up of emerging prevention technologies like PrEP will use race-specific parameter definitions, so we still describe them in detail here in order to outline these broader modeling methods for current and future research activities.

3 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 3.1), and then present the formal statistical modeling methods (Section 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. 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.

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*):

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

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:

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

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:

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 3.1.2 weighted by the proportions in Section 3.1.1. These reflect the overall expected value across all men for one-time AI acts per time step.

3.1.4 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.[1,3,5] 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

3.1.5 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.

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

3.1.6 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

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,[6] since they persist for multiple time steps. One-time contacts, on the other hand, were modeled using cross-sectional ERGMs.[7] 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):

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

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

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

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

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

where:

- $Y_{ij,t}$ = the relational status of persons *i* and *j* at time *t* (1 = in relationship/contact, 0 = not)
- $Y^{C}_{ij,t}$ = 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 $\boldsymbol{g(y)}$ vectors.

Specific model statistics are listed below. Together these sets allow us to retain all of the network features listed in Section 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 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 zeros 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 zeros 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 zeros 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 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 frequencies listed in Section 3.1.6, 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.[8] During the subsequent model simulation, we use the method of Krivitsky et al.[9] 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 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.

4.1 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 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.

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%

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. 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 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.

4.3 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.[10,11] 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, implies an overall rate of condom use of approximately 50% across all acts.

4.4 Sexual role

Men are assigned an individual sexual role preference (exclusively insertive, exclusively receptive, or versatile) as described in Section 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 49%, and is derived from the partner-specific role data described in Section 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 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. 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,[10] 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).[2,12]
- 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.[13,14] 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.[13] But because race was not explicitly represented in these models, we averaged each set of proportions: 1.7% homozygous and 9.9% heterozygous overall.

5.3 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.[15] 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 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 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 8. The parameters governing these processes are provided in the table below.

Parameter	Value	Reference
Time to peak viremia in acute stage	45 days	Little[16]
Level of peak viremia	6.886 $\log_{10}$	Little[16]
Time from peak viremia to viral set point	45 days	Little,[16] Leynaert[17]
Level of viral set point	4.5 $\log_{10}$	Little[16]
Duration of chronic stage infection (no ART)	3550 days	Buchbinder,[18] Katz[19]
Duration of AIDS stage	728 days	Buchbinder[18]
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.

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.[20]

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,[10] 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.[10,21] 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.[22] 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.[23,24]

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.[21] 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.[25] 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.[25] The latter corresponds to an absolute viral load below the standard levels of detection (VL = 50).[26]

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,[23] 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 where 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.[27] 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.

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.[18] 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.

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 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.

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 Section 2). Dyads active were considered active at a specific time step if the terminus of that simulated edge is 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 are 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 wthin each discordant dyad for the time step, as well as condom use and role for each of those acts, was described in Section 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[28]
		Insertive: 0.003379 base probability when HIV+ partner has 4.5 $\log_{10}$ viral load	Vittinghoff[28]
HIV viral load (VL)	HIV+	Multiplier of $2.45^{(VL - 4.5)}$	Wilson[29]
Acute stage	HIV+	Multiplier of 6	Leynaert,[17] Bellan[30]
CCR5 status	HIV-	Δ32 homozygote: multiplier of 0	Marmor[13]
		heterozygote: multiplier of 0.3	Marmor[13]
Condom use	Both	Multiplier of 0.25	Varghese,[31] Weller[32]
Circumcision status	HIV-, insertive	Multiplier of 0.40	Gray[12]
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.

9 PRE-EXPOSURE PROPHYLAXIS (PrEP)

PrEP was modeled as daily oral use of combination tenofovir disoproxil fumarate and emtricitabine (trade name: Truvda) among HIV- MSM.[33] 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.

9.1 PrEP Indications

The indications for PrEP initiation followed the eligibility guidelines for prescription within CDC's recommendations for clinical practice.[34] This paper explicitly models only the 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; and
3. AI in a known serodiscordant partnership.

We modeled PrEP indications based on these three conditions separately and then jointly to estimate their individual and combined prevention impact. Because of potential differences in clinical interpretation of these conditions, we explored two different functional definitions: a more "literal" reading of the specific wording in the guidelines, and a "clinical" version that may be more realistic to assess in practice.

- For Condition 1, we define monogamy as *both* partners in a long-term partnership having no outside partnerships (literal) versus only the person assessed for PrEP exhibiting monogamy (clinical).
- For Condition 2, the literal version considers any UAI outside of a monogamous partnership, whereas the clinical version indicates PrEP if there is any UAI outside of self-defined main partnerships in the risk window.
- For Condition 3, the guideline definition is AI in a known serodiscordant partnership, but we also model a high-risk variant indicating PrEP only if UAI occurred in these partnerships.

The CDC guidelines indicate PrEP based on the union of Conditions 1–3. We modeled three variants of this union based on the different condition definitions, comprising a plausible range of PrEP risk assessment schemes in clinical practice.

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, but sensitivity analyses varied that from 3 months to 12 months.

9.2 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.

9.3 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.[35] 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.[33,36]

10 SIMULATION METHODS

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

10.1 Model Calibration

Instead of modeling the time series of HIV transmission among MSM since the inception of the epidemic in the 1980s, which would require historical empirical data related to behavioral and clinical parameters, we replicate the current HIV epidemic in this population using model parameters measured recently following existing approaches.[1–3] Starting with a population of 10,000 MSM, HIV infection was initially seeded in 25% of the population. A set of burn-in simulations was then used to allow the natural dynamics of HIV 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 the Atlanta-area HIV prevalence of 26%.[10,37]

We used approximate Bayesian computation with sequential Monte Carlo sampling (ABC-SMC) methods[30,38] to calibrate behavioral parameters in which there was measurement uncertainty in order to match the simulated HIV prevalence at the end of the burn-in simulations to the HIV prevalence among Atlanta-area MSM. 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).

In this use of ABC, the parameter to be calibrated was an overall multiplier for the rate of acts within sexual partnerships over time. We chose this parameter based on the assumption that the number of acts may be underreported due to sensitivity biases. We used a uniform prior distribution for this multiplier parameter, with a range from 0.5 to 1.5, where 1 was equal to the act rate observed in the data. The ABC algorithms in the network simulations were particularly computationally intensive so we chose only one parameter to fit in order to keep the sample space smaller in this initial research effort. Future modeling efforts will expand the number of candidate parameters to estimate to allow for a broader source of uncertainty.

For summary statistics against which to measure the performance of the model simulations, we choose two for this research project: 1) the slope of the prevalence curve in the time series of the burn-in model for the last 10 years of calendar time; and 2) the prevalence value at the end of the time series. The target summary statistic for the slope statistic was 0, which reflected the goal of a disease prevalence in an equilibrium state with minimal temporal fluctuations. The target statistic for the latter prevalence statistic was 26% as noted.[10,37] The threshold parameter for the distance statistics was selected iteratively based on the performance of the ABC algorithm to converge towards those two summary statistics. The ABC model calibration was completed using the *abc* package in R.

For the ABC algorithms to calibrate to the observed HIV prevalence, a total of 480 simulations were required for 50 years of calendar time. The posterior distribution for the act rate multiplier parameter was 1.32 (95% CrI = 1.19, 1.44). Given this parameter set, we simulated a burn-in model 250 times to account for the stochastic variability over individual simulations. The individual simulation in which the HIV prevalence at the end of the simulation was closest to the HIV prevalence target statistic of 26% was selected as the starting point for the intervention simulations.

10.2 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 in each simulation. 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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