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Birds of a Feather: Estimating the Population Impact of Assortative Mixing by HIV Diagnosis Status and Pre-Exposure Prophylaxis Use on HIV Incidence Among Men Who Have Sex With Men

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An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
In Epidemiology
2021

Abstract

Birds of a Feather: Estimating the Population Impact of Assortative Mixing by HIV Diagnosis Status and Pre-Exposure Prophylaxis Use on HIV Incidence Among Men Who Have Sex With Men

By Kevin M. Maloney

The advent of pre-exposure prophylaxis (PrEP) was a paradigm shift for human immunodeficiency virus (HIV) prevention. Uptake among men who have sex with men (MSM) was slow, but approximately 20% of PrEP-eligible MSM used PrEP in 2017. Despite optimism, HIV incidence among MSM has not declined as fast as projected given coverage levels. We hypothesize this may be explained by HIV serosorting and assortative mixing among MSM who use PrEP, which creates clusters of PrEP use in sexual networks and decreases the population benefit of PrEP. In this dissertation, we conducted three studies to explore the impact of PrEP sorting on HIV transmission among MSM.

In the first study, we estimated HIV serosorting and PrEP sorting patterns, using an egocentric sexual network study. We found strong evidence of assortative mixing among MSM with diagnosed HIV (39.3%), MSM who used PrEP (31.9%), and MSM who did not use PrEP (82.6%). We showed that naïve estimation of HIV and PrEP mixing matrices is biased. We presented a reclassification analysis to correct information bias.

In the second study, we used network estimation and simulation methods to describe cross-sectional sexual networks of MSM. We estimated that 45% of persistent and 24% of one-time partnerships among MSM are concordant without diagnosed HIV and without PrEP use. Network models based on degree and demographic mixing statistics produced only 70–80% of these partnerships. Our models provide evidence for inefficient network coverage of PrEP.

In the third study, we used a network-based model of HIV transmission to estimate the impact of PrEP sorting on the population benefit of PrEP. Our model showed 2.4% more infections over 10 years in the scenario with PrEP sorting compared to without PrEP sorting. The effect was relatively small, but PrEP sorting may interact with other network-level effects to limit HIV prevention in the real world.

These findings highlight the potential role of network-level factors in mediating the causal relationship between PrEP coverage and HIV incidence. Future research should investigate PrEP sorting in combination with other network properties to inform interventions to increase network coverage and the population benefit of PrEP.

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Acknowledgments

This dissertation is the culmination of many years of work, which was made possible by a village of mentors, colleagues, and friends. My dissertation committee has been insightful and encouraging at each stage – from conception of the research questions to development of the methodology, execution of the analyses, interpretation of findings, and throughout the writing process. I would like to thank each of you for your time and expertise. To Sam Jenness, thank you for holding my hand as I toddled and learned how to model, and for pushing me at each stage to ask more impactful questions. This dissertation would not be what it is without you. Through it all, you tolerated my chaotic approach and aggressive timeline, which are not small tasks. To Patrick Sullivan, thank you for seeing my potential and convincing me to move to Atlanta. Your mentorship and support from the very beginning has helped me keep my head up as I navigated this difficult journey. To Colleen Kelley, thank you for suggesting ways to keep this work grounded in reality and the unwavering positive attitude. And to David Benkeser, thank you for the much needed help working through methods and insightful feedback.

There are many other mentors who have supported me in thinking through my dissertation research and growth as an epidemiologist, including Jeb Jones, Tim Lash, and Allison Chamberlain. Before I came to Emory – and before I even enrolled as an MPH student – Doug Krakower took a chance on me, hired me for my first full-time job in public health, and spent four years opening doors for me, demonstrating kindness in academia, and encouraging my wandering mind. My origin story would not be complete without mentioning Elizabeth Spudich, who wrote a letter of recommendation when I applied to medical school, but told me “I think you care more about public health, not medicine, so you should probably think about that.” Dr. Spudich, thank you!

I would like to dedicate this dissertation to my family. My mother and brothers have been consistent support throughout my entire life, providing encouragement and a dose of reality, even when I didn’t want it. My father couldn’t go to college, so he was unwavering in encouraging my education. Fourteen years ago, the last time I saw him before he died, I promised him I wouldn’t give up on this. With my own son beside me, I can finally say we did it. Cameron, my adorable and curious little boy, has been a light during a very difficult time. I hope to one day inspire him to follow his passions, as my father encouraged me. And finally, Austin, deserves an acknowledgement, at the very least, for putting up with me these past few weeks and months. No other person has supported me more and complained less. Thanks for being everything I could ask for in a husband, partner, friend, and Papa to Cam (and Dax).

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Chapter 1. Background and Significance

Modern HIV Prevention in the US: The PrEP and U=U Era

Forty years after the first report of human immunodeficiency virus (HIV),[1] gay, bisexual, and other men who have sex with men (MSM) are still at increased risk for HIV infection in the United States, with approximately two-thirds of new infections each year attributed to male-to-male sexual contact.[2] In recent years, prevention efforts have been bolstered by biomedical interventions.[3] Antiretroviral treatment for persons living with HIV also prevents onward transmission by suppressing the viral load (Undetectable = Untransmittable; or U=U).[4,5] Antiretroviral medications, usually taken daily, can also reduce or eliminate the risk for HIV infection among persons with HIV, which is a prevention strategy known as pre-exposure prophylaxis (PrEP).[6,7] Clinical trials with MSM have shown that PrEP can reduce individual risk for infection by 99% if taken as recommended.[6–8] MSM are an ideal population for PrEP due to their increased risk for infection.[9] The Centers for Disease Control and Prevention (CDC) estimate that 1.1 million US adults are behaviorally indicated for PrEP.[10] The US Food and Drug Administration approved the first PrEP medication in 2012, but uptake was initially slow and only 20% of MSM with behavioral indications for PrEP used it in 2017.[11] Models of HIV transmission suggest that HIV incidence could decrease substantially if PrEP use increases among MSM, with additional population-level benefits if targeted to MSM with higher behavioral or demographic risk.[12–15] However, even at current PrEP coverage levels, a population-level benefit is expected.[12–15] For example, one model projects a 20% decline in HIV incidence over 10 years if 20% of PrEP-eligible MSM use it.[13]

The PrEP and U=U era has inspired optimism in the fight against HIV. The US federal government has recommitted efforts to end HIV, with the 2019 “Ending the HIV Epidemic” (EHE) initiative calling for increased PrEP use as one pillar of a broader strategy to prevent 90%

of infections by 2030.[16] Among MSM, incidence has declined slowly in recent years, with approximately 26,100 incident infections in 2014 and 24,400 in 2018, a 6.5% decline.[2] Despite increased PrEP use in this time, there is a lack of empiric evidence supporting PrEP impact at the population level.[17] A recent population-level analysis found only a small effect of decreased HIV diagnoses as PrEP use has expanded.[18] The reasons for gaps between the predicted population-level benefit of PrEP and observed trends in HIV incidence are unknown, but myriad factors likely contribute.[17] Racial disparities in PrEP access and uptake overlap with disparities in HIV incidence among MSM, which might partially explain the discrepancy. Despite 43% of new diagnoses among Black MSM and 26% among Hispanic/Latino MSM, White MSM were more likely to report PrEP use in a 2017 study.[2,19] Other disparities exist, including lower uptake in the southeast, where incidence is highest, and among young people.[11,20] Among persons accessing PrEP, early discontinuation (despite ongoing risk) contributes to lower cross-sectional coverage in the population, which undermines efforts to expand coverage by improving awareness, access, and initial uptake.[21–24] Inadequate adherence further decreases effectiveness at the individual and population levels.[22,25] Progress has been made to close disparities in PrEP uptake and effective use, with interventions focusing on various aspects of the PrEP care continuum (i.e., access, adherence, and persistence),[11,26] yet evidence of decreased HIV incidence has lagged.

There is a need to both monitor progress along the stages of the PrEP care continuum and to understand how these factors contribute to decreased incidence on the population level. However, given the lack of empiric evidence for PrEP impact at the population level, alternative hypotheses should be considered. One potential issue is that cross-sectional PrEP coverage (i.e., the fraction of PrEP-eligible MSM using PrEP at any point) may be an incomplete metric to predict the population impact of PrEP. Increased coverage should result in decreased incidence, as has been shown in predictive models.[12–15] However, 20% coverage among PrEP-

eligible MSM could have varying population impact depending on *which* PrEP-eligible MSM are using PrEP.[13] Predicting individual HIV risk is challenging, but risk calculators and other tools have been developed to help patients and clinical providers assess risk based on sexual behavior and demographics,[27–30] and the CDC has defined behavioral indications for PrEP use.[9] However, even after accounting for traditional risk identifiers, such as age, race, geography, and individual behavior, PrEP coverage might be inefficiently distributed in the sexual network of MSM, so that HIV transmission would proceed uninterrupted among MSM not using PrEP, while some MSM who use PrEP have limited risk for infection. Indeed, a recent study found that 6.3% of MSM who used PrEP in 2017 were not behaviorally indicated based on CDC guidelines.[11]

Furthermore, structural properties of the sexual contact network, including the location and density of HIV and PrEP across the network, can influence transmission dynamics and PrEP impact, even if all MSM who use PrEP are behaviorally indicated.[31–35] Clusters of PrEP use in the sexual networks of MSM might form as a result of assortative mixing (preferential partnering) among MSM who use PrEP. Assortative mixing could decrease HIV exposure among MSM who use PrEP (analogous to herd immunity of vaccines), which would reinforce the effectiveness of the intervention among these men. At the same time, PrEP use would remain sparse outside of local clusters, so that opportunities for primary and secondary prevention are limited. The overarching theory of this dissertation is that clustering of PrEP use in the sexual network may contribute to decreased PrEP impact at the population-level.

Network Structure and Sexual Transmission of HIV

Networks are representations of persons (nodes) and their connections (edges).[31,34] The edges can represent any type of specified relationship, including social, professional, or familial.[31] In an infectious disease framework, network edges represent exposures that are opportunities for disease transmission.[31] For studies of sexually transmitted infections, including HIV, the edges represent sexual partnerships.[31,33] The nodes can be characterized by

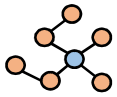
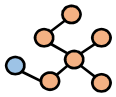
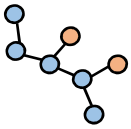
demographic and other descriptors, while characteristics of the edges describe the nature and duration of the edge.[31] The networks can be represented graphically, and data can be stored using vectors and matrices to identify nodes and edges and describe characteristics of each.[36] The networks can be represented cross-sectionally (i.e., a momentary network configuration at a single time point) or temporally (i.e., a series of networks with dynamic edge configurations over time).[36,37] Sexual networks are best represented temporally, because transmission is affected by the timing and sequence of partnerships, as well as the number of partnerships in a given time frame.[38,39] However, cross-sectional network analysis can help identify the mechanisms which contribute to transmission in the network.

Structural properties of networks can directly influence HIV transmission.[31–35] Early examples of network analysis of sexually transmitted infections include studies of the role of assortative sexual mixing (tendency to select partners with shared characteristics; e.g., same race partnering),[40,41] partnership concurrency (having ≥ 2 partners overlapping in time),[38,40,41] and skewed degree distributions (many individuals have few partners, while a few individuals have many partners),[40,41] in transmission dynamics. By analyzing the way in which nodes are connected in space and time, these studies identified network properties which influence epidemic trajectory. Transmission models which do not account for network structure (e.g., compartmental models) may be unable to represent complex interactions between population mixing (e.g., based on multiple attributes), patterns of behavior (e.g., degree by attributes), and biomedical dynamics (e.g., HIV viral load).[34] This may be appropriate for some types of infectious diseases with diffuse exposures (e.g., airborne pathogens). For other disease types, including sexually transmitted infections, in which intimate physical contact is necessary for transmission, repeated contact with the same persons(s) is common, large variation in the number and type of contacts exists, and the process for partner selection may be highly

structured.[31,32,34,39] For this class of diseases, it is necessary to account for network structure when modeling transmission.

The way that a set of nodes are connected (the "geometry" of the network) also can influence HIV transmission. Diagrams of select concepts are shown in **Table 1.1**. Degree centrality is a measure of a node's degree relative to other nodes.[32] Nodes with higher degree have higher centrality and are at greater risk for infection and secondary transmission.[33] In contrast, less central nodes are peripheral to the network.[33] Sets of interconnected nodes are known as components and typically contribute to the growth of an epidemic.[32] When each node in a component is connected to every other node, the component is called a clique.[32] Cliques and otherwise highly interconnected components form because sexual partners may also share social ties (i.e., assortative mixing) or meet in a common venue, such as a bathhouse or bar.[42] As a result of these components, a node that is neighboring a node with HIV will have a higher probability of also having HIV than a node randomly selected from the network.[42] Components with closed loops allow HIV epidemics to grow more rapidly.[33,43] As degree and density increase, the rate of transmission in the component tends to also increase.[33] Assortative mixing with respect to low degree results in long linear components.[32,33,43] In contrast to higher degree components, in which HIV transmission would rapidly saturate, linear components allow endemic transmission to occur.[32,33,43] Sexual networks of MSM contain both highly dense, closed loop components, and linear components.[43] Nodes that connect two separate networks "bridge" these networks and allow an epidemic to move from one network to another. An example of bridging is MSM who inject drugs were found to connect the separate networks of heterosexuals who inject drugs and MSM during the early stages of the HIV epidemic in some locales.[43]

Table 1.1. Examples of network structures

The blue node has **higher centrality** 	The blue node has **lower centrality** 
The interconnected nodes form a **component** 	The component forms a **clique** with fully Interconnected nodes 
The component is interconnected in a **closed loop** 	The nodes form a **linear component** 

Statistical Models for Networks

Many of the structural network properties described above were identified by constructing networks with sociometric techniques, such as contact tracing or chain sampling.[32,33] These methods involve extensive interviewing to identify recent sexual partners. The named partners are then enrolled in the study and interviewed for their sexual partners. The records are linked to identify any mutual partners shared with the seed participant or other members of the network. This process can become unwieldly, as the size of the network grows rapidly, and is susceptible to selection bias if study participants are reluctant to name some partners for recruitment to the study.[33]

Alternatively, network configurations can be estimated and simulated using egocentric data.[34,44,45] Egocentric studies sample a subset of individuals from the network; the study participants (egos) report information about themselves, their contacts (alters), and the duration and nature of the relationship (edge). Pairs of egos and alters form dyads. By design, many studies do not also sample alters, given that recruitment can be challenging. The alters may be enrolled as egos, by chance, but there is usually no formal mechanism (e.g., name matching) to match egos with alters, so the ego-reported information is the only source to define egos, alters

and edges. Statistical models are used with egocentric data to generate plausible realizations of the whole unobserved network.[34,44,45] Common parameters derived from egocentric data include degree distributions and mixing patterns. Mean degree is the expected number of edges for each node.[34,45] Mixing patterns influence the probability of edge formation based on nodal attributes.[34,45] Mixing patterns for categorical attributes (e.g., race) are often just a simple matrix of dyads, stratified by attributes of the partners, and the proportions for each potential pairing.[34,45] For example, the parameters for mixing by race in a simulated population of Black and White MSM could be the expected proportions of Black-Black, White-White, and Black-White dyads.

Using the parameters estimated from egocentric studies, along with summary measures of the whole population, whole networks may be inferred using statistical models estimated with sampled data.[45] Several methods for this data class have been developed, but one widely used approach is exponential random graph models (ERGMs).[46,47] ERGMs are a family of statistical models which use maximum likelihood methods to estimate features of cross-sectional networks.[46,47] ERGMs allow for dependence between nodes and edges [45,47] so that the probability of an edge forming is dependent on the existence of other edges (a feature of sexual networks) and the broader connectivity of the network. The probability distribution for ERGMs is:

$$P(\boldsymbol{Y} = \boldsymbol{y} \mid \theta) = \frac{\exp(\theta' g(\boldsymbol{y}))}{\kappa(\theta)}$$

where y is the observed network of edges, nodes, and nodal attributes; θ is the model coefficients; $g(y)$ is the network statistics; and $\kappa(\theta)$ is a normalizing constant representing all possible network configurations. Calculating $\kappa(\theta)$ can be computationally demanding, so a Markov chain Monte Carlo algorithm is used for efficiency.

One-time sexual contacts or cross-sectional analyses of persistent partnerships are modeled with ERGMs. Temporal ERGMs (TERGMs) are an extension of ERGMs for dynamic

networks which represent edge formation and dissolution over time.[37] TERGMs are necessary to model changes in network structure over time and provide a basis for network-based models of infectious disease simulation.[36] The TERGMs use two parallel ERGMs: one to model edge formation; and one to model edge dissolution. The ERGMs may have different parameters (i.e., the factors influencing edge formation may differ from those which influence edge dissolution). To handle these processes, the ERGMs may be reexpressed in the conditional logit form:

$$logit[P(Y_{ij} = 1 | \boldsymbol{Y^c}) = \theta' \partial(g(y))$$

where Y_{ij} is the edge between nodes i and j; $\boldsymbol{Y^c}$ is the rest of the network; and $\partial(g(y))$ are change statistics that represent the network configuration changes when Y_{ij} changes from 0 to 1. The conditional logit model for edge formation in a TERGM is:

$$logit\left[P(Y_{ij,t+1} = 1 | Y_{ij,t} = 0, \boldsymbol{Y^c})\right] = \theta'_{+} \partial(g_{+}(y))$$

where time is simulated in discrete time steps, and $Y_{ij,t+1}$ is the edge starting between nodes i and j between $time = t$ and $t + 1$ conditional on the edge not existing at t.

A similar expression is used to represent edge dissolution (not shown).[37] The edge formation and dissolution models may include terms reflecting dependencies (i.e., the existence of an edge influences whether another edge forms). Parameter estimates from the ERGM and TERGM models are used to implement the stochastic network simulations. One tool to simulate infectious disease contact networks is the *R* software package *EpiModel*.[36] *EpiModel* integrates ERGMs and TERGMs to estimate and simulate networks based on summary statistics from egocentric and population-representative data.

With egocentric data, alters are not recruited and interviewed to report their own sexual partners (e.g., by chain sampling subjects) so it is impossible to observe higher-order, non-local features of the network.[33] However, by modeling assortative mixing patterns, heterogeneous

degree distributions, and other network constraints, informed by egocentric data, most network features relevant to sexual partnership formation may be represented.[48] However, caution should be exercised when using the simulated network structures to make inferences about the true network from which the egos were sampled.[33,48] Studies of networks using egocentric data can still yield useful summary information, such as degree distributions and mixing statistics, which are properties of the network that influence transmission.[33,48] An advantage to egocentric network simulation is that participants in egocentric studies may be more likely to honestly report certain sexual behaviors and partners since the investigators will not be contacting those partners.[33]

With the addition of mathematical functions to represent other processes, including behavior within dyads, transmission probabilities, entry and exit from the population, and biological features of infection, these networks can be used to simulate complex epidemics.[36] More information about network-based mathematical models of epidemics is described below.

Sexual Partnerships of MSM with Respect to HIV and PrEP

Sexual partners are not selected randomly. As such, the factors influencing partnership selection have a profound effect on sexual networks. Most male-male sexual partnerships occur between men of similar age and the same race.[49–51] Other characteristics which may influence partnership selection include geography, socioeconomic status, and education.[52–54] The tendency to select partners with a shared characteristic is known as homophily or assortative mixing (e.g., homosexual partnerships are assortative with respect to sex); selecting partners with a different characteristic is disassortative mixing (e.g., heterosexual partnerships are disassortative with respect to sex). As a consequence of assortative mixing, characteristics like race tend to be segregated in the sexual network.[49–54]

Assortative mixing by race among MSM is one hypothesis to explain racial disparities in HIV,[55] based on the theory that sexual networks of Black MSM are denser than networks of White MSM. Network density is defined by the number of existing edges relative to the number of possible edges in the network.[32] Typically, higher mean degree creates denser networks. Black MSM do not have higher degree than White MSM,[55] but assortative mixing and smaller population size can increase density in a subgroup of highly interconnected nodes.[33] Although assortative mixing is insufficient to fully explain racial disparities,[56] mixing patterns remain a key area of research.

Partnership formation in the PrEP and U=U era also depends on HIV status and PrEP use, for several reasons. First, HIV and PrEP are independently associated with other factors that influence partnership formation, including age, race, geography, socioeconomic status, and education.[2,11,20,57,58] As a result, individuals with HIV may be more likely to select partners with HIV than would be expected by chance alone (similarly, MSM using PrEP may be more likely to select partners also using PrEP). Second, some MSM may preferentially select partners based on HIV status (either actual or perceived) to reduce the risk of HIV acquisition or transmission.[59,60] For example, MSM without HIV may select other MSM without HIV as sexual partners, while MSM with HIV may select other MSM with HIV. This concept is known as HIV serosorting and is well described in the HIV literature. Gaps in routine screening and diagnosis of HIV infection undermines serosorting as an effective strategy to reduce HIV risk, since MSM with undiagnosed HIV are unaware of their infection and may have a high viral load.[61] A related phenomenon, PrEP sorting, occurs when individuals seek out partners based on their current PrEP use status.[62–66] In this case, the sorting pattern may not be exclusively assortative. MSM without HIV (including those who do and do not use PrEP) may perceive MSM who use PrEP as less likely to have HIV, and therefore lower risk for HIV exposure.[62,63,66] On the other hand, PrEP use may disrupt traditional HIV serosorting, if MSM who use PrEP are less likely to avoid

partnering with MSM living with HIV.[62] Similarly, this concept would apply in the opposite direction; MSM living with HIV may seek out partners who are using PrEP but otherwise would avoid partnering with MSM not living with HIV.[62] In some cases, the temporal order between PrEP use and partnership selection may be reversed (which would not be captured with cross-sectional data). For example, PrEP may be initiated because a sero-discordant partnership already exists, and similarly discontinued if the relationship ends.[21] This type of sorting is not caused by PrEP use, but this mechanism still influences the network distribution of PrEP. Finally, awareness and acceptability of PrEP may spread within social networks (i.e., diffusion of innovations theory[67]) and their overlapping sexual networks,[68] and due to coordinated decision making within persistent partnerships,[69] thus providing additional mechanisms for nonrandom network distribution of PrEP.

As a result of HIV and PrEP sorting, as well as confounding factors that are independently associated with HIV, PrEP, and partnership formation, we hypothesize that the location and density of HIV and PrEP in the sexual networks of MSM is nonrandom. Specifically, assortative mixing by HIV and PrEP may result in clustering of each in the sexual network (i.e., MSM with HIV are more connected to other MSM with HIV, and MSM using PrEP are more connected to other MSM using PrEP). Among MSM without HIV, PrEP use may increase disassortative mixing with respect to HIV, resulting in greater connectivity to MSM with diagnosed HIV. At the same time, assortative mixing among MSM who use PrEP, and disassortative mixing between MSM who use PrEP and MSM with diagnosed HIV, will decrease partnering with other MSM, including those with undiagnosed HIV. Consequently, the probability of exposure to HIV in the network may be differentially associated with both diagnosed HIV status and PrEP use, even after accounting for confounders. Given the complex set of factors which may influence sorting, it is difficult to predict the magnitude of sorting, and what effect this may have on the efficiency of PrEP distribution in the network of MSM.

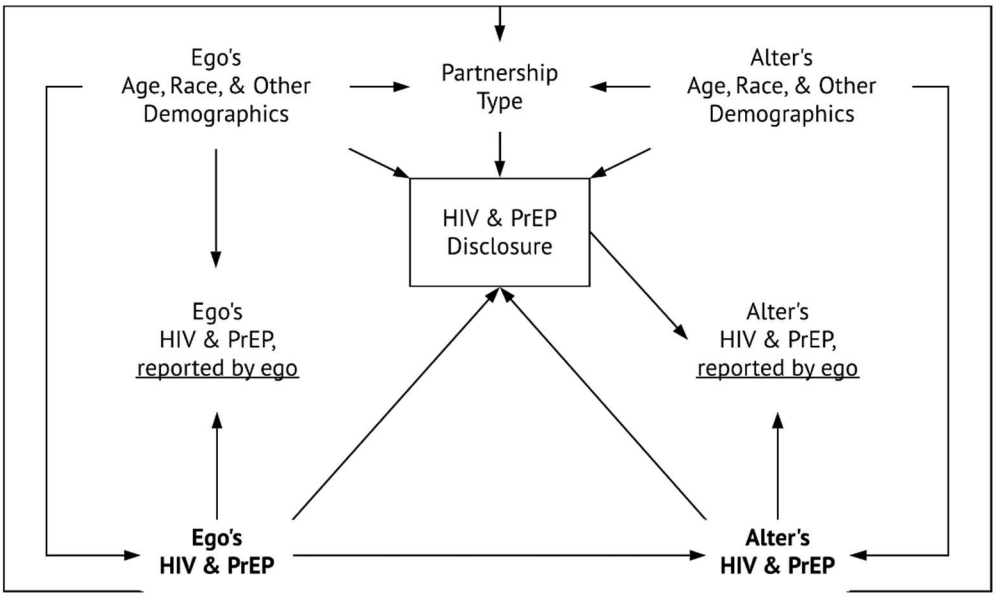
Estimates of HIV and PrEP sorting exist, [59,60,62,64,65,70] but these estimates should be interpreted with caution due to potential bias introduced by misclassification and missing data. The bias may exist because self-reported HIV serostatus is often unverified and research participants are often unable to reliably report the HIV serostatus and PrEP use of their recent sexual partners (we explore this further below, and **Chapter 2**, page 22).[68,71] In addition, PrEP is still relatively new, so there is little research on sorting patterns with respect to PrEP; older estimates of HIV serosorting may not be relevant to the PrEP era. One recent study, however, found nonrandom sorting based on HIV and PrEP in a population representative study of Canadian MSM.[64] The study showed that MSM living with HIV were more likely than MSM without HIV to report sexual partners with HIV (66% vs. 12%). Among MSM without HIV, those who were using PrEP were more likely to report partners with HIV and less likely to report partners of unknown HIV status, compared to those who were not using PrEP (17% and 31% vs 9% and 50%, respectively). Paradoxically, MSM reporting fewer partners with HIV (but more partners of unknown serostatus) may be at increased risk for exposure to HIV, given that MSM with undiagnosed HIV may have a high viral load and condoms may not be used if both men believe the other is without HIV.[4,61] For partnerships in which both men were without HIV, MSM using PrEP were more likely to report their partner also used PrEP, compared to MSM not using PrEP (51% vs. 20%).[64] This study supports our hypothesis that assortative mixing by HIV and PrEP may influence the distribution of each across the network of MSM, and that PrEP use by MSM without HIV may cause disassortative mixing with respect to diagnosed HIV status. Unfortunately, 13% of subjects and 44% of their partners were of unknown serostatus; among partners reported to be without HIV, 10% were of unknown PrEP use status.[64] Given the large amount of missing data and potential for misclassification, it is difficult to determine the true magnitude of HIV and PrEP sorting in this population.

Challenges in Estimating New Network Parameters

Partnership formation in network models of MSM is often determined based on attributes like age and race. HIV and PrEP are differentially assigned to MSM based on age and race, but mixing patterns based on HIV and PrEP may not be explicitly modeled. This approach may account for some of the sorting with respect to HIV and PrEP but may not reproduce the real-world network distribution of HIV and PrEP.

Mixing patterns based on HIV and PrEP require information about the HIV status and PrEP use of both egos (i.e., the study participant) and alters (i.e., the sexual partners that the egos report). These data are prone to error due to misclassification and missing data, because HIV and PrEP are difficult to report reliably.[68,72,73] At the ego-level, misclassification occurs when egos self-report values which are objectively incorrect and missing data arise if egos fail to report values at all. At the alter-level, data are ego-reported and similarly subject to misclassification and missingness. Parameters estimated using misclassified or partially observed data can be biased, depending on the underlying mechanism of the error. Misclassification and missingness in this context arise from similar mechanisms. **Figure 1.1** shows a directed acyclic graph (DAG) summarizing the possible factors contributing to misclassification and missing data among HIV and PrEP values in egocentric studies of MSM.

Figure 1.1. Directed acyclic graph of the mechanisms producing misclassification and missing data among HIV and PrEP values in egocentric studies of MSM



Knowledge of HIV serostatus is not universal among MSM. The CDC recommends that sexually active MSM are screened at least annually for HIV, with more frequent screening among MSM with higher risk behaviors.[73,74] Despite these guidelines, among MSM not previously diagnosed with HIV, approximately 28% have not screened for HIV in the past year and an additional 10% have never screened.[73] As a result, an estimated 16% of HIV infections among MSM are undiagnosed.[2] A systematic review of internet-using MSM found no association between race and having ever screened for HIV, but MSM of older age or higher education were more likely to have ever been screened.[75] Undiagnosed HIV among MSM is more prevalent in the southeast and among young or Black men.[2,76,77] Screening for HIV is a prerequisite to initiate PrEP and clinical practice guidelines recommend quarterly screening of patients using PrEP,[9] so screening (and diagnosis of HIV) is also expected to vary by PrEP use.

Among egos, MSM with undiagnosed HIV may incorrectly self-report their serostatus as negative, resulting in misclassification of HIV. Alternatively, egos with a recent risk exposure or infrequent screening may report their HIV serostatus as unknown, which is a form of missing data. It is unlikely that an ego would incorrectly self-report their HIV serostatus as positive, but stigma surrounding HIV and social desirability bias can influence egos living with HIV to self-report their serostatus as negative.[78,79] Self-reported HIV status can be verified with an HIV test, although this is expensive for studies to implement and generally not feasible for online surveys. Given varying rates of screening and diagnosis, misclassification and missingness are expected to vary differentially with respect to age, race, PrEP use and other demographic and behavioral factors. Knowledge of PrEP use is easier to self-report, in theory, since egos are presumably aware of whether they have used PrEP. However, if an ego does not accurately remember the timing of past PrEP use, then PrEP use during a specific partnership could be misclassified or reported as unknown.

There are additional challenges to collecting HIV and PrEP data for alters. Since egocentric data are usually one-sided (i.e., only one of the two individuals in a dyad is sampled), the information about alters is reliant upon what the ego knows and reports. Effective conversations surrounding HIV and PrEP do not always occur before sexual encounters,[80–88] so egos may be unable to accurately report information about their alters.[68,72] Discussions of HIV occur with differing frequency based on diagnosed HIV status; MSM with diagnosed HIV are more likely to discuss their HIV status with sexual partners than MSM without diagnosed HIV.[68,80,88] Other factors associated with discussing HIV with a sexual partner include age,[84] having a social relationship in addition to sexual,[68] meeting online,[86,87] and having sex more than once with the partner.[88] If HIV and PrEP information is not exchanged, egos may report these values as unknown, resulting in missing data. Some MSM may incorrectly assume that partners who are living with HIV do not have HIV (or vice versa) resulting in misclassification.[68,72] Similarly, it is possible that some MSM may assume that a partner was using PrEP at the time of a sexual encounter, perhaps because the partner was known to use PrEP in the past (e.g., PrEP use is listed on a sexual networking app); however, PrEP may have been discontinued prior to the encounter or never used at all.

The misclassification described affects both egos and alters and we hypothesize this to be differential with respect to the true HIV and PrEP values, as well as factors independently associated with edge formation. As a result, ignoring misclassification could lead to biased estimates of the relationship between HIV and PrEP and the probability of edge formation in network models. Similarly, the probability that HIV or PrEP is reported unknown is related to the true values, as well as important covariate factors. Therefore, the probabilities are missing not at random and complete case analysis would likely introduce additional bias to the estimates of HIV and PrEP mixing.[89] As a result, studies which do not address misclassification and missing data might misestimate the magnitude of mixing by HIV and PrEP. The magnitude and direction

of this bias is challenging to predict intuitively, given the complex set of factors which determine which values are misclassified or reported unknown. However, it is likely that misclassification of HIV results in under-reporting of partners with HIV (and over-reporting of those without HIV),[78,79] which we expect would result in an overestimate of assortative mixing among MSM without HIV, and underestimate assortative mixing among MSM with HIV. In terms of missing data, it is likely that missing values among egos and alters are more commonly negative, given the relatively low prevalence of undiagnosed HIV,[2] and MSM with diagnosed HIV are more likely to disclose their HIV status;[68,80,87] in this case, estimates of assortative mixing would be underestimated for MSM without diagnosed HIV and overestimated for MSM with diagnosed HIV. Similar logic can be applied to PrEP, although there is less information in the published literature to inform the potential direction of the bias. However, underreporting of PrEP use among alters (whether due to misclassification or missing data) would result in an underestimate of assortative mixing with respect to PrEP; and over-reporting of PrEP would result in an overestimate of assortative mixing by PrEP use status.

It may be possible to quantify and reduce the bias by using misclassification correction and missing data imputation methods. This is important because network models of HIV transmission rely on valid mixing statistics to estimate parameters. Furthermore, improving the validity of these estimates could have broader application to studies that use egocentric sexual history data, including studies of HIV serosorting and PrEP sorting, disclosure of HIV and PrEP in sexual partnerships, and behavioral modification because of HIV and PrEP.

Network-Based Mathematical Models for HIV Transmission

Mathematical models of infectious disease transmission are useful tools to estimate epidemic potential and the effectiveness of an intervention at the population level.[34] Clinical trials and observational research studies can provide estimates of an intervention's efficacy or effectiveness on the individual level. The total effects of an intervention on the population level

are difficult to predict in infectious disease epidemiology due to indirect effects, which are not accounted for using a simple function of individual-level effectiveness and coverage level.[34] In order to predict the population-level impact of an intervention like PrEP, it is necessary to use mathematical models which can account for both direct and indirect effects.[34] Traditional approaches to modeling epidemics, such as compartmental models, may not be appropriate for diseases like HIV, because the nature of contact necessary for transmission involves complex human behavior, random-mixing cannot be assumed, and network effects play a large role in transmission dynamics.[31,32,34,39] Network-based mathematical models allow for increased complexity and are suitable for modeling HIV.[36]

Network-based mathematical models of HIV transmission are stochastic simulations that use dynamic contact networks with additional mathematical functions to model transmission.[36] The contact networks can be simulated using the ERGM and TERGM statistical models described above. Algorithms are then added to the model to represent behaviors within partnerships (e.g., condom use, anal sex positioning), biological processes (e.g., HIV viral load), and the per-contact probability of transmission. The models are initialized with a starting population and the epidemic is calibrated to match empirical data. Once calibrated, the model can then be used to project forward in time to predict future epidemic outcomes. Counterfactual scenarios can be represented by modifying the model parameters.[90] For example, a reference scenario may be simulated without PrEP, whereas an experimental scenario may include PrEP allocated to a portion of the population.[13] Under each scenario condition, outcomes are tracked, such as cumulative incidence and person-time of PrEP use. By comparing the outcomes of counterfactual scenarios, the models provide a causal understanding of the mechanisms which impact an epidemic at the population-level.[90]

Prior network-based models have estimated the population impact of PrEP, with uptake based on individual-level attributes, such as age, race and risk level.[12–14,91–93] Recently, we

(KMM & SMJ) published a network-based modelling study that estimated the population impact of long-acting injectable PrEP (an experimental formulation of PrEP) when available concurrently with daily-oral PrEP.[94] In general, mathematical models have helped inform public policy and reinforce the utility of PrEP when uptake is robust. A potential limitation of these models is the assumption of random mixing with respect to diagnosed HIV status and PrEP use, conditional on behavior and a limited set of attributes such as age and race. These models may partially represent HIV and PrEP sorting in the network using mixing patterns based on nodal attributes (e.g., age and race) which are independently associated with HIV and PrEP in the model. However, additional sorting within and between groups is likely, based on the mechanisms described previously. Models which account for HIV and PrEP sorting in the network would overcome this limitation and provide a more realistic estimate of the population-level impact of PrEP given current uptake.

Networks and Mathematical Simulations to Inform Public Health Policy

Simulating the sexual networks of MSM will help identify mechanisms for HIV exposure and transmission. This will extend the knowledge gained using traditional regression techniques to identify groups at risk for infection.[33] In this context, the network structures are a framework to represent risk, in addition to the traditional risk factors such as demographics, behavior, and location. Thus, network structures can guide public health policy and interventions.[95,96] Although network science was not explicitly invoked at the time, a classic example of this concept in HIV is the closing of bathhouses attended by MSM in the early years of the epidemic.[95] The bathhouses served as social venues in which attendees were part of highly interconnected sexual network components which facilitated rapid growth of the epidemic. By closing these venues, the network components were disrupted. There are social and ethical consequences to these types of public health interventions, so this example should be instructive rather than idealized for replication. For example, the network hypothesis for racial disparities in HIV has

been used by some to suggest that sex with Black men should be avoided.[97] This type of "intervention" is impractical in the real world and results in other consequences, including stigma, racism, and discrimination.[97]

Despite challenges, careful use of network concepts can guide effective and ethical interventions,[95,96] even when network segmentation is impractical or unethical. For example, PrEP could be targeted to highly centralized sub-populations and individuals (e.g., people who attend sex parties or exchange sex for money, drugs and other goods).[31] PrEP can disrupt chains of transmission, resulting in both primary and secondary prevention benefits. Targeting PrEP to highly centralized nodes both protects those individuals with higher risk for HIV and maximizes efficiency by disrupting more paths on average. Another delivery strategy is to provide PrEP to the social and sexual contacts of recently infected individuals, similar to the ring vaccination strategy used to contain smallpox,[98] and more recently in response to ebola.[99,100] This strategy is based on the theory that neighboring nodes may have similar risks for HIV,[42] and PrEP use may be sparse in areas of the network with prevalent HIV transmission.

By simulating networks, we can identify opportunities to optimize PrEP delivery. Network-based models of HIV transmission can be used to test various network informed PrEP delivery strategies. To do this, mixing patterns with respect to HIV and PrEP are needed to simulate these networks appropriately.

Dissertation Aims

The purpose of this dissertation is to understand the potential impact of HIV serosorting and assortative mixing among MSM who use PrEP on the population benefit of PrEP. These analyses will test the hypothesis that assortative mixing among MSM who use PrEP produces clusters of PrEP use in the population, which decrease the population benefit of PrEP compared

to modelled projections. We hypothesize that network clustering of PrEP is one factor contributing to decreased PrEP effectiveness at the population-level.

In Aim 1, we used 2017–2019 egocentric sexual network data of MSM to estimate mixing statistics for HIV serosorting and PrEP sorting. This analysis used missing data and reclassification methods to address information bias in egocentric reporting of diagnosed HIV status and PrEP use during the partnership.

In Aim 2, we estimated and simulated cross-sectional sexual networks of MSM in the US to assess mixing by diagnosed HIV status and PrEP use. The network models were fit to summary statistics from an egocentric sexual network study, including degree estimates, assortative mixing by race/ethnicity and age, and mixing matrices for the interaction of diagnosed HIV and PrEP use, weighted to the demographics and MSM in the US We compared fully saturated models of the empiric network statistics to less structured parameterizations, to quantify the magnitude of nonrandom mixing that is expected based on other network properties.

In Aim 3, we used a network-based model of HIV transmission to estimate the impact of network-clustered PrEP use. The model was developed to represent observed patterns of PrEP uptake in our target population of MSM in Atlanta. We compared models with and without PrEP sorting to test the hypothesis that assortative mixing by PrEP use status decreases the overall impact of PrEP even at fixed coverage levels in the population.

Chapter 2. Sexual mixing by diagnosed HIV status and pre-exposure prophylaxis use among men who have sex with men: stochastic reclassification to address information bias in egocentric network data

ABSTRACT

Background: Population-level estimates of sexual network mixing are needed to parameterize prediction models of pre-exposure prophylaxis (PrEP) effectiveness to prevent human immunodeficiency virus (HIV) among men who have sex with men (MSM). Estimates obtained by egocentric sampling are vulnerable to information bias due to incomplete respondent knowledge.

Methods: We estimated patterns of serosorting and PrEP sorting among MSM in the United States using data from a 2017–2019 egocentric sexual network study. Respondents served as proxies to report the HIV status (test-negative, diagnosed HIV, or unknown) and PrEP use (ever, never, or unknown) of recent sexual partners. We contrasted results from a complete-case analysis (unknown HIV and PrEP excluded) versus a sensitivity analysis with respondent-reported data stochastically reclassified to simulate unobserved self-reported data from sexual partners.

Results: We found strong evidence of preferential partnering across analytical approaches. The reclassification analysis showed concordance among MSM with diagnosed HIV (39.3%; 95% simulation interval: 30.9, 46.0), MSM who used PrEP (31.9%; 21.0, 37.4), and MSM who did not use PrEP (82.6%; 79.3, 87.1). The fraction of partners with diagnosed HIV was higher among MSM who used PrEP (11.1%; 8.6, 13.5) compared to MSM who did not use PrEP (3.7%; 2.7, 4.6). Comparatively, the complete-case analysis showed higher fractions of partners with diagnosed HIV and those who used PrEP, across all strata, and lower fractions of partners who did not use PrEP.

Discussion: Serosorting and PrEP sorting among MSM may influence HIV transmission dynamics and effectiveness of PrEP at the population level. Complete-case analyses may misestimate population-level mixing. Sensitivity analyses can reduce bias but validation data are needed to verify results.

BACKGROUND

Gay, bisexual, and other men who have sex with men (MSM) remain at increased risk for human immunodeficiency virus (HIV) in the United States.[101] The federal "Ending the HIV Epidemic" (EHE) initiative calls for increased use of pre-exposure prophylaxis (PrEP), which can decrease individual risk more than 99%.[6–8,16] Modeling studies have shown that PrEP has the highest impact at a population level if targeted to MSM with greater risk for HIV.[12–14] Despite normative guidelines to evaluate individual risk,[9] non-random mixing in sexual networks may influence HIV exposure and decrease the population-level benefit of PrEP.[102] Quantitative estimates of mixing among MSM are needed to parameterize prediction models of HIV epidemics and evaluate progress toward EHE priorities.[103]

Serosorting is the preferential selection of sexual partners with the same HIV diagnosis status to decrease risk for HIV transmission. Approximately 1 in 6 MSM living with HIV are undiagnosed, which limits the effectiveness of serosorting to prevent HIV.[59,60,101] Serosorting patterns among MSM may be evolving in the U=U era (i.e., Undetectable = Untransmittable), as more MSM became aware that HIV treatment prevents onward transmission.[104–106] A newer phenomenon, PrEP sorting, has also emerged in which partners are selected based on current PrEP use.[63,64,62,65,70,66] For example, MSM without HIV may prefer sexual partners who use PrEP based on the perception of decreased risk for HIV.[63] The advent of PrEP and U=U may also disrupt traditional serosorting by decreasing barriers (e.g., stigma and fear) to sero-different partnerships.[62]

Estimates of HIV and PrEP sorting among MSM exist.[59,60,62,64,65,70] However, standard data collection mechanisms may bias the estimates. First, not all MSM know their HIV status: among MSM without an HIV diagnosis, 10% have never screened for HIV and 28% have not screened in the past year.[73] As a result, self-reported data reflect HIV test history and MSM with undiagnosed HIV are not identified. Second, mixing patterns are estimated based on concordance or discordance of individual attributes in a sexual partnership. Adaptive sampling strategies (e.g., chain-sampling of sexual partners) are ideal, but recruitment is challenging and expensive. Egocentric sexual network studies, in which index respondents (i.e., egos) serve as a proxy to report the attributes of recent sexual partners, are a convenient alternative. However, egocentric studies are vulnerable to misclassification if the ego-reported data is different than what the partner would have self-reported.[72]

Discussions surrounding HIV status and PrEP use are common in sexual partnerships of MSM, but still far from universal.[63,65,68,80,87,84,107–109] MSM with diagnosed HIV are more likely to initiate these conversations and disclosure tends to be mutual,[63,68,80,87,107] so knowledge may be differential with respect to HIV diagnosis status.[72] Additional variability occurs based on partnership duration or commitment level,[80,108] overlapping social networks,[68,87] and demographic factors.[68,72,83,84] Less is known about discussions of PrEP which may occur as part of a broader negotiation of HIV risk.[63,109] Nevertheless, recent egocentric estimates of serosorting and PrEP sorting are limited by unknown HIV status and PrEP use in sexual partnerships.[62,64,65]

Given the potential impact of mixing patterns on HIV transmission dynamics, there is a need to address potential bias in egocentric data. In the present study, we estimate HIV serosorting and PrEP sorting patterns using a large egocentric study of MSM in the United States. We present the data in three ways to demonstrate how estimates may be biased depending on analytical decisions: (1) a full-sample analysis, with unknown values included to

summarize the data based on ego-reported knowledge; (2) a complete-case analysis, with unknown values excluded; and (3) a sensitivity analysis, with ego-reported data stochastically reclassified to estimate what the partner would have self-reported had he been surveyed. The goal of the sensitivity analysis is to correct for information bias in egocentric estimates of HIV and PrEP sorting.

METHODS

Study design and sample: We used data from ARTnet, a cross-sectional (2017–2019) egocentric sexual network study of MSM in the United States, recruited from MSM who had participated in the American Men's Internet Study.[103] Cisgender men aged 15–65 years were eligible to participate if they reported a lifetime history of male sexual partners. Respondents self-reported demographic and other individual attributes, including HIV status and PrEP use. Respondents also completed a 12-month sexual history inventory with detailed questions about their most recent oral or anal sexual partners (up to five) including demographics, HIV status, PrEP use, type and frequency of sexual activity, and partnership duration and level of commitment. We refer to respondents as egos and partners as alters. Total enrollment of ARTnet after deduplication was 4,904 egos, who reported on 16,198 alters.

We restricted the sample to anal-sex partnerships, due to the potential for HIV transmission and because serosorting and PrEP sorting decisions may be related to type of sexual activity. We further excluded partnerships with missing (or reported unknown) alter race and/or ethnicity, because the reclassification model uses alter race/ethnicity. For HIV status and PrEP use, we distinguished between responses reported as unknown and less informative missingness by excluding partnerships if the ego skipped or refused to answer questions. Methodological details of ARTnet and descriptive summary statistics of the full sample have been published previously.[103]

Individual-level attributes: Egos self-reported age at survey completion, race, and ethnicity. We grouped continuous age into categories (ages 15–24; 25–34; 35–44; 45–54; and 55–65) and combined race and ethnicity to one categorical variable (non-Hispanic White; non-Hispanic Black; Hispanic/Latino; or other). Alter race and ethnicity was categorized using the same definition. Egos were asked to report alter age or an age that "you think is close." Alternatively, egos could estimate alter age relative to their own (e.g., 2–10 years younger). Numerical age was then estimated using single imputation and assigned to categories (including an additional category for 66 or older). We used the imputation results previously described to maintain consistency across ARTnet analyses.[103]

Egos self-reported their own HIV status at the time of survey completion. Egos with prior HIV test history were classified as either test-negative or diagnosed HIV. Those without HIV test history were classified as HIV unknown (this combined: never tested; did not receive results; unsure of results; or indeterminate results). Egos with test-negative HIV status were asked about PrEP use during each sexual partnership. We classified PrEP use as those who had used PrEP (always or sometimes) or those who had not used PrEP for each alter. Screening for HIV is a prerequisite for PrEP initiation, so egos with unknown HIV status were not asked about PrEP and therefore categorized as never PrEP.

Ego-reported alter HIV status was classified as diagnosed HIV, test-negative, or HIV unknown (combined responses: never tested; has not been tested recently and is uncertain of his HIV status; or I don't know). Egos reported PrEP use for alters with test-negative or unknown HIV. We categorized alter PrEP use as used PrEP, did not use PrEP, or unknown ("I don't know").

Partnership-level attributes: The geographic location of each partnership (based on ego zip-code) was categorized for 15 major cities and the 9 US Census Divisions. Egos indicated whether each alter is someone they feel committed to above all others ("someone you might call

your boyfriend, significant other, life partner or husband"). We created a variable for partnership type based on commitment and frequency of sex: main (committed partner); casual (not committed but sex occurred more than once); or one-time (not committed and sex occurred once).

Mixing patterns: We estimated mixing patterns for HIV serosorting and separately for PrEP sorting (i.e., the interaction of HIV status and PrEP use). For HIV serosorting, we stratified egos by HIV status and reported the proportion of alters with concordant or discordant HIV status. Similarly, for PrEP sorting, we stratified egos by HIV status and PrEP use, and reported the proportion of alters with each combination of HIV and PrEP. We estimated mixing patterns based on three alternative approaches and quantified differences between the methods.

First, we completed a full-sample analysis including unknown values as standalone categories. We disaggregated HIV status by test history and ego knowledge (diagnosed HIV, test-negative, and HIV unknown). Similarly, we reported PrEP use for egos with test-negative HIV, and for alters with test-negative or unknown HIV status. Second, the complete-case analysis excluded partnerships with unknown HIV or PrEP. We calculated HIV serosorting among egos and alters with test-negative HIV or diagnosed HIV. For PrEP sorting, we further excluded alters with unknown PrEP use. Third, the sensitivity analysis used the full sample of partnerships and simulated new values for alters by reclassifying the ego-reported data. We used a dichotomous definition of HIV diagnosis status (with versus without diagnosed HIV) by combining test-negative and unknown HIV. The group of MSM without diagnosed HIV include those who are truly without HIV infection and those with undiagnosed HIV. We categorized PrEP use or nonuse for each ego and alter without diagnosed HIV. We used the self-reported data to classify egos. However, the same dichotomizations for alters would introduce misclassification, because the information reported by egos may be different than the information the alter would have self-reported. Therefore, we simulated alter data using the

methods described below. We reported median results and 95% simulation intervals (SI) across all simulation datasets. We compared the results from the sensitivity analysis to the complete-case analysis by calculating proportion differences and reported the median result and 95% SI.

Sensitivity analysis to reclassify egocentric data: We used multiple imputation with exponential-tilt models to reclassify the ego-reported alter HIV status and PrEP use. The goal of the sensitivity analysis is to quantify potential information bias in ego-reported data by imputing what alters would have self-reported. The method is adapted from prior work in studies of older adults, in which a proxy respondent is used if study subjects are unable to complete a survey.[110] In the present study, we apply the method to egocentric data, in which self-reported alter data is missing by design and egos serve as proxies for one or more alters. The process is repeated multiple times to allow for random variation. In the present study, we used 300 repetitions. We used a larger number of repetitions than is required for simple missing data imputation, due to the large proportion of unknown values and uncertainty of the reclassification parameters. We completed the process in two stages: first to reclassify alter HIV status and second to reclassify PrEP use for the subset of alters assigned without diagnosed HIV in the first stage. Full methodological details are provided in **Appendix A** (page 114).

Briefly, we estimated separate imputation models for alter HIV status and PrEP use, using Bayesian multilevel regression with integrated nested Laplace approximation (INLA).[111] The imputation models included a random intercept for each ego and fixed effects for alter demographics (age group, race/ethnicity, and the interaction of age group and race/ethnicity), ego demographics (age group, race/ethnicity, and the interaction of age group and race/ethnicity), ego HIV status (diagnosed HIV, test-negative, or unknown) and PrEP use (used PrEP or did not use PrEP), partnership type, and location. We also modeled the three-way interaction of partnership type, ego HIV status and PrEP use, to allow mixing patterns to vary by partnership type. Predictive probabilities for each observation (ego-reported known and

unknown) were drawn from the posterior distributions of the imputation models. The probabilities were then adjusted based on assumptions about the sensitivity and specificity of the ego-reported data. New values were then imputed for each alter using the adjusted probabilities. Final specifications of the model parameters were calibrated to the expected prevalence of diagnosed HIV and PrEP use among alters, estimated using the population of egos standardized to the age, race/ethnicity, and geographic distribution of alters.

RESULTS

The final analytic sample included 3,904 egos with 9,914 alters (**Table 2.1**) after excluding: egos with no recent sexual partners (n = 237); oral-sex-only partnerships (n = 4,796); egos missing PrEP use (n = 462); and alters missing race and/or ethnicity (n = 947), HIV status (n = 235), or PrEP use (n = 27).

The egos and alters differed by demographics and ego-reported HIV status and PrEP use (**Table 2.1**). At the partnership-level, 48.0% of egos were aged 35 or older, compared to 39.2% of alters. A greater proportion of egos were non-Hispanic White (71.4%) compared to alters (57.4%), and smaller proportions of egos compared to alters were classified as non-Hispanic Black (4.9% vs 12.1%) or Hispanic/Latinx (14.8% vs 20.6%). At the partnership level, 11.2% of egos self-reported diagnosed HIV and 12.3% were of unknown HIV status. Alternatively, only 6.6% of alters were reported to have diagnosed HIV and 24.2% were of unknown HIV status. Among those without diagnosed HIV, 24.7% of egos used PrEP during the partnership, compared to only 15.5% of alters. A substantial proportion of alters without diagnosed HIV were of unknown PrEP use (48.6%).

Table 2.1. Characteristics of egos and up to five anal-sex alters in the twelve months prior to survey completion in a national egocentric sexual network study of men who have sex with men in the United States (2017–2019)

	Ego-level		Partnership-level			
	Egos		Egos		Alters	
	N	%	n	%	n	%
Total	3904	100.0	9914	100.0	9914	100.0
Age Group						
15-24	1138	29.1	2583	26.1	2470	24.9
25-34	1035	26.5	2573	26.0	3560	35.9
35-44	573	14.7	1558	15.7	1892	19.1
45-54	634	16.2	1801	18.2	1296	13.1
55-65	524	13.4	1399	14.1	612	6.2
66+	---	---	---	---	84	0.8
Race and Ethnicity						
Non-Hispanic Black	186	4.8	484	4.9	1195	12.1
Non-Hispanic White	2810	72.0	7079	71.4	5693	57.4
Hispanic/Latinx	564	14.4	1466	14.8	2042	20.6
Other	344	8.8	885	8.9	984	9.9
HIV Status						
Test-negative	2914	74.6	7578	76.4	6857	69.2
Diagnosed HIV	369	9.5	1114	11.2	655	6.6
Unknown	621	15.9	1222	12.3	2402	24.2
PrEP Use[1]						
Never	---	---	6629	75.3	3320	35.9
Ever	---	---	2171	24.7	1438	15.5
Unknown	---	---	---	---	4501	48.6
Partnership Type						
Main	---	---	---	---	2155	21.7
Casual	---	---	---	---	4053	40.9
One-time	---	---	---	---	3706	37.4

[1]Pre-exposure prophylaxis use during the partnership, among egos or alters without diagnosed HIV

After reclassification, the median prevalence of diagnosed HIV among alters was 9.4% (95% SI: 7.2, 11.1) across all 300 simulated datasets (**Appendix Table A.3.**, page 126). This was similar to the expected prevalence (9.9%) based on the population of egos standardized to alter demographics. Overall, 98.8% (95% SI: 95.7, 99.7) of alters with ego-reported diagnosed HIV remained classified with diagnosed HIV in the simulated data. The fraction reclassified to diagnosed HIV was 1.6% (95% SI: 0.1, 3.1) among alters with ego-reported test-negative HIV and 7.2% (95% SI: 1.5, 11.2) among unknown HIV. Among all alters, the prevalence of ever using PrEP was 17.9% (95% SI: 12.2, 21.6; **Appendix Table A.4.**, page 128). Although widely variable across datasets, the median value was slightly higher than the expected prevalence (16.5%). Stratified by ego-reported knowledge, the median prevalence of ever used PrEP was 92.0% (95% SI: 52.5, 98.6) among ever used PrEP was, 2.6% (95% SI: 1.0, 4.0) among never used PrEP, and 10.6% (95% SI: 4.4, 16.1) among unknown PrEP.

The full-sample analysis of serosorting shows concordance among MSM with test-negative HIV (75.0%) and those with diagnosed HIV (28.7%) (**Figure 2.1** and **Table 2.2**). The fraction of alters with unknown HIV was highest among egos with unknown HIV (39.9%) and lowest for test-negative HIV (20.9%). Overall, 31.6% of partnerships were excluded from the complete-case analysis due to unknown HIV status (**Table 2.3**). Among the remaining 6,777 alters, the prevalence of diagnosed HIV was 9.3%. There was 41.0% concordance of diagnosed HIV and 94.8% of test-negative HIV. The sensitivity analysis showed similar quantitative results, compared to the complete-case analysis, although qualitative interpretation is different based on the definition of HIV status. After reclassification, matching among MSM with diagnosed HIV was 39.3% (95% SI: 30.9, 46.0). Among MSM without diagnosed HIV concordance was 94.4% (95% SI: 93.3, 95.8).

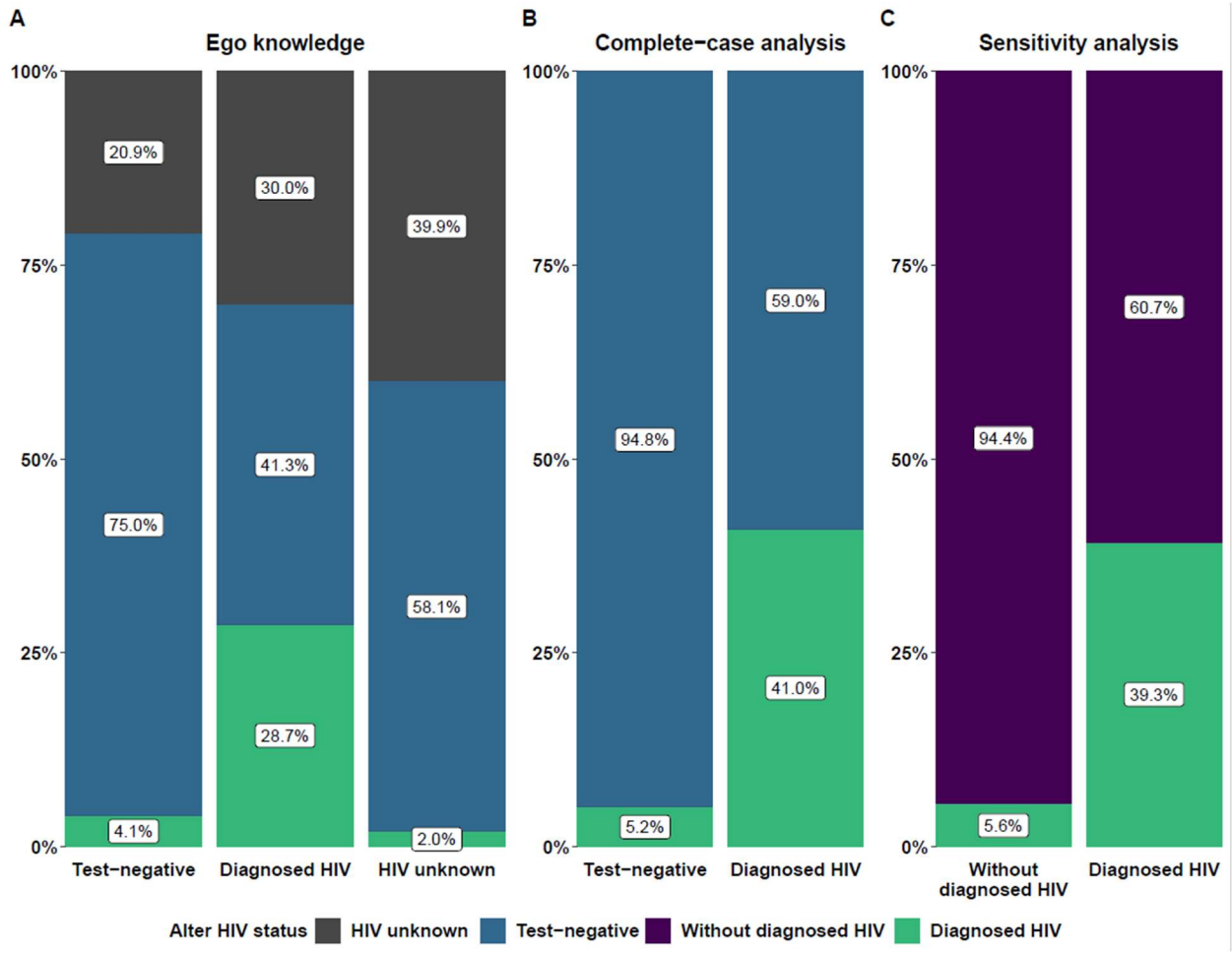
Table 2.2. Partnership-level mixing by HIV serostatus and pre-exposure prophylaxis use among anal-sex partnerships based on ego knowledge in a national egocentric sexual network study of men who have sex with men in the United States (2017–2019)

			HIV Status, Alters					
HIV Status, Egos			**Diagnosed HIV**		**Test-negative**		**Unknown HIV**	
	n	%[1]	n	%[2]	n	%[2]	n	%[2]
Diagnosed HIV	1114	11.2	320	28.7	460	41.3	334	30.0
Test-negative	7578	76.4	310	4.1	5687	75.0	1581	20.9
Unknown HIV	1222	12.3	25	2.0	710	58.1	487	39.9
Total	9914	100.0	655	6.6	6857	69.2	2402	24.2

			HIV Status and PrEP Use, Alters							
HIV Status and PrEP Use, Egos			**Diagnosed HIV**		**Never PrEP**		**Ever PrEP**		**Unknown PrEP**	
	n	%[1]	n	%[2]	n	%[2]	n	%[2]	n	%[2]
Diagnosed HIV	1114	11.2	320	28.7	184	16.5	161	14.5	449	40.3
Never PrEP	5407	54.5	135	2.5	2188	40.5	583	10.8	2501	46.3
Ever PrEP	2171	21.9	175	8.1	453	20.9	604	27.8	939	43.3
Unknown HIV	1222	12.3	25	2.0	495	40.5	90	7.4	612	50.1
Total	9914	100.0	655	6.6	3320	33.5	1438	14.5	4501	45.4

[1]Column percentage (all partnerships). [2]Row percentage (partnerships, conditional on the ego HIV status or PrEP use).

Figure 2.1. Serosorting among men who have sex with men in an egocentric sexual network study in the United States (2017–2019)



Legend: Panel A: Mixing patterns estimated using the ego-reported data to show the full distribution of ego knowledge; Panel B: Data restricted to exclude unknown HIV status; Panel C: Ego-reported data stochastically reclassified to approximate unobserved self-reported alter data. Percentages shown are median results across 300 simulated datasets.

Table 2.3. Partnership-level mixing by HIV diagnosis status among anal-sex partnerships in a national egocentric sexual network study of men who have sex with men in the United States (2017–2019)

		Complete-case[1]		Reclassification Analysis[2]				Absolute Change[3]	
Egos	**Alters**	N[4]	%[5]	N[4]	95% SI	%[5]	95% SI	PD	95% SI
With HIV[6]	With HIV[6]	320	41.0	438	344, 513	39.3	30.9, 46.0	-1.7	-10.1, 5.0
	Without HIV[7]	460	59.0	676	601, 770	60.7	54.0, 69.1	1.7	-5.0, 10.1
Without HIV[7]	With HIV[6]	310	5.2	490	366, 593	5.6	4.2, 6.7	0.4	-1.0, 1.5
	Without HIV[7]	5687	94.8	8310	8207, 8434	94.4	93.3, 95.8	-0.4	-1.5, 1.0
Total	With HIV[6]	630	9.3	932	710, 1102	9.4	7.2, 11.1	0.1	-2.1, 1.8
	Without HIV[7]	6147	90.7	8982	8812, 9204	90.6	88.9, 92.8	-0.1	-1.8, 2.1

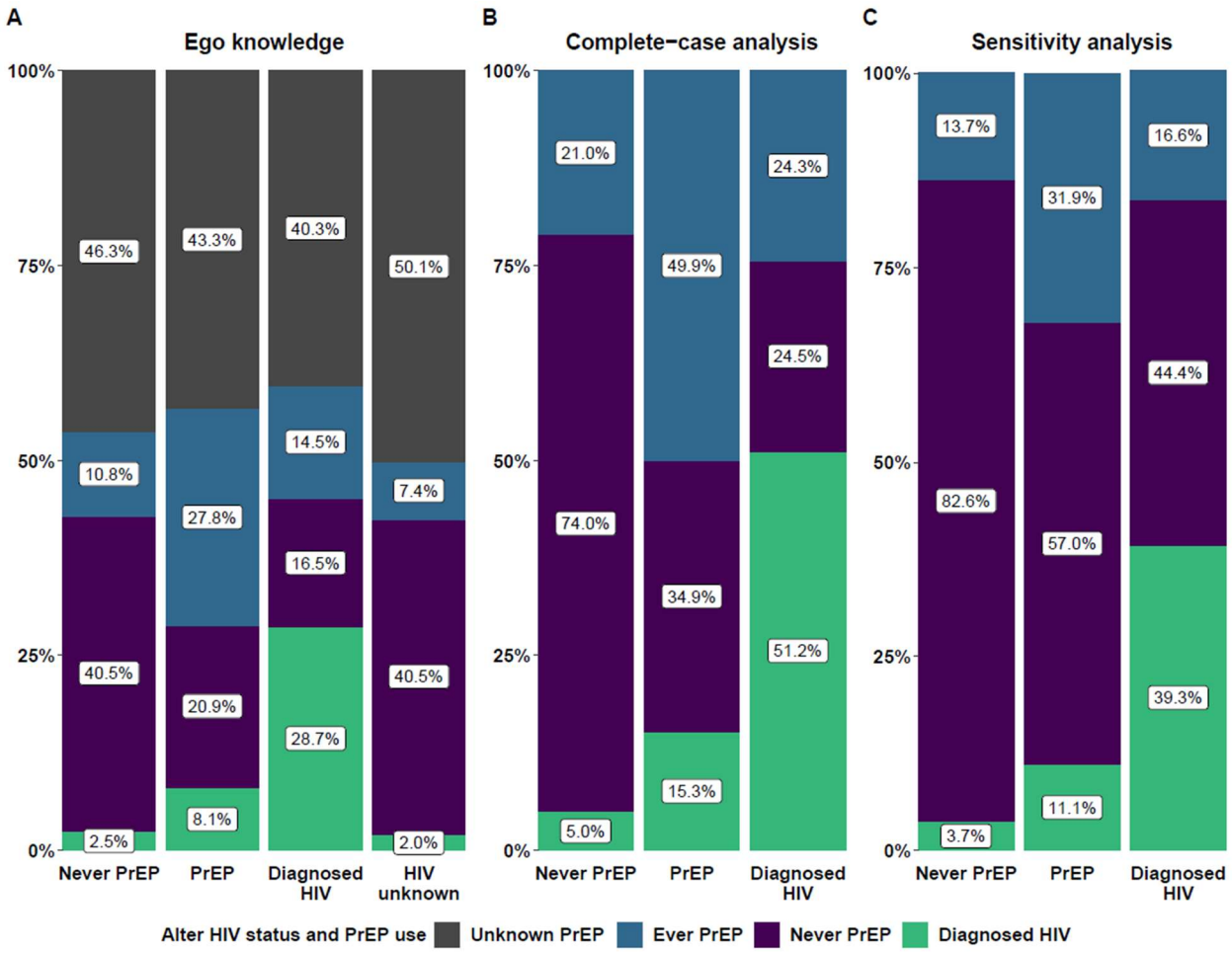
[1]Restricted to partnerships with known ego and alter HIV status. [2]Full sample analysis, with alter HIV status stochastically reclassified. [3] Prevalence difference (PD) comparing proportions in the reclassification analysis to the complete-case analysis. [4]Number of partnerships. [5]Proportion of partnerships, conditional on ego HIV status. [6]Diagnosed HIV. [7]Without diagnosed HIV: complete-case analysis restricted to test-negative HIV; and reclassification analysis includes test-negative or unknown HIV status

The full-sample analysis of PrEP sorting showed varied patterns of alter PrEP use, depending on ego HIV status and PrEP use (**Figure 2.2** and **Table 2.2**). There was evidence of concordant partnering within each group: never used PrEP (40.5%); ever used PrEP (27.8%); and diagnosed HIV (28.7%). The proportion of alters with diagnosed HIV was higher for egos who had ever used PrEP (8.1%) compared to egos who had never used PrEP (2.5%). Similarly, alter PrEP use was higher among egos with diagnosed HIV (14.5%) compared to egos who had never used PrEP (10.8%). Egos with unknown HIV reported the lowest fractions of alters with diagnosed HIV (2.0%) or alters who had ever used PrEP (7.4%). Unknown alter PrEP use was 45.4% overall, with the lowest fraction among egos with diagnosed HIV (40.3%) and the highest among egos with unknown HIV (50.1%).

The complete-case analysis of PrEP sorting was restricted to 4,452 partnerships after excluding unknown HIV and PrEP – comprising only 44.9% of the original sample (**Table 2.4** and **Figure 2.2**). The prevalence of diagnosed HIV among alters was higher (14.2%, versus 9.3% in the complete-case analysis of serosorting and 6.6% in the full sample) due to the shrinking denominator of remaining alters. Similarly, the fraction of alters who had used PrEP was twice as high in the complete-case analysis (28.9%) compared to the full sample (14.5%). By excluding unknown values, concordance increased for each group of MSM: 74.0% had not used PrEP; 49.9% had used PrEP; and 51.2% were with diagnosed HIV. Other patterns remained, including higher prevalence of alters with diagnosed HIV among egos who had used PrEP (15.3%) compared to egos who had not used PrEP (5.0%). In the sensitivity analysis, the median prevalence of diagnosed HIV and ever used PrEP decreased by 4.8% (95% SI: 3.1, 7.0) and 11.0% (95% SI: 7.3, 16.7), respectively, compared to the complete-case analysis. Percent concordance after reclassification was 82.6% (95% SI: 79.3, 87.1) for had not used PrEP, 31.9% (95% SI: 21.0, 37.4) for had used PrEP, and 39.3% (95% SI: 30.9, 46.0) for diagnosed HIV. Compared to the complete-case analysis, this represented an absolute increase of 8.6%

(95% SI: 5.3, 13.1) concordance among those who had not used PrEP, and a decrease of 18.0% (95% SI: 12.5, 28.8) for those who had used PrEP and 11.9% (95% SI: 5.2, 20.3) for diagnosed HIV. Similar absolute decreases of diagnosed HIV and ever used PrEP among alters were observed for each stratum of egos.

Figure 2.2. Pre-exposure prophylaxis (PrEP) sorting among men who have sex with men in an egocentric sexual network study in the United States (2017–2019)



Legend: Panel A: Mixing patterns estimated using the ego-reported data to show the full distribution of ego knowledge; Panel B: Data restricted to exclude unknown HIV status or PrEP use; Panel C: Ego-reported data stochastically reclassified to approximate unobserved self-reported alter data. Percentages shown are median results across 300 simulated datasets, so bar totals may not sum to 100%.

Table 2.4. Partnership-level mixing by HIV diagnosis status and PrEP use among anal-sex partnerships in a national egocentric sexual network study of men who have sex with men in the United States (2017–2019)

		Complete-case[1]		Reclassification Analysis[2]				Absolute Change[3]	
Egos	**Alters**	N[4]	%[5]	N[4]	95% SI	%[5]	95% SI	PD	95% SI
With HIV[6]	With HIV[6]	320	51.2	438	344, 513	39.3	30.9, 46.0	-11.9	-20.3, -5.2
	Never PrEP[7]	153	24.5	495	428, 586	44.4	38.5, 52.6	19.9	14.0, 28.1
	Ever PrEP[7]	152	24.3	185	127, 229	16.6	11.4, 20.5	-7.7	-12.9, -3.8
Never PrEP[7]	With HIV[6]	135	5.0	248	178, 305	3.7	2.7, 4.6	-1.3	-2.3, -0.4
	Never PrEP[7]	1983	74.0	5478	5255, 5776	82.6	79.3, 87.1	8.6	5.3, 13.1
	Ever PrEP[7]	562	21.0	911	591, 1122	13.7	8.9, 16.9	-7.3	-12.1, -4.1
Ever PrEP[7]	With HIV[6]	175	15.3	241	186, 294	11.1	8.6, 13.5	-4.2	-6.7, -1.8
	Never PrEP[7]	400	34.9	1237	1126, 1471	57.0	51.9, 67.8	22.1	17.0, 32.9
	Ever PrEP[7]	572	49.9	692	456, 812	31.9	21.0, 37.4	-18.0	-28.8, -12.5
Total	With HIV[6]	630	14.2	932	710, 1102	9.4	7.2, 11.1	-4.8	-7.0, -3.1
	Never PrEP[7]	2536	57.0	7197	6838, 7848	72.6	69.0, 79.2	15.6	12.0, 22.2
	Ever PrEP[7]	1286	28.9	1779	1206, 2145	17.9	12.2, 21.6	-11.0	-16.7, -7.3

[1]Restricted to partnerships with known ego and alter HIV status and known alter PrEP use. [2]Full sample analysis, with alter HIV status and PrEP use stochastically reclassified. [3]Prevalence difference comparing proportions in the reclassification analysis to the complete-case analysis. [4]Number of partnerships. [5]Proportion of partnerships, conditional on ego HIV status. [6]Diagnosed HIV. [7]PrEP use during the partnership among those without diagnosed HIV: complete-case analysis restricted to test-negative HIV; and reclassification analysis includes test-negative or unknown HIV status

DISCUSSION

We found evidence of HIV serosorting and PrEP sorting among MSM across each of the analytical approaches, including strong concordance by diagnosed HIV status, and among those who had used PrEP and those who had not used PrEP. We also found evidence of sorting between MSM with diagnosed HIV and those who used PrEP. Our findings quantify the role of information bias in egocentric data. Analytical decisions about uncertainty change the magnitude of results as well as qualitative interpretation. This has implications for understanding population-level PrEP impact because these mixing features influence HIV transmission dynamics. Valid estimates are needed to specify model parameters and evaluate PrEP impact based on real-world mixing patterns among MSM.

As PrEP uptake among MSM increases over time and partnering norms potentially evolve,[20,62,63] periodic monitoring of population-level mixing patterns is needed to inform public health modeling and prevention messaging. Our analysis provides a recent (2017–2019) estimate of mixing by diagnosed HIV status and PrEP use among MSM in the United States. Consistent with previous reports of HIV serosorting in high income countries during the U=U era, we found strong concordance of diagnosed HIV status.[62,64,65,70] Our estimates of PrEP sorting are similarly supported by previous studies in Canada and the US, which showed high concordance of PrEP use and nonuse when the overall prevalence of PrEP use exceeds 10%.[62,64,65] In Australian MSM with low prevalence of PrEP use (3%), concordance of PrEP use was uncommon,[70] but still in excess of the fraction expected by chance alone.[112] We also found evidence of sorting between MSM with diagnosed HIV and those who use PrEP, similar to previous findings,[62,64] and consistent with CDC guidelines for PrEP indications.[9]

Taken together, existing evidence and our new results provide evidence for the concentration of biomedical protection against HIV transmission (i.e., PrEP and U=U) in fewer partnerships throughout the sexual network.[63] This may substantially decrease opportunities for

HIV transmission among MSM using PrEP, despite variable PrEP adherence and longitudinal persistence,[8,22,113] and gaps in viral suppression among MSM with diagnosed HIV.[114] However, HIV transmission may proceed uninterrupted in broad components of the sexual network where prevention efforts remain sparse. Indeed, our sensitivity analysis found 83% concordance among MSM not using PrEP. Additional research is needed to understand how mixing patterns interact with other features of sexual network structure (e.g., variable number of partners) to determine the full extent of HIV exposure among MSM.

Quantitative estimates of HIV and PrEP sorting vary across studies, in part because the underlying prevalence of diagnosed HIV and PrEP use may be different for each population. Our analysis also highlights differences in study design that can produce varying results. Complete-case analyses exclude MSM with unknown HIV status or PrEP use; this approach requires strong assumptions, including that the data are reported unknown completely at random and without additional misclassification.[89] We find these assumptions untenable, because knowledge of HIV and PrEP within sexual partnerships is likely differential with respect to each.[72] Our results suggest that bias in complete-case analyses of serosorting may be limited when the prevalence of diagnosed HIV is low and specificity is high, even if unknown HIV is relatively high – over 30% of partnerships in our sample – although validation data are needed to verify this finding. Full mixing patterns of HIV and PrEP sorting may require greater attention to information bias. Altogether, 55% of partnerships in our sample were excluded from the complete-case analysis of PrEP sorting, which artificially inflated the fractions of alters with PrEP use and diagnosed HIV. Our findings suggest that previously reported estimates of PrEP sorting may overestimate nonrandom mixing.[64] Alternatively, analyses may stratify by ego knowledge and include unknown HIV and PrEP as correlates of other behaviors,[62,65] but this approach does not estimate population-level mixing patterns. Our sensitivity analysis

demonstrates a third approach, in which ego-reported data are reclassified to estimate the unobserved self-reported alter information.

LIMITATIONS

Our sensitivity analysis aimed to reduce bias by reclassifying the ego-reported data based on assumptions about the sensitivity and specificity of classification. One strength of the sensitivity analysis is that our assumptions were explicit and quantified. However, residual bias might remain, and new bias could be introduced due to model misspecification. Validation data are needed to verify our assumptions and results. The reclassification model uses sensitivity and specificity parameters, which are familiar concepts to epidemiologists, but implementation of the model is not intuitive. Simpler approaches are possible,[115] but validation data are needed to quantify the interacting selection and classification mechanisms generating the ego-reported data. Future egocentric network studies should chain-recruit a subsample of alters to validate the predictive value of ego-reported data. For example, alters could self-report HIV diagnosis status and PrEP use, to assess the accuracy of ego-reported information. Finally, we only assessed PrEP use among egos who had previously screened for HIV, because HIV screening is a pre-requisite for obtaining a PrEP prescription. Some MSM may obtain PrEP from other sources (e.g., a friend sharing medication) so we may have underestimated PrEP use in this population. However, we expect this bias is minimal.

CONCLUSIONS

We found evidence of HIV and PrEP sorting in a 2017–2019 egocentric sexual network study of MSM in the United States. Unbiased estimates of population-level mixing are needed to understand of PrEP impact.[103] However, mixing patterns estimated with egocentric data are vulnerable to information bias. We used a sensitivity analysis to quantify and correct for potential bias. Our results demonstrate that information bias cannot be ignored, and further

studies are needed to verify our results. Egocentric studies should routinely collect validation data to assess and correct information bias.

Chapter 3. Assortative Mixing by HIV Status and PrEP Use in Sexual Network Models of Men Who Have Sex with Men

ABSTRACT

Background: Assortative mixing among men who have sex with men (MSM) who use pre-exposure prophylaxis (PrEP) and by HIV diagnosis status (serosorting) may decrease the population benefit of PrEP, by concentrating PrEP in the sexual network and resulting in more partnerships in which both men are not using PrEP.

Methods: We used a 2017–2019 egocentric study of MSM in the United States to estimate network statistics. Exponential random graph models (ERGMs) were fit to the observed network data to estimate cross-sectional networks of persistent and one-time partnerships. We compared fully saturated ERGM parameterizations to less saturated parameterizations (including degree heterogeneity and assortative mixing by age and race/ethnicity) to elucidate the mechanisms generating the observed HIV and PrEP mixing statistics.

Results: An estimated 45.3% of persistent and 23.6% of one-time partnerships among MSM were concordant between MSM without diagnosed HIV and not using PrEP. Models based on degree heterogeneity and assortative mixing within demographic groups reproduced only 79.1% and 69.8%, respectively, of these partnerships.

Discussion: Excess partnering among MSM not using PrEP, due to HIV and PrEP sorting, may partially explain sustained HIV diagnoses among MSM despite increased PrEP use. Interventions are needed to expand PrEP use beyond existing clusters in the sexual network.

BACKGROUND

Renewed human immunodeficiency virus (HIV) prevention efforts in the United States, including the federal "Ending the HIV Epidemic" (EHE) initiative, prioritize pre-exposure prophylaxis (PrEP) allocation to populations at increased risk for HIV, including gay, bisexual, and other men who have sex with men (MSM).[16] Uptake among MSM was initially slow, but by 2017 approximately 20% of MSM with indications accessed PrEP.[11] Coverage remains substantially lower than the predicted levels needed to meet the EHE goal of preventing 90% of infections by 2030, but mathematical models project a 20% decline in infections over ten years even at 2017 coverage levels.[116] Despite projections, HIV diagnoses among MSM have remained relatively constant.[117] There are multiple intersecting factors that contribute to the HIV diagnosis rate, but a recent ecological analysis of increasing PrEP coverage over time found only small effects on reducing HIV diagnoses.[17,18]

One hypothesis for gaps between the predicted and observed population impact of PrEP are network effects, including nonrandom sexual partnering by HIV status and PrEP use. Recent studies have found high levels of assortative mixing (i.e., concordance of shared attributes) among MSM who use PrEP,[62,64,65] which may decrease the efficiency of PrEP distribution in the sexual networks of MSM. Network analyses are needed to understand how nonrandom mixing influences PrEP coverage in the sexual network even at fixed coverage levels in the population.

Decades of research has shown high levels of assortative mixing by HIV status, which is attributed to multiple mechanisms.[59,60,118] First, transmission within ongoing partnerships induces concordance among MSM living with HIV.[119] Second, assortative mixing by race, ethnicity, age, and other factors associated with HIV prevalence, increases the probability of randomly selecting a sexual partner with the same HIV status.[120–122] Third, partners may be selected preferentially based on perceived or disclosed HIV diagnosis status (i.e., serosorting)

as an HIV prevention strategy.[59,60,118] The effectiveness of serosorting is undermined by the prevalence of undiagnosed HIV (approximately 15% of MSM living with HIV in the US are undiagnosed).[2,59,60] Serosorting intentions may change in the PrEP era, especially with increasing awareness that treatment of HIV prevents onward transmission (i.e., Undetectable = Untransmittable; or U=U),[4,5] but the results presented in **Chapter 2** (page 22), as well as other recent cross-sectional estimates, show persistent concordance among MSM in high-resource countries.[62,64,65,70,123]

A newer phenomenon of PrEP sorting has been identified, including concordance of both PrEP use and PrEP nonuse among MSM without diagnosed HIV.[62,64,65] Similar to mixing by HIV status, this might be partially explained by assortative mixing within demographic groups and disparities in PrEP coverage. However, this is unlikely to fully explain the high levels of concordance observed among MSM in the US – approximately 30% among MSM who use PrEP and 80% among MSM who do not use PrEP (**Chapter 2**, page 22). Alternative mechanisms include preferential partnering among MSM who use PrEP as an HIV prevention strategy,[66] diffusion of PrEP awareness and uptake along overlapping social and sexual networks,[124] and coordinated decision making within ongoing partnerships.[69] There is also evidence of disassortative mixing between MSM with diagnosed HIV and those who use PrEP (**Chapter 2**, page 22),[64] which is consistent with Centers for Disease Control and Prevention guidelines for PrEP indications.[9] Nonrandom mixing by HIV diagnosis status and PrEP use may impact the total population-level benefit of PrEP by varying the location of HIV and PrEP in sexual networks and opportunities both for primary and secondary prevention.[125] However, it is unclear how observed mixing patterns interact with other network properties, such as degree heterogeneity (number of partners) and assortative mixing within demographic groups, to generate the network-level structures that determine the location and density of HIV and PrEP in the sexual network.

In this study, we used data from a 2017–2019 egocentric network study of MSM in the US to estimate individual and partnership network statistics, including degree, assortative mixing by race/ethnicity and age, and mixing matrices for the interaction of diagnosed HIV status and PrEP use. Using statistical models for networks, we estimated the distribution of diagnosed HIV and current PrEP use in the sexual networks of US MSM. We also compared models fully parameterized to the observed network statistics to models with less structured parameterizations to quantify the magnitude of nonrandom mixing that is expected based on other network properties. This comparative analysis will help elucidate the causal mechanisms which vary the efficiency of PrEP coverage in sexual networks. The results of this study provide a descriptive summary of the sexual networks of MSM in the PrEP and U=U era.

METHODS

Empirical network data: Network data used in this analysis were drawn from ARTnet, a 2017–2019 egocentric sexual network study of cisgender MSM in the United States.[103] A full summary of the ARTnet population and methods has been published previously.[103] Briefly, MSM were recruited from those who completed the American Men's Internet Study who also reported a lifetime history of male-male sexual activity and were aged 15–65 years. Respondents self-reported their own attributes at the time of the study, including age, race, ethnicity, HIV status and test history, and current PrEP use. Respondents also reported their past-year sexual history, including degree of anal-sex partnerships by type: momentary persistent (i.e., sex typically occurs at least one time per month and is expected to continue) or one-time (i.e., sex occurred once). For up to five of their most recent sexual partnerships in the past year, respondents reported: the partner's age, race, ethnicity, HIV status, and PrEP use during the partnership; their own PrEP use during the partnership; type and frequency of sexual activity; duration of the partnership; and level of commitment (main or casual). Race and ethnicity were combined to create a single categorical variable (non-Hispanic White, non-Hispanic Black,

Hispanic/Latinx, or other) and age was categorized in 10-year age groups. We dichotomized HIV status (diagnosed HIV versus test-negative or unknown) for each respondent and partner. Similarly, PrEP use was dichotomized (ever versus never) for each partner and at the partnership-level for each respondent. We calculated partner degree for momentary persistent partners (total), persistent partners stratified by type (main versus casual), and cumulative monthly one-time partners (past-year total divided by 12 for a monthly average). The ARTnet sample included 4,904 egos (study participants) and 16,198 alters (partners egos reported on).

Network estimation and simulation: Exponential random graph models (ERGMs) were fit to the observed network data using the *ergm* R package.[126,127] These models estimated properties of cross-sectional networks of MSM (nodes) and their anal-sex partnerships (edges). ERGMs were fit to alternative network parameterizations, including heterogeneity in degree and mixing, hypothesized as the generative processes for the observed network data. Model fits were assessed by visual inspection of MCMC trace plots. Output parameters from each ERGM were used to simulate 10,000 complete synthetic networks.

Simulated population: We created a synthetic population of 10,000 nodes to represent a cross-section of MSM aged 15–65 years in the US. The nodes were assigned demographic attributes based on post-censal estimates of the US population in 2019,[128] restricted to men aged 15–65 years. Next, we used models of ARTnet data to assign HIV status and PrEP use. We first assigned HIV status (with or without diagnosed HIV) using logistic regression fit to continuous age, age-squared, race/ethnicity, and the interaction of race/ethnicity with each age term. Among nodes without diagnosed HIV, PrEP use was similarly assigned based on current PrEP use (at the time of the study) among ARTnet respondents without diagnosed HIV.

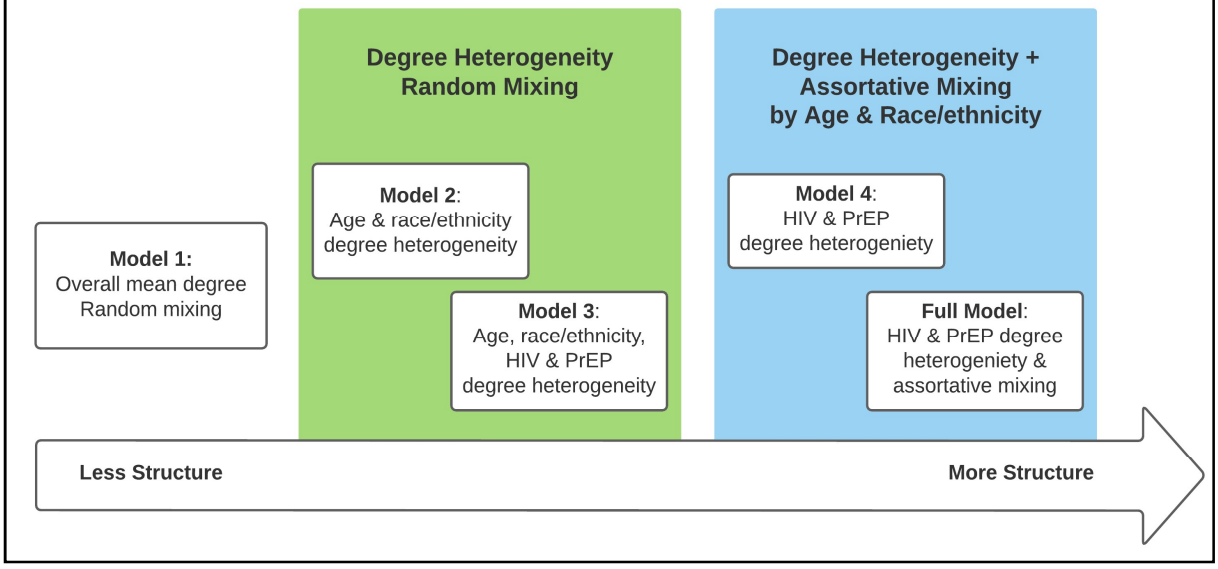
Summary network statistics: Degree and mixing statistics were estimated using the ARTnet sample and stratified by partnership type: main, casual, total persistent (main and casual), and one-time partners. We used the ARTnet respondents to estimate mean degree overall and

stratified by age group, race/ethnicity, diagnosed HIV status, and current PrEP use. Overall and marginal mean degree estimates were standardized to the nodal attributes of the simulated population. We estimated mixing matrices using the subset of partnerships in which anal-sex occurred (n = 9,914). Mixing statistics represented the proportion of partnerships with concordant or discordant attributes conditional on strata of respondents. We estimated assortative mixing statistics both for age group and race/ethnicity (i.e., concordant matching within each stratum). Full mixing matrices were estimated for the interaction of HIV status and PrEP use (concordant between MSM with diagnosed HIV, MSM using PrEP, or MSM not using PrEP; and discordant pairings of the three groups). It can be challenging for survey respondents to accurately report the HIV status and PrEP use of their sexual partners, resulting in misclassification and missing data. Therefore, we used the median results from a previous sensitivity analysis of the ARTnet sample which estimated mixing by diagnosed HIV status and PrEP use (**Chapter 2**, page 22). The sensitivity analysis reclassified partners' HIV status and PrEP use to approximate what the partners would have self-reported had they been surveyed. The mixing statistics represent unobserved partnership-level information that can be challenging to estimate without collecting information from partners directly.

Network model parameterizations: We estimated ERGMs for each partnership type, with models fit to the synthetic nodal attributes and the egocentric network data. The models included standardized mean degree statistics (overall and stratified by age group, race/ethnicity, HIV status, and PrEP use) and mixing statistics for age group, race/ethnicity, and the interaction of HIV status and PrEP use (**Figure 3.1**). We compared the fully parameterized models to less structured models. Nodal attributes remained fixed, and we also held constant overall mean degree for each partnership type so that the total number of edges remained constant. The first three experimental models included varying parameterizations of degree without mixing statistics (i.e., random mixing models). Model 1 included only the overall mean degree. Model 2

added degree heterogeneity by age group and race/ethnicity. Model 3 included the Model 2 parameters and added degree heterogeneity by HIV status and current PrEP use (i.e., fully parameterized degree heterogeneity). Finally, Model 4 used assortative mixing statistics for age group and race/ethnicity plus fully parameterized degree heterogeneity. The four models were used to estimate the magnitude of nonrandom mixing that is expected based on degree heterogeneity and demographic mixing.

Figure 3.1. Network model scenarios



Simulated network outcomes: We tracked the distribution of HIV status and PrEP use in each of the 10,000 simulated networks for each model parameterization. First, we tracked the distribution of edges in each network, including total number of edges, number with concordant HIV statuses (for both with or without diagnosed HIV) or discordant HIV statuses, and number of concordant or discordant edges for each of the combinations of diagnosed HIV and PrEP use. For each pairing, we also calculated the proportion out of all edges in the network. Second, we reported mixing matrices for the interaction of HIV status and PrEP use. To do this, we stratified the nodes by HIV status and PrEP use and calculated the proportions of partners with

diagnosed HIV, and those using PrEP or not using PrEP. Third, we compared the fully parameterized model to Model 4 (fully parameterized degree and assortative mixing within demographic groups) and calculated the population attributable fraction for the proportions of edges concordant with diagnosed HIV, using PrEP, or not using PrEP. For each scenario, we reported median results and 95% simulation intervals (SI) across all 10,000 simulations.

RESULTS

We will first summarize the simulated population attributes and network statistics used to parameterize the models. Next, we will summarize the simulated networks fully parameterized to the empiric network data. Last, we will compare the fully parameterized networks to the four less structured experimental models.

The prevalence of diagnosed HIV in the simulated population was 13.5% (**Appendix Table B.1**). Prevalence was lowest among young MSM and increased by age group (1.4% to 23.2%). Prevalence also varied by race/ethnicity, with 29.3% of Black, 14.7% of Hispanic/Latinx, 10.1% of White, and 9.8% of other. Current PrEP use was 15.1% overall, with variations by age and race/ethnicity. PrEP was lower among MSM aged 15–24 (7.1%) and 55–65 (11.6%), and lowest among Black MSM (11.6%).

Table 3.1 shows the standardized marginal mean degree estimates. Overall mean degree was 0.40 for main, 0.65 for casual, 1.05 for total persistent, and 0.43 for cumulative one-time partners. Mean degree varied only slightly by race/ethnicity or age group. Differences by diagnosed HIV status and PrEP use were negligible for main partner degree, while greater variation was observed for casual and one-time partner degree. MSM who used PrEP had the highest casual (1.22) and one-time (1.10) partner degree, while MSM who did not use PrEP had the lowest (0.47 and 0.24, respectively). MSM with diagnosed HIV had an average of 0.97 casual and 0.69 one-time partner degree.

Table 3.1. Mean momentary degree for persistent partners and cumulative degree for one-time partnerships, stratified by select characteristics, among men who have sex with men in the United States.

	Persistent Partnerships[1]			
	Main[2]	**Casual**	**Total**	**One-time[3]**
	n[4]	n[4]	n[4]	n[5]
Total	0.40	0.65	1.05	0.43
Age Group				
15–24	0.36	0.30	0.66	0.27
25–34	0.46	0.51	0.96	0.40
35–44	0.48	0.75	1.23	0.52
45–54	0.41	0.88	1.29	0.54
55–65	0.28	0.85	1.13	0.45
Race & Ethnicity				
Non-Hispanic				
Black	0.27	0.63	0.91	0.35
White	0.41	0.64	1.05	0.44
Other	0.38	0.73	1.11	0.37
Hispanic/Latinx	0.42	0.69	1.11	0.48
HIV & PrEP				
No PrEP	0.39	0.47	0.87	0.24
PrEP	0.39	1.22	1.60	1.10
Diagnosed HIV	0.42	0.97	1.39	0.69

[1]Partnerships in which anal sex occurs more than one time. [2]Committed to each other above all other partners. [3]Partnerships in which anal sex occurs only one time. [4]Mean momentary degree; cross-sectional frequency of persistent partners. [5]Mean cumulative (monthly) degree; frequency of one-time partners.

Table 3.2 summarizes the mixing statistics from the observed network data. Assortative mixing within race/ethnicity and age groups was stronger for main partners than casual or one-time partners. Younger MSM and White MSM had the highest assortative mixing fractions across partnership types, while assortative mixing was lowest among older MSM and those in the “other” race/ethnicity group. The full mixing patterns of diagnosed HIV and PrEP use showed concordance across partnership types: PrEP nonuse (86.4% main, 71.3% casual, and 74.5% one-time partners), PrEP use (45.3% main, 41.0% casual, and 33.3% one-time partners), and diagnosed HIV (44.7% main, 49.3% casual, and 46.1% one-time partners). We also observed disassortative mixing, with higher fractions of partners with diagnosed HIV among nodes using PrEP (16.4% main, 10.1% casual, and 7.9% one-time partners) compared to nodes not using PrEP (4.0% main, 8.4% casual, and 7.0% one-time partners).

Table 3.2. Sexual partnership mixing by age group, race and ethnicity, HIV diagnosis status and pre-exposure prophylaxis use, stratified by partnership type, among men who have sex with men in the United States.

	Persistent Partnerships[1]			
	Main[2]	Casual	Total	One-time[3]
	%	%	%	%
Age Group[4]				
15-24	71.8	53.5	61.1	49.3
25-34	65.6	52.1	57.5	52.4
35-44	43.1	26.8	32.2	30.1
45-54	33.6	24.7	27.1	22.8
55-65	28.4	15.6	18.4	17.2
Race & Ethnicity[4]				
Non-Hispanic				
Black	50.5	53.9	53.1	48.5
White	70.7	61.3	64.6	60.8
Other	24.7	15.0	18.1	18.6
Hispanic/Latinx	42.9	38.6	40.1	37.0
HIV & PrEP[5]				
No PrEP				
No PrEP	86.4	71.3	76.9	74.5
PrEP	9.6	20.3	16.3	18.5
Diagnosed HIV	4.0	8.4	6.8	7.0
PrEP				
No PrEP	38.3	48.8	45.9	58.7
PrEP	45.3	41.0	42.3	33.3
Diagnosed HIV	16.4	10.1	11.8	7.9
Diagnosed HIV				
No PrEP	31.2	22.1	25.5	30.7
PrEP	24.2	28.6	27.0	23.2
Diagnosed HIV	44.7	49.3	47.6	46.1

[1]Partnerships in which anal sex occurs more than one time. [2]Committed to each other above all other partners. [3]Partnerships in which anal sex occurs only one time. [4]Expected assortative (within group) mixing fraction. [5]Expected mixing fractions for the interaction of HIV diagnosis status and PrEP use.

Table 3.3 summarizes the edge distribution in simulated networks fully parameterized to the empiric network data, including degree heterogeneity, assortative mixing within demographic groups, and the mixing matrices for diagnosed HIV and PrEP use. Of all edges in the networks, the fraction between nodes with diagnosed HIV was 6.9% (95% SI: 5.8, 8.1) of main, 10.3% (95%: 9.3, 11.3) of casual, and 11.0% (95% SI: 9.7, 12.3) of one-time partnerships. The remaining 93.1% (95% SI: 91.9, 94.2) of main, 89.7% (95% SI: 88.7, 90.7) of casual, and 88.0% (95% SI: 87.7, 90.3) of one-time partnerships in each network are opportunities for HIV transmission to occur. The prevalence of edges with discordant diagnosed HIV statuses was lower in main partner networks (13.3%; 95% SI: 11.8, 14.9) compared to casual (17.7%; 95% SI: 16.3, 19.0) and one-time (17.9%; 95% SI: 16.3, 19.6) partner networks. PrEP use varied by partnership type, resulting in similar prevalence of discordant edges with one node with diagnosed HIV and one node without diagnosed HIV and not using PrEP: 8.6% (95% SI: 7.9, 9.4) of all persistent edges and 6.8% (95% SI: 5.8, 7.8) of one-time edges. The prevalence of edges concordant without diagnosed HIV was 74.8% (95% SI: 73.6, 76.0) of all persistent and 71.1% (95% SI: 69.1, 72.9) of one-time edges. Variable PrEP coverage and assortative mixing resulted in 61.4% (95% SI: 59.1, 63.5) of main, 36.0% (95% SI: 34.5, 37.8) of casual, and 23.6% (95% SI: 21.8, 25.4) of one-time partnership edges concordant among those not using PrEP.

Table 3.3. Distribution of network edges in fully parameterized models stratified by partnership type

	Median (95% Simulation Interval)			
	Persistent Partnerships[1]			
	Main	**Casual**	**Total**	**One-time**[2]
Edges (total N)	1975 (1889, 2058)	3248 (3130, 3359)	5223 (5076, 5378)	2148 (2056, 2241)
HIV Mixing (%)				
Concordant				
Without HIV[3]	79.7 (77.9, 81.5)	72.0 (70.6, 73.5)	74.8 (73.6, 76.0)	71.1 (69.1, 72.9)
With HIV[3]	6.9 (5.8, 8.1)	10.3 (9.3, 11.3)	8.9 (8.1, 9.9)	11.0 (9.7, 12.3)
Discordant	13.3 (11.8, 14.9)	17.7 (16.3, 19.0)	16.2 (15.2, 17.3)	17.9 (16.3, 19.6)
HIV & PrEP Mixing (%)				
Concordant				
No PrEP	61.4 (59.1, 63.5)	36.0 (34.5, 37.8)	45.3 (43.9, 46.6)	23.6 (21.8, 25.4)
PrEP	6.1 (5.1, 7.2)	12.0 (10.9, 13.0)	9.6 (8.8, 10.4)	18.0 (16.5, 19.6)
With HIV[3]	6.9 (5.8, 8.1)	10.3 (9.3, 11.3)	8.9 (8.1, 9.9)	11.0 (9.7, 12.3)
Discordant				
No PrEP–PrEP	12.2 (10.9, 13.7)	24.0 (22.6, 25.5)	19.9 (18.7, 21.0)	29.5 (27.6, 31.4)
No PrEP–With HIV[3]	7.5 (6.4, 8.7)	8.5 (7.5, 9.5)	8.6 (7.9, 9.4)	6.8 (5.8, 7.8)
PrEP–With HIV[3]	5.9 (4.8, 6.9)	9.2 (8.2, 10.3)	7.6 (6.9, 8.3)	11.0 (9.8, 12.5)

[1]Momentary persistent partnerships. [2]Cumulative (monthly) one-time partnerships. [3]With or without diagnosed HIV.

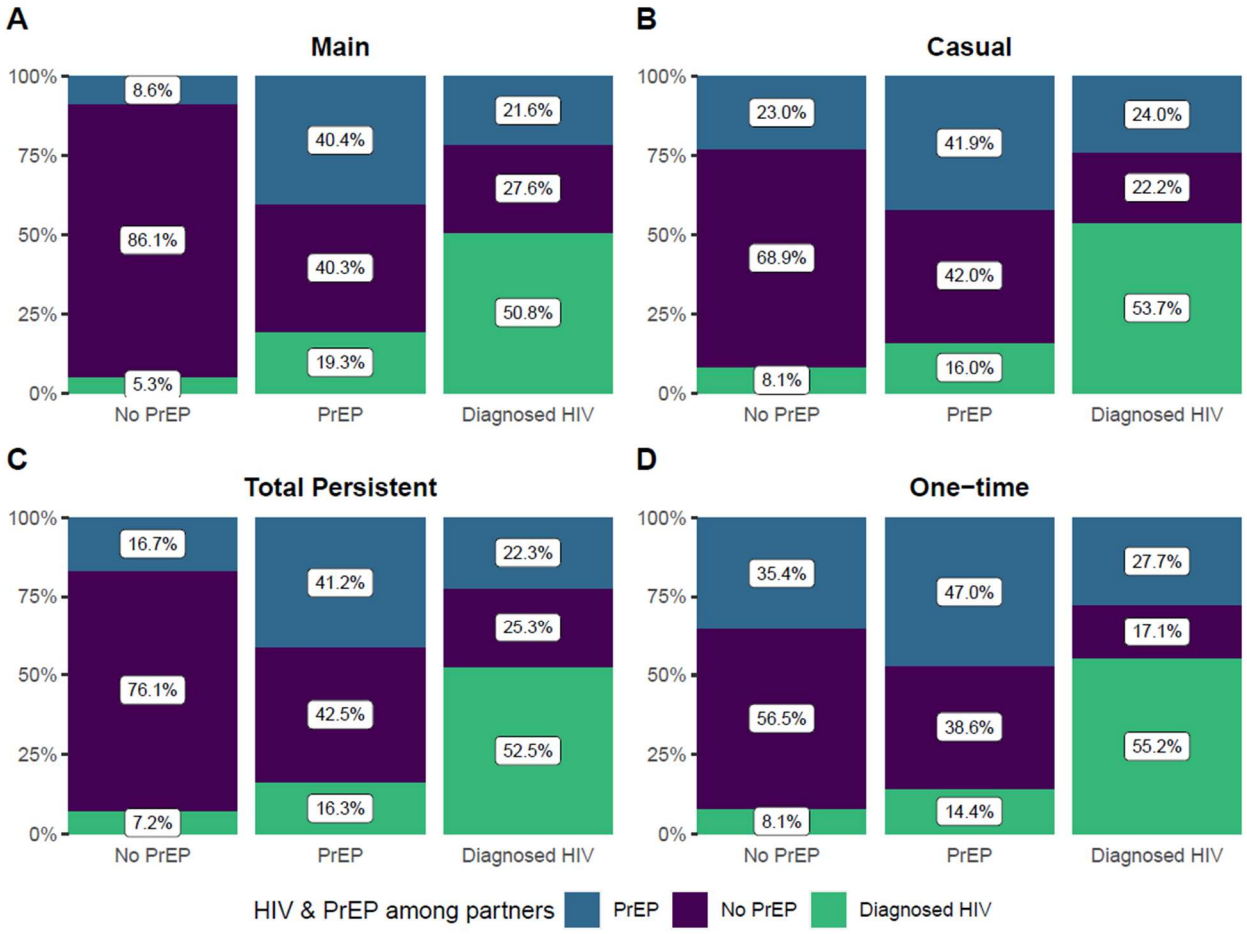
Table 3.4 summarizes the mixing matrices for diagnosed HIV status and PrEP use from the fully parameterized network simulations. Median results from these analyses are presented in **Figure 3.2**. Across partnership types, MSM with diagnosed HIV had the highest proportion of partnerships to other MSM with diagnosed HIV: 52.5% (95% SI: 49.2, 55.7) of all persistent and 55.2% (95% SI: 51.2, 59.0) of one-time edges. Similarly, among nodes with PrEP use, 41.2% (95% SI: 38.8, 43.6) of all persistent and 47.0% (95% SI: 44.2, 49.8) of one-time edges were concordant with PrEP use. Concordance among nodes not using PrEP varied more substantially by partnership type. Among nodes not using PrEP, 86.1% (95% SI: 84.7, 87.4) of main, 68.9% (95% SI: 67.1, 70.8) of casual, and 56.5% (95% SI: 53.7, 559.2) of one-time partners were concordant and also not using PrEP. Nodes using PrEP, compared to nodes not using PrEP, had higher fractions of partners with diagnosed HIV: 16.3% (95% SI: 14.7, 17.8) versus 7.2% (95% SI: 6.6, 7.9) among all persistent, and 14.4% (95% SI: 12.8, 16.3) versus 8.1% (95% SI: 6.9, 9.4) among one-time partners.

Table 3.4. Mixing by HIV status and PrEP use in fully parameterized models stratified by partnership type

	Median (95% Simulation Interval)			
	Persistent Partnerships[1]			
	Main	**Casual**	**Total**	**One-time[2]**
No PrEP (N[3])	2812 (2673, 2952)	3397 (3248, 3554)	6218 (6029, 6428)	1794 (1689, 1901)
With HIV (%[4])	5.3 (4.4, 6.1)	8.1 (7.2, 9.1)	7.2 (6.6, 7.9)	8.1 (6.9, 9.4)
No PrEP (%[4])	86.1 (84.7, 87.4)	68.9 (67.1, 70.8)	76.1 (74.9, 77.2)	56.5 (53.7, 59.2)
PrEP (%[4])	8.6 (7.6, 9.7)	23.0 (21.4, 24.5)	16.7 (15.7, 17.7)	35.4 (32.8, 37.9)
PrEP (N[3])	599 (543, 660)	1856 (1754, 1952)	2444 (2319, 2557)	1644 (1547, 1740)
With HIV (%[4])	19.3 (16.1, 22.7)	16.0 (14.4, 18.0)	16.3 (14.7, 17.8)	14.4 (12.8, 16.3)
No PrEP (%[4])	40.3 (36.1, 44.8)	42.0 (39.5, 44.7)	42.5 (40.2, 44.8)	38.6 (36.0, 41.2)
PrEP (%[4])	40.4 (35.5, 45.2)	41.9 (39.0, 44.7)	41.2 (38.8, 43.6)	47.0 (44.2, 49.8)
With HIV (N[3])	537 (480, 593)	1242 (1162, 1320)	1783 (1681, 1909)	856 (789, 927)
With HIV (%[4])	50.8 (45.4, 56.3)	53.7 (50.4, 57.2)	52.5 (49.2, 55.7)	55.2 (51.2, 59.0)
No PrEP (%[4])	27.6 (23.6, 31.8)	22.2 (19.7, 24.7)	25.3 (23.0, 27.6)	17.1 (14.5, 19.6)
PrEP (%[4])	21.6 (17.8, 25.4)	24.0 (21.5, 26.9)	22.3 (20.2, 24.5)	27.7 (24.6, 31.2)

[1]Momentary persistent partnerships. [2]Cumulative (monthly) one-time partnerships. [3]Total network edges by HIV status and PrEP use of nodes; each edge is counted twice (once for each node in a dyad). [4]Proportion of edges based on partner HIV status and PrEP use.

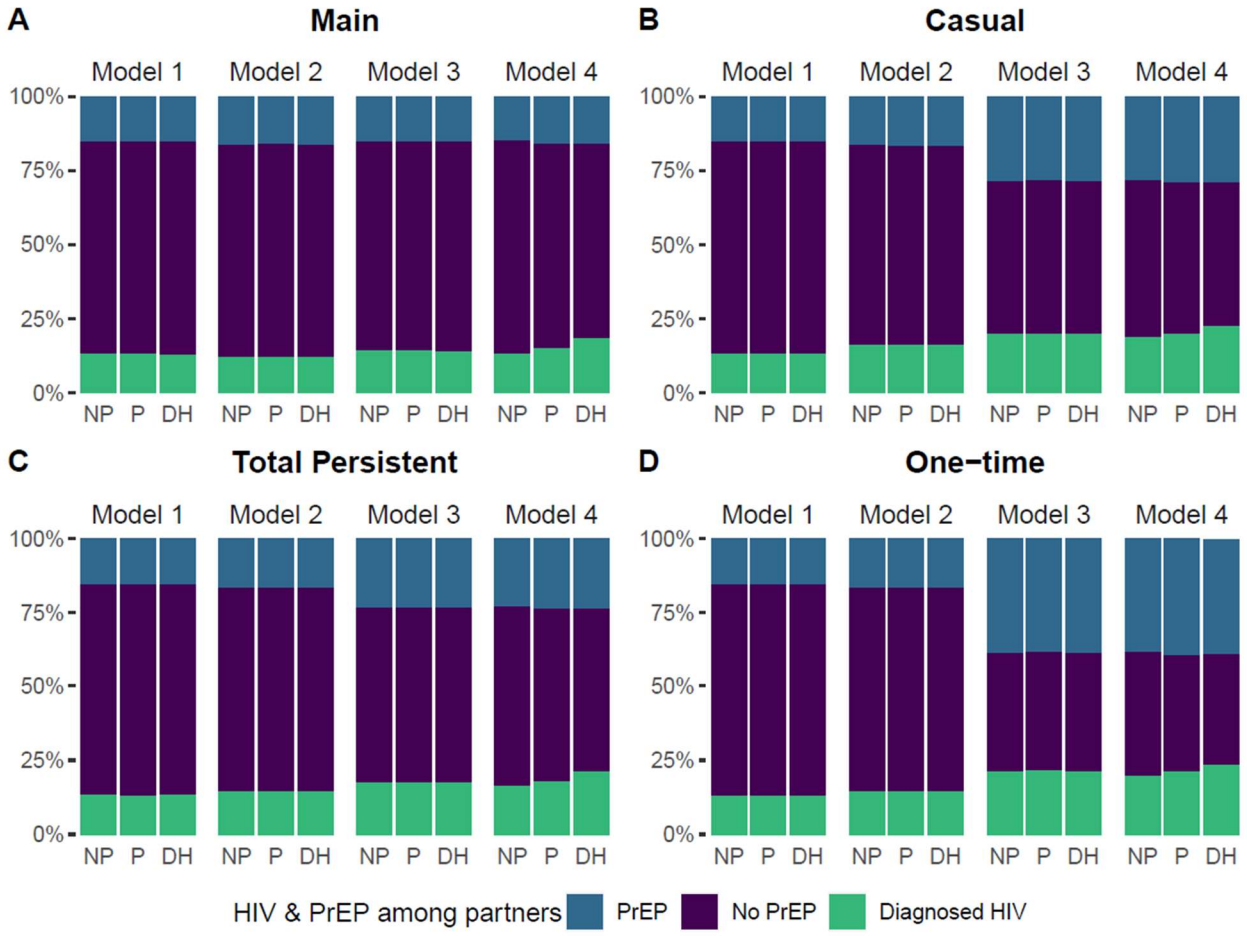
Figure 3.2. Mixing by human immunodeficiency virus (HIV) diagnosis status and current pre-exposure prophylaxis (PrEP) use in simulated sexual networks of 10,000 men who have sex with men.



Legend: Cross-sectional networks stratified by partnership type and fully specified to observed network data in an egocentric sexual network study of MSM in the US. Results are median values across 10,000 simulations per scenario. Proportions represent partnership mixing by HIV status and PrEP use. Panel A: Main persistent partnerships; Panel B: Casual persistent partnerships; Panel C: Total (main and casual) persistent partnerships; Panel D: Cumulative (monthly) one-time partnerships.

We were unable to reproduce the observed levels of HIV serosorting and PrEP sorting with less structured ERGM parameterizations. **Appendix Tables B.3–B.6** (pages 132–135) summarize the distribution of network edges, while **Figure 3.3** and **Appendix Tables B.7–B.10** (pages 136–139) summarize the mixing matrices for each parameterization of network structure. First, we compared Models 1–3 to isolate the influence of degree on network structure. The overall number of edges remained constant across model parameterizations, on average, due to fixed overall mean degree. However, the marginal mean degree parameters changed the average number of edges for nodes with different attributes. There was little variation between the models with homogenous degree (Model 1) and those with degree heterogeneity by age group and race/ethnicity (Model 2), despite differences in HIV prevalence and PrEP uptake between demographic groups. The number of edges among nodes with PrEP use and those with diagnosed HIV increased slightly, but larger changes were observed when adding degree heterogeneity by HIV status and PrEP use (Model 3). For example, the fraction of edges concordant without PrEP use in casual partner networks was 51.0% (95% SI: 49.3, 52.8) in Model 1 but only 26.6% (95% SI: 25.1, 28.1) in Model 3. The absolute difference is greater in one-time partner networks and smaller in main partner networks. In casual partner networks, discordant partnering between MSM with different HIV statuses increased from 23.2% (95% SI: 21.8, 24.7) in Model 1 to 32.1% (95% SI: 30.5, 33.7) in Model 3. The net change in partnering between MSM with different HIV statuses was entirely attributable to partnerships in which PrEP was used, with no net change in the overall fraction without PrEP use. Similar changes were observed for discordant partnering among one-time partners, but no change was observed for main partners. Despite varying edge distribution and mixing matrices across Models 1–3, the mixing matrices within each model were undifferentiated when comparing nodes with different HIV or PrEP use statuses.

Figure 3.3. Mixing by human immunodeficiency virus (HIV) diagnosis status and current pre-exposure prophylaxis (PrEP) use in simulated sexual networks of 10,000 men who have sex with men (MSM), stratified by partnership type.



Legend: Cross-sectional networks stratified by partnership type. Alternative parameterizations based on observed network data in an egocentric sexual network study of MSM in the US: Model 1 = homogenous degree, random mixing; Model 2 = degree heterogeneity by age and race/ethnicity, random mixing; Model 3 = degree heterogeneity by age, race/ethnicity, HIV status and PrEP use, random mixing; Model 4 = degree heterogeneity by age, race/ethnicity, HIV status and PrEP use, and mixing by age and race/ethnicity. Results are median values across 10,000 simulations per scenario. Proportions represent partnership mixing by HIV status and PrEP use. Panel A: Main persistent partnerships; Panel B: Casual persistent partnerships; Panel C: Total (main and casual) persistent partnerships; Panel D: Cumulative (monthly) one-time partnerships.

Mixing matrices begin to differentiate after adding assortative mixing statistics for age group and race/ethnicity (Model 4). However, a comparison of Model 4 and Model 3 shows only small changes. The models also remain substantially different than the fully parameterized models, as evidenced by the population attributable fractions presented in **Table 3.5**. For example, compared to the fully parameterized model, Model 4 underestimated the proportion of all edges concordant with diagnosed HIV: 8.9% (95% SI: 8.1, 9.9) versus 3.8% (95% SI: 3.3, 4.3) of all persistent edges, and 11.0% (95% SI: 9.7, 12.3) versus 5.1% (95% SI: 4.2, 6.1) of one-time partnership edges. This means that the fraction of edges concordant with diagnosed HIV attributable to degree heterogeneity and assortative mixing was only 42.6% (95% SI: 37.0, 48.8) in persistent partnership networks and 46.5% (95% SI: 38.5, 55.4) in one-time partnership networks. The population attributable fractions were higher for concordance among nodes using PrEP and nodes not using PrEP. Model 4 only accounted for 79.1% (95% SI: 76.1, 82.1) of persistent partnerships concordant without PrEP use and 69.8% (95% SI: 62.9, 77.4) of one-time partnerships. These partnerships were the largest group in the networks, including 45.3% (95% SI: 43.9, 46.6) of all persistent edges and 23.6% (95% SI: 21.8, 25.4) of all one-time partnership edges in the fully parameterized models, so even small or moderate relative differences may translate to large absolute differences on the population-level.

Table 3.5. Assortative mixing by HIV status and PrEP use attributable to degree heterogeneity and assortative mixing within demographic groups compared to models fully parameterized to empiric mixing statistics.

	Model 4[1]	**Full Model**[1]	**PAF**[2]
	%[3]	%[3]	%[3]
Main Partners			
No PrEP	50.8 (48.6, 53.0)	61.4 (59.1, 63.5)	82.8 (79.1, 86.8)
PrEP	2.3 (1.7, 3.0)	6.1 (5.1, 7.2)	38.3 (28.9, 49.9)
With HIV	2.7 (2.0, 3.5)	6.9 (5.8, 8.1)	39.2 (29.8, 50.3)
Casual Partners			
No PrEP	27.2 (25.8, 28.8)	36.0 (34.5, 37.8)	75.6 (71.1, 80.3)
PrEP	8.2 (7.2, 9.2)	12.0 (10.9, 13.0)	68.4 (60.1, 77.1)
With HIV	4.6 (3.9, 5.2)	10.3 (9.3, 11.3)	44.6 (38.2, 51.4)
Total Persistent			
No PrEP	35.8 (34.5, 37.1)	45.3 (43.9, 46.6)	79.1 (76.1, 82.1)
PrEP	5.4 (4.7, 6.0)	9.6 (8.8, 10.4)	56.2 (49.7, 62.6)
With HIV	3.8 (3.3, 4.3)	8.9 (8.1, 9.9)	42.6 (37.0, 48.8)
One-time			
No PrEP	16.5 (14.9, 18.1)	23.6 (21.8, 25.4)	69.8 (62.9, 77.4)
PrEP	15.2 (13.9, 16.7)	18.0 (16.5, 19.6)	84.8 (76.3, 94.4)
With HIV	5.1 (4.2, 6.1)	11.0 (9.7, 12.3)	46.5 (38.5, 55.4)

[1]Model 4 includes parameters for overall mean degree, degree heterogeneity by age group, race/ethnicity, HIV status and PrEP, and assortative mixing within age groups and race/ethnicity. The Full Model adds full mixing patterns by HIV status and PrEP use to the Model 4 parameters.
[2]Population attributable fraction; proportion of assortative mixing in the full model attributable to Model 4 parameters.
[3]Median percentage and 95% simulation interval

DISCUSSION

This study estimated PrEP coverage in the sexual networks of MSM in the United States during the PrEP and U=U era. Our network modeling approach combined sexual partnership network degree and mixing statistics derived from egocentric network data in a simulated population representing MSM in the US. We found evidence of assortative partnering by HIV status and PrEP use, including excess clustering of PrEP in the sexual network. This likely provides a high level of protection among MSM who use PrEP, but HIV transmission may proceed uninterrupted in areas of the network with relatively sparse PrEP use. This has implications for projecting future PrEP impact, as well as public health planning for PrEP distribution.

Our study adds to the literature describing HIV and PrEP mixing among MSM in high-resource countries. Recent studies using egocentric network data have shown that traditional HIV serosorting (assortative mixing by perceived or disclosed HIV status) has persisted in recent years,[62,64,65,70,123] while new patterns have emerged, including assortative mixing by PrEP use status and discordant mixing between MSM with diagnosed HIV and those who use PrEP.[62,64,65] The findings have been qualitatively consistent across studies, although quantitative estimates vary based on study design and population. Mixing matrices reflect the underlying prevalence of diagnosed HIV and PrEP use in the sampled population of respondents and their reported sexual partners, which may not be generalizable to all MSM in the target population. The network modeling approach provides adjusted mixing estimates using the observed network data with a synthetic population representative of US MSM (analogous to population weighting of prevalence or risk estimates).[129]

Our models provide evidence of inefficient network coverage of PrEP, which may partially explain the sustained HIV diagnosis rate among MSM despite increasing PrEP coverage in the population.[17,18] One study estimates that PrEP use in the past 12 months increased from less than 2% in 2013 to approximately 20% in 2017.[11] The US EHE initiative

calls for increased PrEP use to decrease incidence,[16] but PrEP is expensive and interventions to increase PrEP coverage will use finite public health resources.[17] Efforts should therefore prioritize strategies which maximize coverage in the network for the greatest impact on HIV incidence.[91,130] This can be achieved in part by targeting distribution to MSM with more partners, but our models show that assortative partnering among MSM who use PrEP can partially offset the benefit of increased PrEP use among MSM with higher degree. This means that progress also requires expanding PrEP use beyond the population subgroups where it is already concentrated. This has proven challenging. Progress has been made to close disparities by race and ethnicity, but not age,[11] and PrEP remains clustered within demographic groups.

Network-based models of PrEP should include full mixing patterns of HIV and PrEP sorting to model gaps in the network coverage of PrEP. We estimated that 45% of all persistent partnerships and 24% of all one-time partnerships were between men without diagnosed HIV and not using PrEP. Models based on degree heterogeneity and assortative partnering within demographic groups accounted for only 70–80% of partnerships between men not using PrEP. There were also differences in the fraction of partnerships with different HIV statuses, including those with and without PrEP use, so it is difficult to predict the net impact on HIV transmission dynamics. A recent study showed increased PrEP impact in scenarios with HIV serosorting,[125] but this model did not consider additional PrEP sorting mechanisms. Few other models of PrEP incorporate HIV serosorting,[131–133] and none explore the impact of assortative partnering among PrEP users.

LIMITATIONS

First, our observed network data come from a convenience sample of US MSM. This was our motivation for using a synthetic population with population-based demographic weights. We also standardized the marginal mean degree estimates to the synthetic population. However, oversampling of MSM with higher or lower degree could bias our estimates regardless of

standardization. We are unable to assess whether our sampled population differs from the broader population of MSM in terms of number of partners or sorting behaviors. Second, egocentric network data like ARTnet are limited by what the egos know about their sexual partners. As shown in **Chapter 2** (page 32), 24% of partners were of unknown HIV status and 49% of partners not known to have diagnosed HIV were of unknown PrEP use status. This study attempted to reduce bias due to unknown or misreported partner information using a reclassification sensitivity analysis. The present study is based on these results. Our network models may be biased if the reclassification sensitivity analysis did not minimize bias in the sorting estimates. Third, our network models are cross-sectional, but diagnosed HIV status and PrEP use may change over time. We were therefore unable to determine the extent to which sorting patterns arose due to HIV transmission within persistent partnerships or due to PrEP initiation within HIV discordant partnerships. We also may have overestimated the prevalence of PrEP use in the persistent partnership networks because we defined PrEP use as ever/never throughout the partnership. Finally, we did not model geography or other factors which may partially explain the observed sorting patterns.

CONCLUSIONS

This study provides several new findings which describe the sexual network structure of MSM and the distribution of diagnosed HIV status and PrEP use. We showed that observed patterns of assortative mixing by diagnosed HIV status and PrEP use cannot be fully explained by other network properties, including degree heterogeneity and assortative mixing by age and race/ethnicity. Our future work will incorporate these mixing estimates in mechanistic models of HIV transmission to assess the potential impact of HIV serosorting and PrEP sorting on the population benefit of PrEP. Our findings show that efforts to increase PrEP use among MSM may be ineffective to reduce HIV transmission at the population level, if distribution is not targeted to expand beyond existing clusters of PrEP.

Chapter 4. Modeling the impact of network clustered HIV pre-exposure prophylaxis on HIV incidence

ABSTRACT

Background: Approximately 20% of men who have sex with men (MSM) with behavioral indications for pre-exposure prophylaxis (PrEP) used PrEP in 2017. However, ecological studies of PrEP impact have not found an association between increased PrEP use over time and decreasing HIV diagnoses among MSM.

Methods: We used a network-based model of HIV among MSM to test the hypothesis that assortative mixing among MSM who use PrEP decreases the population benefit of PrEP, compared to a scenario without PrEP mixing, due to clustering of PrEP use in the sexual network. We allocated PrEP based on estimates of degree heterogeneity and mixing statistics from an egocentric network study.

Results: There were 2.4% more (95% simulation interval: 10.3 less, 16.8 more) infections over 10 years in the scenario with PrEP sorting compared to without PrEP sorting. The excess transmission was attributable to partnerships in which both men were not using PrEP and partnerships between MSM with diagnosed HIV and MSM not using PrEP.

Discussion: The total effect of PrEP sorting was relatively small in our model. However, PrEP sorting may interact with other network-level factors to decrease PrEP impact in the real world. Public health interventions to increase PrEP use should seek to increase coverage in the sexual network to maximize the prevention benefit of PrEP coverage in the population.

BACKGROUND

Daily-oral pre-exposure prophylaxis (PrEP) for the prevention of human immunodeficiency virus (HIV) is more than 99% effective.[8,134] Uptake of PrEP among men who have sex with men (MSM) in the United States was initially slow, but by 2017 approximately 20% of MSM with indications for PrEP were using it.[11] Mathematical models predict a 20% decline in HIV incidence over ten years at 2017 PrEP coverage levels,[116] yet diagnoses among MSM have remained relatively constant over the past decade.[117] A recent population-level analysis of PrEP found only a small effect on the HIV diagnosis rate.[18] The federal "Ending the HIV Epidemic" initiative aims to increase PrEP use among MSM to meet the goal of 90% fewer incident infections by 2030.[16] Yet it is unclear whether current policies for PrEP allocation are sufficient to meet these targets, given the lack of empiric evidence for PrEP impact at the population level. The reasons for gaps between the predicted and observed epidemic trajectory are not fully understood.[17] Progress has been made to increase PrEP uptake and effective use by focusing on various aspects of the PrEP care continuum (i.e., access, adherence, and persistence).[11,26] However, PrEP impact may also depend on network-level factors. Inefficient PrEP coverage in the sexual network may facilitate sustained transmission and decrease the impact of PrEP at the population level.

The location and density of PrEP in the sexual network is influenced by various individual-level behaviors and partnership-level decisions.[31,35] Assortative mixing within demographic groups segments the sexual network by race/ethnicity, age, geography, and other factors.[120–122] Disparities in HIV prevalence and PrEP coverage within these groups generates unequal distribution of each across the sexual network. There is also evidence of sorting by HIV status and PrEP use beyond the levels expected based on demographics alone (**Chapter 3**, page 43).[62,64,65,70,123] Preferential partnering by HIV status (i.e., serosorting) is an HIV prevention strategy used by some MSM, but effectiveness depends on frequent screening to limit

transmission by undiagnosed HIV infection.[59,60,118] Concordant partnering between MSM with HIV can also occur due to transmission within ongoing partnerships, even if one or both men were without HIV when the sexual partnership began.[119] More recently, egocentric sexual network studies of MSM describe PrEP sorting, including assortative mixing among MSM who use PrEP.[62,64,65] This may produce clusters of PrEP use in the sexual network and increases the number of partnerships in which neither man is using PrEP (**Chapter 3**, page 43). Assortative mixing among MSM who use PrEP might therefore decrease PrEP impact at the population level by varying opportunities for both primary and secondary prevention. The potential impact of network clustered PrEP use on HIV transmission dynamics has not been evaluated.

In this study, we used a network-based model of HIV transmission dynamics to explore the impact of PrEP sorting among MSM.[15,36,116] The model was developed to represent observed patterns of PrEP uptake in our target population of MSM in Atlanta. We modeled estimates of PrEP sorting by varying the propensity for partnership formation based on current PrEP use as well as coordinated PrEP decision making within ongoing partnerships. We compared models with and without PrEP sorting to test the hypothesis that assortative mixing by PrEP use status decreases the overall impact of PrEP even at fixed PrEP coverage levels in the population. Our models may inform strategies to allocate PrEP efficiently to meet EHE goals of 90% fewer infections by 2030.

METHODS

We used a mathematical model of HIV transmission dynamics among MSM in the Atlanta area with a time horizon of 10 years. The model was calibrated to the diagnosed HIV prevalence of Black, White, and Hispanic/Latinx MSM, aged 15–65 years, in Atlanta. We used *EpiModel*,[36] a software package for modeling infectious disease transmission over dynamic contact networks with temporal exponential random graph models (TERGMs).[37] The model builds on previous

work exploring PrEP impact among MSM,[15,116] by incorporating PrEP sorting patterns to the dynamic sexual network. Full methodological details can be found in **Appendix C** (page 140).

Sexual Network Model: We used ARTnet, a 2017–2019 egocentric sexual network study of 4,904 MSM reporting on 16,198 sexual partnerships, to estimate all network and behavioral parameters, including mean degree (number of partners), partnership durations, and mixing statistics.[103] Target statistics for HIV serosorting and PrEP sorting were based on the median results of the analysis described in **Chapter 2** (page 22). Selected target statistics used in this study can be found in **Table 4.1**. Statistical network models were fit to summary statistics from ARTnet to estimate formation and dissolution parameters for main, casual, and one-time sexual partnerships. We estimated three sets of network parameters for each of the partnership types: one set of base parameters; and one set for each of the two PrEP scenarios (i.e., with and without PrEP sorting).

The base model parameters were used to calibrate the HIV epidemic prior to PrEP introduction. The base models included formation parameters for partnership type, degree (including heterogeneity by diagnosed HIV status), assortative mixing within age and race/ethnicity groups, and mixing by anal-sex position preferences (i.e., receptive and insertive). Dissolution of main and casual partnerships was based on the estimated median partnership durations and modeled with a constant hazard which was stratified by age of the partners. We also included HIV serosorting parameters for the one-time partnership network. We did not model serosorting for the persistent partnership networks, because cross-sectional estimates of HIV serosorting in persistent partnerships overestimate serosorting, compared to mixing at the time of partnership formation, due to transmission within partnerships over time. In other words, the prevalence of partnerships with different HIV statuses decreases with relationship age, while there is an increase in partnerships concordant with diagnosed HIV. The persistent partnership networks based on other model parameters approximated HIV serosorting in the real world, but

this is a simplification of mixing in the population. Both PrEP models were fit to the same summary statistics included in the base models, and included parameters for degree heterogeneity by PrEP use status. The PrEP sorting model also included assortative mixing statistics for the group of MSM using PrEP.

Table 4.1. Target degree, rate of one-time partners, and mixing statistics for cross-sectional network structure, stratified by partnership type

	Main	**Casual**	**One-time**
Degree	n[1]	n[1]	n[2]
Without Diagnosed HIV[3]	0.39	0.48	0.06
Not Using PrEP	0.39	0.35	0.03
Using PrEP	0.38	0.92	0.17
With Diagnosed HIV	0.42	0.72	0.11
Mixing	%	%	%
Without Diagnosed HIV[3,4]	93.2	90.9	92.4
Not Using PrEP	86.4	71.3	74.5
Using PrEP	45.3	41.0	33.3
With Diagnosed HIV[4]	44.7	49.3	46.1
Discordant HIV[5]	19.6	22.7	24.3

[1]Mean momentary degree

[2]Mean weekly rate of one-time partners

[3]MSM without diagnosed HIV include those with undiagnosed HIV infection

[4]Fraction of within-group mixing

[5]Fraction of all partnerships

The network was initialized with 10,000 MSM and relationship formation and dissolution occurred stochastically under the base model conditions. The population varied in size due to entry (sexual debut) and exit (death or aging out at 65 years). The network parameters were substituted along with the introduction of PrEP according to each of the model scenarios. This process retained the existing sexual network (i.e., persistent partnerships were not disrupted)

but relationship formation and dissolution at subsequent time steps followed the new network parameters.

HIV Transmission and Disease Progression: HIV transmission occurred stochastically with a per-act probability, which varied based on condom use,[135] sexual positioning,[136] circumcision status of the insertive partner,[137] PrEP use of the partner without HIV,[25] and HIV viral load of the partner with HIV.[4,138] Condom use varied based on demographic attributes of the partners, duration and type of partnership, and PrEP use within each partnership. Individuals with HIV were diagnosed, initiated antiretroviral therapy (ART), and maintained viral suppression, based on variable rates of HIV screening, HIV care engagement, and ART adherence.[139,140] Viral loads varied continuously according to the natural history of HIV infection in the absence of ART.[141,142] Disease progression occurred in stages (acute, chronic, and AIDS) with corresponding changes in viral load and mortality rates.

PrEP Uptake, Adherence, and Persistence: Uptake of PrEP was determined with both individual and partnership-dependent mechanisms. Individuals without HIV were eligible to initiate PrEP based on CDC guidelines for PrEP indications.[9] First, individual initiation occurred stochastically among all PrEP-eligible MSM at each time step, based on an overall initiation probability which varied with main and casual partner degree, and quintiles of one-time partner rates (**Table 4.2**). Second, to generate concordant partnering by PrEP use status, we simulated mutual PrEP decision making within persistent partnerships. This was operationalized by identifying main and casual partnerships, at each time step, in which both MSM are PrEP-eligible but only one partner initiated PrEP under the individual initiation mechanism. The partner who did not initiate PrEP was then given a second chance to initiate PrEP, within the same time step, based on different probabilities for main and casual partnerships. Individuals were limited to one chance at partnership-based PrEP initiation, even if multiple persistent partnerships met the criteria in the same time step; in these cases, if the qualifying partnerships were a mixture of main and

casual partners, initiation was based on the main partnership probability. Finally, if PrEP was not initiated during the time step, then the individual returns to the pool of PrEP-eligible MSM. The initiation cycle repeated at each time step and was memoryless (i.e., initiation probabilities did not depend on individual PrEP use history or PrEP initiation by a persistent partner at a previous time step).

Following PrEP initiation, MSM were assigned a PrEP adherence level, with 78.4% maintaining the high-adherence level associated with a 99% relative reduction in HIV transmission.[25,143] PrEP indications were reassessed annually and PrEP was discontinued if indications had lapsed. Spontaneous discontinuation also occurred, at a constant rate, based on an estimated median 224 days to discontinuation.[15,144] Similar to initiation mechanisms, we simulated partnership-dependent discontinuation by identifying persistent partnerships in which both men are using PrEP at the beginning of the time step, but only one discontinues. We implemented partnership-dependent discontinuation with varying probabilities for main and casual partners.

PrEP Sorting Scenarios: We modeled two scenarios of PrEP distribution in the sexual networks: (1) without PrEP sorting; and (2) with PrEP sorting. Degree distributions were held constant across scenarios, to isolate the impact of varying sorting mechanisms. We modeled PrEP sorting among persistent partners with assortative mixing targets for MSM using PrEP, by substituting the dynamic network parameters and varying the PrEP uptake and discontinuation probabilities. We did not directly model PrEP sorting for one-time partners, because the model without PrEP sorting generated assortative mixing among MSM using PrEP (median = 30.9%, **Appendix Table C.14**) that is similar to the observed mixing statistics from ARTnet (33.3%, **Table 4.1**). We were unable to model this slight increase to PrEP sorting among one-time partners without inadvertently increasing the magnitude of HIV serosorting. Among main and casual partners, respectively, the model without PrEP sorting generated only 12.1% and 24.1%

assortative mixing among MSM using PrEP (**Appendix Table C.14**). The ARTnet targets were 45.3% and 41.0% for main and casual partners, respectively, so there was a larger difference between the models with and without PrEP sorting.

Assortative mixing among MSM using PrEP caused changes throughout the network in the distribution of partnerships with concordant or discordant PrEP use statuses, due to the constraints imposed by fixed degree distributions, overall PrEP coverage, and the base network model conditions. By increasing the number of partnerships which are concordant with PrEP use, there were fewer opportunities for MSM who use PrEP to partner with either MSM who are not using PrEP or MSM with diagnosed HIV. In turn, the prevalence of other partnering combinations increased, including concordant partnering among MSM who are not using PrEP and discordant partnering between MSM with diagnosed HIV and MSM who are not using PrEP.

Calibration, Simulation, and Analysis: The model was initialized with the base network model conditions, to establish a stable HIV epidemic before PrEP was introduced. The model was calibrated to 2013–2014 prevalence estimates of diagnosed HIV infection among Atlanta MSM (33.3% Black; 12.7% Hispanic/Latinx; and 8.4% White).[145]

The calibrated PrEP uptake parameters are shown in **Table 4.2**. PrEP was introduced to the model in two stages over a five-year phase-in period. The first stage maintained the base network model parameters (i.e., without PrEP degree or sorting parameters) for one year, to allow PrEP use to increase steadily before substituting the network model parameters. This was necessary because the network models including PrEP parameters require >0% PrEP use in the population. The rate of PrEP initiation in the first stage was calibrated to reach a steady state of 20% PrEP use among PrEP-eligible MSM after 5 years, based on 2017 estimates of US MSM,[11] if the simulations continued beyond 1 year. The second stage (years 2–5 of the PrEP phase-in) was repeated twice: once without PrEP sorting and once with PrEP sorting. The network model parameters were substituted at the beginning of year 2, using the network

models either with or without PrEP sorting. The PrEP initiation probabilities were calibrated to maintain an average of 20% PrEP coverage among PrEP-eligible MSM at the end of year 5.[11] The calibrated initiation probabilities also varied by main and casual partner degree, and quintiles of one-time partner rates, based on target statistics from ARTnet, and to maintain similar distributions between the scenarios.

Table 4.2. Calibrated probabilities for PrEP uptake based on individual initiation and partnership-dependent mechanisms

	Without PrEP Sorting	With PrEP Sorting
Individual Initiation		
Overall Initiation Probability[1]	0.00479	0.00257
Main Partner Degree[2]		
0	1.38	1.35
1	0.75	0.7
2	1.0	1.0
Casual Partner Degree[2]		
0	0.82	0.77
1	2.1	2.1
2	2.3	2.5
3	2.3	2.5
One-time Partner Rate[2,3]		
0	0.3	0.05
0.61	1.0	0.8
2.22	1.2	2.75
16.94	1.64	3.5
Partnership-dependent PrEP		
Main Partners		
Initiation[4]	0	0.7
Discontinuation[5]	0	0.7
Casual Partners		
Initiation[4]	0	0.75
Discontinuation[5]	0	0.5

[1]Base probability of PrEP initiation per week, conditional on PrEP eligibility.

[2]Multiplicative scalar for relative changes to the base initiation probability.

[3]Based on quintiles of one-time partner rates (yearly); quintiles 1 and 2 each have a rate of 0 one-time partners and the same PrEP initiation probability.

[4]Probability of initiating PrEP concordant with a persistent partner.

[5]Probability of discontinuing PrEP concordant with a persistent partner.

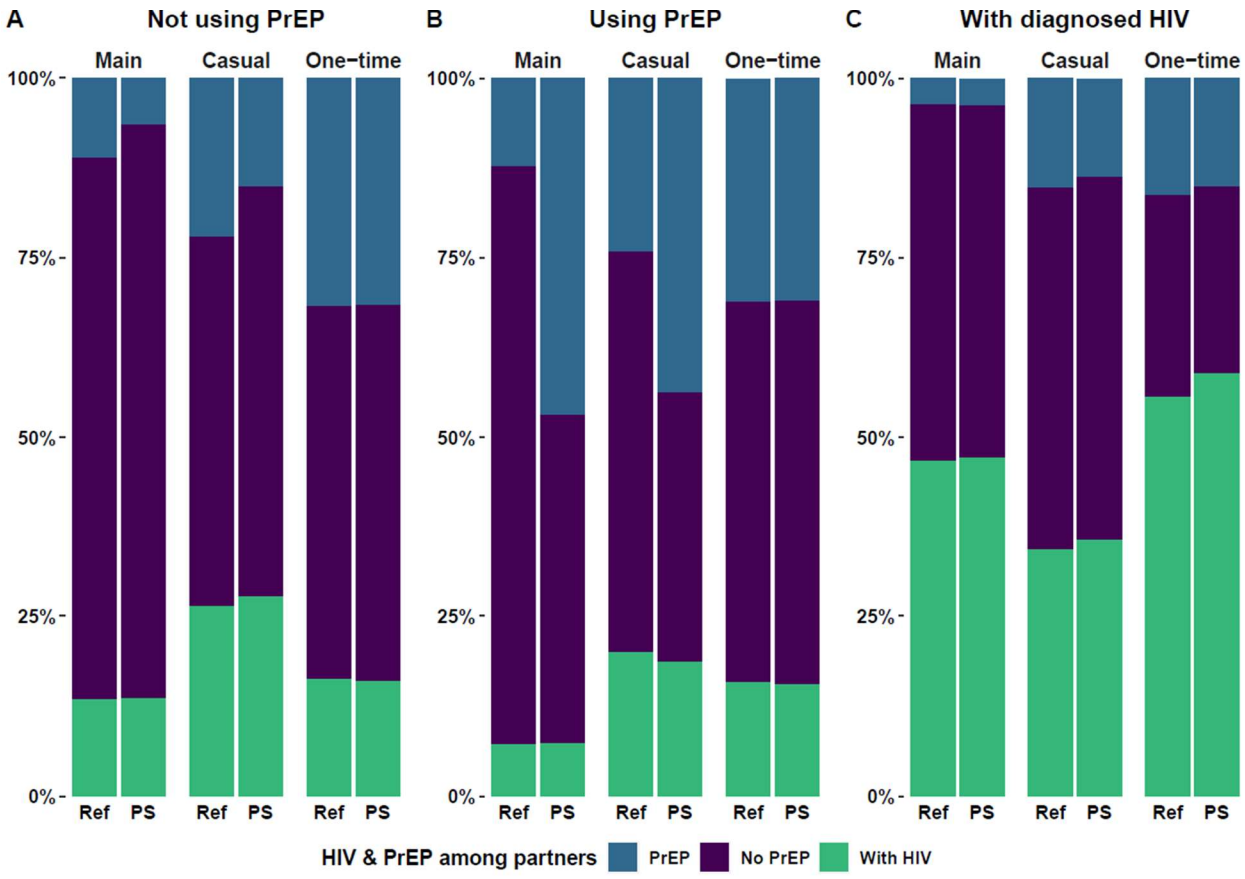
The scenarios were simulated 500 times for 10 years each, following the initial five-year phase-in of PrEP. For each scenario, we tracked network outcomes, including mean degree by diagnosed HIV status and PrEP use status; HIV serosorting and PrEP sorting statistics (i.e., mixing matrices); and the overall prevalence of partnerships with each combination of diagnosed HIV status and PrEP use status. We also tracked HIV outcomes, including HIV prevalence at the end of 10 years; HIV incidence rates per 100 person-years at risk, overall and stratified by PrEP use; per-act probabilities of HIV transmission; and cumulative incidence over 10 years, overall and for each combination of partnerships with concordant or discordant PrEP use and HIV diagnosis statuses. Cumulative incidence differences (CID) and relative cumulative incidence differences (RCID) were calculated by comparing cumulative incidence in the scenario with PrEP sorting to the reference scenario without PrEP sorting. The CID is the absolute difference between cumulative incidence in the scenario with PrEP sorting and the scenario without PrEP sorting. The RCID is the CID divided by the cumulative incidence without PrEP sorting. We summarized the results with the median values and 95% simulation intervals (SI) across all simulations.

RESULTS

Figure 4.1 compares mixing statistics in the referent scenario without PrEP sorting to the scenario with PrEP sorting (full numerical results presented in **Appendix Table C.14**). Assortative mixing among MSM with diagnosed HIV was similar to the ARTnet target statistics (**Table 4.1**) for main partners, but the magnitude of assortative mixing in casual partner networks (34.3% without PrEP sorting and 35.7% with PrEP sorting) was less than the target statistic (49.3%). At the same time, there was excess assortative mixing among MSM with diagnosed HIV in the one-time partner networks (55.6% without PrEP sorting and 58.8% with PrEP sorting) compared to the target statistic (46.1%). This means that there were more casual partnerships and fewer one-time partnerships with different diagnosed HIV statuses than the

target network statistics. The models with and without PrEP sorting were similar with respect to these differences.

Figure 4.1. Mixing statistics in scenarios with and without PrEP sorting, average over year 10



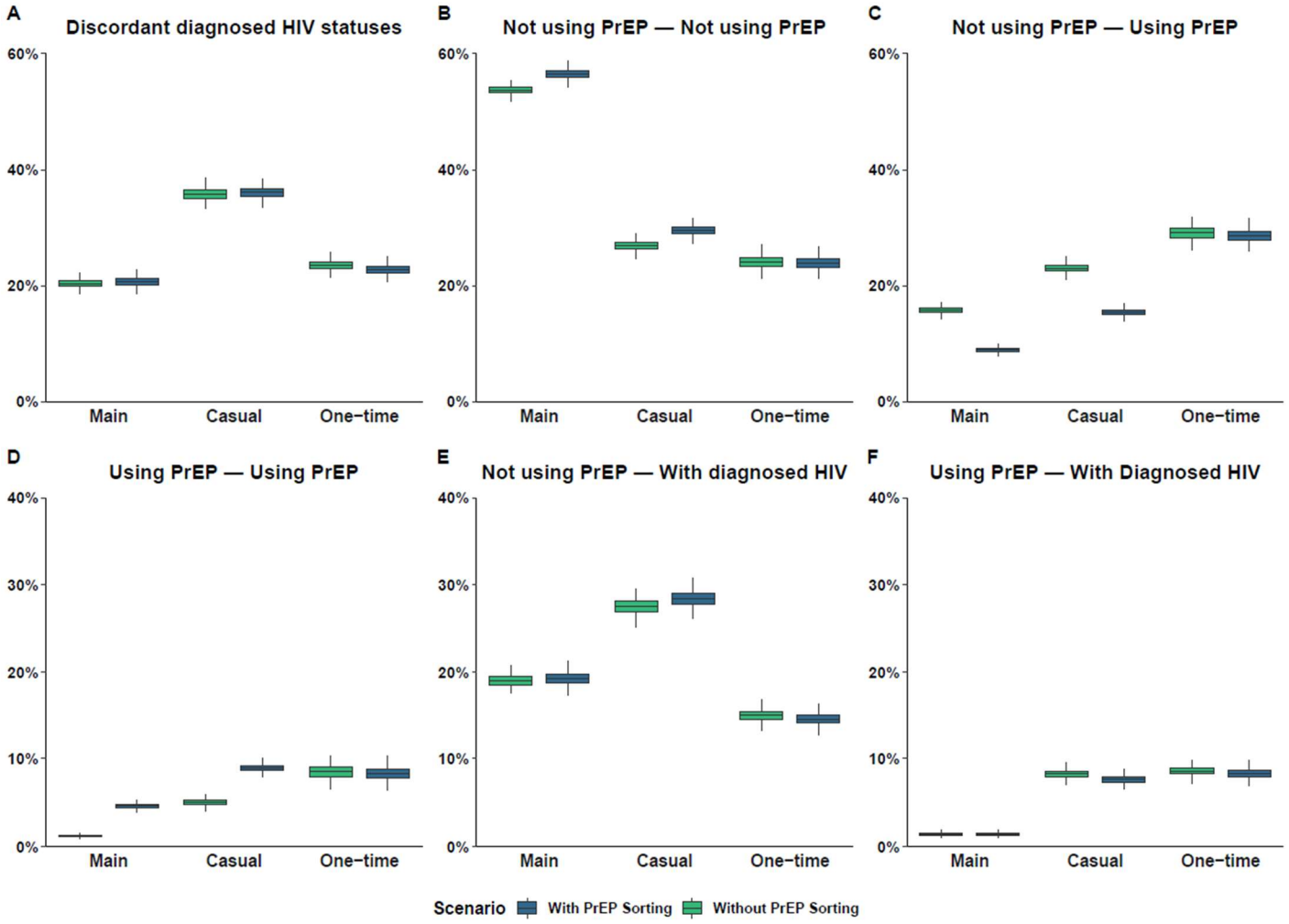
Legend: Ref = referent scenario without PrEP sorting; PS = PrEP sorting scenario; Values shown are median results across 500 simulations in each scenario

Assortative mixing among MSM using PrEP was 12.1% among main partners and 24.1% among casual partners, in the scenario without PrEP sorting. These proportions increased to 46.9% for main partners and 43.7% for casual partners, in the scenario with PrEP sorting. These were similar to the target statistics of 45.3% and 41.0%, respectively. In both scenarios, assortative mixing for one-time partners (30.9%; no change between scenarios) was slightly less than the fraction estimated in ARTnet (33.3%). The increased assortative mixing among main and casual partners using PrEP was balanced by decreased mixing with MSM not using PrEP. There was no change to mixing with MSM with diagnosed HIV for main partners, while mixing decreased only slightly for casual partners (20.0% without PrEP sorting vs. 18.6% with PrEP sorting). Among MSM not using PrEP, there was an increase to assortative mixing in main (75.6% without PrEP sorting vs. 80.1% with PrEP sorting) and casual (51.6% without PrEP sorting vs. 57.3% with PrEP sorting) partnerships. Assortative mixing among one-time partners not using PrEP was 52.1% without PrEP sorting and 52.5% with PrEP sorting. Across partnership types and in both scenarios, assortative mixing among MSM not using PrEP was lower than the fraction estimated in ARTnet: 86.4% for main, 71.3% for casual, and 74.5% for one-time.

Figure 4.2 compares the scenarios with respect to the prevalence of partnerships with different combinations of diagnosed HIV status and PrEP use status (full numerical results presented in **Appendix Table C.15**). The number of main, casual, and one-time partnerships was similar across the two scenarios, due to fixed degree distributions (**Appendix Table C.16**). The prevalence of persistent partnerships concordant with PrEP use (i.e., the proportion out of all partnerships, stratified by type) was higher in the scenario with PrEP sorting compared to without (1.2% vs. 4.6% for main; and 5.0% vs. 9.0% for casual). Increased assortative mixing among MSM using PrEP results in fewer partnerships between MSM using PrEP and MSM not using PrEP (15.7% vs. 9.0% for main; and 23.0% vs. 15.4% for casual). There was also an

increase to the prevalence of partnerships between men not using PrEP (53.7% vs. 56.5% for main, and 26.9% vs. 29.5% for casual). Among casual partners, there was a small decrease to discordant partnerships between MSM using PrEP and MSM with diagnosed HIV (8.3% vs. 7.6%) and corresponding increase to partnering between MSM not using PrEP and MSM with diagnosed HIV (27.5% vs. 28.4%). There was no similar change for main partnerships. Among one-time partners, there was a small decrease to the fraction of partnerships with different diagnosed HIV statuses (23.6% vs. 22.8%).

Figure 4.2. Prevalence of partnerships with different combinations of diagnosed HIV status and PrEP use status, stratified by partnership type, in scenarios with and without PrEP sorting



Legend: Panels A–C use a different y-axis scale than Panels D–F

Table 4.3 summarizes HIV outcomes across the two scenarios. The relative cumulative incidence difference shows that there were 2.4% more (95% SI: 10.3% less, 16.8% more) incident infections over 10 years in the scenario with PrEP sorting compared to without PrEP sorting. The final HIV prevalence, fraction diagnosed versus undiagnosed, and prevalence of PrEP use among PrEP-eligible MSM, was similar across the two scenarios. The median HIV incidence rate in year 10 was the same in both scenarios, although the 95% simulation interval indicates a slightly higher rate in the scenario with HIV sorting. Among all MSM susceptible to HIV acquisition, the HIV incidence rate per 100 person-years at risk was 0.84 (95% SI: 0.59, 1.06) without PrEP sorting and 0.84 (95% SI: 0.63, 1.09) with PrEP sorting. However, there were diverging effects based on PrEP use. Among MSM not using PrEP, the trend was similar to overall incidence rates: 0.94 (95% SI: 0.66, 1.19) without PrEP sorting vs. 0.94 (95% SI: 0.71, 1.21) with PrEP sorting. For MSM using PrEP, the HIV incidence rate was lower in the scenario with PrEP sorting: 0.16 (95% SI: 0.00, 0.49) without PrEP sorting vs. 0.09 (95% SI: 0.00, 0.41) with PrEP sorting. The per-act probability of HIV transmission in partnerships with different HIV statuses was the same in both scenarios (**Appendix Table C.17**) so differences in the HIV incidence rates are attributable to varying mixing in the networks.

Table 4.3. HIV incidence and prevalence outcomes in scenarios without versus with HIV pre-exposure prophylaxis (PrEP) sorting

	Without PrEP Sorting	**With PrEP Sorting**
	Median (95% SI)[1]	Median (95% SI)[1]
PrEP Prevalence,[2] %	19.7 (18.9, 20.5)	19.7 (18.8, 20.6)
HIV Prevalence,[3] %	20.0 (19.3, 20.7)	20.1 (19.4, 20.9)
Diagnosed,[4] %	89.0 (87.7, 90.5)	89.1 (87.8, 90.4)
Undiagnosed,[4] %	11.0 (9.5, 12.3)	10.9 (9.6, 12.2)
Incidence Rate[5]		
Overall, 100^{-1} PYAR	0.84 (0.59, 1.06)	0.84 (0.63, 1.09)
Not Using PrEP, 100^{-1} PYAR	0.94 (0.66, 1.19)	0.94 (0.71, 1.21)
Using PrEP, 100^{-1} PYAR	0.16 (0.00, 0.49)	0.09 (0.00, 0.41)
Cumulative incidence,[6] N	832 (755, 906)	850 (777, 939)
Relative Cumulative Incidence Difference,[7] %		2.4 (-10.3, 16.8)

[1]Median and 95% simulation interval over 500 simulations in each scenario

[2]Among PrEP-eligible MSM, mean over year 10

[3]HIV prevalence at the end of 10 years

[4]Percent of all infections diagnosed versus undiagnosed, mean over year 10

[5]HIV incidence per 100 person-years at risk, mean over year 10

[6]Total infections over 10 years

[7]Difference of the cumulative incidence in the scenario with PrEP sorting compared to without PrEP sorting, divided by cumulative incidence in the scenario without PrEP sorting, mean over 10 years

Table 4.4 presents cumulative incidence stratified by attributes of the two partners. There were 20 more (95% SI: 92 less, 132 more) infections over 10 years, in the scenario with PrEP sorting compared to without PrEP sorting. Most incident infections, in both scenarios, occurred among MSM not using PrEP and were attributable to partners with diagnosed HIV. Cumulative incidence increased for partnerships in which both partners were without diagnosed HIV and not using PrEP (n = 8; 95% SI: -56, 69) and in partnerships in which one partner is not using PrEP and the other partner is with diagnosed HIV (n = 14; 95% SI: -55, 86). There were fewer infections attributable to partnerships in which one man is using PrEP and the other is not using PrEP (n = -4; 95% SI: -15, 7).

Table 4.4. HIV incidence over 10 years, overall and stratified by individual and partnership level attributes at the time of HIV transmission, in scenarios without and with PrEP sorting

	Without PrEP Sorting		With PrEP Sorting		
	N[1,2]	%[2,3]	N[1,2]	%[2,3]	CID[2,4]
Total	832 (755, 906)	---	850 (777, 939)	---	20 (-92, 132)
PrEP Use, Susceptible Partner					
Not Using PrEP	814 (737, 887)	97.9 (92.8, 100.0)	832 (764, 920)	98.4 (93.7, 100.0)	21 (-82, 129)
Using PrEP	20 (11, 29)	2.1 (0.0, 7.2)	17 (10, 28)	1.6 (0.0, 6.3)	-2 (-14, 10)
Diagnosis Status, Partner with HIV					
With Diagnosed HIV	607 (556, 657)	73.4 (61.0, 85.4)	621 (569, 673)	74.3 (60.6, 85.2)	15 (-57, 87)
With Undiagnosed HIV	227 (184, 275)	26.6 (14.6, 39.0)	230 (187, 277)	25.7 (14.8, 39.4)	4 (-62, 67)
Partnership Level PrEP Use and HIV Diagnosis Status					
Not Using PrEP – Not Using PrEP	212 (170, 256)	24.7 (13.6, 36.9)	220 (178, 264)	24.6 (14.3, 37.7)	8 (-56, 69)
Not Using PrEP – Using PrEP	13 (6, 22)	1.2 (0.0, 6.0)	9 (3, 18)	0.6 (0.0, 4.8)	-4 (-15, 7)
Using PrEP – Using PrEP	0 (0, 2)	0.0 (0.0, 0.0)	0 (0, 3)	0.0 (0.0, 0.8)	0 (-2, 3)
Not Using PrEP – With Diagnosed HIV	594 (542, 644)	71.6 (58.7, 84.4)	608 (557, 660)	72.9 (59.3, 83.2)	14 (-55, 86)
Using PrEP – With Diagnosed HIV	12 (6, 20)	1.1 (0.0, 5.6)	12 (6, 20)	1.1 (0.0, 5.5)	0 (-10, 10)

[1]Median and 95% simulation interval across 500 simulations of each scenario; [2]Cumulative incidence over 10 years; [3]Fraction of all incident infections; [4]Cumulative incidence difference in simulations with PrEP sorting vs. without PrEP sorting

DISCUSSION

In this study, we projected a minor increase to HIV incidence when MSM who use PrEP are clustered in the sexual network due to assortative mixing. However, the results were widely variable, and incidence decreased in many simulations. The magnitude of effect was not large enough to explain gaps between the predicted and observed population-level impact of PrEP. However, analyses of the mechanisms contributing to transmission dynamics provide support for our hypothesis that assortative mixing among MSM who use PrEP may contribute to sustained HIV incidence despite increased PrEP coverage among MSM in the US. Our model demonstrates that individual and partnership-level decisions among MSM who use PrEP can impact transmission dynamics by varying opportunities for primary and secondary prevention.

Despite the minor impact of PrEP sorting on HIV incidence in our model, we presented mechanisms by which network-level factors may influence the population benefit of PrEP. We showed that assortative mixing among MSM who use PrEP results in decreased HIV incidence in this group (analogous to herd immunity of vaccines). At the same time, concentration of PrEP in fewer partnerships caused HIV incidence to increase among MSM not using PrEP – yielding a net increase to cumulative incidence in the population. The magnitude of assortative mixing among MSM not using PrEP was lower in our model, compared to the target statistics, because we were unable to model serosorting in persistent partnerships or modify the sorting mechanisms in one-time partnerships. Therefore, we may have underestimated excess transmission in the group of MSM not using PrEP, along with the net negative influence of PrEP sorting on transmission dynamics. Previous mathematical models have explored the varying impact of PrEP on HIV incidence depending on individual-level factors, including which PrEP-eligible MSM are using PrEP,[91,116,130,133,146] and PrEP-mediated sexual behavior changes,[125,132,147] while other models have explored various systems-level factors, including PrEP care delivery models and combination prevention packages.[15,92,132,148] This study adds to

the literature by demonstrating the potential role of network-level factors in further limiting the population benefit of PrEP.

Prior models of mixing among MSM have explored the impact of HIV serosorting, but not PrEP sorting. A recent modeling study of MSM in Canada found a minor decrease to the population benefit of PrEP if MSM who use PrEP discontinue HIV serosorting following PrEP initiation,[125] due to increased partnering between MSM with diagnosed HIV and MSM using PrEP. Wang et al employed a partnership balancing mechanism in which the overall number of partnerships was fixed, so decreased HIV serosorting among MSM using PrEP caused cascading effects in the population. These effects included increased assortative mixing among MSM not using PrEP, with a corresponding increase to infections attributable to these partnerships. Although the research question was different (the Wang model explored HIV serosorting, while our model explored PrEP sorting) these two studies highlight related phenomena of nonrandom mixing among MSM. Both models have limitations. Wang et al used a deterministic compartmental model, which facilitated successful implementation of the partnership balancing mechanism; however, models of this kind are not individual based, so many of the complex factors which influence transmission dynamics were not represented (e.g., individual variation in sexual behavior). Our model was more complex, but we were unable to vary mixing with the same degree of success. The net effect was small in both studies, but serosorting and PrEP sorting decisions may interact to produce a larger impact on HIV transmission dynamics. Future research should explore the combined effect of these phenomena.

Our model was part of a broader set of questions about which MSM are using PrEP. Following others,[15,116] we allocated PrEP by first identifying which MSM are PrEP-eligible based on CDC indications.[9] However, there are multiple ways that MSM may be indicated for PrEP, so individual risk and location in the sexual network are variable among PrEP-eligible MSM.[149] For

example, some PrEP-eligible MSM have more than one concurrent partner of unknown HIV status, while others may be in a monogamous partnership with a partner living with diagnosed HIV. Uptake of PrEP varies based on which indications establish eligibility, and some MSM who report PrEP use are not considered eligible based on CDC indications.[11] We partially accounted for this variability by allocating PrEP according to degree estimates from ARTnet. However, we did not model other differences, including increased uptake among MSM with main or casual partners living with HIV. A future model should build on our work modeling assortative mixing among MSM who use PrEP, by exploring other ways that PrEP coverage varies in the network.

LIMITATIONS

There are several important limitations to our model. First, as discussed earlier, we were unable to calibrate the model to estimated serosorting patterns in the population. This means that our model underestimated the number of partnerships concordant without PrEP use. We also did not model other ways that mixing varies (e.g., the interaction of PrEP use status and HIV serosorting). Our future work will include a model of HIV serosorting, to further explore the role of variable population mixing. Second, we modeled PrEP coverage based on degree and mixing, so we were unable to also stratify by race/ethnicity and age. This would require increasing the population size, with a trade-off of increased computation time required to complete the simulations. PrEP sorting may impact communities differently, due to disparities in HIV incidence and PrEP coverage, so these are important factors to explore in a future model. Third, we modeled concordant PrEP use in persistent partnerships using probabilities selected during calibration. This mechanism could be improved with empiric estimates of coordinated decision making in main and casual partnerships. Finally, our estimate of PrEP sorting was based on a sensitivity analysis of the ARTnet data. We used the median results from this analysis, but it is possible that there was residual bias. We did not vary the magnitude of PrEP sorting (e.g., by using the lower and upper values of the 95% simulation interval from the

sensitivity analysis) because of the challenges of calibrating the model to HIV serosorting and imposing further PrEP sorting. The mechanisms presented with the current model are unlikely to vary with different estimates of mixing, but the magnitude of effect may be different than projected.

CONCLUSIONS

The federal “Ending the HIV Epidemic” initiative calls for increased PrEP use to decrease HIV incidence by 90% in the next decade, but there has yet to be empiric evidence supporting PrEP impact at the population level. In the present study, we explored the potential role of network clustered PrEP in limiting the population benefit of PrEP. The overall effect in our model was small. However, assortative mixing among MSM who use PrEP might be just one factor among several which decrease the efficiency of PrEP coverage in the sexual network. A future model should build on our work by exploring the interaction of multiple network-level factors.

Chapter 5. Conclusions and Public Health Implications

The goal of this dissertation was to explore the potential impact of HIV serosorting and assortative mixing among MSM who use PrEP on the population benefit of PrEP. Reinvigorated efforts to end the HIV epidemic in the US rely heavily on PrEP as a core component of a broader strategy to decrease HIV incidence by 90% by 2030.[16] Clinical trials show that PrEP can reduce individual risk by 99%.[6,8] Approximately 20% of PrEP-eligible MSM used PrEP in 2017.[11] Mathematical models suggest that HIV incidence could decrease by 20% over 10 years at 2017 coverage levels,[12–15] yet ecological estimates of PrEP coverage and HIV diagnoses among MSM have found limited impact.[17,18] There are likely many factors contributing to gaps between the observed and predicted HIV epidemic trajectory. Public health efforts have centered on improving overall PrEP coverage and effective use in the population, and decreasing demographic disparities along the PrEP continuum of care. However, PrEP coverage may be unequal in the sexual network beyond levels expected based on demographic disparities.

Assortative mixing among MSM who use PrEP could produce clusters of PrEP use in the sexual network, which we hypothesized would decrease opportunities for primary and secondary prevention, compared to counterfactual scenarios with less clustered PrEP, and decrease the overall population benefit of PrEP. In the current studies, we estimated mixing statistics for the interaction of diagnosed HIV status and PrEP use in the sexual networks of MSM. We used these statistics to estimate and simulate cross-sectional sexual networks of MSM in the US, to quantify the magnitude of excess HIV serosorting and PrEP sorting beyond the levels expected based on other network properties. Finally, we used a network-based model of HIV transmission to estimate the impact of assortative mixing among MSM who use PrEP on the population benefit of PrEP. In this chapter, we review the findings of this dissertation and discuss innovations, public health implications, and future directions.

Review of major findings

In **Chapter 2**, we estimated HIV serosorting and PrEP sorting patterns among MSM in the US, using a 2017–2019 egocentric sexual networking study. Respondents reported their own attributes, as well as sexual and medical history, including HIV status and PrEP use. The respondents also served as proxies to report information about their recent sexual partners. Mixing matrices estimated with egocentric data are vulnerable to information bias, due to incomplete respondent knowledge.[68,71,72] We used a reclassification sensitivity analysis to minimize information bias and compared the results to a complete-case analysis.

We found strong evidence of preferential partnering across analytical approaches. The reclassification analysis showed concordance among MSM with diagnosed HIV (39.3%) and among MSM who used PrEP (31.9%) and MSM who had not used PrEP (82.6%). The fraction of partners with diagnosed HIV was higher among MSM who used PrEP (11.1%) compared to MSM who had not used PrEP (3.7%). Comparatively, the complete-case analysis overestimated the fractions of partners with diagnosed HIV or partners who used PrEP, across all strata, and underestimated partners who had not used PrEP. This is because of our assumption that MSM with diagnosed HIV and MSM who use PrEP are more likely to discuss their HIV status and PrEP use with sexual partners, compared to MSM without diagnosed HIV and not using PrEP. Our analysis provides a recent estimate of HIV serosorting and PrEP sorting among MSM, which is supported by previous estimates in the literature.[62,64,65] Quantitative estimates vary across studies, which is to be expected given varying prevalence of diagnosed HIV and PrEP use in the underlying populations. However, our results show that differences in analytical decisions surrounding incomplete or misclassified data can bias results. We concluded that complete-case analyses of PrEP sorting likely overestimate assortative mixing.

In **Chapter 3**, we estimated and simulated cross-sectional sexual networks of MSM in the US. Exponential random graph models (ERGMs) were fit to egocentric summary statistics,

weighted to the demographics of MSM in the US. Model parameters from the fit models were used to simulate cross-sectional networks. We estimated models fully parameterized to the observed network data, including summary statistics for degree heterogeneity, assortative mixing by race/ethnicity and age, and full mixing matrices for the interaction of diagnosed HIV status and PrEP use. We compared fully saturated model parameterizations to less saturated parameterizations to elucidate the mechanisms generating the observed HIV and PrEP mixing statistics.

We estimated that 45% of all persistent partnerships and 24% of one-time partnerships among MSM are between men without diagnosed HIV and not using PrEP. Models based on degree heterogeneity and assortative mixing within demographic groups accounted for only 70–80% of these partnerships. The excess partnering among MSM not using PrEP is due to assortative mixing among MSM who use PrEP and among MSM with diagnosed HIV. Our models provide evidence for inefficient network coverage of PrEP, which may partially explain sustained incidence despite increasing PrEP use over time.[11,17,18] The US EHE initiative aims to decrease HIV incidence by expanding PrEP use,[16] but our results show that PrEP coverage in sexual networks can vary depending on which PrEP-eligible MSM are using PrEP. We propose using network coverage as an additional metric to measure progress, as policies continue to focus on increased PrEP use in the population. Maximizing network coverage can be achieved by targeting PrEP to MSM with more partners, but our results show that assortative mixing among MSM who use PrEP can undermine this strategy. Efforts should prioritize expanding PrEP use outside the population subgroups where it is already concentrated.

In **Chapter 4**, we used a network-based model of HIV transmission dynamics among MSM to estimate the impact of assortative mixing among MSM who use PrEP. The model was developed to represent observed patterns of PrEP use in our target population of MSM in Atlanta, including 20% coverage among PrEP-eligible MSM. We allocated PrEP based on

degree estimates by partnership type, so that MSM using PrEP had more casual and one-time partners, on average, than MSM not using PrEP. We compared models with and without PrEP sorting for differences in HIV incidence and network structure, to test the hypothesis that network clustering of PrEP decreases the population benefit of PrEP.

Our model projected a minor increase to HIV incidence when MSM who use PrEP are clustered in the sexual network. Compared to the model without PrEP sorting, there were 2.4% more incident infections over 10 years in the model with PrEP sorting. However, the results were variable and incidence was lower in some simulations (95% simulation interval: 10.3% less, 16.8% more). The excess incidence was attributable to increased partnering between MSM not using PrEP, and partnering between MSM not using PrEP and MSM with diagnosed HIV. The overall effect was relatively minor, but analyses of the mechanisms involved support our hypothesis that assortative mixing among MSM who use PrEP decreases the population benefit of PrEP by concentrating its use in fewer partnerships. Our model also showed that PrEP sorting decreases the HIV incidence rate among MSM who use PrEP, even though overall incidence is greater than the scenario without PrEP sorting. This is because assortative mixing among MSM who use PrEP decreases exposure to HIV (either diagnosed or undiagnosed) for these men. This further supports our hypothesis that clustering of PrEP use in the sexual network increases the prevention benefit for MSM using PrEP, while decreasing opportunities for primary and secondary prevention throughout the network.

Innovations

This dissertation represents a number of innovations, both with respect to methodology and HIV prevention more broadly. First, we estimated HIV serosorting and PrEP sorting patterns among MSM in the PrEP and U=U era. There has been decades of research summarizing HIV serosorting among MSM.[60] More recently, studies have described the newer phenomenon of PrEP sorting.[62,64,65] The reported outcomes, mixing matrices, are relatively simple summary

statistics. Nevertheless, *valid* estimation of these matrices is not a simple task, due to bias that is introduced when respondents are unable to accurately report information about their sexual partners, as is the case for HIV status and PrEP use. Bias of this kind threatens the validity of HIV serosorting and PrEP sorting estimates obtained by egocentric study design. Our reclassification sensitivity analysis is a novel approach to addressing information bias in mixing matrices and other network statistics. The method can be improved by estimating bias parameters with a validation sub-study to the main sample. For example, a small portion of the sample (e.g., 10%) could be selected to refer their sexual partners to participate in the study. The records would be linked, in order to assess the ego-reported information for accuracy. The results of such analyses could serve as bias parameters for a reclassification model. This would substantially reduce uncertainty in the results and researchers could use simpler reclassification mechanisms. We propose routine collection of validation data for egocentric studies of hard-to-report information, such as a sexual partner's HIV status and PrEP use. We present our current work as evidence of the substantial impact of bias and as a guide for reclassification methods.

Second, we used network models to estimate PrEP coverage in the sexual networks of MSM. The most common metric to summarize PrEP coverage uses individuals (e.g., PrEP-eligible MSM) as the denominator. For example, 20% of PrEP-eligible MSM used PrEP in 2017.[11] Increasing PrEP coverage among MSM is a central goal of the US "Ending the HIV Epidemic" initiative,[16] but population-level analyses of PrEP impact have not found a substantial effect of decreased HIV incidence as PrEP coverage has increased.[17,18] Our analyses show that PrEP coverage in the sexual network may vary, even if coverage in population remains fixed, which could mediate the casual relationship between PrEP coverage in the population and HIV incidence. Network coverage depends on coverage in the population, but also varies based on degree distributions and mixing patterns. Coverage in the population is both intuitive and simple to calculate, but coverage in the network may be more proximal to prevention outcomes. We

present network coverage as a new metric to monitor public health progress, to evaluate the population-level association between PrEP coverage and HIV incidence, and to define targets for increased PrEP use.

Third, our analysis is the first to use network estimation and simulation analyses to elucidate the mechanisms generating the observed patterns of HIV serosorting and PrEP sorting among MSM. We showed that network coverage of PrEP increases if PrEP is used by MSM with higher degree, but this benefit can be partially offset by assortative mixing which produces clusters of PrEP use. We also found that only 70–80% of concordant partnering among MSM not using PrEP is attributable to degree heterogeneity and demographic mixing. This means that increasing PrEP coverage in the sexual network will require a mixed strategy of targeting MSM with more partners and MSM outside of existing clusters.

Fourth, we used a mathematical model of HIV to provide the first estimates of the population-level impact of assortative mixing among MSM who use PrEP. The model was adapted from a previously published model of HIV transmission among MSM in Atlanta,[13,15,36] and includes a number of new features. The model is network-based, so we varied mixing by substituting the parameters governing the dynamic network. This required multiple versions of the network parameterizations. We adapted the Krivitsky[150] method for adjusting the network parameters to the population size (which typically occurs automatically at each time-step) for seamless substitution of the network parameters to the existing network structure. Population mixing is influenced by degree distributions, so we included network parameters for degree heterogeneity by diagnosed HIV status and PrEP use. Prior studies have used a fixed nodal attribute (“risk group”) to model a skewed distribution of one-time partner rates in the population; we modified this mechanism so that one-time partner rates could change over time (i.e., individual nodes could change “risk groups”) so that mean rates by group remain stable. Network parameters govern partnership formation and dissolution, but HIV and PrEP

concordance can change over time within persistent partnerships, due to HIV transmission (or diagnosis) and intermittent PrEP use. Therefore, we also modified the mechanisms to allocate PrEP among PrEP-eligible MSM. Following prior models,[13,15] we used an overall initiation probability to vary the rate of PrEP uptake and calibrated overall coverage to 20% among PrEP-eligible MSM. In this process, we varied PrEP initiation based on main, casual, and one-time partner degree, and calibrated these probabilities so that degree distributions were the same for the models with and without PrEP sorting. We modeled coordinated decision making in persistent partnerships by incorporating a partner-dependent mechanism for PrEP initiation and discontinuation. These mechanism can be used in future research to vary PrEP coverage in the sexual network. Finally, we assessed the mechanisms contributing to increased HIV incidence by tracking network propertied over time and attributing incident infections to partnerships with different combinations of diagnosed HIV status and PrEP use.

Relevance and public health impact

The advent of both PrEP and U=U, with major clinical trials published in 2010 and 2011,[4,6] respectively, was a paradigm shift for HIV prevention. A decade later, however, we have yet to observe the predicted decrease in HIV incidence among MSM following increased PrEP use.[17,18] Myriad factors contribute to HIV transmission dynamics. Public health efforts have prioritized individual (e.g., awareness) and systems-level (e.g., normative guidelines defining PrEP indications) factors of the PrEP care continuum. The goal of these efforts is to increase effective PrEP use among MSM at risk for HIV acquisition and limit transmission in the population. This dissertation investigated the role of assortative mixing among MSM who use PrEP, a network-level factor, as an additional mechanism contributing to sustained HIV incidence among MSM. We demonstrated that network coverage of PrEP can vary depending on which PrEP-eligible MSM are using PrEP, which may undermine prevention efforts despite increased PrEP coverage in the population.

Our models of HIV transmission predicted a relatively small effect of PrEP sorting on decreasing the population-level HIV prevention benefit of PrEP. However, the mechanisms presented support our hypothesis that network clustering decreases PrEP impact at the population level. One implication of these findings is that interventions to increase PrEP coverage should be designed to maximize PrEP coverage in the network. The US EHE already prioritizes specific communities of MSM, defined by demographic attributes and geography, for interventions to increase PrEP access and use.[16] These efforts, if successful, are likely to increase PrEP coverage in the network, but progress may be slow and inefficient without concerted effort to deliver PrEP outside of the community clusters where it is already concentrated. It will be challenging to target interventions to individuals based on their location in the sexual network (which is unobservable in practice) but strategies exist to leverage networks (both sexual and social) for targeted diffusion of interventions.[151] Alternatively, existing public health systems for HIV screening can be used for PrEP delivery. For example, individuals newly diagnosed with HIV are referred to contact tracing systems to identify sexual partners for HIV screening. This is a convenient way to identify MSM who may be located in the sexual network where PrEP use is sparse. Screening remains a priority, but negative results should be followed by linkage to PrEP services. Finally, normative guidelines, such as CDC guidance for PrEP prescribing,[9] can incorporate partner PrEP use in algorithms to assess risk and define indications.

This dissertation also has implications for mathematical modeling of PrEP. Previous models have explored the varying impact of PrEP on HIV incidence depending on individual-level factors, including which PrEP-eligible MSM are using PrEP,[91,116,130,133,146] and PrEP-mediated sexual behavior changes,[125,132,147] while other models have explored various systems-level factors, including PrEP care delivery models and combination prevention packages.[15,92,132,148] Our results show that PrEP impact can also vary depending on mixing, as

well as modelling decisions about which PrEP-eligible MSM are using PrEP. The magnitude of effect was small, but we were unable to fully model the observed network structures. Our work can be extended, so that PrEP sorting patterns are routinely built into models of PrEP impact. This is important to investigate the role of network-level factors in mediating the causal relationship between PrEP coverage in the population and HIV incidence.

Future Directions

Our work has generated a number of new research questions which warrant investigation. First, assortative mixing among MSM who use PrEP is just one way that PrEP coverage varies in the network. Our analyses show that coverage also varies by degree and the full mixing pattern of diagnosed HIV status and PrEP use. We focused on assortative mixing among MSM who use PrEP, because of the overarching hypothesis for this dissertation, but our future work will explore the independent and combined impact of other network-level factors. We will begin by re-calibrating the base model to cross-sectional estimates of HIV serosorting, which will increase assortative mixing among MSM without diagnosed HIV. We will then vary PrEP coverage based on our mean degree estimates and the full mixing pattern of HIV and PrEP. Second, we modeled PrEP allocation among PrEP-eligible MSM based on CDC guidelines for PrEP indications,[9] but a recent study shows that some MSM who use PrEP are not considered PrEP-eligible.[11] As we continue to model network coverage of PrEP, it will be important to account for these men and understand their place in the sexual network. Third, we did not vary PrEP coverage based on race/ethnicity or age. It will be important to explore how network-level factors interact with demographic disparities in PrEP coverage to reinforce unequal HIV burden in the population. This will require a larger simulated population (e.g., beginning with 25,000 nodes instead of 10,000) so that we can vary PrEP use by more factors.

Fourth, our reclassification sensitivity analysis to estimate HIV serosorting and PrEP sorting with egocentric sexual network data used parameters (i.e., assumptions about sensitivity

and specificity) derived from external literature sources and expert knowledge. Future studies should collect validation sub-study data. For example, egos would be surveyed as usual (i.e., self-report their own information and serve as a proxy to report information about sexual partners) then refer their sexual partners to participate in the study. The records would be linked and compared for accuracy. The results of this analysis could be used to parameterize a reclassification model. This would decrease uncertainty by tying the bias parameters to the parent study. This would also enable researchers to use a simpler reclassification model with direct estimates of information bias (opposed to indirect assumptions about knowledge within sexual partnerships). As technology evolves, it is also possible to mail HIV screening kits to sub-study participants, in order to estimate the prevalence of undiagnosed HIV in the population and verify self-reported data. Finally, the sub-study could generate other network statistics, such as mixing with respect to degree (e.g., the tendency of MSM with many partners to partner with MSM who have few partners) which may influence overall network structure and HIV transmission dynamics.

Finally, this dissertation was focused on HIV prevention, but other sexually transmitted infections (STIs) are transmitted along the same sexual networks. A prior model showed that PrEP could act to decrease bacterial STI incidence, because clinical practice guidelines call for quarterly screening which would decrease the prevalence of asymptomatic and undiagnosed infections.[9,152] However, this effect could be undermined by PrEP sorting, if bacterial STIs proliferate rapidly within dense clusters of PrEP use and emanate outward to other regions of the sexual network where MSM are not using PrEP (and screening for STIs may be less frequent on average). Future models of bacterial STIs should explore these dynamics as a hypothesis for increasing incidence among MSM.

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Appendix A. Chapter 2 Technical Supplement

General approach

We used multiple imputation with exponential-tilt models to stochastically reclassify the ego-reported alter HIV status and PrEP use.[110] The method uses multiple imputation techniques from the missing data literature to estimate a joint probability distribution of the ego-reported data. Predictive probabilities for each observation (ego-reported known and unknown) are drawn from the posterior distribution of the model parameters. The probabilities are then adjusted based on assumptions about the sensitivity and specificity of the ego-reported data. Finally, new values are imputed for each alter using the adjusted probabilities. The approach is similar to probabilistic methods used to correct misclassification.[115] However, the imputation model is used to estimate which observations are likely candidates for reclassification. This is especially useful for the observations initially reported unknown. The process is repeated multiple times to allow for random variation, for a total of M = 300 datasets. We completed the process in two stages: first to reclassify alter HIV status and second to reclassify PrEP use for alters without diagnosed HIV.

Reclassification model

We define Y_{ij} as the unobserved alter-reported outcome (e.g., HIV diagnosis status) for the ith ego and jth alter. We consider modeling Y_{ij} as a function of X_{ij}, a fully-observed exposure (e.g., the ith ego's HIV diagnosis status), and $\boldsymbol{Z}$, a set of fully-observed covariates, $P(Y_{ij} = y_{ij}|X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$. This probability is inestimable with standard egocentric data. Instead, we specify an imputation model with the ego-reported Y_{ij}^{*} to estimate $P(Y_{ij}^{*} = y_{ij}^{*}|X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$. Egocentric data typically include multiple observations (i.e., alters) for each ego, so the imputation model must account for correlated outcomes. In the present analysis, we used

Bayesian multilevel regression with integrated nested Laplace approximation (INLA).[111] The models used random intercepts for each ego to account for correlation among alters. The Bayesian approach allowed us to use the observations with known values in the response, to estimate a predictive distribution for the observations with unknown values.[153]

We can relate $P(Y_{ij}^* = y_{ij}^* | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$ to $P(Y_{ij} = y_{ij} | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$ with the following equation[110]:

$$P(Y_{ij} = 1 | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z}) = \frac{P(Y_{ij}^* = 1 | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z}) + Spec\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right) - 1}{Sens\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right) + Spec\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right) - 1} \quad (1)$$

Equation (1) is derived from methods to adjust aggregate cell counts of misclassified prevalence estimates using the sensitivity and specificity of the classification mechanism.[154] Here, we apply the equation to individual-level data and allow the sensitivity and specificity to vary based on x_{ij}, y_{ij}^* and $\boldsymbol{Z}$. We define the sensitivity, $Sens\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right) = P(Y_{ij}^* = 1 | Y_{ij} = 1, X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$, and specificity, $Spec\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right) = P(Y_{ij}^* = 0 | Y_{ij} = 0, X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$. In other words, the sensitivity is the probability that the ego-reported values is 1, given that the alter would have reported 1, conditional on the covariates x_{ij} and $\boldsymbol{Z}$. Similarly, the specificity is the probability that the ego-reported value is 0, given that the alter would have also reported 0. Larger $Sens\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right)$ will decrease $P(Y_{ij} = 1 | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$, relative to $P(Y_{ij}^* = 1 | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$; whereas larger $Spec\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right)$ will increase $P(Y_{ij} = 1 | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$. As a binomial probability, $P(Y_{ij} = 1 | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$ is constrained by [0, 1], so $Sens\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right)$ and $Spec\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right)$ are also constrained:

$$1 - Spec\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right) < P(Y_{ij}^* = 1 | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z}) < Sens\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right) \quad (2)$$

It can be challenging to supply values for all strata of x_{ij}, y_{ij}^* and $\boldsymbol{Z}$, especially if high-dimensional, while also satisfying Equation (2) for varying $P(Y_{ij}^* = 1 | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$ estimated

for each observation. As a simplification, we can reduce the parameter set and specify target values for sensitivity and specificity based on important strata of x_{ij}, y_{ij}^* and $\boldsymbol{Z}$. $Sens(x_{ij}, y_{ij}^*, \boldsymbol{z})$ and $Spec(x_{ij}, y_{ij}^*, \boldsymbol{z})$ are then varied using exponential-tilt models.

Exponential-tilt model

Exponential-tilt models are used in the missing data literature when data are missing not at random and researchers must specify the mechanism for selection, which may vary for strata of the outcome, exposure, or covariates. Exponential-tilt models can be used to "tilt" (i.e., vary) $Sens(x_{ij}, y_{ij}^*, \boldsymbol{z})$ and $Spec(x_{ij}, y_{ij}^*, \boldsymbol{z})$ based on x_{ij}, y_{ij}^* and $\boldsymbol{Z}$. The exponential-tilt model for misclassification is as follows:

$$P(Y_{ij}^* = y_{ij}^* | Y_{ij} = y_{ij}, X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z}) = \frac{P(Y_{ij}^* = y_{ij}^* | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z}) e^{q(y,y^*)}}{P(Y_{ij}^* = 0 | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z}) e^{q(y,0)} + P(Y_{ij}^* = 1 | X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z}) e^{q(y,1)}} \quad (3)$$

The parameter $q(y, y^*)$ is used to vary $Sens(x_{ij}, y_{ij}^*, \boldsymbol{z})$ and $Spec(x_{ij}, y_{ij}^*, \boldsymbol{z})$. The parameters $q(1,1)$ and $q(0,0)$ relate to the sensitivity and specificity, respectively, and $q(1,0)$ = $q(0,1)$ = 0. Conveniently, if $q(1,1) > 0$ and $q(0,0) > 0$, then $Sens(x_{ij}, y_{ij}^*, \boldsymbol{z})$ and $Spec(x_{ij}, y_{ij}^*, \boldsymbol{z})$ can vary without violating Equation (2).

The parameters $q(1,1)$ and $q(0,0)$ are not immediately intuitive, but can be defined using target values for sensitivity and specificity, $Sens_{Target}$ and $Spec_{Target}$, respectively, and a median value of $P(Y_{ij}^* = y_{ij}^* | X_i = x_i, \boldsymbol{Z} = \boldsymbol{z})$, denoted π. The parameters $q(1,1)$ and $q(0,0)$ relate to $Sens_{Target}$, $Spec_{Target}$, and π, with the following equations:

$$Sens_{Target} = \frac{\pi e^{q(1,1)}}{(1-\pi) + \pi e^{q(1,1)}} \quad (4)$$

$$Spec_{Target} = \frac{(1-\pi)e^{q(0,0)}}{(1-\pi)e^{q(0,0)} + \pi} \quad (5)$$

Equations (4) and (5) can be rearranged to solve for the parameters: $q(1,1) = logit\left(Sens_{Target}\right) - logit(\pi)$ and $q(0,0) = logit\left(Spec_{Target}\right) + logit(\pi)$. Researchers can then vary $Sens_{Target}$ and $Spec_{Target}$ based on y_{ij}^*, x_i and $\boldsymbol{z}$ to obtain stratum specific values for $q(1,1)$ and $q(0,0)$. Used with Equation (3), the parameters provide unique values of $Sens\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right)$ and $Spec\left(x_{ij}, y_{ij}^*, \boldsymbol{z}\right)$ for each observation to satisfy Equation (2).

Specifying reclassification parameters

There are multiple approaches to parameterization of the reclassification model, depending on data availability, purpose of the analysis, and strength of the assumptions.[110] Gold-standard methods to correct for misclassification require a validation sub-study or external validation data to quantify the magnitude of potential bias and estimate parameters for reclassification.[115] When validation data are unavailable or imperfect, researchers may specify parameter estimates (or a range of estimates) based on plausible values from the literature or expert opinion, or calibrated to reach some pre-specified target prevalence. Alternatively, the target values may represent extreme scenarios (maximum and minimum possible values) to demonstrate the robustness of the effect estimate; however, extreme scenarios can be uninformative if the goal is to reduce bias in the estimate. Therefore, we specified target values representing a range of plausible values obtained from a review of the published literature, a validation dataset, and calibration of the model to the data. We assigned a uniform distribution to vary each parameter stochastically and drew a complete set of parameters for each of the $M = 300$ reclassification datasets. Other probability distributions (e.g., beta distribution) may better describe the shape and magnitude of variability, but we used uniform distributions to

reflect uncertainty without validation data. We used an algorithm to ensure larger or smaller values depending on strata of x_{ij}, y_{ij}^{*} and $\boldsymbol{Z}$.

Reclassification of alter HIV status

The expected prevalence of diagnosed HIV among alters was 9.9%, based on the prevalence among egos standardized to the age, race, ethnicity, and geographic distribution of alters. We first specified an imputation model for the joint binomial probability distribution of ego-reported alter HIV status (diagnosed HIV vs test-negative). From the posterior distribution of the model, we randomly drew 300 sets of linear predictors for each observation (known and unknown) and transformed each with the inverse-logit function to obtain binomial predictive probabilities. We then drew 300 sets of reclassification parameters and adjusted the predictive probabilities using Equation (3). We then imputed 300 sets of new values using Equation (1). We retained each dataset to reclassify alter PrEP use and for final analysis of the data. Results of the reclassification model (Appendix Table 3) were similar to the expected prevalence of diagnosed HIV.

Imputation model

We specified an imputation model for the joint binomial probability distribution of ego-reported alter HIV status (diagnosed HIV vs test-negative) using Bayesian regression with INLA. The models included a random intercept for each ego. We modeled as fixed effects the alter demographics (age group, race/ethnicity, and the interaction of age group and race/ethnicity), ego demographics (age group, race/ethnicity, and the interaction of age group and race/ethnicity), ego HIV status (diagnosed HIV, test-negative, or HIV unknown) and PrEP use (ever or never), partnership type, and location. We also modeled the three-way interaction of partnership type with ego HIV status and PrEP use to allow ego-alter mixing patterns to vary by partnership type. From the posterior distribution of the model, we randomly drew 300 sets of

linear predictors for each observation (known and unknown) and transformed each with the inverse-logit function to obtain binomial predictive probabilities.

Reclassification parameters

We varied the sensitivity and specificity parameters stochastically, drawing a new set for each of the 300 datasets. A 2011–2013 study chain-sampled MSM to compare ego-reported alter HIV status to alter self-report.[72] Overall, the study showed 98.6% specificity (combined test-negative and HIV unknown) and 64.9% sensitivity (unpublished data). In other words, few of the ego-reported values were considered false-positives, when compared to the alter-reported data. Alternatively, the false-negative fraction was higher. The data are informative, but may not be generalizable to our analysis due to differences in study design, population and years of data collection (i.e., 2011–2013, before the PrEP era).

Therefore, we reviewed the literature for estimates of HIV status disclosure in sexual partnerships of MSM.[68,80,84,87,108] The studies were varied in terms of geography and characteristics of the sample populations, as well as the outcomes reported. A 2017 study of European MSM found that disclosure of HIV status to most recent sexual partner was 56% among MSM with diagnosed HIV and 35% among those without HIV.[80] Similar findings of greater disclosure among MSM with diagnosed HIV, compared to those without, was reported in other studies (although prevalence estimates were not consistently reported).[68,87] This supports the hypothesis that alters with test-negative HIV would be disproportionately misclassified as unknown HIV. The disclosure findings varied by partnership type, with increased disclosure for persistent partners compared to one-time partners, and increased disclosure for committed (main) partners compared to casual.[80,88] Finally, disclosure tends to be mutual.[68,80,88]

We assumed high $Spec_{Target}$ for all observations using a uniform distribution $\sim U[0.97, 1.00]$. Given the relatively narrow range of values, we did not vary $Spec_{Target}$ for strata

of covariates. However, the mean predictive probability (i.e., $P(Y_{ij}^{*} = 1|X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$) for alters with diagnosed HIV (by ego report) was only 0.406. To ensure that the adjusted predictive probability (i.e., $P(Y_{ij} = 1|X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$) was closer to 1.00 (i.e., low false-positive fraction) we calibrated the model by setting $q(1,1) = 0.01$ for alters with diagnosed HIV (by ego-report). By Equation (3), this sets $Sens(x_{ij}, y_{ij}^{*}, \boldsymbol{z}) \approx P(Y_{ij}^{*} = 1|X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$. Using Equation (1) with high specificity, this approach ensures that $P(Y_{ij} = 1|X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$ is high for all alters with diagnosed HIV (by ego-report), with relatively higher or lower values based on $P(Y_{ij}^{*} = 1|X_{ij} = x_{ij}, \boldsymbol{Z} = \boldsymbol{z})$.

For alters with test-negative or unknown HIV status, we varied $Sens_{Target}$ based on assumptions about the sensitivity of disclosing diagnosed HIV in sexual partnerships of MSM. To represent uncertainty, we specified a broad range of values for sensitivity (36%–100%) with variability based on the ego-reported alter HIV status and PrEP use, partnership type, and the ego HIV status. We first drew a starting value for sensitivity from a uniform distribution $\sim U[0.98, 1.00]$ for each of the 300 reclassification datasets. The starting value represented the highest possible $Sens_{Target}$ for each dataset, and was used for alters classified as a main partner with ego-reported test-negative HIV status. We then decreased the target sensitivity if the alter was classified as a casual or one-time partner, or if the ego-reported HIV status was unknown. We increased the sensitivity if the alter used PrEP (ego-reported) to represent greater certainty of the ego-reported alter HIV status (i.e., decrease probability of reclassification to diagnosed HIV). Finally, we considered mutual disclosure and increased the sensitivity if the ego self-reported diagnosed HIV and reported the alter HIV status as test-negative. We used uniform distributions to specify the magnitude of the absolute decrease relative to the starting values (Appendix Table 1) and used the following Equation to calculate the target sensitivity for each strata of partnership type, alter HIV status and PrEP use (ego-reported), and ego HIV status:

$$Sens^{*}_{Target} = Sens_{Starting} - (A_{Main} + A_{Casual} + A_{One-time}) * B * C * D \quad (6)$$

Where $Sens^{*}_{Target}$ is the target sensitivity for strata of partnership type, alter HIV status and PrEP use (ego-reported), and ego HIV status; $Sens_{Starting}$ is the starting sensitivity parameter; A is a set of linear modifiers based on partnership type; B is a scalar based on alter HIV status (ego-reported); $C \sim U[0,1]$ if the alter PrEP use is Ever (by ego-report), else $C = 1$; and $D \sim U[0,1]$ if the ego self-reports diagnosed HIV and the alter HIV status is test-negative (by ego-report), else $D = 1$. The scalars C and D offset decreases in sensitivity based on partnership type or unknown HIV status, with a broad range of possible values due to uncertainty. The parameters were drawn from uniform distributions, so that each of the 300 datasets used a unique set of parameters. By using Equation (6) we can vary the parameters stochastically, while maintaining higher or lower values based on the assumptions. The median prevalence of diagnosed HIV among alters after reclassification was 9.4% (95% simulation interval: 7.2, 11.1; Appendix Table 3) which is similar to the expected prevalence (9.9%). Therefore, no additional calibration of the parameters was necessary.

Appendix Table A.1. Alter HIV status reclassification parameters

Parameter	Distribution			
$Sens_{Starting}$	$\sim U[0.98, 1.00]$			
A_{Main}	$\sim U[0.03, 0.05]$			
A_{Casual}	$\sim U[0.01, 0.03]$			
$A_{One-time}$	$\sim U[0.035, 0.045]$			
Partnership Type	**Alter HIV status**	$\boldsymbol{A}$	$\boldsymbol{B}$	**Possible values[1] for** $\boldsymbol{Sens^*_{Target}}$
Main	Test-negative	A_{Main}	0	[0.98, 1.00]
Main	Unknown	A_{Main}	5	[0.73, 0.85]
Casual	Test-negative	$A_{Main} + A_{Casual}$	1	[0.90, 0.96]
Casual	Unknown	$A_{Main} + A_{Casual}$	5	[0.58, 0.80]
One-time	Test-negative	$A_{Main} + A_{Casual} + A_{One-time}$	1	[0.86, 0.93]
One-time	Unknown	$A_{Main} + A_{Casual} + A_{One-time}$	5	[0.36, 0.63]

[1]Based on $C = D = 1$. If $C < 1$ or $D < 1$, then the minimum possible value for $Sens^*_{Target}$ remains the same and the maximum possible value is 1.00.

Reclassification of alter PrEP use

The expected prevalence of PrEP use among alters was 16.5%, based on the distribution among egos standardized to the age, race, ethnicity, and geographic distribution of alters. We specified imputation models for PrEP use using the varying subset of alters classified without diagnosed HIV status in each of the 300 datasets. From the posterior distribution of each model, we randomly drew 1 set of linear predictors for each observation (known and

unknown) and transformed each with the inverse-logit function to obtain binomial predictive probabilities (for a total of 300 sets of predictive probabilities). We randomly drew 300 sets of reclassification parameters and adjusted the predictive probabilities using Equation (3). We then imputed 300 sets of new values using Equation (1). We retained each dataset for final analysis of the data. Results of the reclassification model are shown in (Appendix Table 4).

Imputation model

We specified imputation models for the joint binomial probability distribution of ego-reported alter PrEP use (ever vs never) using Bayesian regression with INLA. We fit 300 unique models to the varying subset of alters classified without diagnosed HIV. We used the same modelling approach and set of predictors used for the model of HIV diagnosis status. From the posterior distribution of each model, we drew one predictive value for each observation (for a total of 300 unique values across all datasets).

Reclassification parameters

Less is known about discussions of PrEP use in sexual partnerships of MSM. Overall, we assumed higher sensitivity (65%–100%) compared to classification of diagnosed HIV, due to decreased stigma compared to HIV infection and motivations to disclose PrEP use to negotiate other sexual behaviors (i.e., condom use). At the same time, we used a broader range of values for specificity (70%–100%) because motivations to discuss PrEP may be lower for MSM not using PrEP, compared to motivations to disclose test-negative HIV status. In addition, this allowed for more false-positive misclassification. This may occur because PrEP use among MSM is inconsistent longitudinally and may be discontinued prior to the onset of a sexual partnership,[113] even if previously discussed or reported passively (e.g., on sexual networking apps).[63,109] Similar to HIV reclassification, we varied the PrEP reclassification parameters based on strata of partnership type, alter PrEP use (ego-reported), and ego HIV status and PrEP use.

We varied the target specificity by partnership type, assigning different values to main, casual and one-time partners. We used the distribution $\sim U[0.70\ 1.00]$ for each strata of partnership type, but restricted each so that values were always highest for main partners and lowest for one-time partners, for each of the 300 sets of parameters. The mean predictive probability for alters with ever PrEP was 0.56, which would result in ~44% reclassification to never PrEP based on the imputation model alone. Similar to the calibration of the HIV reclassification model, we varied $q(1,1)$ for alters with Ever PrEP using a uniform distribution $\sim U[0.01, 0.1]$. Using this approach, the adjusted probabilities for alters with ever PrEP was increased closer to 1.00, with variability based on the imputation model and the target specificity parameters.

We varied target sensitivity using a similar mechanism as the HIV reclassification (Appendix Table 2). We first drew a starting value from the distribution $\sim U[0.98, 1.00]$, which was used for alters classified as main partners and Never PrEP. We decreased the sensitivity for casual or one-time partners, and for alters with unknown PrEP. To account for mutual disclosure, we increased the sensitivity if the ego self-reported diagnosed HIV or PrEP use. We varied target sensitivity using the following Equation:

$$Sens^{*}_{Target} = Sens_{Starting} - (A_{Main} + A_{Casual} + A_{One-time}) * B * C * D \quad (7)$$

Where $Sens^{*}_{Target}$ is the target sensitivity for strata of partnership type, alter PrEP use (ego-reported), and ego HIV status and PrEP use; $Sens_{Starting}$ is the starting sensitivity parameter; A is a set of linear modifiers based on partnership type; B is a scalar based on alter PrEP use (ego-reported); $C \sim U[0,1]$ if the ego self-reports diagnosed HIV and the alter PrEP use is Never, else $C = 1$; and $D \sim U[0,1]$ if the ego self-reports PrEP use (by ego-report) and the alter PrEP use is Never, else $D = 1$. The scalars C and D offset decreases in sensitivity based on partnership type, with a broad range of possible values due to uncertainty. The parameters were

drawn from uniform distributions, so that each of the 300 datasets used a unique set of parameters. By using Equation (7) we can vary the parameters stochastically, while maintaining higher or lower values based on the assumptions.

Appendix Table A.2. Alter PrEP use reclassification parameters

Parameter	**Distribution**			
$Sens_{Starting}$	$\sim U[0.98, 1.00]$			
A_{Main}	$\sim U[0.02, 0.04]$			
A_{Casual}	$\sim U[0.01, 0.03]$			
$A_{One-time}$	$\sim U[0.02, 0.04]$			
Partnership Type	**Alter HIV status**	$\boldsymbol{A}$	$\boldsymbol{B}$	**Possible values[1] for** $\boldsymbol{Sens^*_{Target}}$
Main	Never PrEP	A_{Main}	0	[0.98, 1.00]
Main	Unknown	A_{Main}	3	[0.86, 0.94]
Casual	Never PrEP	$A_{Main} + A_{Casual}$	1	[0.91, 0.97]
Casual	Unknown	$A_{Main} + A_{Casual}$	3	[0.77, 0.91]
One-time	Never PrEP	$A_{Main} + A_{Casual} + A_{One-time}$	1	[0.87, 0.95]
One-time	Unknown	$A_{Main} + A_{Casual} + A_{One-time}$	3	[0.65, 0.85]

[1]Based on $C = D = 1$. If $C < 1$ or $D < 1$, then the minimum possible value for $Sens^*_{Target}$ remains the same and the maximum possible value is 1.00.

Chapter 2 Supplementary Results

Appendix Table A.3. Mean HIV reclassification parameters and results across 300 datasets

						% HIV+ (after reclassification)		
	% HIV+	P(Y* = 1)	Sens(x,z,y*)	Spec(x,z,y*)	P(Y = 1)	Median	95% SI	
Total	6.6%	9.1%	74.5%	94.0%	9.4%	9.4%	7.2%	11.1%
Age Group								
15-24	1.5%	2.3%	58.6%	98.6%	2.5%	2.5%	1.7%	3.3%
25-34	4.9%	6.7%	76.0%	95.7%	7.0%	7.1%	5.3%	8.7%
35-44	10.0%	13.9%	82.2%	90.8%	14.1%	14.2%	10.8%	16.9%
45-54	12.7%	17.2%	83.9%	88.5%	17.4%	17.4%	13.5%	20.7%
55-65	12.6%	16.7%	83.3%	88.8%	17.0%	16.8%	13.6%	20.5%
66+	15.5%	21.5%	86.2%	84.9%	20.9%	20.2%	15.5%	28.6%
Race/ethnicity								
Non-Hispanic Black	9.4%	15.4%	79.8%	90.0%	14.6%	14.6%	10.5%	18.1%
Non-Hispanic White	6.7%	8.6%	75.0%	94.3%	9.1%	9.1%	7.2%	10.6%
Hispanic/ Latinx	5.9%	8.5%	73.2%	94.5%	8.7%	8.8%	6.3%	10.6%
Other	4.2%	5.6%	67.4%	96.2%	6.0%	6.0%	4.5%	7.7%
Ego-reported								
Diagnosed HIV	100.0%	40.3%	40.5%	74.2%	98.8%	98.8%	95.7%	99.7%

Test-negative	0.0%	6.0%	84.0%	95.3%	1.6%	1.6%	0.1%	3.1%
Unknown	0.0%	9.7%	56.0%	95.0%	7.2%	7.2%	1.5%	11.2%
Main								
Total	8.4%	9.2%	86.9%	93.5%	10.0%	10.0%	8.5%	11.5%
Diagnosed HIV	100.0%	39.6%	39.7%	74.6%	98.8%	98.9%	95.0%	100.0%
Test-negative	0.0%	6.4%	94.9%	94.9%	1.7%	1.6%	0.1%	3.3%
Unknown	0.0%	6.6%	60.5%	96.7%	4.6%	4.3%	0.5%	8.9%
Casual								
Total	7.9%	10.7%	77.6%	92.9%	10.9%	10.9%	8.5%	12.8%
Diagnosed HIV	100.0%	41.9%	42.1%	72.9%	98.8%	98.8%	95.8%	100.0%
Test-negative	0.0%	6.8%	84.7%	94.6%	1.8%	1.8%	0.1%	3.6%
Unknown	0.0%	12.4%	66.4%	93.2%	8.7%	8.6%	1.8%	14.1%
One-time								
Total	4.2%	7.3%	63.6%	95.6%	7.3%	7.3%	4.8%	9.2%
Diagnosed HIV	100.0%	38.1%	38.3%	76.2%	98.8%	98.7%	95.5%	100.0%
Test-negative	0.0%	4.5%	74.5%	96.4%	1.2%	1.1%	0.0%	2.6%
Unknown	0.0%	8.3%	48.6%	95.9%	6.6%	6.7%	1.3%	10.5%

Appendix Table A.4. Mean PrEP reclassification parameters and results across 300 datasets

						% Ever PrEP (after reclassification)		
	%Ever PrEP	P(Y* = 1)	Sens(x,z,y*)	Spec(x,z,y*)	P(Y = 1)	Median	95% SI	
Total	15.5%	34.5%	76.4%	70.3%	19.8%	19.8%	13.6%	23.7%
Age Group								
15-24	9.4%	19.9%	67.6%	83.1%	12.2%	12.3%	8.3%	14.9%
25-34	17.4%	38.5%	79.5%	67.0%	22.1%	22.0%	14.9%	26.3%
35-44	19.6%	44.2%	81.4%	61.7%	25.0%	25.1%	16.5%	29.8%
45-54	18.3%	43.2%	81.2%	62.5%	23.8%	23.7%	16.2%	28.7%
55-65	13.3%	29.2%	74.1%	75.1%	17.1%	16.9%	12.0%	20.8%
66+	12.7%	22.8%	66.6%	80.4%	14.9%	14.3%	8.1%	20.8%
Race/ethnicity								
Non-Hispanic Black	11.9%	32.9%	73.4%	71.5%	17.1%	17.2%	11.3%	21.9%
Non-Hispanic White	16.6%	34.5%	77.0%	70.4%	20.5%	20.5%	13.9%	24.4%
Hispanic/ Latinx	14.9%	36.3%	76.7%	68.8%	19.9%	19.8%	13.5%	24.2%
Other	14.8%	32.8%	75.5%	71.8%	19.1%	19.1%	12.8%	23.4%
Ego-reported								
Ever PrEP	100.0%	56.0%	57.0%	58.7%	91.7%	92.0%	52.5%	98.6%
Never PrEP	0.0%	19.1%	85.0%	82.4%	2.6%	2.6%	1.0%	4.0%

Unknown	0.0%	39.1%	75.9%	64.6%	10.7%	10.6%	4.4%	16.1%
Main								
Total	14.7%	16.2%	76.8%	88.6%	15.4%	15.4%	13.8%	16.5%
Ever PrEP	100.0%	45.5%	46.3%	82.2%	96.0%	96.1%	86.2%	99.6%
Never PrEP	0.0%	10.7%	85.7%	90.3%	1.4%	1.3%	0.4%	2.3%
Unknown	0.0%	15.1%	56.4%	86.7%	4.3%	4.0%	0.5%	8.2%
Casual								
Total	17.9%	34.8%	75.9%	70.5%	22.1%	22.2%	13.3%	25.6%
Ever PrEP	100.0%	55.6%	56.5%	60.3%	94.4%	94.5%	47.2%	99.1%
Never PrEP	0.0%	24.3%	85.2%	77.5%	3.3%	3.2%	1.3%	5.6%
Unknown	0.0%	34.5%	76.9%	69.2%	9.1%	8.9%	3.8%	13.7%
One-time								
Total	13.5%	44.3%	76.3%	59.7%	20.2%	20.1%	9.2%	26.4%
Ever PrEP	100.0%	63.4%	64.3%	42.3%	87.3%	86.8%	7.0%	98.1%
Never PrEP	0.0%	29.0%	83.5%	72.8%	4.1%	4.0%	1.3%	7.0%
Unknown	0.0%	44.5%	76.9%	59.4%	12.4%	12.4%	5.1%	18.7%

Appendix B. Chapter 3 Supplementary Results

Appendix Table B.1. Characteristics of a simulated population of 10,000 men who have sex with men in the United States

	Total		Without diagnosed HIV				Diagnosed HIV	
			No PrEP		PrEP			
	N	%[1]	N	%[2]	N	%[2]	N	%[2]
Total	10000	100.0	7141	71.4	1514	15.1	1345	13.5
Age group								
15–24	2006	20.1	1834	91.4	143	7.1	29	1.4
25–34	2117	21.2	1655	78.2	332	15.7	130	6.1
35–44	1927	19.3	1216	63.1	428	22.2	283	14.7
45–54	1838	18.4	1059	57.6	365	19.9	414	22.5
55–65	2112	21.1	1377	65.2	246	11.6	489	23.2
Race & ethnicity								
Non-Hispanic								
Black	1306	13.1	771	59.0	152	11.6	383	29.3
White	6045	60.5	4521	74.8	915	15.1	609	10.1
Other	736	7.4	546	74.2	118	16.0	72	9.8
Hispanic/ Latinx	1913	19.1	1303	68.1	329	17.2	281	14.7

[1]Column percent

[2]Row percent

Appendix Table B.2. Characteristics of ARTnet egos

	Total		Without diagnosed HIV				Diagnosed HIV	
			No PrEP		PrEP			
	N	%[1]	N	%[2]	N	%[2]	N	%[2]
Total	4502	100.0	3437	76.3	638	14.2	427	9.5
Age group								
15–24	1248	27.7	1164	93.3	73	5.8	11	0.9
25–34	1160	25.8	894	77.1	199	17.2	67	5.8
35–44	643	14.3	440	68.4	122	19.0	81	12.6
45–54	767	17.0	473	61.7	150	19.6	144	18.8
55–65	684	15.2	466	68.1	94	13.7	124	18.1
Race & ethnicity								
Non-Hispanic								
Black	232	5.2	140	60.3	28	12.1	64	27.6
White	3423	72.0	2483	76.6	476	14.7	284	8.8
Other	404	9.0	326	80.7	53	13.1	25	8.7
Hispanic/ Latinx	623	13.8	488	78.3	81	13.0	54	6.2

[1]Column percent

[2]Row percent

Appendix Table B.3. Distribution of network edges – all persistent partnerships

	Median (95% simulation interval)				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Full Model**
Edges (total N)	5241 (5099, 5387)	5235 (5108, 5375)	5238 (5101, 5391)	5236 (5093, 5384)	5223 (5076, 5378)
HIV mixing (%)					
Concordant					
Without HIV	74.9 (73.8, 76.1)	72.6 (71.4, 73.8)	67.5 (66.2, 68.8)	68.0 (66.8, 69.3)	74.8 (73.6, 76.0)
With HIV	1.8 (1.5, 2.2)	2.2 (1.8, 2.6)	3.2 (2.7, 3.6)	3.8 (3.3, 4.3)	8.9 (8.1, 9.9)
Discordant	23.3 (22.1, 24.4)	25.2 (24.0, 26.4)	29.3 (28.1, 30.6)	28.2 (26.9, 29.4)	16.2 (15.2, 17.3)
HIV & PrEP mixing (%)					
Concordant					
No PrEP	51.0 (49.6, 52.4)	47.6 (46.3, 49.0)	34.9 (33.7, 36.2)	35.8 (34.5, 37.1)	45.3 (43.9, 46.6)
PrEP	2.3 (1.9, 2.7)	2.6 (2.2, 3.1)	5.3 (4.7, 5.9)	5.4 (4.7, 6.0)	9.6 (8.8, 10.4)
With HIV	1.8 (1.5, 2.2)	2.2 (1.8, 2.6)	3.2 (2.7, 3.6)	3.8 (3.3, 4.3)	8.9 (8.1, 9.9)
Discordant					
No PrEP–PrEP	21.7 (20.5, 22.8)	22.4 (21.2, 23.5)	27.3 (26.0, 28.5)	26.8 (25.6, 28.0)	19.9 (18.7, 21.0)
No PrEP–With HIV	19.2 (18.1, 20.2)	20.4 (19.3, 21.5)	21.1 (20.0, 22.2)	19.8 (18.7, 20.8)	8.6 (7.9, 9.4)
PrEP–With HIV	4.1 (3.5, 4.6)	4.8 (4.3, 5.4)	8.2 (7.5, 8.9)	8.4 (7.6, 9.1)	7.6 (6.9, 8.3)

Model 1: Null model – homogenous degree; random mixing
Model 2: Degree heterogeneity by age and race/ethnicity; random mixing
Model 3: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; random mixing
Model 4: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age and race/ethnicity
Model 5: Fully parameterized model – degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age, race/ethnicity, HIV status and PrEP use

Appendix Table B.4. Distribution of network edges – main persistent partnerships

	Median (95% simulation interval)				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Full Model**
Edges (total N)	1978 (1894, 2066)	1975 (1884, 2060)	1977 (1892, 2063)	1971 (1885, 2056)	1975 (1889, 2058)
HIV mixing (%)					
Concordant					
Without HIV	75.0 (72.9, 76.9)	77.2 (75.3, 79.0)	73.3 (71.3, 75.2)	73.8 (71.8, 75.7)	79.7 (77.9, 81.5)
With HIV	1.8 (1.2, 2.4)	1.5 (1.0, 2.0)	2.1 (1.5, 2.7)	2.7 (2.0, 3.5)	6.9 (5.8, 8.1)
Discordant	23.3 (21.4, 25.2)	21.4 (19.5, 23.2)	24.7 (22.8, 26.6)	23.5 (21.6, 25.4)	13.3 (11.8, 14.9)
HIV & PrEP mixing (%)					
Concordant					
No PrEP	51.0 (48.8, 53.2)	51.6 (49.5, 53.8)	49.8 (47.7, 52.0)	50.8 (48.6, 53.0)	61.4 (59.1, 63.5)
PrEP	2.3 (1.7, 2.9)	2.5 (1.9, 3.3)	2.2 (1.6, 2.9)	2.3 (1.7, 3.0)	6.1 (5.1, 7.2)
With HIV	1.8 (1.2, 2.4)	1.5 (1.0, 2.0)	2.1 (1.5, 2.7)	2.7 (2.0, 3.5)	6.9 (5.8, 8.1)
Discordant					
No PrEP–PrEP	21.7 (19.8, 23.6)	23.0 (21.2, 24.9)	21.2 (19.5, 23.0)	20.6 (18.9, 22.5)	12.2 (10.9, 13.7)
No PrEP–With HIV	19.2 (17.4, 21.0)	17.5 (15.8, 19.2)	20.3 (18.6, 22.1)	18.9 (17.1, 20.6)	7.5 (6.4, 8.7)
PrEP–With HIV	4.1 (3.2, 5.0)	3.9 (3.1, 4.8)	4.3 (3.4, 5.2)	4.6 (3.7, 5.5)	5.9 (4.8, 6.9)

Model 1: Null model – homogenous degree; random mixing
Model 2: Degree heterogeneity by age and race/ethnicity; random mixing
Model 3: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; random mixing
Model 4: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age and race/ethnicity
Model 5: Fully parameterized model – degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age, race/ethnicity, HIV status and PrEP use

Appendix Table B.5. Distribution of network edges – casual persistent partnerships

	Median (95% simulation interval)				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Full Model**
Edges (total N)	3264 (3156, 3375)	3268 (3157, 3378)	3267 (3154, 3375)	3268 (3150, 3383)	3248 (3130, 3359)
HIV mixing (%)					
Concordant					
Without HIV	74.9 (73.4, 76.4)	69.8 (68.2, 71.4)	63.9 (62.2, 65.5)	64.5 (62.9, 66.1)	72.0 (70.6, 73.5)
With HIV	1.8 (1.4, 2.3)	2.7 (2.2, 3.3)	4.0 (3.4, 4.7)	4.6 (3.9, 5.2)	10.3 (9.3, 11.3)
Discordant	23.2 (21.8, 24.7)	27.5 (26.0, 29.1)	32.1 (30.5, 33.7)	30.9 (29.5, 32.4)	17.7 (16.3, 19.0)
HIV & PrEP mixing (%)					
Concordant					
No PrEP	51.0 (49.3, 52.8)	45.2 (43.5, 46.9)	26.6 (25.1, 28.1)	27.2 (25.8, 28.8)	36.0 (34.5, 37.8)
PrEP	2.3 (1.8, 2.8)	2.7 (2.1, 3.2)	8.0 (7.1, 8.9)	8.2 (7.2, 9.2)	12.0 (10.9, 13.0)
With HIV	1.8 (1.4, 2.3)	2.7 (2.2, 3.3)	4.0 (3.4, 4.7)	4.6 (3.9, 5.2)	10.3 (9.3, 11.3)
Discordant					
No PrEP–PrEP	21.6 (20.2, 23.0)	21.9 (20.4, 23.2)	29.3 (27.8, 30.9)	29.0 (27.5, 30.7)	24.0 (22.6, 25.5)
No PrEP–With HIV	19.2 (17.8, 20.5)	22.2 (20.8, 23.6)	20.7 (19.3, 22.1)	19.4 (18.1, 20.8)	8.5 (7.5, 9.5)
PrEP–With HIV	4.1 (3.4, 4.8)	5.4 (4.6, 6.2)	11.4 (10.3, 12.5)	11.5 (10.4, 12.7)	9.2 (8.2, 10.3)

Model 1: Null model – homogenous degree; random mixing
Model 2: Degree heterogeneity by age and race/ethnicity; random mixing
Model 3: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; random mixing
Model 4: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age and race/ethnicity
Model 5: Fully parameterized model – degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age, race/ethnicity, HIV status and PrEP use

Appendix Table B.6. Distribution of network edges – cumulative (monthly) one-time partnerships

	Median (95% simulation interval)				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Full Model**
Edges (total N)	2159 (2069, 2252)	2159 (2068, 2249)	2158 (2066, 2255)	2160 (2073, 2255)	2148 (2056, 2241)
HIV mixing (%)					
Concordant					
Without HIV	75.0 (73.1, 76.8)	72.8 (70.9, 74.7)	61.5 (59.5, 63.4)	62.2 (60.3, 64.2)	71.1 (69.1, 72.9)
With HIV	1.8 (1.2, 2.4)	2.2 (1.6, 2.8)	4.7 (3.8, 5.6)	5.1 (4.2, 6.1)	11.0 (9.7, 12.3)
Discordant	23.2 (21.4, 25.0)	25.0 (23.2, 26.9)	33.9 (32.0, 35.7)	32.7 (30.7, 34.5)	17.9 (16.3, 19.6)
HIV & PrEP mixing (%)					
Concordant					
No PrEP	51.1 (48.9, 53.2)	47.6 (45.5, 49.8)	15.8 (14.2, 17.3)	16.5 (14.9, 18.1)	23.6 (21.8, 25.4)
PrEP	2.3 (1.7, 2.9)	2.6 (2.0, 3.4)	14.9 (13.4, 16.4)	15.2 (13.9, 16.7)	18.0 (16.5, 19.6)
With HIV	1.8 (1.2, 2.4)	2.2 (1.6, 2.8)	4.7 (3.8, 5.6)	5.1 (4.2, 6.1)	11.0 (9.7, 12.3)
Discordant					
No PrEP–PrEP	21.6 (19.9, 23.4)	22.5 (20.7, 24.4)	30.8 (28.9, 32.7)	30.5 (28.6, 32.5)	29.5 (27.6, 31.4)
No PrEP–With HIV	19.2 (17.5, 20.9)	20.3 (18.6, 22.0)	17.2 (15.6, 18.7)	15.9 (14.3, 17.4)	6.8 (5.8, 7.8)
PrEP–With HIV	4.1 (3.2, 4.9)	4.8 (3.9, 5.7)	16.7 (15.2, 18.1)	16.8 (15.3, 18.3)	11.0 (9.8, 12.5)

Model 1: Null model – homogenous degree; random mixing
Model 2: Degree heterogeneity by age and race/ethnicity; random mixing
Model 3: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; random mixing
Model 4: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age and race/ethnicity
Model 5: Fully parameterized model – degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age, race/ethnicity, HIV status and PrEP use

Appendix Table B.7. Mixing by HIV status and PrEP use – all persistent partnerships

	Median (95% simulation interval)				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Full Model**
No PrEP (N)	7485 (7267, 7708)	7231 (7032, 7444)	6193 (6001, 6399)	6189 (5995, 6380)	6218 (6029, 6428)
With HIV (%)	13.4 (12.6, 14.2)	14.8 (13.9, 15.7)	17.9 (16.8, 18.9)	16.7 (15.8, 17.7)	7.2 (6.6, 7.9)
No PrEP (%)	71.4 (70.2, 72.6)	69.0 (67.8, 70.2)	59.1 (57.6, 60.5)	60.6 (59.1, 62.0)	76.1 (74.9, 77.2)
PrEP (%)	15.2 (14.3, 16.1)	16.2 (15.3, 17.1)	23.1 (21.9, 24.2)	22.7 (21.5, 23.8)	16.7 (15.7, 17.7)
PrEP (N)	1589 (1507, 1677)	1694 (1608, 1784)	2415 (2317, 2521)	2405 (2291, 2529)	2444 (2319, 2557)
With HIV (%)	13.4 (11.7, 15.2)	14.8 (13.2, 16.6)	17.8 (16.3, 19.3)	18.2 (16.6, 19.8)	16.3 (14.7, 17.8)
No PrEP (%)	71.4 (68.8, 74.0)	69.1 (66.4, 71.6)	59.1 (56.9, 61.4)	58.3 (55.9, 60.8)	42.5 (40.2, 44.8)
PrEP (%)	15.1 (12.8, 17.6)	16.1 (13.7, 18.5)	23.0 (20.8, 25.4)	23.5 (21.0, 25.7)	41.2 (38.8, 43.6)
With HIV (N)	1409 (1332, 1490)	1550 (1467, 1632)	1868 (1779, 1960)	1873 (1786, 1973)	1783 (1681, 1909)
With HIV (%)	13.5 (11.1, 15.9)	14.7 (12.3, 17.4)	17.7 (15.5, 20.1)	21.4 (18.9, 23.8)	52.5 (49.2, 55.7)
No PrEP (%)	71.4 (68.8, 74.2)	69.1 (66.3, 71.7)	59.2 (56.7, 61.7)	55.3 (52.6, 57.8)	25.3 (23.0, 27.6)
PrEP (%)	15.1 (13.3, 17.0)	16.2 (14.5, 18.0)	23.0 (21.2, 25.0)	23.4 (21.4, 25.4)	22.3 (20.2, 24.5)

Model 1: Null model – homogenous degree; random mixing
Model 2: Degree heterogeneity by age and race/ethnicity; random mixing
Model 3: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; random mixing
Model 4: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age and race/ethnicity
Model 5: Fully parameterized model – degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age, race/ethnicity, HIV status and PrEP use

Appendix Table B.8. Mixing by HIV status and PrEP use – main persistent partnerships

	Median (95% simulation interval)				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Full Model**
No PrEP (N)	2825 (2694, 2962)	2838 (2699, 2974)	2792 (2660, 2928)	2781 (2654, 2915)	2812 (2673, 2952)
With HIV (%)	13.4 (12.1, 14.8)	12.2 (10.9, 13.4)	14.4 (13.1, 15.8)	13.4 (12.0, 14.7)	5.3 (4.4, 6.1)
No PrEP (%)	71.4 (69.4, 73.3)	71.8 (70.0, 73.7)	70.6 (68.7, 72.4)	72.0 (70.1, 73.9)	86.1 (84.7, 87.4)
PrEP (%)	15.2 (13.8, 16.7)	16.0 (14.6, 17.5)	15.0 (13.7, 16.4)	14.6 (13.3, 16.1)	8.6 (7.6, 9.7)
PrEP (N)	600 (549, 652)	631 (579, 686)	593 (543, 643)	590 (541, 642)	599 (543, 660)
With HIV (%)	13.4 (10.8, 16.3)	12.1 (9.7, 14.9)	14.4 (11.5, 17.3)	15.3 (12.4, 18.4)	19.3 (16.1, 22.7)
No PrEP (%)	71.6 (67.1, 75.7)	72.0 (67.6, 76.2)	70.7 (66.5, 74.9)	69.0 (64.7, 73.3)	40.3 (36.1, 44.8)
PrEP (%)	15.0 (11.3, 18.9)	15.8 (11.9, 19.8)	14.9 (11.0, 19.0)	15.7 (11.8, 19.6)	40.4 (35.5, 45.2)
With HIV (N)	531 (483, 581)	480 (435, 525)	569 (522, 618)	569 (519, 621)	537 (480, 593)
With HIV (%)	13.2 (9.4, 17.3)	12.1 (8.2, 16.2)	14.3 (10.5, 18.5)	18.7 (14.4, 23.1)	50.8 (45.4, 56.3)
No PrEP (%)	71.6 (67.0, 75.9)	71.8 (67.4, 76.5)	70.7 (66.2, 75.0)	65.4 (60.8, 70.0)	27.6 (23.6, 31.8)
PrEP (%)	15.1 (12.1, 18.4)	16.0 (12.8, 19.4)	15.0 (12.1, 18.0)	15.8 (12.9, 19.0)	21.6 (17.8, 25.4)

Model 1: Null model – homogenous degree; random mixing
Model 2: Degree heterogeneity by age and race/ethnicity; random mixing
Model 3: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; random mixing
Model 4: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age and race/ethnicity
Model 5: Fully parameterized model – degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age, race/ethnicity, HIV status and PrEP use

Appendix Table B.9. Mixing by HIV status and PrEP use – casual persistent partnerships

	Median (95% simulation interval)				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Full Model**
No PrEP (N)	4664 (4490, 4836)	4395 (4230, 4557)	3372 (3233, 3512)	3366 (3227, 3504)	3397 (3248, 3554)
With HIV (%)	13.4 (12.4, 14.5)	16.5 (15.3, 17.7)	20.1 (18.7, 21.5)	18.9 (17.6, 20.2)	8.1 (7.2, 9.1)
No PrEP (%)	71.4 (70.0, 72.9)	67.3 (65.6, 68.7)	51.6 (49.5, 53.5)	52.9 (50.9, 54.9)	68.9 (67.1, 70.8)
PrEP (%)	15.1 (14.1, 16.2)	16.3 (15.1, 17.4)	28.4 (26.8, 30.2)	28.2 (26.6, 30.0)	23.0 (21.4, 24.5)
PrEP (N)	988 (921, 1053)	1064 (996, 1136)	1850 (1758, 1948)	1859 (1757, 1968)	1856 (1754, 1952)
With HIV (%)	13.4 (11.3, 15.7)	16.4 (14.2, 18.9)	20.1 (18.3, 22.0)	20.2 (18.3, 22.3)	16.0 (14.4, 18.0)
No PrEP (%)	71.5 (68.0, 74.7)	67.1 (63.9, 70.4)	51.7 (49.2, 54.2)	51.1 (48.4, 53.7)	42.0 (39.5, 44.7)
PrEP (%)	15.1 (12.1, 18.2)	16.4 (13.5, 19.5)	28.2 (25.6, 30.7)	28.8 (25.8, 31.6)	41.9 (39.0, 44.7)
With HIV (N)	877 (818, 941)	1075 (1007, 1145)	1311 (1232, 1384)	1310 (1231, 1385)	1242 (1162, 1320)
With HIV (%)	13.6 (10.4, 16.9)	16.3 (13.4, 19.5)	20.0 (17.2, 22.9)	22.9 (20.0, 25.5)	53.7 (50.4, 57.2)
No PrEP (%)	71.3 (67.7, 74.9)	67.4 (64.0, 70.7)	51.6 (48.6, 54.6)	48.5 (45.7, 51.4)	22.2 (19.7, 24.7)
PrEP (%)	15.1 (12.7, 17.6)	16.3 (14.1, 18.7)	28.3 (25.9, 31.0)	28.6 (26.1, 31.4)	24.0 (21.5, 26.9)

Model 1: Null model – homogenous degree; random mixing
Model 2: Degree heterogeneity by age and race/ethnicity; random mixing
Model 3: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; random mixing
Model 4: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age and race/ethnicity
Model 5: Fully parameterized model – degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age, race/ethnicity, HIV status and PrEP use

Appendix Table B.10. Mixing by HIV status and PrEP use – cumulative (monthly) one-time partnerships

	Median (95% simulation interval)				
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Full Model**
No PrEP (N)	3085 (2946, 3231)	2979 (2842, 3118)	1718 (1623, 1818)	1713 (1619, 1813)	1794 (1689, 1901)
With HIV (%)	13.4 (12.2, 14.7)	14.7 (13.3, 16.0)	21.6 (19.6, 23.6)	20.0 (18.0, 22.0)	8.1 (6.9, 9.4)
No PrEP (%)	71.4 (69.6, 73.3)	69.0 (67.1, 70.9)	39.7 (36.8, 42.6)	41.6 (38.5, 44.5)	56.5 (53.7, 59.2)
PrEP (%)	15.1 (13.8, 16.5)	16.3 (14.8, 17.8)	38.7 (36.2, 41.3)	38.4 (35.9, 41.2)	35.4 (32.8, 37.9)
PrEP (N)	653 (599, 708)	703 (647, 760)	1667 (1572, 1763)	1679 (1592, 1775)	1644 (1547, 1740)
With HIV (%)	13.4 (10.8, 16.2)	14.7 (12.0, 17.4)	21.6 (19.6, 23.6)	21.6 (19.7, 23.5)	14.4 (12.8, 16.3)
No PrEP (%)	71.5 (67.5, 75.6)	69.1 (65.0, 73.2)	39.9 (37.3, 42.4)	39.2 (36.7, 42.0)	38.6 (36.0, 41.2)
PrEP (%)	15.1 (11.3, 18.9)	16.2 (12.6, 20.1)	38.5 (35.6, 41.5)	39.2 (36.6, 42.2)	47.0 (44.2, 49.8)
With HIV (N)	579 (529, 630)	634 (580, 688)	933 (870, 998)	927 (861, 992)	856 (789, 927)
With HIV (%)	13.4 (9.6, 17.3)	14.7 (11.2, 18.6)	21.6 (18.0, 25.1)	23.8 (20.2, 27.7)	55.2 (51.2, 59.0)
No PrEP (%)	71.5 (67.3, 75.9)	69.0 (64.9, 72.9)	39.7 (36.4, 43.1)	37.0 (33.6, 40.4)	17.1 (14.5, 19.6)
PrEP (%)	15.1 (12.2, 18.3)	16.3 (13.3, 19.3)	38.6 (35.4, 41.9)	39.1 (35.9, 42.5)	27.7 (24.6, 31.2)

Model 1: Null model – homogenous degree; random mixing
Model 2: Degree heterogeneity by age and race/ethnicity; random mixing
Model 3: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; random mixing
Model 4: Degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age and race/ethnicity
Model 5: Fully parameterized model – degree heterogeneity by age, race/ethnicity, HIV status and PrEP use; mixing by age, race/ethnicity, HIV status and PrEP use

Appendix C. Chapter 4 Technical Supplement

The following technical appendix is based on a document written by Samuel Jenness (Dissertation Advisor). The original document has been modified for various studies with the *EpiModel* software,[15,152,155–157] by several contributing authors, and adapted by Kevin Maloney for this dissertation.

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 network-based transmission models in which uniquely identifiable sexual partnership dyads were simulated and tracked over time. This partnership structure is represented through the use of temporal exponential-family random graph models (TERGMs), described in Section 3. On top of this dynamic network simulation, the epidemic model represents demography (entries, exits, and aging), interhost epidemiology (disease transmission), intrahost epidemiology (disease progression), and clinical epidemiology (disease diagnosis and treatment and prevention interventions). 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 utilize and extend the *EpiModel* software platform to incorporate HIV-specific epidemiology and transmission dynamics. 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,[158–160] and subsequently used for a model for HIV preexposure prophylaxis (PrEP) among US MSM.[15,152,155–157] The most recent innovation in our modeling platform has been to incorporate primary data from the

ARTnet study of MSM in the United States directly into the workflow for parameterizing the network and behavioral components.[161]

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 sexually transmitted infections (STIs).[162] *EpiModel* depends on *Statnet* [http://statnet.org/], a suite of software in R for the representation, visualization, and statistical analysis of complex network data.[163]

EpiModel allows for a modular expansion of its built-in modeling tools to address novel research questions. We have developed a set of extension modules into a software package called *EpiModelHIV*. This 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 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 repository architecture on Github; the branch of the repository associated with this research project is *CombPrev.*
- [http://github.com/EpiModel/PrEP-Mixing] contains the scripts to execute the models and to run the statistical analyses provided in the manuscript.

1.3 Core Model Specifications

We started with a network size of 10,000 MSM aged 15 to 65 to represent the larger population of sexually active MSM in the Atlanta metropolitan area. The population size was allowed to increase and decrease with arrivals into the sexually active population at age 15 and departures

related to mortality or aging out of the sexually active population at age 65. MSM were stratified by Black, Hispanic, and White/other race/ethnicity in proportions equivalent to Census-derived proportions. Further details on the demography (race and age) are provided in Section 5. We used a four-stage simulation framework, first calibrating the model to diagnosed HIV prevalence for 60 years of burn-in time (Stage 1), then calibrating the model to current estimated levels of PrEP coverage for 5 years of burn-in time (Stages 2 and 3). Stage 2 introduced PrEP for 1 year, in order to establish PrEP use in the population before Stage 3. At the beginning of Stage 3 (year 2 of PrEP phase-in) the network model parameters were substituted for each of the scenarios with and without PrEP sorting. The models with and without PrEP sorting were simulated for 10 years each (Stage 4). The time unit used throughout the simulations was one week. Unless otherwise noted, all rate-based parameters listed below are to be interpreted as the rate per week and all duration-based estimates are to be interpreted as the duration in weeks.

2 THE ARTnet STUDY

This model featured an innovative parameterization design in which primary individual-level and partnership-level data were used to estimate statistical models for summary statistics that were then entered into the epidemic model. The primary data source for network structure and behavioral data was the ARTnet study, described below. Wherever possible, we used primary data from this study for model parameterization, and only relied on the secondary published literature for model parameters that could be generalized across target populations (e.g., HIV natural history or clinical response parameters).

2.1 Study Design

This analysis used data collected in the ARTnet study of MSM in the United States in 2017–2019.[161] MSM were recruited directly after participating in the American Men's Internet Study (AMIS),[164] a parent web-based study about MSM sexual health that recruited through banner

ads placed on websites or social network applications. At the completion of AMIS, MSM were asked to participate in ARTnet, which focused on sexual network features. ARTnet data collection occurred in two waves (following AMIS): July 2017 to February 2018 and September 2018 to January 2019.

Eligibility criteria for ARTnet were male sex at birth, current male cisgender identity, lifetime history of sexual activity with another man, and age between 15 and 65. Respondents were deduplicated within and across survey waves (based on IP and email addresses), resulting in a final sample of 4904 participants who reported on 16198 sexual partnerships. The Emory University Institutional Review Board approved the study.

2.2 Primary Measures

ARTnet participants were first asked about demographic and health-related information. Covariates used in this analysis included race, age, ZIP Code of residence, and current HIV status. ZIP Codes were transformed into Census regions/divisions and urbanicity levels by matching against county databases (using standardized methods for selecting county in the small number of cases when ZIP Codes crossed county lines). Participants reporting as never testing for HIV, having indeterminate test results, or never receiving test results were classified as having an unknown HIV status.

Participants were then asked detailed partner-specific questions for up to 5 most recent partners. The detailed partner-specific questions included attributes of the partner and details about the partnership itself. Partner attributes considered here included age, race/ethnicity, and HIV status. Participants were allowed to report any partner attribute as unknown. When partner age was unknown, age was imputed based on a response to a categorical question (e.g., 5–10 years younger/older, 2–5 years younger/older). Partner HIV status and PrEP use was imputed with a reclassification analysis to estimate mixing matrices for HIV diagnosis status and PrEP use status. The methods and results of this analysis are presented in **Chapter 2** (page 22) of

this dissertation. Partnerships were classified into three types: “main” (respondent reported they considered this partner a “boyfriend, significant other, or life partner”) casual (someone they have had sex with more than once, but not a main partner), and one-time.[165] For one-time partners, we asked for the date that sexual activity occurred. For persistent (main and casual) partnerships, we asked for the date of most recent sex, the date first sex (which could have been prior to the past year), and whether the partnership was ongoing (if the participant expected sexual activity would occur in the future). For each partnership, we asked whether (for one-time) or how frequently (for persistent) anal sex occurred.

Outcome measures include descriptive statistics for characteristics of participants and their reported partnerships, and the aggregate network statistics used to estimate the TERGMs underlying epidemic simulations on dynamic networks. The network statistics include ego degree, attribute mixing in partnerships, and the current length of ongoing partnerships, stratified by the attributes of persons and partnerships. Degree is a property of individuals, whereas mixing and length are properties of partnerships. Degree was defined as the ongoing number of persistent partners measured on the day of the survey (includes main and casual partnerships). Degree is not defined for one-time partnerships, so for these we instead calculated a weekly rate of new contacts by subtracting the total main and casual partners from the total past-year partners, and dividing by 52. Partnership length for main and casual partnerships was calculated by taking the difference between the survey date and the partnership start date. The mean length of ongoing partnerships is the network statistic needed for TERGM estimation; the logic and derivation are explained here.[162] Mixing was measured by the relative frequency of partnerships that occurred within and between groups defined by race/ethnicity, age group, HIV diagnosis status, and PrEP use status.

2.3 Statistical Analysis

We fit a series of general linear models (GLMs) to estimate summary statistics for features of the sexual network structure and the behavior within partnerships. Specific GLM parameterizations are detailed below in the discussion of each set of model parameters. Common across all models was the general approach of including geography of residence as a main effect with two levels (Atlanta versus all other areas). This allowed for the model coefficients and predicted summary statistics to vary by geography while ensuring stability of outcomes under the assumption of conditional exchangeability.

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 contacts. We first describe the methods conceptually, including the parameters used to guide the model and their derivation, and then present the formal statistical modeling methods. Consistent with our parameter derivations, all relationships are defined as those in which anal intercourse 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 observed in our primary data, while also allowing for mean relational durations to be targeted to those reported for different groups and relational types. Our methods do so within the context of changing population size (due to births, deaths, arrivals and departures from the population) and changing composition by attributes such as age. The broader motivation, methodological details, and link between models and primary data are described here.[162]

The network features that we aim to preserve are as follows:

- Persistent (Main and Casual) Partnerships
    - The mean degree (number of ongoing partners), stratified by main and casual partnership types, and the proportion of men with concurrency (2 or more ongoing partners) for each partnership type, at any time point.
    - Variations in the mean degree specific to each persistent partnership type by:
        - Race/ethnicity group (3 categories for Black, Hispanic, and White/other MSM).
        - Age group (5 categories for 15–24, 25–34, 35–44, 45–54, and 55–64).
        - Diagnosed HIV status (with diagnosed HIV; and without diagnosed HIV, including MSM without HIV and MSM with undiagnosed HIV)

      Cross-type degree: Degree in the other persistent partnership type (e.g., mean degree of MSM for main partnerships given current casual degree of 0, 1, 2, 3).
    - Selection of partners within the same race/ethnicity group (mixing by race/ethnicity).
    - Selection of partners within the same age group (mixing by age).
    - Mean partnership durations, stratified by main and casual partnership types, and by mixing within age groups.
- One-Time Partnerships
    - The overall rate of having one-time anal intercourse partnerships per week.
    - Variations in this contact rate by:
        - Race/ethnicity group.
        - Age group.
        - Diagnosed HIV status.
        - Total persistent degree (sum of main and casual partnerships ongoing).
        - Risk level heterogeneity above variations by the other four factors (mean partnership rates for five quintiles of MSM stratified by mean one-time rates).

    - Selection of partners within the same race/ethnicity group (mixing by race/ethnicity).
    - Selection of partners within the same age group (mixing by age).
    - Selection of partners with the same HIV diagnosis status (HIV serosorting).
- Common to Persistent and One-Time Partnership Types
    - Prohibitions against MSM with incompatible sexual positioning roles (e.g., no partnerships between exclusively receptive MSM).

3.1.1 Overall Mean Degree for Persistent Partnerships

Ongoing persistent partnerships (whether main or casual) were defined from the partnership-level ARTnet dataset as those in which sex had already occurred more than once, and in which the respondent anticipated having sex again. The momentary main or casual mean degree is then defined as the mean of the degree of all MSM for main or casual partnerships on the day of study. We estimated this with a Poisson model with main or casual degree as the outcome and a dummy variable for Atlanta residence as the predictor and then exponentiating the coefficients, resulting in an estimated mean main degree of 0.396 and a mean casual degree of 0.541.

In addition, we modeled the proportion of MSM with concurrency (degree of 2 or more) by partnership type. This was estimated with logistic regression models for binary outcomes with a dummy variable for Atlanta residence as the predictor. Taking the inverse of the logit of the coefficient yielded the predicted probabilities of 0.9% for main concurrency and 14.5% for casual concurrency.

3.1.2 Heterogeneity in Mean Degrees for Persistent Partnerships

We estimated the heterogeneity in main and casual mean degree by fitting three Poisson regression models. For race/ethnicity, we estimated the mean degree for each group within the target population by including dummy variables for city and race/ethnicity. For age, we modeled

the semi-parametric relationship between age and mean degrees by including city, age group, and square root of age group to allow for a non-linear relationship between age and the outcome. For HIV and PrEP, we estimated mean degree for MSM with diagnosed HIV, MSM without diagnosed HIV and not using PrEP, and MSM without diagnosed HIV and using PrEP, with a dummy variable for city. We then calculated a weighted average of MSM with and without PrEP to estimate an overall mean degree for MSM without diagnosed HIV. For cross type degree, we modeled the mean degree for main partnerships as a function of degree of casual partnerships, and vice versa, again with city also as a predictor. For each of the 6 models (2 partnership types times three predictors of interest), we estimated the statistical models and then exponentiated the coefficients to obtain the rates for each stratum. Those are shown in the Table below.

Appendix Table C.1. Heterogeneity in Mean Main and Casual Degree by Race/Ethnicity, Age Group, diagnosed HIV status, and Cross Type Degree of Ego (Respondent)

Predictor	Main Mean Degree	Casual Mean Degree
Race/Ethnicity		
Black	0.279	0.605
Hispanic	0.423	0.513
White	0.412	0.534
Age Group		
15–24	0.374	0.297
25–34	0.469	0.479
35–44	0.449	0.615
45–54	0.373	0.701
55–64	0.284	0.742
HIV status		
Without diag. HIV	0.387	0.483
With diag. HIV	0.424	0.719
Cross Type Degree		

0	0.440	0.632
1	0.352	0.401
2	0.282	0.254
3	0.225	—

3.1.3 Mixing by Race/Ethnicity and Age for Persistent Partnerships

Respondents reported on their perception of the race and ethnicity (Hispanic/non-Hispanic) for each partner. We categorized the respondents' and partners' races into three mutually exclusive groups: Black, Hispanic, and White/other. Using logistic regression models, we estimated the proportion of partnerships were between MSM of the same race (within-group mixing) by evaluating relationship between the respondent group and partner group as a binary outcome (using geography of residence predictor as a main effect with two levels, Atlanta versus all other areas). The inverse logit of the coefficients is then interpreted as the predicted probability of a same-race/ethnicity partnership. The values were 76.5% for main partnerships and 63.3% for casual partnerships.

For mixing by age, we used a model parameterization for the 5-category age group that allowed for differences in the level of age mixing that could vary by age group (differential homophily). We fit a logistic regression model for partnerships, with being in a partnership of the same age group as the outcome and the age group of the respondent as the main predictor. With the inverse logit transformation, the probabilities of partnerships within the same age group, stratified by partnership type are shown in the table below.

Appendix Table C.2. Proportion of Main and Casual Partnerships within the Same Age Group, by Age of Ego (Respondent)

Age Group	Main Within Group	Casual Within Group
15–24	79.5%	56.4%
25–34	69.7%	43.8%
35–44	57.8%	31.9%

45–54	44.8%	22.1%
55–64	32.6%	14.6%

3.1.4 Duration of Persistent Partnerships

We model partnership dissolution as a heterogenous, geometrically distributed process with unique parameters for each relational type. The geometric distribution for relational durations implies a “memoryless process,” which is a common assumption within ordinary differential equation modeling. Although this assumption implies that the rate of dissolution does not depend on the current age of the partnership, the overall exponential shape of the dissolution distribution matches reasonably well to empirical data on relational durations. The fit is improved considerably when the partnership types are stratified, as we do here, implying a mixture of geometric distributions. Once one-time contacts are removed, and longer-duration main partnerships are separated from shorter-term causal partnerships, the hypergeometric distribution fits the empirical data on partnership durations well.

The fit is improved further by stratifying based on the interaction between partnership type and age of the both members within the dyad. For this analysis, we explored how relationship duration varied by multiple demographic characteristics, and unsurprisingly age was most strongly associated with duration. For this model parameterization, we specifically elected to estimate and input based on matched age groups (that is, partnerships between two persons of the same age).

As detailed in previous work,[158,162] for memoryless processes, the expected age of an extant (ongoing) relationship at any moment in time is an unbiased estimator of the expected uncensored duration of relationships, given the balancing effects of right-censoring and length bias for this distribution. Raw relational ages were calculated as the difference between first sex date and the study date for each dyad the ego reported sex with more than once in the interval. To derive our estimator of relational age, we take the median of the observed distribution and

then calculate the mean for the geometric distributions associated with that median. To account for estimation within the Atlanta target population, we weighted this estimator by the inverse of the relative differences in Atlanta partnerships to non-Atlanta partnerships.

The resulting expected relational ages are summarized in the table below.

Appendix Table C.3. Duration of Main and Casual Partnerships by Dyadic Age Group of Ego (Respondent) and Alter (Partner)

Dyadic Age Group	Main Relational Age (Weeks)	Casual Relational Age (Weeks)
Both 15–24	71.2	50.5
Both 25–34	253.5	72.5
Both 35–44	523.3	112.1
Both 45–54	637.1	161.3
Both 55–64	903.1	147.4
Different Groups	217.9	106.4

3.1.6 Overall Mean One-Time Contact Rate

In addition to persistent main and casual partnerships, we modeled one-time sexual contacts involving anal intercourse based on ARTnet reports on the number and variation in these types of relations. As noted above, degree is not defined for one-time contacts, so for these we instead calculated a weekly rate of new contacts by subtracting the total main and casual partners from the total past-year partners. We estimated the weekly rate by fitting a Poisson regression model with the count of one-time contacts as a function of city, exponentiating the coefficient to get the predicted count, and dividing by 52 to get the week rate. The overall mean one-time contact rate was 0.076 AI contacts per week.

3.1.7 Heterogeneity in One-Time Contact Rates

Individuals were assigned a risk level strata at entry to the population, with 20% probability for each of the quintiles, which correspond to different rates of one-time partners. Individuals with

more one-time partners are at higher risk for HIV acquisition, so over time the distribution of risk levels becomes imbalanced between MSM with and without HIV. This results in MSM with HIV disproportionately in higher risk quintiles, while relatively few are in the lower risk quintiles, so the overall mean degree among MSM with HIV is higher than the specified target statistic. Therefore, we reassigned risk levels at each time step for the group of MSM screening for HIV (regardless of test results) by randomly shuffling risk levels within the group. This ensures that, on average, quintiles of risk level are equally distributed among MSM with and without diagnosed HIV. We excluded MSM who are using PrEP from this mechanism, because PrEP initiation probabilities varied with risk level (i.e., MSM with higher rates of one-time partners are more likely to initiate PrEP). This stabilizes the mean one-time partner rates among MSM using PrEP. For MSM using PrEP who screen positive for HIV infection (disproportionately those with more one-time partners) we re-assigned risk level along with the pool of MSM not using PrEP who are screening for HIV.

Heterogeneity in one-time contact rates was modeled with four Poisson regression models to estimate the rates as a function of race/ethnicity, age group, diagnosed HIV status, risk level strata, and total persistent (main plus casual) degree. We fit these models with geography of residence as a main effect (which had two levels, Atlanta versus all other areas, with the former level used for predictions) and exponentiated the coefficients and then divided by 52 to get the group-specific rates. For age group, similar to the estimation of degree, we modeled this semi-parametrically by including age group and the square root of age group as the joint predictors (along with city). The results are shown in the table below.

Appendix Table C.4. Weekly One-Time Contact Rates by Race/Ethnicity, Age Group, diagnosed HIV status, Risk Level, and Total Persistent Degree of Ego (Respondent)

Predictor	Weekly Contact Rate
Race/Ethnicity	
Black	0.062
Hispanic	0.071
White	0.079
Age Group	
15–24	0.048
25–34	0.075
35–44	0.089
45–54	0.093
55–64	0.087
HIV status	
Without diag. HIV	0.064
With diag. HIV	0.112
Risk Level Quintile	
1	0.000
2	0.000
3	0.012
4	0.043
5	0.326
Total Persistent Degree	
0	0.049
1	0.057
2	0.121
3+	0.284

3.1.8 Mixing by Race/Ethnicity, Age, and diagnosed HIV status, for One-Time Contacts

We used a similar approach to within-group mixing by race/ethnicity and age group for one-time contacts to the one used for persistent contacts, with one difference that we did not model differential homophily by age group to improve model stability. Therefore, the overall proportion of one-time contacts that were within the same race/ethnic group was 67.6% and the proportion of one-time contacts that were within the same age group was 32.8%. Unlike persistent partnerships, we included HIV serosorting targets for one-time contacts. We did not model differential homophily and instead specified the proportion of partnerships with discordant diagnosed HIV statuses, which was 24.3%.

3.1.9 Mixing by Sexual Role Across All Partnership Types

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. We estimated the proportion men were in each category (insertive, receptive, and versatile) by analyzing whether men had only insertive anal intercourse, only receptive anal intercourse, or both insertive and receptive anal intercourse (respectively) in their past five anal partnerships over the past year. These proportions were stratified (restricted) by geography of residence to the city of Atlanta. The proportions were: 18.5% exclusively insertive, 27.1% exclusively receptive, and 54.4% versatile.

3.2 Statistical Representation of Sexual Networks

Exponential-family random graph models (ERGMs) and their dynamic extension temporal ERGMs (TERGMs) 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 TERGMs,[166] since they persist for multiple time steps. One-time contacts, on the other hand, were modeled using cross-sectional ERGMs.[167] Formally, our statistical models for relational dynamics can be represented as five equations for the

conditional log odds (logits) of relational formation and persistence at time *t* (for main and casual relationships) or for relational existence at time *t* (for one-time contacts):

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

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

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

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

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

where:

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

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

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

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 demographics (race/ethnicity and age) based on Census data for Atlanta and assign men sexual roles based on frequencies listed above, as well as one-time risk quintiles (20% of the men in each race per quintile).
3. Calculate the target statistics (i.e., the expected count of each statistic at any given moment in time) associated with the terms in the formation model (for the main and casual partnerships) and in the existence model (for one-time contacts).
4. Assign each node a place-holder main and casual degree (number of on-going partnerships) that is consistent with the estimated distributions, and store these numbers as a nodal attribute. (Note: this does not actually require individuals to be paired up into the partnerships represented by those degrees).
5. For the main and casual networks, use the mean relational durations by age group combination to calculate the parameters of the persistence model, using closed-form solutions, given that the models are dyadic-independent (each relationship's persistence probability is independent of all others).
6. For the main and casual networks, estimate the coefficients for the formation model that represent the maximum likelihood estimates for the expected cross-sectional network structure.
7. For the one-off network, estimate the coefficients for the existence model that represent the maximum likelihood estimates for the expected cross-sectional network structure.

Steps 5–7 occur within the *EpiModel* software, and use the ERGM and STERGM methods therein. They are completed efficiently by the use of an approximation in Step 6.[168] During the subsequent model simulation, we use the method of Krivitsky[169] 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.

3.3 Addition of PrEP Degree and Sorting Network Parameters

The two experimental scenarios (with and without PrEP sorting) required different network parameterizations than the base network models. We first estimated new network parameters by fitting network models to the base model target statistics, plus additional statistics for PrEP use status. For the model without PrEP sorting, we added degree distribution estimates for the subsets of MSM with and without PrEP use among all MSM without diagnosed HIV (a group that includes those without HIV and those with undiagnosed HIV). Similarly, the models with PrEP sorting added degree distributions for PrEP use status, as well as assortative mixing statistics for MSM using PrEP. We modeled assortative mixing among MSM using PrEP for main and casual partners, but not one-time partners. This is because the target for assortative mixing among one-time partners using PrEP is 33.3%, while the model without PrEP sorting already produces an average of 30.9% assortative mixing among one-time partners using PrEP. We were unable to increase assortative mixing to 33.3% without inadvertently inducing changes to serosorting, so we decided to model PrEP sorting for persistent partnerships only. The target statistic for main partnerships was 45.3% and for casual partnerships it was 41.0%. Assortative mixing in models without PrEP sorting was 12.1% for main partners, and 24.1% for casual partners, so the difference in assortative mixing was more substantial and important to model.

We did not model full mixing matrices for the interaction of PrEP use status and diagnosed HIV status (i.e., assortative mixing among MSM not using PrEP; mixing between MSM with and without PrEP use; mixing between MSM with/without PrEP use and MSM with diagnosed HIV). However, by modeling within group mixing for MSM using PrEP (in the scenario with PrEP sorting) the prevalence of other partnership combinations also varies. This is

because of the constraints imposed by fixed degree targets and the other network parameters. As the number of partnerships concordant with PrEP use increases, MSM with PrEP use have fewer partnerships with (1) MSM not using PrEP; and (2) MSM with diagnosed HIV. In turn, there is an increase to within group mixing for MSM not using PrEP, and discordant mixing between MSM not using PrEP and MSM with diagnosed HIV. This partnership balancing mechanism avoids over-parameterizing the network models, so that degree distributions and HIV serosorting do not vary between the two scenarios.

The network models with PrEP parameters were substituted into the simulation one year after the introduction of PrEP. To do this, we performed the initial calibration of the model to burn-in the HIV epidemic. We were unable to incorporate network parameters based on PrEP use at the same time step as PrEP introduction, because network simulation with PrEP parameters requires >0% PrEP use in the population. Therefore, we introduced PrEP using an initiation probability compatible with 20% PrEP use among PrEP-eligible MSM after five years. After one year of PrEP introduction, the simulation was stopped in order to supply the new network parameters.

The network parameters for the respective scenarios were added to the simulation. Each set of parameters (estimated for a population of N = 10,000) was adjusted for the population size at the time of substitution to the model, using the Krivitsky[169] method. The simulations proceeded for four years, for a total of five years of PrEP burn-in for each scenario.

4 BEHAVIOR WITHIN SEXUAL PARTNERSHIPS

In this study, we model three phenomena consecutively within relationships at each time step: the number of anal intercourse sex acts, condom use per sex act, and sexual role per sex act. We simulate these within all relationships regardless of HIV status (whether diagnosed or not).

4.1 Anal Intercourse Acts Per Partnership

The rate of anal intercourse is applicable to persistent (main and casual) partnerships in which there are repeated AI acts between the start and end of the partnership. We use ARTnet data on the overall rate and predictors of variation in rates unique to each partnership type. For one-time contacts, we assumed that the number of AI exposures was one by definition, although there could have been multiple AI acts within an exposure due to role versatility (see Section 4.4).

4.1.1 Measurement of Acts in ARTnet

We measured the number of acts within each reported partnership within the ARTnet study by asking participants about the frequency of AI acts. Study participants could report on the average number of acts within the partnership over the past year by week, month, year, or total partnership duration. We then scaled this into a total weekly act rate. The final ARTnet partnership-level dataset on 16198 partnerships includes this weekly rate as the outcome and predictors at the individual and dyadic level that we used for statistical modeling as described below.

4.1.2 Statistical Models of Act Rates

With this partnership-level dataset, we then modeled the count of acts per year per partnership based on the Poisson regression formula:

$$Y_i \sim \beta_0 + \beta_1 X_1 + \beta_2 X_1^2 + \beta_3 X_2 + \beta_4 X_3 + \beta_5 X_1 X_3 + \beta_6 X_4 + \beta_7 X_4^2 + \beta_8 X_5 + \beta_9 X_6$$

where:

Y_i = Log of the count of acts per year

X_1 = Duration of partnership in weeks at the survey date.

X_2 = Racial/ethnic combination of the ego (respondent) and alter (partner), coded in 6 categories to capture within and across group mixing: Black-Black, Black-Hispanic/White, Hispanic-Black/White, Hispanic-Hispanic, White-Black/Hispanic, White-White.

X_3 = Partnership type (main or casual).

X_4 = The combined age of ego and alter in years.

X_5 = The concordant diagnosed HIV-positive status of both ego and alter (as perceived by the ego), compared to all other combinations of dyadic HIV status.

X_6 = Residence in the Atlanta metropolitan area.

Note that we modeled the partnership duration and combined age of partners quadratically, and we modeled the interaction of partnership duration and partnership type. Terms within the prediction model were selection based on a combination of *a priori* theory and exploratory data analysis. The coefficients for the model, and their lower and upper 95% confidence intervals, are presented in the table below. Exponentiating any linear combination of coefficients will yield the yearly rates, which may be converted to weekly through division.

Appendix Table C.5. Statistical Model of Act Rates in Main and Casual Partnerships

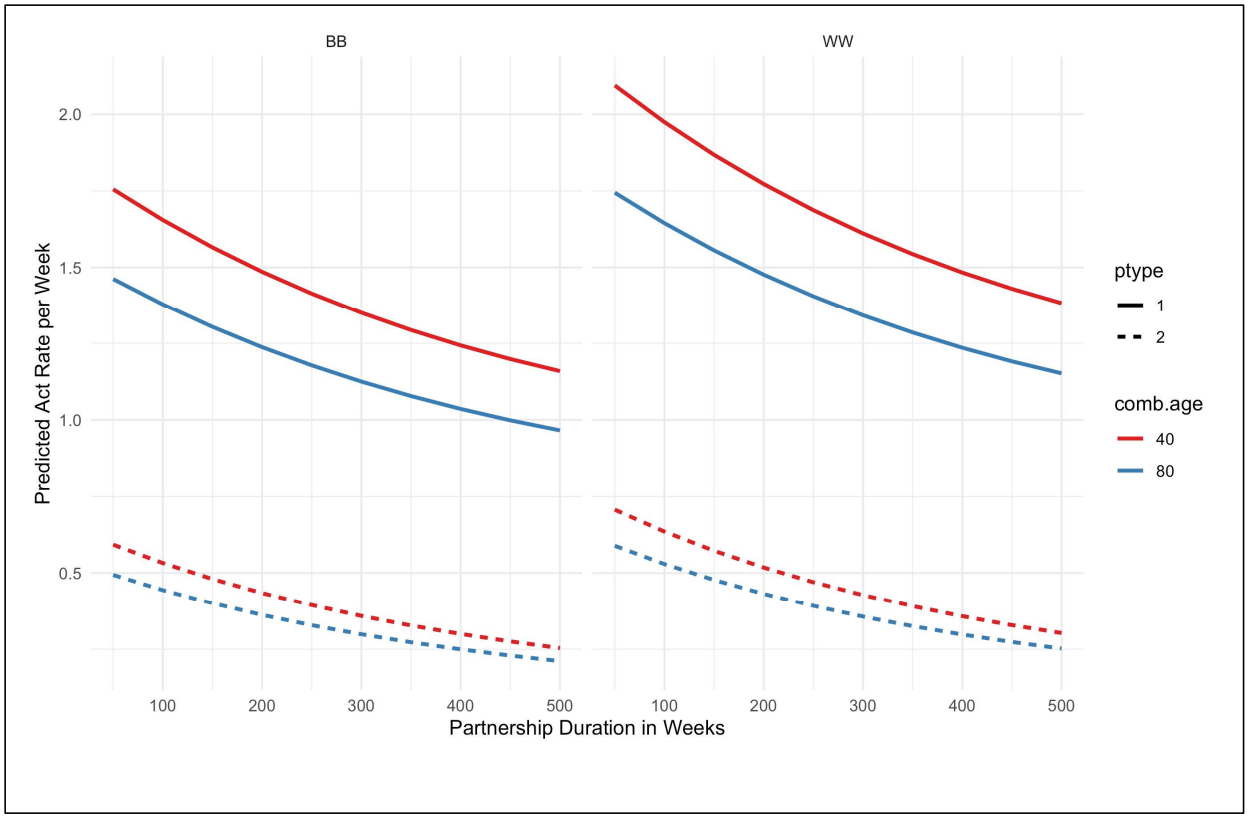
Model Parameter	Estimate	Lower 95% CI	Upper 95% CI
β_0 (Intercept)	4.9615	4.9208	5.002
β_1 (Duration)	-0.0013	-0.0013	-0.0012
β_2 (*D*uration^2)	6.3197E-07	6.0598E-07	6.5781E-07
β_3 (B-H/W Combo)	0.5196	0.4888	0.5505
β_3 (H-B/W Combo)	0.2178	0.1908	0.2449
β_3 (H-H Combo)	0.1967	0.1687	0.2250
β_3 (W-B/H Combo)	0.4758	0.4505	0.5013
β_3 (W-W Combo)	0.1765	0.1516	0.2016
β_4 (Casual Type)	-1.0373	-1.0458	-1.0287
β_5 (Duration x Casual Type)	-0.0009	-0.0010	-0.0009
β_6 (Combined Age)	-0.0113	-0.0122	-0.0104
β_7 (Combined Age^2)	5.6269E-05	5.0154E-05	6.2374E-05
β_8 (HIV+ Concordant)	0.3614	0.3452	0.3776
β_9 (Atlanta residence)	-0.0229	-0.0396	-0.0063

4.1.3 Predicted Rates in Epidemic Model

Predicted weekly rates of AI based on the linear combination of partnership and individual attributes is then obtained dynamically by predicting from the statistical model with inputs based on the current simulated population. *EpiModel* tracks the current age of partners, the duration of their partnership, their racial combination, and the partnership type. This set of predictors was input into a predict function in R to obtain the weekly mean rates in each strata. The size of the potential set of strata and corresponding predicted means is therefore nearly infinite based on all the potential combinations of input values.

In Supplemental Figure 1 below, we display some example weekly rates based on a subset of model inputs. This figure shows that rates decline in partnerships with a longer duration, that they are higher in partnerships in which both partners are younger, they are lower for casual partnerships (ptype = 2) compared to main partnerships, and that they are higher in White-White partnerships compared to Black-Black partnerships. The act rates generally ranged from 0.5 acts per week to 2 acts per week. Other predicted rates may be obtained by exponentiating the coefficients in the table above and dividing by 52 (to convert from yearly rates to weekly rates).

Appendix Figure C.1. Predicted Weekly AI Rates from the Poisson Statistical Model, by Partnership Duration, Partnership Type (1 = Main; 2 = Casual), Combined Partner Age, and Racial Combination.



Based on these model predictions, which represent means for each linear combination, we then drew individual counts of acts per partnership per time step in *EpiModel* using the rpois function to draw randomly from the Poisson distribution with a vector of parameters, one value for each partnership. In addition to these data-driven statistical calculations, we also assumed that MSM in late stages of AIDS (HIV viral load above 5.75), had no acts due to active disease that would limit their sexual activity. We had no primary data in ARTnet on sexual partnerships in this late disease stage, but prior analysis and modeling studies support a general decline in sexual activity due to AIDS.[170]

4.2 Condom Use Per Act

We modeled condom use within all three partnership types (main, casual, and one-time contacts) based on ARTnet data on the frequency of condom use within reported partnerships. We followed the same general approach to measuring, fitting statistical models, and dynamically predicting condom use within *EpiModel* as we used for rates of AI.

4.2.1 Measurement of Condom Use in ARTnet

We measured condom use within partnerships in the ARTnet study by asking about the frequency of condom use (for persistent partnerships) or whether condom use occurred (for one-time partnerships) during anal intercourse. Study participants first reported on the number of AI acts that occurred in the time intervals described above, and then we followed-up with a question on the number of those total acts that involved condom use. We then transformed these subsetted counts into proportions of acts that were condom-protected. This resulted in a U-shaped distribution of proportions, with most persistent partnerships involving either always or never condom use. For this current study, we simplified the outcome variable to any condom use (yes, no) over the past year.

4.2.2 Statistical Models of Condom Use Probabilities

With the outcome described above, we used the partnership-level dataset to fit two logistic regression models for any condom use in the partnership, with one model for persistent (main and casual) and another model for one-time partnerships. The linear model formula for persistent partnerships was as follows:

$$Y_i \sim \beta_0 + \beta_1 X_1 + \beta_2 X_1^2 + \beta_3 X_2 + \beta_4 X_3 + \beta_5 X_1 X_3 + \beta_6 X_4 + \beta_7 X_4^2 + \beta_8 X_5 + \beta_9 X_6 + \beta_{10} X_7$$

where:

Y_i = Log odds of the probability of condom use per act.

X_1 = Duration of partnership in weeks at the survey date.

X_2 = Racial/ethnic combination of the ego (respondent) and alter (partner), coded in 6 categories to capture within and across group mixing: Black-Black, Black-Hispanic/White, Hispanic-Black/White, Hispanic-Hispanic, White-Black/Hispanic, White-White.

X_3 = Partnership type (main or casual).

X_4 = The combined age of ego and alter in years.

X_5 = The concordant diagnosed HIV-positive status of both ego and alter (compared to all other combinations of dyadic HIV status).

X_6 = Current use of pre-exposure prophylaxis (PrEP) by the ego (respondent).

X_7 = Residence in the Atlanta metropolitan area.

Note that we modeled the partnership duration and combined age of partners quadratically, and we modeled the interaction of partnership duration and partnership type. Terms within the prediction model were selected based on a combination of *a priori* theory and exploratory data analysis. The coefficients for the model, and their lower and upper 95% confidence intervals, are presented in the table below. Taking the inverse logit of the linear combination of coefficients will yield to the strata-specific predicted probabilities of condom use within the partnership.

Appendix Table C.6. Statistical Model of Per Act Condom Use Probability for Main and Casual Partnerships

Model Parameter	Estimate	Lower 95% CI	Upper 95% CI
β_0 (Intercept)	2.008	1.3020	2.7144
β_1 (Duration)	-0.0031	-0.0040	-0.0023
β_2 (*D*uration^2)	1.2561E-06	5.8878E-07	1.8614E-06
β_3 (B-H/W Combo)	-0.3355	-0.8549	0.1802
β_3 (H-B/W Combo)	-0.3692	-0.7798	0.04214
β_3 (H-H Combo)	-0.3989	-0.8314	0.0336
β_3 (W-B/H Combo)	-0.4402	-0.8235	-0.0557
β_3 (W-W Combo)	-0.5031	-0.8738	-0.1310
β_4 (Casual Type)	0.5710	0.4084	0.7347
β_5 (Duration x Casual Type)	-0.0467	-0.0638	-0.0294
β_6 (Combined Age)	0.0002	9.5502E-05	0.0003
β_7 (Combined Age^2)	-1.6150	-2.1624	-1.1322
β_8 (HIV+ Concordant)	-0.5248	-0.6790	-0.3724
β_9 (PrEP Use)	0.1701	-0.1385	0.4743
β_{10} (Atlanta residence)	0.0012	0.0005	0.0019

For the logistic regression model of one-time partnerships, we used a similar logistic regression approach as for persistent partnerships but dropped the partnership duration and partnership type (since there was only one type for this model) predictor variables. The corresponding linear model formula for persistent partnerships was as follows:

$$Y_i \sim \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_2^2 + \beta_4 X_3 + \beta_5 X_4 + \beta_6 X_5$$

where:

Y_i = Log odds of the probability of condom use per one-time contact.

X_1 = Racial/ethnic combination of the ego (respondent) and alter (partner), coded in 6 categories to capture within and across group mixing: Black-Black, Black-Hispanic/White, Hispanic-Black/White, Hispanic-Hispanic, White-Black/Hispanic, White-White.

X_2 = The combined age of ego and alter in years.

X_3 = The concordant diagnosed HIV-positive status of both ego and alter (compared to all other combinations of dyadic HIV status).

X_4 = Current use of pre-exposure prophylaxis (PrEP).

X_5 = Residence in the Atlanta metropolitan area.

The coefficients for the model, and their lower and upper 95% confidence intervals, are presented in the table below. Taking the inverse logit of the linear combination of coefficients will yield to the strata-specific predicted probabilities of condom use within the partnership.

Appendix Table C.7. Statistical Model of Per-Act Condom Use Probability for One-Time Sexual Contacts

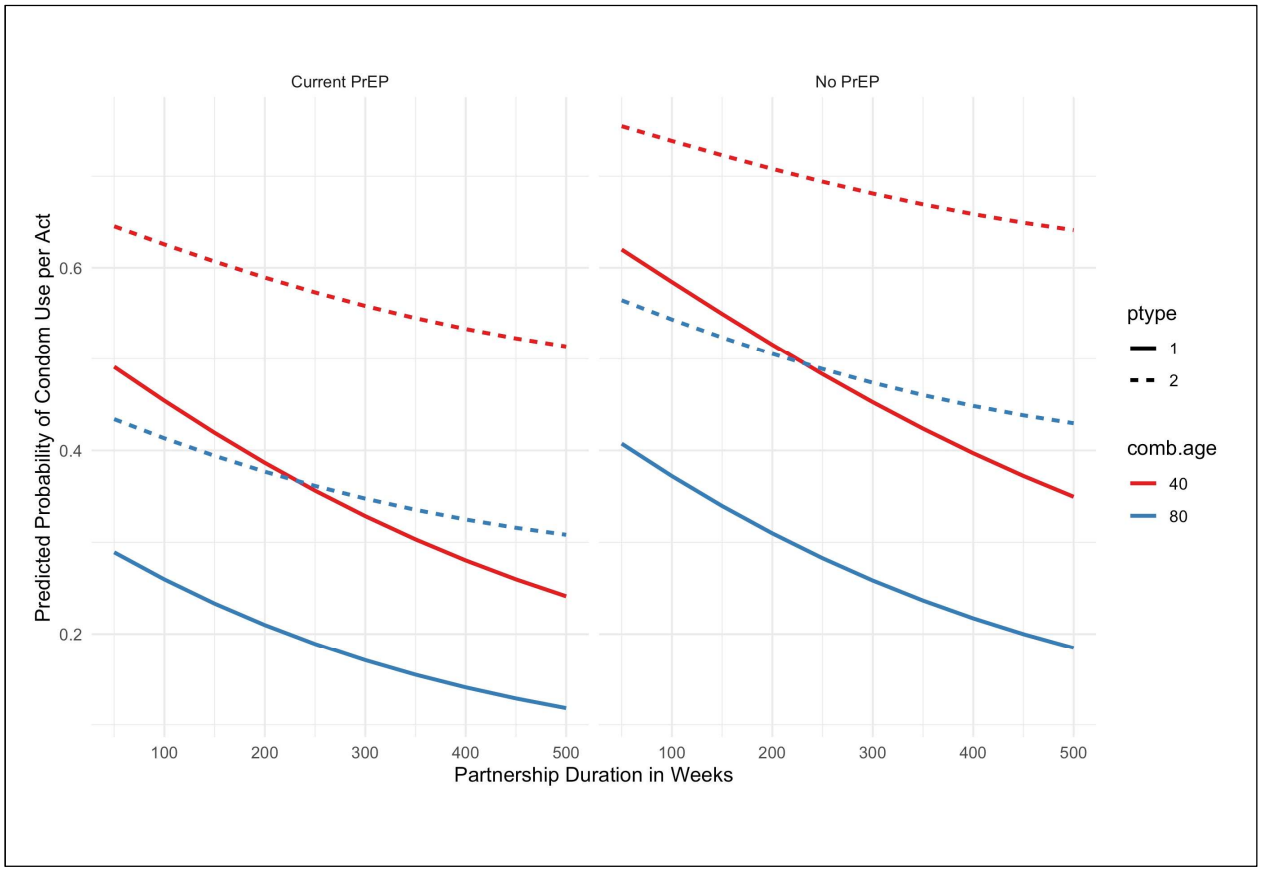
Model Parameter	Estimate	Lower 95% CI	Upper 95% CI
β_0 (Intercept)	2.4287	1.6597	3.2007
β_1 (B-H/W Combo)	0.1526	-0.3728	0.6785
β_1 (H-B/W Combo)	-0.1042	-0.5311	0.3221
β_1 (H-H Combo)	-0.10538	-0.5617	0.3506
β_1 (W-B/H Combo)	-0.1189	-0.5205	0.2825
β_1 (W-W Combo)	-0.2507	-0.6414	0.1396
β_2 (Combined Age)	-0.0542	-0.0733	-0.0351
β_2 (Combined Age^2)	0.0003	0.0001	0.0004
β_3 (HIV+ Concordant)	-1.8369	-2.6547	-1.1610
β_4 (PrEP Use)	-0.7133	-0.8732	-0.5553
β_5 (Atlanta residence)	0.3102	0.0107	0.6095

4.2.3 Predicted Probabilities in Epidemic Model

Predicted probabilities of condom use conditional on an AI act were calculated based on the linear combination of partnership and individual attributes obtained dynamically by predicting from the statistical model with inputs based on the current simulated population. This set of predictors was input into a predict function in R to obtain the expected mean probabilities.

In Supplemental Figure 2 below, we display some example probabilities based on a subset of model inputs. This figure shows that condom use is lower in partnerships of a longer duration, generally higher in casual compared to main partnerships, lower in partnerships in which both partners are older, and lower in partnerships in which the ego (respondent) reported currently using PrEP. Other predicted probabilities may be obtained from Supplemental Table 6 by taking the inverse logit of the linear combination of coefficients of interest.

Appendix Figure C.2. Predicted Probabilities of Condom Use Per AI Act in Persistent Partnerships from the Logistic Regression Model, by Partnership Duration, Partnership Type (1 = Main; 2 = Casual), Combined Partner Age, and PrEP Use.

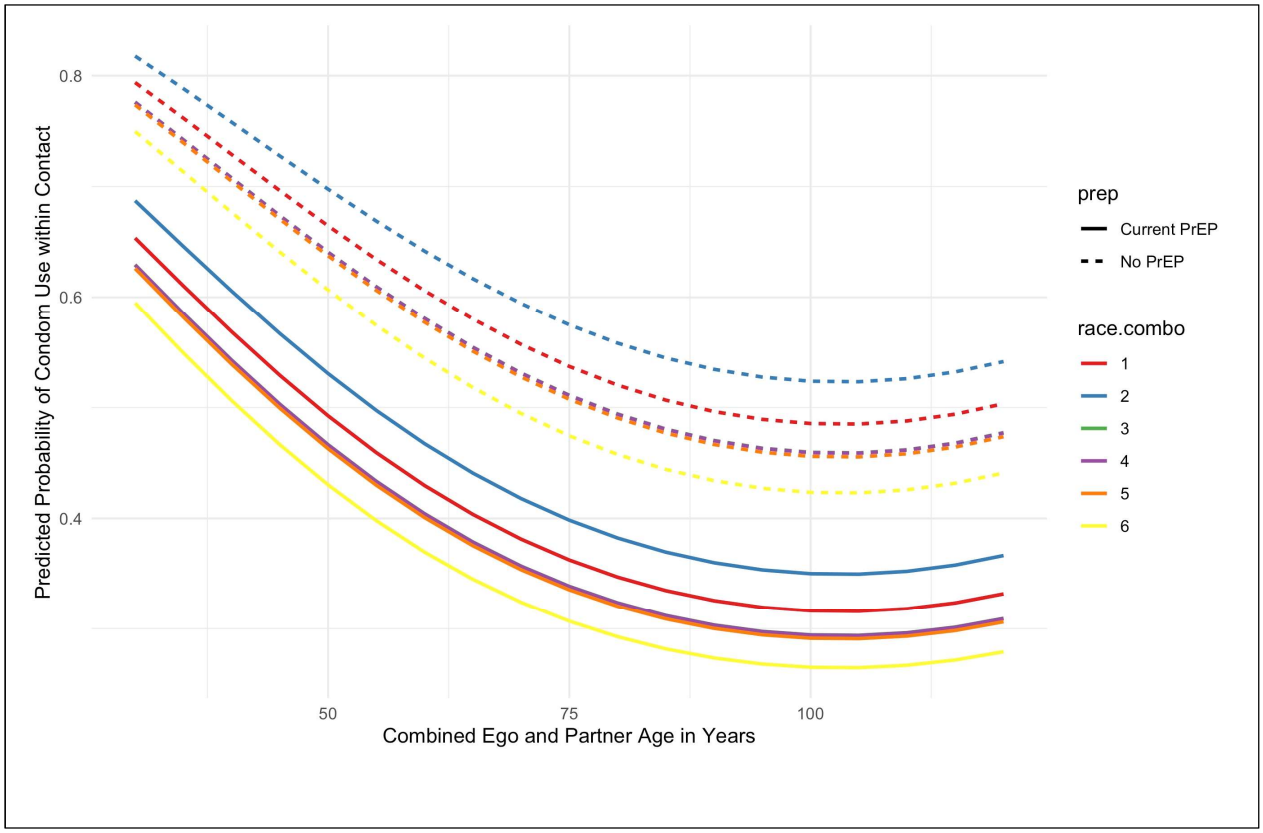


Supplemental Figure 3 shows the predicted probabilities for the second logistic model, for condom use within one-time AI contacts. Here we display variation in condom use by combined age of the partners, current PrEP use, and racial combination of the partners. As the figure shows, condom use is lower within partners of a lower combined age, higher in partnerships involving Black MSM (race.combo = 1 or 2), and lower among current PrEP users.

Based on these model predictions, which represent expected probabilities for each linear combination, we then drew individual probabilities of condom use per act in *EpiModel* using the rbinom function to draw randomly from the binomial (Bernoulli) distribution with a vector of

parameters, one value for each act. This generated a set of 0's and 1's for whether condom use occurred within the act as a function of the predictors in the statistical model.

Appendix Figure C.3. Predicted Probabilities of Condom Use in One-Time AI Contacts from the Logistic Regression Model, by Combined Partner Age, Current PrEP Use, and Racial Combination of Partners.



4.4 Sexual Role

Men were assigned an individual sexual role preference (exclusively insertive, exclusively receptive, or versatile) as described in Section 3.1.9. Relationships between two exclusively insertive or two exclusively receptive men are prohibited via the TERGM models. Versatile men were further assigned a preference for being an the insertive partner drawn from a uniform distribution between 0 and 1 upon entry into the population; we refer to this proportion as the 'insertivity quotient'. When two versatile men were simulated to have an AI act, their sexual

positions during that act must be determined (all other combinations have only one allowed direction). One option is for men to engage in intra-event versatility (IEV; i.e. both men engage in insertive and receptive AI during the act). The probability of this is was derived from the partner-specific role data described in Section 3.1.9. 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 AND INITIAL CONDITIONS

In this model, there are three demographic processes: entries, exits, and aging. Entries and exits are conceptualized as flows into and out of the sexually active population of interest: MSM aged 15 to 65 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 associated with sexual debut and ending at an age potentially before death (age 65). This age range also mapped directly on to the eligibility criteria of the ARTnet study.[161]

5.1 Arrivals at Sexual Onset

All persons enter the network at age 15, which was the lower age boundary of ARTnet. The number of new entries at each time step was based on a fixed rate (0.052 per 100 person-weeks) that kept the overall network size in a relatively stable state. The model parameter governing this rate was tuned iteratively in order to generate simulations with a population size at equilibrium, given the inherent variability in population flows related to background mortality, sexual cessation (i.e., reaching the upper age limit of 65), 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 in different categories. Some attributes remained fixed by definition (e.g., race/ethnicity), others were fixed by assumption (e.g., insertive versus receptive sexual role), and others were allowed to vary over time (e.g., age and disease status). Here we describe attributes initialized at the outset in the model and for arrivals into the population at each time step:

- **Race/ethnicity.** This model was based on a race/ethnic population composition categorized into three mutually exclusive groups: Black, Hispanic, and White/other. At the outset of the model simulations, individuals were randomly assigned into one of these three groups with a probability equal to the proportions each represented in the Atlanta metropolitan target population based on 2018 Census data estimates for men aged 15 to 65. Those probabilities were: 51.5% Black, 4.6% Hispanic, and 43.9% White. Incoming nodes during the dynamic simulation were also randomly assigned a race/ethnicity in these proportions.
- **Age.** In the dynamic simulation, as noted above, all nodes were assigned an age of 15, which incrementally grew in weekly time steps. At the outset of the model simulations, we assigned nodes an age based on a uniform distribution, with ages from 15 to 65. This population-level age distribution was expected to converge to a more realistic distribution during model burn-in and calibration (explained in Section 9.2).
- **HIV Status.** In the dynamic simulation, all nodes were assigned an HIV status of uninfected upon arrival into the population. This reflects the assumption that arrival corresponded with sexual debut, before which exposure to HIV would be very rare. At the outset of the model simulations, we randomly seeded the nodes with HIV infection by fitting and predicting from a logistic regression of diagnosed HIV status from the ARTnet data. This model incorporated city (residence in Atlanta), age, and race/ethnicity as the primary predictors based on the self-reported diagnosed HIV status reported by ARTnet

respondents. These initial infections were all assumed to be diagnosed based on this outcome. We did not expect that this initial condition of diagnosed HIV prevalence at the outset of the burn-in model to match the calibrated disease prevalence prior to experimental intervention models; instead this statistical modeling approach allowed for a data-driven seeding of HIV infection in the population that was distributed according to known demographic and geographic heterogeneity. Further description of the transition from initial HIV conditions to calibrated levels are provided in Section 8.2.

- **Circumcision Status.** Circumcision status was randomly assigned to incoming nodes at arrival and for all nodes as initial conditions in the simulations. Based on empirical data from Atlanta MSM,[171] 89.6% of men were circumcised before sexual onset. As described in Section 8, 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).[159,172]

5.3 Departures from the Network

All persons exited the network by age 65, either from mortality or by reaching the upper age bound of the MSM target population of interest. This upper limit of 65 was modeled deterministically (probability = 1), but other exits due to mortality were modeled stochastically. Departures included both natural (non-HIV) and disease-induced mortality causes before age 65. Background mortality rates were based on US all-cause mortality rates specific to age and race/ethnicity from the National Vital Statistics life tables.[173] The following table shows the probability of mortality per year by age and race/ethnicity.

Appendix Table C.8. Age- and Race/Ethnicity-Specific Probabilities of Mortality among Men in the United States

Age	Black	Hispanic	White
15–19	0.00124	0.00062	0.00064
20–24	0.00213	0.00114	0.00128
25–29	0.00252	0.00127	0.00166
30–34	0.00286	0.00132	0.00199
35–39	0.00349	0.00154	0.00226
40–44	0.00422	0.00186	0.00272
45–49	0.00578	0.00271	0.00382
50–54	0.00870	0.00440	0.00591
55–59	0.01366	0.00643	0.00889
60–64	0.02052	0.00980	0.01266

These yearly probabilities were transformed into weekly risks. Natural mortality was then applied to persons within the population at each time step stochastically by drawing from a Bernoulli distribution for each eligible person with a probability parameter corresponding to that the age- and race-specific risk of death. 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 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 (15 and 65 years old). Evolving age impacted background mortality, age-based mixing in forming new partnerships, and other 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,[152,155,158,159,174] 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. The HIV viral load has a direct impact on the rates of HIV transmission within serodiscordant pairs in the model, and this interaction is detailed in Section 8. A starting viral load of 0 is assigned to all persons upon infection. From there, the natural viral load curve is fit with the following parameters.

Appendix Table C.9. HIV Natural History Parameters

Parameter	Value	Reference
Time to peak viremia in acute stage	45 days	Little[175]
Level of peak viremia	6.886 $\log_{10}$	Little[175]
Time from peak viremia to viral set point	45 days	Little,[175] Leynaert[176]
Level of viral set point	4.5 $\log_{10}$	Little[175]
Duration of chronic stage infection (no ART)	3550 days	Buchbinder,[177] Katz[178]
Duration of AIDS stage	728 days	Buchbinder[177]
Peak viral load during AIDS	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 $\log_{10}$. Changes occur linearly on the log scale. 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 on the log scale from 4.5 log_{10} to 7 log_{10}. 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 7. These transitions are deterministic for all ART-naïve persons. In the AIDS stage, disease-related mortality is imposed stochastically with a homogenous risk of 1/104, corresponding to average duration of the AIDS stage in weeks. This is accomplished by drawing from a binomial (Bernoulli) distribution for all eligible individuals in the AIDS stage.

7 CLINICAL EPIDEMIOLOGY

Clinical epidemiological processes in the model refer to all steps along the HIV care continuum after initial HIV infection: diagnosis, linkage to ART care, adherence to ART, and HIV viral load suppression. In this model, these clinical features have interactions with behavioral features detailed above, as well as impacts on the rates of HIV transmission, detailed in the next section. 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 ART initiation to HIV viral suppression.[179]

7.1 HIV Diagnostic Screening

Both HIV-uninfected and HIV-infected persons in our model were exposed to regular interval-based HIV screening that served as a common entry point for HIV prevention and HIV treatment services, respectively. Individuals screened at routine intervals first based on whether they were currently using PrEP or not. For HIV screening outside of PrEP care, we used race/ethnicity stratified rates estimated and calibrated for a previous model of the HIV care continuum.[15] The numerical results from this parameterization are shown in Supplemental Table 10.

Appendix Table C.10. Model Parameterization for HIV Screening

	Black MSM	Hispanic MSM	White MSM
Target Statistic: Diagnosed Fraction[180]	80.4%	79.9%	88.0%
Simulations: Diagnosed Fractions	80.8%	79.4%	88.0%
Calibrated Rates (per Week)	0.00385	0.00380	0.00690
Inter-Test Interval (Years)	5.00	5.06	2.79
Diagnostic Delay (Years)	3.20	3.21	2.32

The target statistics for the diagnosed fraction were drawn from a Georgia Department of Public Health surveillance report based on laboratory data for MSM in 2017, the most recent year for which the data were available. The diagnosed fraction was higher for White MSM compared to black and Hispanic MSM. After calibration, the simulated diagnosed fractions were nearly identical to those targets. The calibrated screening rates per week were higher among White MSM, and lower among Black and Hispanic MSM, consistent with producing the differentials in the diagnosed fractions across the groups. These weekly rates were consistent with average inter-test intervals, or the average time between HIV negative screening events, of 2.8 to 5.1 years. Note that these intervals represent marginal averages across the target population; some MSM may screen more frequently while others screen very rarely.

Diagnostic testing was simulated stochastically using draws from a binomial distribution with probability parameters equal to these stratified probabilities. This generated a population-level geometric distribution of times since last test.

For PrEP users, we modeled HIV screening practice based on CDC clinical practice guidelines.[181] The guidelines recommend ongoing screening at 3-month intervals for MSM actively using PrEP. This schedule was imposed for all PrEP users active in their PrEP use,

regardless of PrEP adherence categories. We also assumed no racial/ethnic variation in HIV screening rates for PrEP users.

Finally, 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.[182] 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

Following HIV diagnosis, individuals were linked to HIV care that provided ART. In the absence of quantitative data and based on current clinical practice guidelines for MSM in the US, we assumed no gap between treatment entry and ART initiation. Although the intermediate steps of the HIV care continuum are often characterized by any linkage to HIV care and/or ART, we selected a second HIV care continuum target of linkage to HIV care specifically within one month of diagnosis for two reasons. First, in the dynamic modeling context, the temporally defined threshold easily mapped on to the tracking implemented for simulated individuals in the model. Second, there were readily available surveillance estimates for this outcome. With respect to the latter, we used data from the Georgia Department of Public Health care continuum estimates for 2017, stratified by transmission risk level and race/ethnicity. We used race/ethnicity stratified rates estimated and calibrated for a previous model of the HIV care continuum.[15]

Supplemental Table 11 shows the numerical results of the calibration. The rate of care establishment was highest for White MSM, and lower for Black and Hispanic MSM. With the calibrated rates, the model simulations matched these target statistics. The inverse of these

rates implied that the average time to ART initiation after HIV diagnosis was between 4 to 6 weeks on average.

Appendix Table C.11. Model Parameterization for ART Linkage After Diagnosis

	Black MSM	Hispanic MSM	White MSM
Target Statistic: Fraction Linked within 1m[180]	62%	65%	76%
Simulations: Fraction Linked	62.4%	65.1%	76.5%
Calibrated Rates (per Week)	0.1775	0.1900	0.2521
Time to ART (in Weeks)	5.6	5.3	4.0

7.3 ART Adherence and HIV Viral Load 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.[183] Individuals on ART could reach full suppression with sustained ART use. The nadir HIV viral load level was assumed to be 1.5 $\log_{10}$ among those at full suppression levels.[183] The latter corresponds to an absolute viral load below the standard levels of detection (VL = 50).[184] Viral load was tracked and updated continuously over time based on the natural history of HIV disease by stage, and current use of ART.

The patterns of ART adherence (cycling on and off ART) leading to full HIV viral suppression were estimated based on an analysis of HIV care patterns among MSM in the United States[185] and model calibration was based on a previous model of the HIV care continuum.[15] The rates of cycling off ART after initially starting (the “halting rate”) and the rates of cycling back on after a period of stopping (the “reinitiation rate”) controlled overall levels of HIV viral suppression.

Supplemental Table 12 shows the numerical results of the calibration. Georgia Department of Public Health data for MSM in 2017 were the target statistics for the proportion of diagnosed MSM with a suppressed viral load in the cross-section. The “halting rate” was calibrated in a

previous model of the HIV care continuum.[15] Supplemental Table 12 shows the numerical results of the calibration.

Appendix Table C.12. Model Parameterization for ART Retention Rates After Linkage

	Black MSM	Hispanic MSM	White MSM
Target Statistic: Fraction VL Suppressed[180]	55%	60%	72%
Simulations: Fraction VL Suppressed	55.7%	58.7%	71.8%
Calibrated Halting Rates (per Week)	0.0062	0.0055	0.0031
Time to First ART Stoppage (in Weeks)	161.3	181.8	322.6
Time to First ART Stoppage (in Years)	3.1	3.5	6.2

The corresponding halting rates were therefore lowest in White MSM and highest in Black MSM. The inverse of these rates implied a time to first stopping ART after initiation of 161 to 323 weeks.

7.4 AIDS Disease Progression and AIDS-Related Mortality

Progression to AIDS after ART initiation was modeled based on the cumulative time on and off ART for individuals who had been linked to treatment (persons never linked to ART progressed according the rates in Section 6). The maximum untreated time between infection and the start of AIDS was 9.7 years.[177] Therefore, an individual who spent this much time off ART during the course of infection progressed to AIDS. We assumed a maximum time off ART of 15 years, similar to previous models.[158] Persons who had ever initiated ART progressed through AIDS at a similar rate as those who were ART-naïve, but ART use during the AIDS stage was associated with the same declines in HIV VL as in pre-AIDS stages. However, to account for treatment failure during the AIDS stage, the same mortality rate (1/104 weeks) was applied to persons on active ART and those not on active ART within the AIDS stage.

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 is calculated as a function of the intrahost epidemiological profile of each member of a partnership, and behavioral features within the dyad.

8.1 HIV-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 3). From the full edgelist, a disease-discordant subset was created by removing those dyads in which both members were HIV- or both were HIV+. This left dyads that were discordant with respect to HIV status, which was the set of potential partnerships over which infection may be transmitted at that time step.

8.2 HIV Transmission Rates

Within HIV-discordant dyads, transmission was simulated stochastically across separate sexual acts at each timestep. The per-act probabilities were a combined function of attributes of the HIV-negative and HIV-positive partner, these probabilities were calibrated to reach the empirical diagnosed HIV prevalence. The final per-partnership transmission rates per time step were then a function of these per-act transmission probabilities raised to the number of acts within the partnership during that time step.

8.2.1 Base Per-Act Transmission Probabilities

Within disease-discordant dyads, HIV transmission was modeled based on a sexual act-by-act basis, in which multiple acts of varying infectiousness could occur within one partnership within a weekly time step. Determination of the number of acts within each discordant dyad for the time step, as well as condom use and role for each of those acts, was described in Section 4. 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, as shown in Supplemental Table 13 below.

Appendix Table C.13. Per-Act Transmission Probabilities and Modifiers

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[186]
		Insertive: 0.003379 base probability when HIV+ partner has 4.5 $\log_{10}$ viral load	Vittinghoff[186]
HIV viral load (VL)	HIV+	Multiplier of $2.45^{(VL - 4.5)}$	Wilson[187]
Acute stage	HIV+	Multiplier of 9	Leynaert,[176] Bellan[188]
Condom use	Both	Multiplier of 0.05 plus 0.25	Varghese,[189] Weller,[190] Smith[191]
Circumcision status	HIV-, insertive	Multiplier of 0.40	Gray[172]
PrEP	HIV-	High adherence: Multiplier of 0.01 Medium adherence: Multiplier of 0.19 Low adherence: Multiplier of 0.69	Grant[192]

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.[188] Three covariates could reduce the risk of infection: condom use within the act by either the HIV- or HIV+ partner, circumcision status of the HIV- partner (only if the HIV- partner was insertive in that act), and PrEP use at the time of the act by the HIV- partner.

For condom use, we updated our previous approach to explicitly represent condom failure that would result in a transmission event. Our previous models used estimates of HIV incidence comparing consistent condom users to occasional or non-condom users, resulting in a condom "efficacy" of 75–80%. However, this efficacy gap of 20–25% is the function of both the biological/physiological gaps in protection given perfect and consistent condom use during anal intercourse as well as the human error resulting in impact use. Such error could represent condom breakage, misapplication, incomplete use during sexual activity, and other related causes.[191] For this model, we assumed a 95% efficacy for the former, and a 25% absolute reduction in that efficacy as a function of condom failure to arrive at the previous range of 75–80% total effectiveness. Therefore, the condom failure rate was set to 25%, so the total multiplier was 0.30.

8.2.2 Calibration of Transmission Probabilities

In addition to the calibration of the HIV care continuum parameters described in Section 7, we also calibrated the per-act transmission probabilities so that the diagnosed HIV prevalence was consistent with empirical data on HIV burden in this target population. Our target statistic for this calibration step was diagnosed HIV prevalence by race/ethnicity, which was estimated in Rosenberg.[193] The target statistics of diagnosed HIV prevalence for MSM in the Atlanta area were 33.3% for Black MSM, 12.7% for Hispanic MSM, and 8.4% for White MSM. The per-act transmission probabilities defined above were then multiplied by a factor unique to each race/ethnic group. The final factor levels were 2.65 for Black MSM, 0.424 for Hispanic MSM, and 0.247 for White MSM. These calibration factors represent the additional sources of potential

error in the transmission parameters that would generate the current HIV epidemic. These include co-factors not included in this model, such as untreated sexually transmitted infections.[194] The upweighting of the transmission probabilities for Black MSM and down-weighting for White and Hispanic MSM is due to the long-standing finding that race-stratified behavioral and network data do not, by themselves, explain the excess burden of HIV among Black MSM.[55,56] We also increased the acute HIV RR to 9, in order to compensate for HIV serosorting among one-time partners. Prior models without HIV serosorting used a RR of 6.

8.2.3 Final Per-Partnership-Week Transmission Rates

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 Bernouli distribution with the probability parameter equal to the per-act transmission probabilities detailed above.

9 MODEL CALIBRATION

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

9.1 Calibration Methods

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

We used approximate Bayesian computation with sequential Monte Carlo sampling (ABC-SMC) methods[188,195] to calibrate behavioral parameters in which there was measurement uncertainty in order to match the simulated HIV prevalence and STI incidence at the end of the burn-in simulations to the targeted HIV prevalence and STI incidence. The details of ABC depend on the specific algorithm used, but in this case, ABC-SMC proceeded as follows.

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

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

9.2 Calibration Steps

We used a three-stage approach to implementing the model calibration. First, we calibrated the model to match target statistics for the diagnosed HIV prevalence (Stage 1). Stage 1 used the base network model parameters (i.e., without PrEP degree or sorting parameters) to establish a stable HIV epidemic prior to the introduction of PrEP. This involved simulating the model at least 500 times for 60 years (the first burn-in period) and evaluating the distance between the selected target statistics and the simulations at the final year of the period. Once that calibration was complete, we simulated 500 replicates of the fitted model and selected the single simulation with the values of the target statistics closest to the targets (with total absolute deviance). We did not calibrate parameters pertaining to the HIV care continuum (screening, linkage, and HIV

viral load suppression) and instead used the model specification calibrated for a previously published study with similar model framework.[15]

We then calibrated PrEP initiation and discontinuation parameters over a 5 year phase-in period (Stages 2 and 3), Stage 2 introduced PrEP to the population for 1 year, so that ~10% of PrEP-eligible MSM were using PrEP at the end of the year. This was necessary to generate >0% PrEP use in the population, prior to substituting the network model parameters for the scenarios with and without PrEP sorting. The PrEP initiation parameters in Stage 2 were calibrated to generate 20% PrEP coverage among PrEP-eligible MSM after 5 years, based on the degree and one-time partner distributions observed in ARTnet, so that PrEP allocation during Stage 2 would be similar to the Stage 3 model without PrEP sorting. Similar to Stage 1, this involved simulating the model at least 500 times for 5 years and evaluating the distance between the selected target statistics (20% PrEP coverage and degree distributions) and the simulations during year 5. Once the parameters were calibrated, we then simulated the model 500 times for 1 year only and selected the single simulation with values of the HIV prevalence target statistics closest to the targets used in Stage 1. We based the model selection on HIV prevalence, so that Stage 3 begins with a stable HIV epidemic (i.e., HIV incidence is not increasing or decreasing substantially due to stochasticity in one simulation).

Stage 3 completed the 5 year phase-in of PrEP. We completed the Stage 3 calibration twice: once for the scenario without PrEP sorting and once for the scenario with PrEP sorting. At the beginning of Stage 3, the network model parameters were substituted to include PrEP degree parameters, and assortative mixing among persistent partners using PrEP in the model with PrEP sorting. Beginning with the model without PrEP sorting, we calibrated the PrEP initiation parameters to generate 20% PrEP use at the end of the 5 year PrEP phase-in. The calibrated parameters were similar to the parameters used in Stage 2. We simulated the model 500 times for 4 years and evaluated the distance between the selected target statistics (20% PrEP

coverage and degree distributions) and the simulations during year 5. Similarly, we repeated the calibration for the scenario with PrEP sorting. Once the PrEP parameters were calibrated for both scenarios, we simulated each model 500 times for 14 years. The first 4 years completed the 5 year phase-in of PrEP, so that both model scenarios begin with the same simulation selected in Stage 2. The simulations then continue for an additional 10 years. We retained the final 10 years of each simulation for analysis of network and HIV outcomes.

10 SUPPLEMENTAL RESULTS

Appendix Table C.14. Mixing statistics, average over year 10

	Main		Casual		One-time	
	Without PrEP sorting	**With PrEP sorting**	**Without PrEP sorting**	**With PrEP sorting**	**Without PrEP sorting**	**With PrEP sorting**
No PrEP, N[1]	3840	3837	2684	2663	339	341
	(3721, 3957)	(3723, 3945)	(2543, 2816)	(2545, 2806)	(316, 363)	(316, 365)
No PrEP (%)	75.6%	80.1%	51.6%	57.3%	52.1%	52.5%
	(74.3, 76.8)	(78.8, 81.2)	(49.6, 53.3)	(55.5, 59.2)	(49.9, 54.5)	(50.0, 54.5)
PrEP (%)	11.1%	6.3%	22.1%	15.0%	31.6%	31.5%
	(10.3, 11.9)	(5.7, 7.0)	(20.7, 23.6)	(13.7, 16.2)	(29.3, 34.1)	(29.2, 33.8)
With HIV (%)	13.4%	13.6%	26.4%	27.6%	16.2%	16.0%
	(12.4, 14.4)	(12.6, 14.7)	(24.6, 28.2)	(25.8, 29.7)	(14.6, 18.0)	(14.4, 17.8)
PrEP, N[1]	526	531	1060	1064	201	200
	(487, 564)	(487, 575)	(980, 1147)	(973, 1140)	(177, 228)	(177, 225)
No PrEP (%)	80.7%	45.9%	55.9%	37.8%	53.2%	53.5%
	(77.3, 83.4)	(42.6, 49.5)	(53.3, 58.5)	(35.5, 39.8)	(50.3, 56.5)	(50.7, 56.7)
PrEP (%)	12.1%	46.9%	24.1%	43.7%	30.9%	30.9%
	(9.6, 15.1)	(43.3, 50.3)	(21.6, 26.5)	(41.2, 46.1)	(27.7, 34.7)	(27.2, 34.2)
With HIV (%)	7.2%	7.3%	20.0%	18.6%	15.8%	15.6%

	(5.4, 9.4)	(5.5, 9.3)	(18.0, 22.2)	(16.6%, 20.7%)	(13.6, 17.8)	(13.6, 17.9)
With HIV, N[1]	1035	1065	1402	1456	195	207
	(979, 1095)	(997, 1129)	(1307, 1493)	(1352, 1565)	(167, 226)	(182, 240)
No PrEP (%)	49.6%	49.1%	50.5%	50.6%	28.2%	26.1%
	(46.3, 53.1)	(45.8, 52.4)	(47.8, 53.1)	(48.1, 53.5)	(25.2, 31.2)	(23.6, 29.2)
PrEP (%)	3.6%	3.6%	15.2%	13.6%	16.3%	15.0%
	(2.8, 4.8)	(2.8, 4.7)	(13.6, 16.8)	(12.1, 15.1)	(13.7, 18.8)	(12.8, 17.5)
With HIV (%)	46.8%	47.2%	34.3%	35.7%	55.6%	58.8%
	(43.1, 50.0)	(43.8, 50.6)	(31.3, 37.5)	(33.0, 38.7)	(50.9, 59.8)	(54.4, 63.0)

Appendix Table C.15. Proportion of partnership types in the network, average over year 10

	Main		Casual		One-time	
	Without PrEP sorting	**With PrEP sorting**	**Without PrEP sorting**	**With PrEP sorting**	**Without PrEP sorting**	**With PrEP sorting**
Partnerships (N)	2701 (2638, 2769)	2715 (2650, 2782)	2577 (2456, 2703)	2591 (2477, 2708)	369 (340, 395)	374 (348, 404)
HIV mixing (%)						
Concordant						
Without diag. HIV	70.6% (69.0, 72.0)	70.1% (68.4, 71.7)	54.8% (52.8, 57.1)	53.9% (51.6, 56.1)	61.7% (58.1, 65.4)	60.8% (57.3, 64.0)
With diag. HIV	9.0% (8.1, 10.0)	9.2% (8.3, 10.3)	9.4% (8.3, 10.6)	10.1% (8.9, 11.4)	14.7% (12.0, 17.6)	16.4% (13.7, 19.4)
Discordant HIV statuses	20.4% (19.1, 21.8)	20.7% (19.2, 22.2)	35.7% (33.7, 37.7)	36.1% (34.3, 38.1)	23.6% (21.7, 25.2)	22.8% (21.1, 24.6)
HIV & PrEP mixing (%)						
Concordant						
Not using PrEP	53.7% (52.1, 55.2)	56.5% (54.8, 58.1)	26.9% (25.4, 28.6)	29.5% (27.9, 31.2)	24.0% (22.1, 26.3)	23.9% (21.8, 26.0)
Using PrEP	1.2% (0.9, 1.5)	4.6% (4.1, 5.1)	5.0% (4.2, 5.7)	9.0% (8.0, 9.9)	8.5% (7.1, 10.2)	8.3% (6.9, 9.7)
With diag. HIV	9.0% (8.1, 10.0)	9.2% (8.3, 10.3)	9.4% (8.3, 10.6)	10.1% (8.9, 11.4)	14.7% (12.0, 17.6)	16.4% (13.7, 19.4)
Discordant						
Not using PrEP – Using PrEP	15.7% (14.6, 16.8)	9.0% (8.1, 9.9)	23.0% (21.6, 24.6)	15.4% (14.2, 16.5)	29.1% (26.9, 31.3)	28.6% (26.5, 30.7)
Not using PrEP – With diag. HIV	19.0% (17.7, 20.4)	19.2% (17.9, 20.7)	27.5% (25.8, 29.2)	28.4% (26.7, 30.2)	15.0% (13.5, 16.3)	14.5% (13.2, 15.9)
Using PrEP – With diag. HIV	1.4% (1.1, 1.9)	1.4% (1.1, 1.8)	8.3% (7.4, 9.1)	7.6% (6.8, 8.4)	8.6% (7.5, 9.7)	8.3% (7.3, 9.4)

Appendix Table C.16. Mean partnership degree, stratified by HIV diagnosis status and PrEP use status, in scenarios with and without PrEP sorting

	Without PrEP Sorting	With PrEP Sorting
	Median (95% SI)[1]	Median (95% SI)[1]
Main Partners[2]		
Without diagnosed HIV[3]	0.44 (0.43, 0.45)	0.44 (0.43, 0.45)
Not using PrEP	0.44 (0.43, 0.45)	0.44 (0.43, 0.45)
Using PrEP	0.43 (0.41, 0.46)	0.44 (0.41, 0.46)
With diagnosed HIV	0.48 (0.45, 0.50)	0.48 (0.46, 0.51)
Casual Partners[2]		
Without diagnosed HIV	0.38 (0.36, 0.39)	0.37 (0.36, 0.39)
Not using PrEP	0.31 (0.29, 0.32)	0.30 (0.29, 0.32)
Using PrEP	0.87 (0.83, 0.92)	0.88 (0.83, 0.92)
With diagnosed HIV	0.64 (0.60, 0.68)	0.66 (0.62, 0.70)
One-time Partners[4]		
Without diagnosed HIV	0.05 (0.05, 0.06)	0.05 (0.05, 0.06)
Not using PrEP	0.04 (0.04, 0.04)	0.04 (0.04, 0.04)
Using PrEP	0.17 (0.15, 0.19)	0.16 (0.15, 0.18)
With diagnosed HIV	0.09 (0.08, 0.10)	0.09 (0.08, 0.11)

[1]Median and 95% simulation interval for all 500 simulations in each scenario

[2]Mean momentary degree, averaged over the final year in each simulation

[3]MSM without diagnosed HIV include those with undiagnosed HIV infection

[4]Mean weekly rate of one-time partners, averaged over the final year in each simulation

Appendix Table C.17. Risk ratios of per-act probabilities of HIV transmission, in the scenario with PrEP sorting compared to the scenario without PrEP sorting, overall and stratified by PrEP use of the susceptible partner and diagnosed HIV status of the partner with HIV.

	All susceptible	Not using PrEP	Using PrEP
	RR[1]	RR[1]	RR[1]
All partners with HIV	1.00 (0.79, 1.24)	0.99 (0.79, 1.23)	0.98 (0.36, 2.19)
Diagnosed	1.01 (0.83, 1.25)	1.00 (0.82, 1.23)	1.02 (0.41, 2.21)
Undiagnosed	1.06 (0.63, 1.86)	0.99 (0.58, 1.80)	1.08 (0.16, 6.44)

[1]Risk ratio per-act in partnerships with different HIV statuses; median and 95% simulation intervals