**Proportion of Incident HIV Cases among Men Who Have Sex with Men Attributable to Gonorrhea and Chlamydia: A Modeling Analysis**

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*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 models of HIV preexposure prophylaxis (PrEP) among US MSM.4,5

The model algorithms and methods presented here generalize these prior MSM HIV transmission models to investigate the interaction between HIV and STIs and the implications of these interactions for HIV prevention 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.6

*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 *syph\_ept.*
* [http://github.com/EpiModel/sti\_paf] 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 both 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*

Respondentsin 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.1,3,7 For instance, a relationship between a 23-year-old and a 28-year-old would represent = 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.

|  |  |
| --- | --- |
|  | **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,8 since they persist for multiple time steps. One-time contacts, on the other hand, were modeled using cross-sectional ERGMs.9 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):

Main partnership formation

Casual partnership formation

Main partnership persistence

Casual partnership persistence

One-time contact existence

where:

* = the relational status of persons *i* and *j* at time *t* (1 = in relationship/contact, 0 = not)
* = the network complement of *i,j* at time *t*,i.e. all relations in the network other than *i,j*
* = vector of network statistics in each model
* = vector of parameters in the formation model

For and , 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 vectors given the 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 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: vector:

* = number of main partnerships
* = number of men with 2+ main partners
* = number of main partnerships for men with 1 casual partner
* = number of main partnerships for men with 2 casual partners
* = sum of the absolute difference in the square root of partners’ ages across main partnerships
* = number of main partnerships between men who were both exclusively insertive
* = number of main partnerships between men who were both exclusively receptive

There are structural zeroes as coefficient constraints for the terms , , . 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: vector:

* = number of main partnerships

Casual partner formation model terms: vector:

* = number of casual partnerships
* = number of casual partnerships for men with 1 main partner
* = number of men with 2 casual partners
* = number of men with 3+ casual partners
* = sum of the absolute difference in the square root of partners’ ages across casual partnerships
* = number of casual partnerships between men who were both exclusively insertive
* = number of casual partnerships between men who were both exclusively receptive

There are structural zeroes as coefficient constraints for the terms , , . 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: vector:

* = number of casual partnerships

One-time contact existence model terms: vector:

* = number of one-time contacts
* = total # of one-time contacts for men with 0 main and 1 casual partnership
* = total # of one-time contacts for men with 0 main and 2 casual partnerships
* = total # of one-time contacts for men with 1 main and 0 casual partnerships
* = total # of one-time contacts for men with 1 main and 1 casual partnership
* = total # of one-time contacts for men with 1 main and 2 casual partnerships
* = total # of one-time contacts for men in risk quintile 1
* = total # of one-time contacts for men in risk quintile 2
* = total # of one-time contacts for men in risk quintile 4
* = total # of one-time contacts for men in risk quintile 5
* = sum of the absolute difference in the square root of partners’ ages across one-time contacts
* = number of one-time contacts between men who were both exclusively insertive
* = number of one-time contacts between men who were both exclusively receptive

There are structural zeroes as coefficient constraints for the terms , . 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 6.10 During the subsequent model simulation, we use the method of Krivitsky et al.11 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.12,13 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,12 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).2,14
* 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.15,16 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.15 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.17 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 heightened 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 | Little18 |
| Level of peak viremia | 6.886 log10 | Little18 |
| Time from peak viremia to viral set point | 45 days | Little,18 Leynaert19 |
| Level of viral set point | 4.5 log10 | Little18 |
| Duration of chronic stage infection (no ART) | 3550 days | Buchbinder20,Katz21 |
| Duration of AIDS stage | 728 days | Buchbinder20 |
| Peak viral load during AIDS (at death) | 7 log10 | 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.22

## 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,12 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.12,23 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.24 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.25,26

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.23 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 log10. 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.27 Men on treatment could achieve partial or full suppression. Men who with partial suppression were assumed to have a log10 viral load of 3.5, compared to 1.5 among those who were fully suppressed.27 The latter corresponds to an absolute viral load below the standard levels of detection (VL = 50).28

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,25 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.29 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.20 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 Sections 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 log10 viral load | Vittinghoff30 |
| *Insertive:* 0.003379 base probability when HIV+ partner has 4.5 log10 viral load | Vittinghoff30 |
| HIV viral load (VL) | HIV+ | Multiplier of 2.45(VL - 4.5) | Wilson31 |
| Acute stage | HIV+ | Multiplier of 6 | Leynaert19, Bellan32 |
| CCR5 status | HIV- | Δ32 homozygote: multiplier of 0 | Marmor15 |
| heterozygote: multiplier of 0.3 | Marmor15 |
| Condom use | Both | Multiplier of 0.25 | Varghese33, Weller34 |
| Circumcision status | HIV-, insertive | Multiplier of 0.40 | Gray14 |

For each act, the overall transmission probability was determined first with a base probability that was a function of whether the HIV- partner was in the receptive or insertive role, with the former at a 2.6-fold infection risk compared to the latter. The HIV+ partner’s viral load modifies this base probability in a non-linear formulation, upwards if the VL was above the VL set point during chronic stage infection in the absence of ART, and downwards if it was below the set point. Following others, we modeled an excess transmission risk in the acute stage of infection above that predicted by the heightened VL during that period. Three predictors of the HIV- partner could reduce the risk of infection: the Δ32 allele on the CCR5 gene, condom use within the act, circumcision status (only if the HIV- partner was insertive in that act).

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 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, respectively, NG and CT infection status, which was the set of potential partnerships in which the infections could be transmitted at that time step.

NG and CT were modeled with susceptible-infected-susceptible (SIS) dynamics, with no immunity. 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 Effect of NG/CT on HIV Acquisition Probability

We modeled a range of plausible values for increased risk of HIV transmission and acquisition based on current STI status. We isolated the effects of STI on HIV transmission from HIV-infected partners and the effects of STI on HIV acquisition by HIV-uninfected partners. These effects are difficult to estimate empirically and data are sparse. Estimates are primarily available for the effect of STI on HIV acquisition, which is described in this section. The effect of NG/CT on HIV transmission is described in the next section.

Chesson et al.35 have described the effect of STI on HIV acquisition 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.36 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.37 estimated a similar risk ratio for the effect of rectal NG or CT infection on HIV transmission, which was slightly elevated over estimates not taking site-specific infection into account.38 Using these estimates, we established a Bayesian prior distribution of 1.50–3.00 for the relative increase in per-act HIV acquisition risk for rectal STI infections, and 1.00–2.50 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 1.97 for rectal NG and CT at a rectal site, 1.48 for urethral NG and CT. These posterior values were obtained in the absence of an effect of NG/CT on HIV transmission. Therefore, we examined a range of plausible values for multipliers of HIV acquisition risk conditional on NG/CT infection at rectal and urethral sites. These risk multipliers were 1.0, 2.0, and 3.0. The effect of NG/CT on HIV transmission (described below) was held constant as the risk multipliers for HIV acquisition were varied to isolate the effect of NG/CT on HIV acquisition.

## 8.3. Effect of NG/CT on HIV Transmission Probability

Fewer data are available to estimate the effect of NG/CT on HIV transmission from HIV-infected to HIV-uninfected partners. We are unaware of any studies that explicitly estimate this quantity among MSM; however, an estimate is available based on heterosexual partnerships in an African cohort.39 Based on these data, we selected a plausible multiplier of 1.3 for the effect of NG/CT on HIV transmission from rectal and urethral sites. This value was used to hold the effect of NG/CT on HIV transmission constant in sensitivity analyses examining the effect of NG/CT on HIV acquisition. To examine a possible range of values for the effect of NG/CT on HIV transmission, we held the risk multipliers for the effect of NG/CT on HIV acquisition constant at the model-derived values (1.97 for rectal infection, 1.48 for urethral infection) and modeled scenarios with the same values from the HIV acquisition sensitivity analysis (1.0, 2.0, and 3.0).

## 8.4 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 0.09–0.2040–54 with a wider range of 0.025 to 0.6.55–62 Estimated per-act transmission risk was generally higher in non-main partnerships when models incorporated or characterized different risk estimates by partnership types.45 Per-partnership transmission risk estimates ranged widely from 0.09 to 0.7,52,63–66 and per-day infection probabilities ranged from 0.001571 to 0.154, with higher estimates for casual partnerships relative to main partnerships.67–70 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,41,42,49,54,55,57,68 although some models did estimate that the FTM transmission probability was greater.40,69

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 0.1–0.24,71 0.4 for receptive AI,72 0.32 for insertive AI,72 and 0.35 per-partner.73 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 0.10–0.50 for urethral CT transmission to incorporate site-specific infection. The estimated posterior means were 0.2813 for per sex-act rectal CT transmission probability and 0.2195 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.74,75

## 8.5 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 0.60,40–44,49,54–56,58,61,64,76–86 with an outer range of 0.1 to 1.83,87,88 Per-day infection probability estimates ranged from 0.011 to 0.6,68,78,89 with higher probabilities estimates for non-main partnerships. Per-partnership estimates differed widely, ranging from 0.10 to 0.80.57,90,91 When FTM transmission was distinguished, the per-act40–42,54,57,68,76,77,79,83–85,90 and per-partnership55,91 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.49,79,86

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 0.8,72,73,92–95 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 0.10–0.50 for urethral NG transmission to incorporate site-specific infection. Bayesian calibration generated posterior values of 0.5161 for per sex-act rectal NG transmission probability and 0.4362 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 SYMPTOMS AND TREATMENT

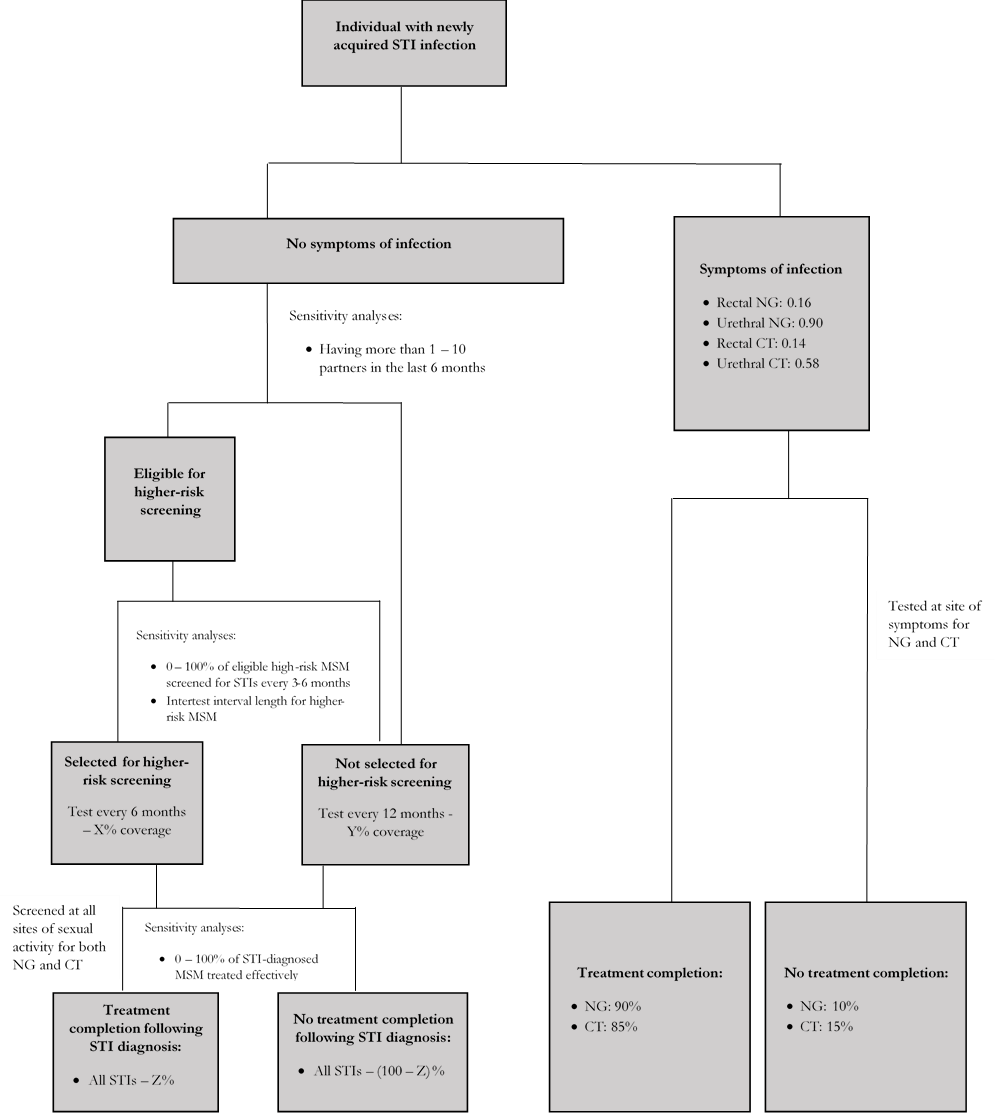
## 9.1 Treatment

Testing and treatment for NG and CTs 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.96 Symptoms-driven testing was correlated, in that a man presenting with rectal symptoms was tested for both NG and CT at a rectal site.

The average time on treatment/in recovery was 1 week for NG and CT, with a stochastic recovery process described below. A background screening process for the identification of asymptomatic infection was newly implemented, with more details in Section 11. Any individual who had been sexually active, e.g. in an edgelist in a non-dissolved partnership, in the previous year was eligible for screening. Screening was implemented as a deterministic process for each STI, stratified by HIV serostatus, with a certain proportion of individuals who met eligibility criteria for a particular screening testing every 365 days for both NG and CT.

A flow diagram showing the trajectories of STI testing and treatment off 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.97 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. Treatment of asymptomatic infection required diagnosis through the screening process that is described further in Section 11.

**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 0.3–0.5,40,46,49,51,54,55,58,61,65,66,70,71,76 with an outer range of 0–0.7544,50,53,98,99 and a sizable cluster of estimates at 0.75.59,60,68,69,73 Beck et al.72 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,40,46,49–51,54,55,65,66,68–70,76 with a few exceptions where women are estimated to be more symptomatic.53,61,99 In our prior STI model5, we used a Bayesian approach to address uncertainty, establishing 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. These estimated posterior values were 0.1035 for the probability of symptomatic rectal CT, and a probability of 0.8850 for symptomatic urethral CT. For this model, however, we reverted to the Beck values of 0.14 for the probability of symptomatic rectal CT infection and 0.58 for the probability of symptomatic urethral CT infection, increasing the probability of symptoms at a rectal site but decreasing the probability of symptoms at a urethral site.

## 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 varied. The middle 50% of estimates of this proportion from STI or HIV/STI models for men has ranged from 0.35–0.88,40,54,58,61,76,78,84,88,93,94 with a lower quartile of 0.11 to 0.2544,55,83,98 with a sizable group of estimates between 0.9 to 0.95.49,68,73,91,100 Beck et al.72 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.40,49,54,55,68,76,83,84,88,91,100 In our prior STI model5, we used a Bayesian approach to address uncertainty, establishing 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. These generated posterior values of 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. For this model, however, we reverted to the Beck values of 0.16 for the probability of symptomatic rectal NG infection and 0.90 for the probability of symptomatic urethral NG infection, increasing the probability of symptoms at both rectal and urethral sites.

# 10 STI DURATION AND RECOVERY

We modeled recovery from NG or CT according to whether men were treated for their infection. Recovery from infection back to susceptibility could 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. 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 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,46,47,50–53,60,66,68,69 but some models have estimates closer to 13–14 days for treated men58,65,72 or at a higher range between 112–365 days.49,54,55,72 Models which have not specified whether the infection is symptomatic or asymptomatic have widely divergent estimates ranging from 60 days up to 370 days.45,48,62,67,73,101,102 Some models specify the length of an infectious stage ranging from 3 weeks in treated infection up to 457 days,43,76 while Welte et al. estimate the incubation time of CT as 12 days.52

For models specifying the duration of an asymptomatic CT infection, estimates tend to cluster between 200–240 days46,49–52,58,68,69,71 and 433–497 days.47,60,70,103 Some models estimated 180 days,53,65 365 days,66 or 622 days,40,54 reflecting a range of uncertainty. Beck et al.72 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, or 310 days, for the duration of asymptomatic CT infection, consistent with our previous STI model.5

## 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,58,68,72,79,91, generally for treated or care-seeking persons, and others between 105–185 days, including for untreated symptomatic infection.40,49,54,72 Models which have not specified whether the infection is symptomatic or asymptomatic have widely divergent estimates of duration, ranging from 10–60 days73,81,82,85–87,104 to 330–365 days83,101 with estimates also observed at 30-day intervals between 60 days and 200 days.55,90,94,104 Estimates of the duration of the infectious stage of NG ranged from 14 days in treated individuals6 to 180–185 days in untreated individuals72,80,84 but varied widely between those extremes.43,76,77,100

For models specifying the duration of an asymptomatic NG infection, estimates were also bimodal, with clusters at 105–135 days40,49,54,68 and 180–185 days.58,91 Beck et al.72 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, or 246 days, for the duration of asymptomatic rectal and urethral NG infection, consistent with our previous STI model.5

# 11 STI SCREENING

A background screening process for the identification of asymptomatic infections was newly implemented. Any individual who had been sexually active, e.g. in an edgelist in a non-dissolved partnership, in the previous year was eligible for screening. Screening was implemented as a deterministic process for each STI, stratified by HIV serostatus, with a certain proportion of individuals who met eligibility criteria for a particular screening testing every 365 days for both NG and CT.

## 11.1 STI Screening Indications and Screening Eligibility

STI screening was simulated following CDC’s guidelines105, which indicate sexually active MSM for site-specific testing at sites of sexual contact at least annually, irrespective of condom use, and more frequent screening (every 3-6 months) “if at increased risk.” We did not implement more frequent screening for men at increased risk in the current model. Thus, men were eligible for screening if they had exhibited any sexual activity in the previous 12 months.

## 11.2 STI Screening Process

Eligibility for STI screening based on sexual activity was assessed using a rolling lookback window. At each time step, men who were in a sexual partnership in the previous 52 weeks were eligible for STI screening based on the recommendations described above. Screening was implemented as a deterministic process for each STI, stratified by HIV serostatus, with a certain proportion of individuals who met eligibility criteria for a particular screening testing every 365 days for both NG and CT.

We selected 44% of sexually active HIV-negative MSM in the model to test regularly on an annual basis for gonorrhea and chlamydia, respectively, and 61% of sexually active HIV-positive MSM in the model were chosen to test regularly on an annual basis for gonorrhea and chlamydia respectively.106 These values were selected to be slightly lower than empirical data (Table S1) from NHBS on NG and CT testing in the prior 12 months to allow for symptoms-based testing to boost the overall proportion of those who had tested for a particular STI in the past 12 month to empirical levels.107

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table S1: Testing targets for calibration | | | | |
|  | HIV-negative MSM | |  | |
| Statistic | Tested for gonorrhea in the past 12 months | Tested for chlamydia in the past 12 months | Tested for gonorrhea in the past 12 months | Tested for chlamydia in the past 12 months |
| Target | 45.8% | 45.8% | 64.1% | 62.8% |
| Source | 107 | 107 | 107 | 107 |

## 11.3 Testing Adherence and Progression to STI Treatment

Positive diagnoses resulted from the presence of an active STI at the time at which screening occurred, and all diagnosed men progressed to treatment.

# 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 10% of the population, urethral NG and CT in 0.15% of the population, rectal NG and CT in 0.15% 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 15% from the national estimate of HIV prevalence among MSM, which harmonized MSM population size estimates with publicly available HIV surveillance data.108 This differs from our previous models, which were calibrated to HIV incidence and prevalence obtained from previous network and incidence studies of Atlanta MSM.109,110

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 S2 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 S2, 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. 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 S2.** Parameters, Posterior Value, Prior Distributions, and Sources for STI-related Model Parameters | | | |
| **Parameter** | **Value** | **Priors** | **Source** |
| *Per-act acquisition probability* |  |  |  |
| Rectal Gonorrhea | 0.5161 | 0.30 – 0.60 | 49,64,94 |
| Urethral Gonorrhea | 0.4362 | 0.10 – 0.50 | 49,64,94 |
| Rectal Chlamydia | 0.2813 | 0.30 – 0.60 | 40,94,111 |
| Urethral Chlamydia | 0.2195 | 0.10 – 0.50 | 9,93,96 |
| *Probability of symptomatic infection* |  |  |  |
| Rectal Gonorrhea | 0.1600 | N/A | 72 |
| Urethral Gonorrhea | 0.9000 | N/A | 72 |
| Rectal Chlamydia | 0.1400 | N/A | 72 |
| Urethral Chlamydia | 0.5800 | N/A | 72 |
| *Duration of asymptomatic, untreated infection* |  |  |  |
| Gonorrhea (days) | 246.0000 | N/A | 5,44,72 |
| Chlamydia (days) | 310.0000 | N/A | 5,55,58 |
| *HIV acquisition risk ratio multiplier* |  |  |  |
| Rectal STI Infection | 1.9700 | 1.50 – 3.00 | 36,37 |
| Urethral STI Infection | 1.4800 | 1.00 – 2.50 | 38 |
| *STI transmission multipliers* |  |  |  |
| Condom use | 0.3000 | N/A | 74,75 |
| *Probability of treatment given symptomatic infection* |  |  |  |
| Gonorrhea | 0.9000 | --- | 72,96,97 |
| Chlamydia | 0.8500 | --- | 72,96,97 |
| *Duration of complete recovery (days)* |  |  |  |
| Gonorrhea | 7.0000 | N/A | Assumption |
| Chlamydia | 7.0000 | N/A | Assumption |
|  |  |  |  |

The targeted NG and CT incidence rates were based on results from a HIV and STI incidence cohort of both black and white Atlanta MSM.109,110 NG incidence rates were complemented by an estimate of incidence among MSM attending STD clinics that were part of the STD Surveillance Network (SSuN).112 An HIV prevalence target of 15% was extracted from a published analysis of rates of prevalent infection which combined MSM population size estimates with public HIV surveillance data.108

|  |  |  |  |
| --- | --- | --- | --- |
| Table S3: Epidemiological targets for calibration | | | |
| Statistic | Gonorrhea incidence | Chlamydia incidence | HIV prevalence |
| Target | 3.5 cases / 100 person-years | 5.6 cases/ 100 person-years | 15% |
| Source | 109,112 | 109 | 108 |

We used approximate Bayesian computation with sequential Monte Carlo sampling (ABC-SMC) methods32,113 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, , to be estimated, we:

1. Sampled a candidate from a prior distribution
2. Simulated the epidemic model with candidate value, .
3. Tested if a distance statistic, (e.g., the difference between observed HIV prevalence and model simulated prevalence) was greater than a tolerance threshold, .
   1. If then discard
   2. If then add the candidate to the posterior distribution of .
4. Sample the next sequential candidate, , either independently from (if 3a) or from 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 100 years of calendar time each. The posterior values for the calibrated parameters are listed in Table S2. The target statistics were matched during this burn-in model.

## 12.2 Model Simulations

The intervention scenarios are described fully within the main paper and in the table below (Table S4). For each scenario, we simulated the model scenario 256 times for 10 calendar years each. Data from each simulation were merged, and a complete 256-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.

|  |  |
| --- | --- |
| Table S4: Modeled Scenarios | |
| **Analysis** | **Details** |
| Effect of NG/CT on HIV Acquisition | * Implemented relative risks (RRs) to alter the risk of HIV acquisition risk based in the presence of NG/CT   + RRs for urethral and rectal NG/CT infection were varied independently across the following range of value: 1.0, 2.0, 3.0 * HIV transmission RR held constant at 1.3 across all scenarios * It is unclear from the literature if infection with >1 STI at a single anatomical site increases the risk of HIV acquisition additively or multiplicatively   + We modeled both scenarios   + Results in which the effects of dual STI infection at a single anatomical site were additive are presented in the main paper   + Results in which the effects of dual STI infection at a single anatomical site were multiplicative are presented below   + No meaningful differences were observed between the assumptions of additive and multiplicative effects |
| Effect of NG/CT on HIV Transmission | * Implemented relative risks (RRs) to alter the risk of HIV transmission risk based in the presence of NG/CT   + RRs for urethral and rectal NG/CT infection were varied independently across the following range of value: 1.0, 2.0, 3.0 * HIV acquisition RR held constant at 1.97 for rectal infections and 1.48 for urethral infections across all scenarios * It is unclear from the literature if infection with >1 STI at a single anatomical site increases the risk of HIV transmission additively or multiplicatively   + We modeled both scenarios   + Results in which the effects of dual STI infection at a single anatomical site were additive are presented in the main paper   + Results in which the effects of dual STI infection at a single anatomical site were multiplicative are presented below * No meaningful differences were observed between the assumptions of additive and multiplicative effects |

# 13 SUPPLEMENTAL RESULTS

Table S5. The effect of relative risk for HIV transmission on HIV incidence. This analysis assumes that when dual STI infection occurs at a single anatomical site that the RRs for each STI multiply.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Relative Risk of HIV Transmission by STI | | HIV Incidence Rate | | Population Attributable Fraction | |
| Gonorrhea | Chlamydia | | Rate per 100 PYAR\* (IQR) | | % (IQR) | |
| 1.0 | 1.0 | | 1.90 (1.87, 1.95) | | Ref | |
| 1.0 | 2.0 | | 2.02 (1.97, 2.07) | | 6.1 (3.7, 8.1) | |
| 1.0 | 3.0 | | 2.11 (2.05, 2.16) | | 10.0 (7.5, 12.1) | |
| 2.0 | 1.0 | | 1.97 (1.93, 2.01) | | 3.6 (1.4, 5.4) | |
| 2.0 | 2.0 | | 2.12 (2.07, 2.17) | | 10.2 (8.3, 12.4) | |
| 2.0 | 3.0 | | 2.26 (2.19, 2.32) | | 15.7 (13.2, 18.1) | |
| 3.0 | 1.0 | | 2.00 (1.96, 2.05) | | 5.0 (2.8, 7.2) | |
| 3.0 | 2.0 | | 2.20 (2.15, 2.26) | | 13.7 (11.5, 15.9) | |
| 3.0 | 3.0 | | 2.41 (2.33, 2.50) | | 21.2 (18.3, 23.9) | |

\*Person years at risk; HIV acquisition relative risks were held constant at base case values, rectal RR = 1.97, urethral RR = 1.48.

Table S6. The effect of relative risk for HIV acquisition on HIV incidence. This analysis assumes that when dual STI infection occurs at a single anatomical site that the RRs for each STI multiply.

|  |  |  |  |
| --- | --- | --- | --- |
| Relative Risk of HIV Acquisition by STI Site | | HIV Incidence Rate | Population Attributable Fraction |
| Rectal | Urethral | Rate per 100 PYAR\* (IQR) | % (IQR) |
| 1.0 | 1.0 | 1.95 (1.91, 2.00) | Ref |
| 1.0 | 2.0 | 1.81 (1.77, 1.86) | 1.7 (-0.8, 4.2) |
| 1.0 | 3.0 | 1.85 (1.80, 1.89) | 3.2 (1.2, 5.5) |
| 2.0 | 1.0 | 1.88 (1.84, 1.92) | 5.3 (3.0, 7.3) |
| 2.0 | 2.0 | 1.92 (1.87, 1.96) | 7.8 (5.9, 10.1) |
| 2.0 | 3.0 | 1.97 (1.93, 2.02) | 9.9 (7.7, 12.1) |
| 3.0 | 1.0 | 2.01 (1.97, 2.06) | 9.9 (7.9, 12.0) |
| 3.0 | 2.0 | 2.01 (1.97, 2.06) | 12.7 (10.7, 14.8) |
| 3.0 | 3.0 | 2.08 (2.03, 2.13) | 13.5 (11.5, 15.5) |

\*Person years at risk; HIV transmission relative risks were held constant at rectal RR = 1.3, urethral RR = 1.3.

Table S7. Proportion of transmission events in which site- and role-specific rectal and/or urethral STI were present. This analysis assumes that when dual STI infection occurs at a single anatomical site that the RRs for each STI multiply.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Relative Risk of HIV Transmission by STI** | | | **Sites of Sexual Activity with Prevalent STI** | | | |
| **Median (IQR) Proportion of Transmission Events** | | | |
| Gonorrhea | Chlamydia | Rectal and Urethral | | Rectal Only | Urethral Only | Neither |
| 1.0 | 1.0 | 6.4 (6.1, 6.9) | | 5.3 (5, 5.8) | 2.7 (2.3, 3) | 85.6 (86.6, 84.3) |
| 1.0 | 2.0 | 8.5 (8.2, 8.8) | | 5.4 (5.1, 5.7) | 3.9 (3.6, 4.2) | 82.2 (83.2, 81.2) |
| 1.0 | 3.0 | 10.3 (9.8, 10.7) | | 5.8 (5.4, 6) | 5 (4.7, 5.3) | 78.9 (80.1, 77.9) |
| 2.0 | 1.0 | 7.7 (7.3, 7.9) | | 5.7 (5.3, 6) | 3.1 (2.9, 3.4) | 83.6 (84.5, 82.6) |
| 2.0 | 2.0 | 10.2 (9.8, 10.5) | | 6 (5.9, 6.4) | 4.5 (4.1, 4.8) | 79.3 (80.2, 78.4) |
| 2.0 | 3.0 | 11.9 (11.7, 12.3) | | 6.9 (6.5, 7.1) | 5.8 (5.4, 6.1) | 75.5 (76.4, 74.5) |
| 3.0 | 1.0 | 8.4 (8.1, 8.8) | | 5.9 (5.6, 6.2) | 3.5 (3.2, 3.7) | 82.3 (83.2, 81.3) |
| 3.0 | 2.0 | 11.4 (11, 11.7) | | 6.9 (6.6, 7.3) | 4.9 (4.6, 5.3) | 76.7 (77.7, 75.6) |
| 3.0 | 3.0 | 13.3 (13, 13.5) | | 8.1 (7.8, 8.5) | 6.8 (6.6, 7.1) | 71.7 (72.6, 70.9) |
| **Relative Risk of HIV Acquisition by STI Site** | | | **Sites of Sexual Activity with Prevalent STI** | | | |
| **Median (IQR) Proportion of Transmission Events** | | | |
| Rectal | Urethral | Rectal and Urethral | | Rectal Only | Urethral Only | Neither |
| 1.97 | 1.48 | 7.2 (6.8, 7.6) | | 5.2 (4.8, 5.5) | 3 (2.7, 3.3) | 84.5 (85.6, 83.6) |
| 1.0 | 1.0 | 4.5 (4.2, 4.9) | | 3.4 (3.1, 3.7) | 2.8 (2.5, 3.1) | 89.3 (90.2, 88.3) |
| 1.0 | 2.0 | 5.2 (4.9, 5.6) | | 4.0 (3.7, 4.4) | 3.3 (3.0, 3.5) | 87.5 (88.5, 86.6) |
| 1.0 | 3.0 | 5.8 (5.4, 6.1) | | 4.4 (4.2, 4.7) | 3.6 (3.4, 3.9) | 86.2 (87.1, 85.3) |
| 2.0 | 1.0 | 7.0 (6.5, 7.3) | | 4.9 (4.6, 5.3) | 2.9 (2.6, 3.2) | 85.2 (86.3, 84.2) |
| 2.0 | 2.0 | 7.8 (7.4, 8.2) | | 5.6 (5.3, 5.9) | 3.2 (2.9, 3.5) | 83.4 (84.4, 82.4) |
| 2.0 | 3.0 | 8.5 (8.2, 8.8) | | 6.1 (5.7, 6.5) | 3.6 (3.3, 3.9) | 81.7 (82.8, 80.8) |
| 3.0 | 1.0 | 8.7 (8.4, 9.0) | | 6.3 (6.0, 6.6) | 2.9 (2.7, 3.1) | 82.2 (83.0, 81.2) |
| 3.0 | 2.0 | 9.5 (9.2, 9.8) | | 6.9 (6.5, 7.2) | 3.2 (3.0, 3.5) | 80.4 (81.2, 79.5) |
| 3.0 | 3.0 | 10.1 (9.8, 10.4) | | 7.3 (6.9, 7.5) | 3.6 (3.2, 3.8) | 79.0 (80.0, 78.3) |

Table S8. Proportion of transmission events in which the newly HIV-infected partner had site- and role-specific gonorrhea and/or chlamydia.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Relative Risk of HIV Transmission by STI** | | | **STI Status of Newly HIV-Infected Partner** | | | |
| **Median (IQR) Proportion of Transmission Events** | | | |
| Gonorrhea | Chlamydia | Gonorrhea and Chlamydia | | Gonorrhea Only | Chlamydia Only | Neither |
| 1.0 | 1.0 | 0.3 (0.2, 0.6) | | 3 (2.7, 3.3) | 7.7 (7.4, 8.1) | 89 (89.7, 88) |
| 1.0 | 2.0 | 0.4 (0.2, 0.6) | | 3 (2.7, 3.4) | 9.6 (9.2, 10) | 87 (87.8, 86) |
| 1.0 | 3.0 | 0.5 (0.4, 0.7) | | 3.4 (3, 3.8) | 11 (10.7, 11.3) | 85 (85.9, 84.1) |
| 2.0 | 1.0 | 0.4 (0.3, 0.7) | | 4.1 (3.7, 4.6) | 7.6 (7.2, 8) | 87.8 (88.7, 86.8) |
| 2.0 | 2.0 | 0.7 (0.6, 0.9) | | 4.3 (4, 4.6) | 9.8 (9.4, 10.2) | 85.2 (86.1, 84.3) |
| 2.0 | 3.0 | 0.9 (0.7, 1.1) | | 4.9 (4.6, 5.2) | 11 (10.6, 11.3) | 83.1 (84.1, 82.4) |
| 3.0 | 1.0 | 0.6 (0.3, 0.7) | | 4.8 (4.5, 5.2) | 7.5 (7.2, 7.9) | 87.1 (87.9, 86.2) |
| 3.0 | 2.0 | 0.8 (0.6, 1.1) | | 5.7 (5.3, 6.1) | 9.6 (9.4, 10) | 83.8 (84.7, 82.8) |
| 3.0 | 3.0 | 1.1 (0.8, 1.3) | | 6.3 (5.9, 6.6) | 11.3 (10.9, 11.6) | 81.4 (82.3, 80.5) |
| **Relative Risk of HIV Acquisition by STI Site** | | | **STI Status of Newly HIV-Infected Partner** | | | |
| **Median (IQR) Proportion of Transmission Events** | | | |
| Rectal | Urethral | Gonorrhea and Chlamydia | | Gonorrhea Only | Chlamydia Only | Neither |
| 1.97 | 1.48 | 0.3 (0.2, 0.5) | | 3.1 (2.8, 3.4) | 8.1 (7.6, 8.5) | 88.5 (89.4, 87.6) |
| 1.0 | 1.0 | 0.2 (0.1, 0.3) | | 1.9 (1.6, 2.2) | 4.9 (4.6, 5.2) | 92.9 (93.6, 92.2) |
| 1.0 | 2.0 | 0.2 (0.1, 0.5) | | 2.4 (2.1, 2.8) | 5.6 (5.3, 6.0) | 91.8 (92.5, 90.8) |
| 1.0 | 3.0 | 0.4 (0.1, 0.5) | | 2.6 (2.3, 2.8) | 6.3 (6.0, 6.8) | 90.8 (91.6, 89.9) |
| 2.0 | 1.0 | 0.3 (0.2, 0.6) | | 3.0 (2.6, 3.2) | 7.7 (7.3, 8.1) | 89.0 (89.8, 88.2) |
| 2.0 | 2.0 | 0.4 (0.3, 0.6) | | 3.5 (3.1, 3.8) | 8.5 (8.1, 8.8) | 87.5 (88.4, 86.7) |
| 2.0 | 3.0 | 0.4 (0.3, 0.6) | | 3.8 (3.4, 4.1) | 9.3 (9.0, 9.6) | 86.4 (87.3, 85.6) |
| 3.0 | 1.0 | 0.5 (0.3, 0.6) | | 3.9 (3.4, 4.2) | 9.8 (9.5, 10.2) | 85.7 (86.8, 85.0) |
| 3.0 | 2.0 | 0.5 (0.4, 0.7) | | 4.3 (3.9, 4.6) | 10.6 (10.4, 11) | 84.6 (85.3, 83.7) |
| 3.0 | 3.0 | 0.6 (0.4, 0.8) | | 4.4 (4.0, 4.7) | 11.4 (10.9, 11.7) | 83.6 (84.6, 82.8) |

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