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Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study

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Key messages:

- Several barriers exist to the successful implementation of PrEP in local settings, and optimizing the efficiency of PrEP delivery is a public health priority
- Targeting MSM infected with *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* increases the efficiency and effectiveness of PrEP delivery
- Expanding levels of STI screening among MSM can significantly improve the impact of PrEP (with PrEP offered to those testing positive)

ABSTRACT

Objectives: *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) increase the risk of HIV transmission among men who have sex with men (MSM). Diagnosis of NG/CT may provide an efficient entry point for prevention of HIV through delivery of pre-exposure prophylaxis (PrEP).

Methods: To quantify the added value of targeting PrEP to those diagnosed with NG/CT, we simulated the co-epidemic of NG/CT and HIV among MSM in Baltimore City, and compared various strategies for implementation of PrEP in this population.

Results: Assuming 60% uptake and 60% adherence, targeting PrEP to MSM diagnosed with NG/CT could reduce HIV incidence among MSM in Baltimore City by 12.4% [95% uncertainty range (UR): 10.3 – 14.4%] in 20 years, relative to no PrEP. Expanding the coverage of NG/CT screening (such that individuals experience a 50% annual probability of NG/CT screening and evaluation for PrEP upon NG/CT diagnosis), can further increase the impact of targeted PrEP to generate a 22.0% [95% UR 20.1 – 23.9%] reduction in HIV incidence within 20 years. When compared to alternative implementation scenarios, PrEP evaluation at NG/CT diagnosis increased impact of PrEP on HIV incidence by 1.7 [95% UR 1.0 – 2.6] relative to a scenario in which PrEP evaluation happened at the time of NG/CT screening/testing, and by 1.9 [95% UR 1.1 – 3.4] relative to evaluating random MSM from the community.

Conclusions: Targeting MSM infected with NG/CT increases the efficiency and effectiveness of PrEP delivery. If high levels of STI screening can be achieved at the community level, NG/CT diagnosis may be a highly effective entry point for PrEP initialization.

Strengths and limitations of this study

- Given the epidemiologic link between *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT) infection and HIV among men who have sex with (MSM), new NG/CT diagnoses may serve as a useful means to identify high-risk MSM for PrEP evaluation and delivery. At present, the impact of such a strategy is not clear. Using surveillance data from Baltimore City, Maryland, this study applies a modeling framework to evaluate the added value of targeting PrEP to MSM diagnosed with NG/CT, in terms of population-level impact on disease incidence over time.
- We base our depiction of HIV on a published agent-based model of HIV transmission among MSM in Baltimore City, and we extend this model to include coinfection of HIV with NG and CT infections modeled at the individual level.
- Our simulation model is calibrated against aggregate estimates of HIV and NG/CT incidence and prevalence, as well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City Health Department as part of the STD Surveillance Network Project.
- Our findings are limited by simplifying assumptions including (but not limited to) exclusion of other STIs such as syphilis, simplified representation of NG/CT natural history, simplification of sexual networks for NG/CT and HIV transmission, exclusion of HIV transmission through injection drugs or heterosexual sex, and exclusion of transgender and bisexual individuals from the simulated population.
- Given the controversies on existence of behavior change among MSM taking PrEP and lack of supporting data from our local population of MSM in Baltimore City, we excluded behavioral disinhibition from this analysis. Future studies can extend this analysis by evaluating changes in population-level impact of PrEP for HIV and STI control under potential levels of behavioral disinhibition for those on PrEP.

Keywords: HIV Infections; Gonorrhoea; Chlamydia; Pre-Exposure Prophylaxis; Homosexuality, Computer Simulation

BACKGROUND

Infection with *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT) may impact HIV transmission in multiple ways, particularly among men who have sex with men (MSM). From a biological standpoint, NG/CT infection may increase one's susceptibility to HIV acquisition: rectal infection in particular has been linked to an increased risk of HIV acquisition [1,2]. HIV and NG/CT also share many risk factors at the individual level (e.g., condomless sex) and network level (e.g., having sex within a high-prevalence network), such that the three conditions are often epidemiologically linked [3]. Additionally, HIV-negative men have an increased risk of HIV acquisition when in partnership with a HIV-positive partner who is also co-infected with NG/CT [4,5]. As a result, better diagnosis and treatment of NG/CT can potentially reduce HIV incidence [6], and help to identify individuals at high risk of future HIV infection.

Pre-Exposure Prophylaxis (PrEP) is part of comprehensive HIV prevention services in which HIV-negative people take daily antiretroviral medication to lower risk of HIV transmission upon exposure. The U.S. Centers for Disease Control and Prevention (CDC) has recommended PrEP for HIV-negative individuals at substantial risk of infection [7]. Among MSM, this includes HIV-negative men who are either diagnosed with a sexually transmitted infection (STI) in the last 6 months, are in a HIV discordant partnership, or report a condomless sex act in the last 6 months. Despite this broad recommendation, the potential population-level impact of PrEP remains uncertain. Several barriers exist to the successful implementation of PrEP, including providers' perceived inability to deliver PrEP in primary care settings [8], individuals' limited knowledge of PrEP effectiveness [9], low self-perceived risk for HIV infection [10], patients' difficulty in maintaining adherence [11], and high costs (at over $10,000 per person-year for those without insurance or access to a medication assistance plan) [12,13].

Given these challenges, optimizing the efficiency of PrEP delivery is a public health priority. Specifically, it is important to tailor PrEP delivery to those who stand to gain the most from its preventive efficacy. Given the epidemiologic link between NG/CT infection and HIV among MSM, new NG/CT diagnoses may serve as a useful means to identify high-risk MSM for PrEP evaluation and delivery [7]. At present, the impact of such a strategy—in terms of reducing HIV and NG/CT incidence at a population level—is not clear. To address this question, we used surveillance data from Baltimore City, Maryland, to construct an agent-based simulation model of the co-transmission of HIV and NG/CT among MSM, [14] and applied this model to study the added value of targeting PrEP to MSM diagnosed with NG/CT, in terms of population-level impact on HIV incidence over time.

METHODS

We base our depiction of HIV on a published agent-based model of HIV transmission among MSM in Baltimore City [14] (Figure 1-top panel), and we extend this model to include coinfection of HIV with NG and CT infections (see section 1 of the Supplementary Material).

NG/CT infection: NG and CT share similarities in natural history, including their acute nature, symptomatology, frequent co-diagnosis, and co-treatment [15]. Given these similarities, and for simplicity of modeling, we model NG/CT as a single biological entity. We assume that NG/CT infection may occur at the urethral, rectal or pharyngeal site – each with different probabilities of symptomatic presentation, diagnosis and treatment, and effects on HIV transmission, as shown in Table 1. We include both asymptomatic and symptomatic infection and fit the model to the annual number of diagnoses at each clinical site (urethral, rectal, or pharyngeal) among MSM in Baltimore City (see section 2 of the Supplementary Material).

Table 1: List of selected simulation parameters and calibration targets.

Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT) Parameters	Value	Reference
Proportion of cases symptomatic[1]		
• **Urethral**	74%	[16]
• **Rectal**	20%	[17,18]
• **Pharyngeal**	10%	[18,19]
Duration of infection (at each site) in the absence of treatment	[3 – 12] months[2]	[4,20–33]
Coefficient of NG/CT transmission per week	0.294	Calibrated to provide the incidence of NG/CT
Proportion of NG/CT infections assigned to each site		
• **Urethral**	0.35	Calibrated to provide the site-specific incidence of NG/CT
• **Rectal**	0.49	
• **Pharyngeal**	0.16	
Increase in HIV transmissibility (for those with urethral or rectal infection)	[1.5 – 2] fold [1]	[34–38]
Increase in HIV susceptibility (for those with urethral or rectal infection)	[1 – 2.5] fold [1]	[19,20,38,39]
NG/CT Calibration Targets	**Mean**[3] **[Range]**	
Annual diagnosis of NG/CT among MSM in Baltimore City		Values estimated from local data on gonorrhea surveillance and STI clinic visitis in Baltimore City (See section 2 in the Supplementary Material)
• **Urethral**	337 [269 – 405]	
• **Rectal**	25 [18 – 33]	
• **Pharyngeal**	42 [23 – 60]	
Site specific annual incidence of NG/CT among MSM in Baltimore City		
• **Urethral**	944 [753 – 1135]	
• **Rectal**	1251 [998 – 1505]	
• **Pharyngeal**	409 [326 – 492]	
HIV Parameters		
Disease duration		
• **Acute**	[6 – 9] weeks[1]	[40,41]
• **Chronic**	[8 –10] years[1]	[42,43]
• **Late stage** [4]	[1 –3] years[1]	[42–44]
Mortality rate[3]		
• **Acute & Chronic, no ART**	5 per 1000 person years	[45–47]
• **Late stage, no ART**	1/duration of late stage	
Reduction in mortality due to ART	0.58	
Time from ART discontinuation to pre-ART CD4 nadir[5]	ART treatment duration up to one year	[48–51]
Time from ART initiation to full viral suppression	[4 – 24] weeks[1]	[52]

[1] Values represent a pooled estimate of the reported measures for NG and CT infections

[2] Values are selected over uniform distributions across the ranges presented.

[3] Values represent the reported levels of NG/CT diagnosis among Baltimore City's MSM, and they are likely to underestimate the proportion of ongoing rectal and pharyngeal infections. We therefore consider such potential underestimation in estimating the annual incidence of NG/CT (see section 2 of the Supplementary Material) and have calibrated the model to represent realistic levels of prevalence (see the section on population overview in the main text).

[4] Mortality rate in late stage is defined as 1/(duration of late stage disease).

[5] Infectiousness assumed equal to that of the chronic disease.

Average viral load (log10 copies/mL)		[42]
• **Acute, no ART**	6.5	
• **Chronic, no ART**	4.5	
• **Late stage, no ART**	5	
• **On ART, partially suppressed**	3.5	
• **On ART, fully suppressed**	1.5	
Infectiousness per sexual contact	$2.45^{(\log(VL)-4.5)}$	[42]
Weekly probability of engagement in HIV care	0.006	[53–55]
Weekly probability of ART discontinuation	0.015	[56]
Gap in care after ART discontinuation	26 weeks	[57]
Relative probability of accessing HIV care among black MSM compared to white MSM	0.5	[58]
HIV calibration targets		
HIV prevalence	0.22 per 100,000 person/year	[59]
HIV continuum of care: Proportion of cases		[59]
• **Diagnosed**	0.86	
• **Linked to care**	0.62	
• **Engaged in care**	0.5	
• **On ART**	0.39	
• **Virally suppressed**	0.27	

STI Screening: In addition to testing of symptomatic NG/CT diagnosis, we also assume screening of asymptomatic individuals as follows (Figure 1- bottom panel):

- **Guidelines-based screening for HIV and NG/CT:** MSM may present to HIV/STI care providers (e.g., STI clinics, community health centers, HIV counseling programs) for a variety of reasons, and get tested for HIV and other STIs. We model visits for STI screening as a fixed weekly probability that reflects an individual's age-group and sexual activity such that younger MSM with higher propensity of partnerships experience a higher likelihood of visits [60,61]. We further assume that NG/CT is always screened at the urethral site, and a proportion of patients are also screened at the rectal and pharyngeal sites (calibrated to match the reported level of NG/CT infections diagnosis at each site among MSM in Baltimore City, as shown in Table 1).

- **NG/CT screening for HIV-positive MSM in care:** Based on CDC recommendations, most MSM who are continuously engaged in HIV care should undergo repeated NG/CT screening at least annually [15]. More frequent screening, such as screening every 3-6 months, is recommended for high-risk MSM, including those with an NG/CT diagnosis in the last year. Based on data from Baltimore City and a conservative estimate, we assume 40% adherence to these guidelines [62,63].

HIV Testing: In addition to combined HIV/STI testing that takes place as part of STI screening, we assume that all MSM experience an additional probability of HIV testing (in excess of testing though the STI program) can calibrate this probability to match the reported level of HIV diagnosis among MSM in Baltimore City.

Calibration: The model was calibrated against aggregate estimates of HIV and NG/CT incidence and prevalence, as well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City Health Department as part of the STD Surveillance Network Project (see section 2 of the Supplementary Material).

PrEP: Our primary outcome for this analysis is the projected incidence of HIV after 20 years of delivering PrEP to MSM. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the added benefit of targeting PrEP at individuals diagnosed with NG/CT. In all three scenarios, indication for PrEP use (eligibility) is considered in accordance with CDC recommendations and Baltimore City PrEP guidelines [64] (See

section 1 of the Supplementary Material) and includes HIV-negative individuals who are diagnosed with NG/CT in the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual partnership in the last 6 months. The three scenarios are thus:

- **PrEP delivery at NG/CT diagnosis** ("targeted" strategy & primary analysis)**:** all MSM diagnosed with NG/CT are offered PrEP at the time of diagnosis
- **PrEP evaluation at NG/CT screening/testing** ("at-testing")**:** PrEP eligibility is evaluated at the time of screening/testing for NG/CT, and all eligible individuals are offered PrEP
- **Untargeted PrEP:** PrEP eligibility is evaluated at random, and all eligible MSM are offered PrEP

All else being equal, increasing the number of MSM on PrEP will result in larger effects on HIV incidence (as more people are protected from HIV transmission). However, for a given number of MSM screened – or a given number of MSM on PrEP (e.g., if resource constraints are such that not all MSM meeting the criteria for PrEP can be placed/maintained on PrEP) – targeting PrEP to those screened for/diagnosed with NG/CT may be more efficient. Our primary aim was to quantify the extent of this gain in efficiency; thus, we compared scenarios in which the same number of MSM would be evaluated for PrEP, or alternatively the same number of MSM would be maintained on PrEP. Furthermore, to illustrate the potential impact of reaching highly ambitious targets for improved STI screening, we considered a hypothetical scenario for improving the underlying level of NG/CT screening (such that individual MSM not on PrEP experience a 50% annual probability of NG/CT screening and evaluation for PrEP upon NG/CT diagnosis), and studied the additional gain in effectiveness of NG/CT-targeted PrEP under this assumption.

In all scenarios, we assume that PrEP eligibility is reassessed every 3 months among patients receiving PrEP, and those who remain eligible for PrEP continue to receive it over time. Furthermore, we assume that in each scenario, a given proportion of eligible MSM who are offered PrEP will initiate prophylaxis (PrEP uptake ranging [0%-100%]) and adhere to it (PrEP adherence ranging [0%-100%]), with adherence defined as taking a sufficient number of doses to provide 60% protection against HIV transmission [65]. As a criterion for initiation of PrEP, all eligible MSM are also screened and treated for NG/CT infection before starting PrEP.

Sensitivity Analysis: A variety of sensitivity analyses were performed with the model. Using the HIV incidence at 10 years in absence and presence of PrEP (via all 3 scenarios) as the main output of interest, one-way sensitivity analyses were performed to variation of all model parameters to +/- 25% of their original value. We also varied condom usage among MSM on PrEP to model behavioral disinhibition (section 3 of the Supplementary Material).

Patient and Public Involvement: Patients and/or public were not involved in this study.

RESULTS

Population overview

The simulation models a population of 15,000 MSM in Baltimore City, projecting an average of 215 [95% UR: 181 – 251] incident HIV cases per year. Within this population, the co-epidemic of NG/CT is calibrated to 2598 [2204 – 2996] incident cases annually among which 35.0% [33.4 – 36.5%] of cases appear with urethral infection, 49.0% [47.4 – 50.6%] with non-urethral/rectal infection and 16.0% [14.8 – 17.2%] with pharyngeal-only infection. Point prevalence of NG/CT infection is estimated as 9.9% [8.4 – 11.5%], with 68.0% [63.5 – 72.5%] of infections occurring among black MSM (accounting for 58% of the MSM population) and 56.0% [54 – 58.2%] among MSM younger than 30 years old (accounting for 28% of the MSM population). Overall, 81.5% [81.0 – 82.1%] of MSM diagnosed with NG/CT in the model were tested on the basis of symptomatic presentation (rather than asymptomatic screening), and 29.1% [23.1 – 35.0%] of MSM diagnosed with NG/CT were coinfected with HIV.

Epidemiological impact of PrEP at NG/CT diagnosis

At baseline, and in the absence of PrEP (steady-state equilibrium), 361 [95% UR: 298 – 427] MSM were annually diagnosed and treated for NG/CT infection (calibrated). If 60% of MSM diagnosed with NG/CT could be started on PrEP (i.e., uptake = 60%) and maintained at a degree to which 60% of subsequent HIV infections were averted (i.e., adherence = 60%), HIV incidence was estimated to decline by 12.4% [10.3 – 14.4%] over 20 years (Figure 2A). This corresponds to averting 318 [253 – 385] potential HIV transmissions through 5808 [5730 – 5886] person-years of PrEP delivered, or 5479 [4330 – 6632] infections averted per 100,000 person-years of PrEP (Figure 2B). Under the current level of NG/CT diagnosis, the number of MSM receiving PrEP is projected to increase through the first 8 years of the program (reaching a total of 332 [327 – 338] MSM on PrEP) and to fall afterward with declining incidence of NG/CT (Figure 2C). Due to the increased level of NG/CT screening/treatment among those on PrEP (through reassessment every 3 months), the prevalence of NG/CT was estimated to decline by 43.3% [41.6 – 44.9%] over 20 years of PrEP implementation (Figure 2D).

The impact of PrEP on HIV incidence can be further increased by expanding the coverage of NG/CT screening at the community level. In our baseline model, 25.0% [95% UR: 24.0 – 26.0%] of MSM undergo NG/CT screening/testing at least once annually (CDC recommendation). In an expanded-screening scenario in which all MSM experienced a 50% probability of screening for NG/CT annually, we projected a 180% increase in the baseline estimate of 4033 [3883 – 4182] annual NG/CT testing/screening events. Offering PrEP to those testing positive for NG/CT subsequently provided a 22.0% [20.1 – 23.9%] decline in HIV incidence over 20 years, corresponding to 648 [589 – 710] potential HIV transmissions averted.

Relative impact of targeted versus untargeted PrEP

NG/CT-integrated PrEP increased efficiency of PrEP delivery in at least two ways (Figure 3A). First, a higher percentage of MSM were eligible for PrEP among those evaluated for PrEP (Figure 3B and 3C). In our model, 71.1% [95% UR: 65.0 – 77.2%] of all MSM diagnosed with NG/CT were eligible to receive PrEP (as 29% of this population is HIV-positive), compared to 45.2% [43.2 – 48.2%] of MSM screened for NG/CT, and 41.3% [39.1 – 43.5%] of randomly selected MSM. Second, providing PrEP to MSM diagnosed with NG/CT targets individuals at higher risk of potential HIV infection (due to both biological factors and high-risk behavior), such that – under the baseline assumption of equal numbers of people receiving PrEP—impact of NG/CT-targeted PrEP on HIV incidence was greater than the other two scenarios (Figure 3D). Specifically, over 20 years of implementation, targeting PrEP to MSM diagnosed with NG/CT infection increased impact of PrEP by 1.5 [1.1 – 1.9] relative to PrEP evaluation at NG/CT screening/testing, and by 1.6 [1.2 – 2.2] relative to untargeted PrEP. In another comparison, if the same number of individuals were evaluated for PrEP, the efficacy of NG/CT-integrated PrEP was increased even further relative to other scenarios (Figure 3E through 3H).

In one-way sensitivity analyses, the projected HIV incidence at 10 years in the absence of PrEP was sensitive to parameters relating to HIV and NG/CT transmission (including level of HIV viral load, condom use, and condom effectiveness) and parameters describing overall sexual activity (including the probabilities of starting new partnerships and the level of sexual activity in the most sexually active class). A similar variation in HIV incidence was observed in scenarios modeling PrEP evaluation at the time of NG/CT diagnosis, NG/CT screening or at random. Impact of PrEP in terms of reduction in HIV incidence in all scenarios relative to baseline was robust to reasonable variation of most model parameters (section 3 of the Supplementary Material). In additional sensitivity analyses, we studied the impact of decreased condom use among MSM on PrEP (behavioral disinhibition) on the outcome of NG/CT-targeted PrEP, and the relative efficacy of STI-targeted scenario compared to the other comparators. As expected, the projected impact of NG/CT-targeted PrEP on incidence of HIV and NG/CT declined with reduced levels of condom use among PrEP users. This further highlights the need for additional behavioural surveillance data characterizing changes in level of condom use and risky behaviours among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis (increased

effectiveness of PrEP implementation through an NG/CT targeted approach) remains robust to variation in rate of condom use reduction.

DISCUSSION

This agent-based simulation of HIV transmission among MSM suggests that screening for NG/CT may be an important and efficient entry point for PrEP evaluation and delivery. Specifically, if all MSM who currently test positive for NG/CT could be offered PrEP – assuming 60% uptake and sufficient adherence to maintain 60% protection – HIV incidence could be reduced by approximately 12%, averting one HIV infection annually per 1,000 MSM population, with fewer than 20 per 1,000 taking PrEP every year. On the basis of infections averted per PrEP dose delivered, providing PrEP to MSM with NG/CT diagnosis is nearly twice as efficient as providing PrEP randomly among eligible MSM. Thus, use of NG/CT diagnosis as an entry point is a highly efficient and feasible mechanism for PrEP delivery. If NG/CT screening could be expanded to 50% of MSM every year (with PrEP offered only to those testing positive), this impact could be more than doubled. Given this substantial potential impact, it will be important to assess willingness and uptake and identify best practices to support PrEP uptake and adherence among MSM diagnosed with NG/CT.

These findings are consistent with other studies of PrEP delivery among MSM [66,67]. Previous studies have shown that the population-level impact of PrEP depends strongly on PrEP uptake and adherence [14,66], as suggested in our study as well. Importantly, NG/CT diagnosis may be useful in this regard, as MSM who have recently been diagnosed with an STI may be more aware of their HIV risk and more likely to accept and initiate PrEP. Past research has shown that HIV interventions may be more effective when they are conducted or initiated at the time of an STI diagnosis [68]. Initiation of PrEP simultaneously with NG/CT diagnosis may also be a clinically feasible approach – as an STI diagnosis is already likely to prompt an HIV test (if not already performed), and MSM who are diagnosed with NG/CT have at least some level of health care access. Unlike performing detailed sexual histories, offering PrEP to all HIV-negative MSM diagnosed with NG/CT is a simple guideline that is easy for most clinicians to follow [69,70]. Further research is needed to assess the feasibility of this approach in the field, especially in ascertaining the degree to which the continuum of PrEP care (including linkage to care and longer-term maintenance on PrEP) can be maintained in this population. Furthermore, the potential tradeoff between the positive impact of PrEP on STI prevalence through enhanced screening and its negative impact through behavioral disinhibition (if MSM on PrEP adopt riskier sexual behaviors) merits further investigation. Additional implementation research is also needed to identify effective mechanisms for improving adherence to CDC PrEP guidelines and overcoming barriers to acceptance and uptake of PrEP such as lack of awareness, lack of access, financial strain, and stigma [11,71].

As with any modeling analysis, our findings are limited by necessary simplifying assumptions. These assumptions include exclusion of other STIs such as syphilis infection, combined estimates of NG/CT natural history parameters (e.g., pooled estimate of NG/CT symptomatic disease for each anatomic site), treating multi-site NG/CT infections as occurring at a single primary site, the simplified approach for modeling the transmission of site-specific infections, applying the same sexual network for NG/CT and HIV transmission, simplification of sexual networks as comprising only stable and casual partnerships, exclusion of serosorting on HIV or PrEP, exclusion of HIV transmission through injection drugs or heterosexual sex, and exclusion of transgender and bisexual individuals from the simulated population.

There are strong racial disparities in HIV incidence and healthcare access in the US, such that the highest risk populations may be the ones least likely to have access to PrEP [72]; these disparities are not included in our simplified cascade of PrEP. We excluded the potential existence of behavioral disinhibition for MSM on PrEP in the main analysis, and applied a simplified approach for modeling the combined role of PrEP uptake/adherence

for HIV protection (explored further in sensitivity analyses). Our model calibration was limited to the scope of local surveillance data, and available literature for values lacking direct empiric estimates from Baltimore City (e.g., probability of symptomatic infection). We also assume a future trajectory of HIV infection in the future that represents continuation of current trends; this trajectory is unlikely to remain constant for the next 20 years but may help to provide a useful conceptual construct for present-day decision-making, which is the ultimate goal of this analysis. Furthermore, our results are limited by exclusion of syphilis infection, another STI that is often transmitted in the same populations and may affect transmission and acquisition of HIV. Finally, we did not incorporate cost or other resource constraints into the present model; future analyses could evaluate the efficiency of NG/CT-targeted PrEP delivery from a cost-effectiveness or budget impact perspective.

In summary, this stochastic agent-based model representing the co-dynamics of NG/CT and HIV transmission among MSM suggests that NG/CT diagnosis may serve as an efficient and effective entry point for PrEP. If linkage between STI and HIV control programs can be effectively developed, further investment in NG/CT screening (followed by PrEP initiation) can have major impact, not only on the incidence and prevalence of NG/CT, but also on transmission of HIV – potentially averting up to 20% of all HIV infections through NG/CT-targeted PrEP alone. Future analyses could evaluate whether such approaches could even be cost-saving in the long term. Ultimately, ending the HIV epidemic in MSM populations will require a combination of multiple activities, including strengthening the continuum of HIV care, ensuring continued access to clinical services, and prevention through both behavioral approaches (e.g., condom use) and PrEP. Using NG/CT diagnosis as an entry point for PrEP initiation may serve as an important component of such a combined prevention approach.

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Contributions

Designed the study [PK and DWD]; Wrote the model code [PK]; Provided data [CS,JJ,ST,DG], Analyzed the data [PK]; supervised the analyses [DWD]; reviewed results [MS,SB, KH, TG, HC]; wrote the first draft of the manuscript [PK]; revised the manuscript and contributed intellectual content [PK, SB, MS, ER, KH, TG, HC]; All authors saw and approved the final manuscript.

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Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention, or the authors' affiliated institutions.

Data sharing statement:

Additional data are presented in the online Supplementary Material.

REFERENCES

1 Katz D, Dombrowski J, Bell T. HIV incidence among men who have sex with men after diagnosis with sexually transmitted infections. *Sex Transm Dis* 2016;**43**:249–54.

2 Pathela P, Braunstein S, Blank S. HIV incidence among men with and without sexually transmitted rectal infections: estimates from matching against an HIV case registry. *Clin Infect Dis* 2013;**57**:1203–9.

3 Ward H, Rönn M. Contribution of sexually transmitted infections to the sexual transmission of HIV. *Curr Opin HIV AIDS* 2010;**5**:305–10.

4 Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. *J Acquir Immune Defic Syndr* 2000;**24**:48–56.

5 Fleming DTDT, Wasserheit JNJN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;**75**:3–17.

6 Grosskurth H, Mosha F, Todd J, *et al.* Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530–6.

7 Centers for Disease Control Prevention. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline. 2014.

8 Krakower D, Ware N, Mitty JA, *et al.* HIV providers' perceived barriers and facilitators to implementing pre-exposure prophylaxis in care Settings: a qualitative study. *AIDS Behav* 2014;**18**:1712–21.

9 Eaton L, Driffin D, Bauermeister J. Minimal awareness and stalled uptake of pre-exposure prophylaxis (PrEP) among at risk, HIV-negative, black men who have sex with men. *AIDS Patient Care STDS* 2015;**29**:423–9.

10 Galindo G, Ja'Nina J. Community member perspectives from transgender women and men who have sex with men on pre-exposure prophylaxis as an HIV prevention strategy: implications for implementation. *Implement Sci* 2012;**7**:116.

11 Golub SA, Gamarel KE, Rendina HJ, *et al.* From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among MSM and transgender women in New York City. *AIDS Patient Care STDS* 2013;**27**:248–54.

12 Juusola JL, Brandeau ML, Owens DK, *et al.* The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Ann Intern Med* 2012;**156**:541–50.

13 Koppenhaver RRT, Sorensen SSW, Farnham PG, *et al.* The cost-effectiveness of pre-exposure prophylaxis in men who have sex with men in the United States: an epidemic model. *AIDS J Acquir Immune Defic Syndr* 2011;**58**:e51–2.

14 Kasaie P, Pennington J, Berry SA, *et al.* The impact of pre-exposure prophylaxis among men who have sex Withmen in Baltimore City: an agent-based simulation. *JAIDS J Acquir Immune Defic Syndr*

2017;**75**:175–83.

15 Workowski KA, Bolan GA. Sexually Transmitted Diseases Treatment Guidelines, 2015. *Morb Mortal Wkly Rep* 2015;**64(RR3)**:1–137.

16 Kent CK, Chaw JK, Wong W, *et al.* Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. *Clin Infect Dis* 2005;**41**:67–74.

17 Lister N, Smith A, Tabrizi S, *et al.* Screening for neisseria gonorrhoeae and chlamydia trachomatis in men who have sex with men at male-only saunas. *Sex Transm Dis* 2003;**30**:886–9.

18 Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. *Genitourin Med* 1996;**72**:422–6.

19 Morris SR, Klausner JD, Buchbinder SP, *et al.* Prevalence and incidence of pharyngeal gonorrhea in a longitudinal sample of men who have sex with men: the EXPLORE study. *Clin Infect Dis* 2006;**43**:1284–9.

20 Beck EEC, Birkett M, Armbruster B, *et al.* A data-driven simulation of HIV spread among young men who Hhave sex with men: role of age and race mixing and STIs. *JAIDS J Acquir Immune Defic Syndr* 2015;**70**:186–94.

21 Kretzschmar M, Duynhoven Y van. Modeling prevention strategies for gonorrhea and chlamydia using stochastic network simulations. *Am J Epidemiol* 1996;**144**:306–17.

22 Korenromp EL, Sudaryo MK, de Vlas SJ, *et al.* What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *Int J STD AIDS* 2002;**13**:91–101.

23 Althaus CL, Heijne JCM, Roellin A, *et al.* Transmission dynamics of chlamydia trachomatis affect the impact of screening programmes. *Epidemics* 2010;**2**:123–31.

24 Price MJ, Ades AE, Angelis D De, *et al.* Mixture-of-exponentials models to explain heterogeneity in studies of the duration of Chlamydia trachomatis infection. *Stat Med* 2013;**32**:1547–60.

25 Turner KM, Adams EJ, Gay N, *et al.* Developing a realistic sexual network model of chlamydia transmission in Britain. *Theor Biol Med Model* 2006;**3**:3.

26 Chesson HW, Bernstein KT, Gift TL, *et al.* The cost-effectiveness of screening men who have sex with men for rectal chlamydial and gonococcal infection to prevent HIV Infection. *Sex Transm Dis* 2013;**40**:366–71.

27 Tuite A, Jayaraman G, Allen V. Estimation of the burden of disease and costs of genital Chlamydia trachomatis infection in Canada. *Sex Transm Dis* 2012;**39**:260–7.

28 Vries R De, Bergen J Van. Systematic screening for Chlamydia trachomatis: estimating cost-effectiveness using dynamic modeling and Dutch data. *Value in* 2006;**9**:1–1.

29 Adams EJ, Turner KME, Edmunds WJ. The cost effectiveness of opportunistic chlamydia screening in England. *Sex Transm Infect* 2007;**83**:267-74-5.

30 Andersen B, Gundgaard J, Kretzschmar M. Prediction of costs, effectiveness, and disease control of a population-based program using home sampling for diagnosis of urogenital Chlamydia

trachomatis. *Sex Transm Dis* 2006;**33**:407–15.

31 Gillespie P, O'Neill C, Adams E, *et al.* The cost and cost-effectiveness of opportunistic screening for Chlamydia trachomatis in Ireland. *Sex Transm Dis* 2012;**88**:222–8.

32 Roberts T, Robinson S, Barton P, *et al.* Cost effectiveness of home based population screening for Chlamydia trachomatis in the UK: economic evaluation of chlamydia screening studies (ClaSS) project. *Bmj* 2007;**335**:291.

33 Welte R, Kretzschmar M, Leidl R, *et al.* Cost-effectiveness of screening programs for Chlamydia trachomatis: a population-based dynamic approach. *Sex Transm Dis* 2000;**27**:518–29.

34 Cohen M. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. *Lancet* 1998;**351**:S5–7.

35 Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;**75**:3–17.

36 Winter AJ, Taylor S, Workman J, *et al.* Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. *Sex Transm Infect* 1999;**75**:261–3.

37 Cohen MS, Hoffman IF, Royce RA, *et al.* Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet* 1997;**349**:1868–73.

38 Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV. *Sex Transm Dis* 2001;**28**:579–97.

39 Jin F, Prestage GP, Imrie J, *et al.* Anal sexually transmitted infections and risk of HIV infection in homosexual men. *J Acquir Immune Defic Syndr* 2010;**53**:144–9.

40 Little SJ, McLean AR, Spina CA, *et al.* Viral dynamics of acute HIV-1 infection. *J Exp Med 1* 1999;**90**:841–50.

41 Leynaert B n d., Downs AM, de Vincenzi I. Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. *Am J Epidemiol* 1998;**148**:88–96.

42 Beyrer C, Baral SD, van Griensven F, *et al.* Global epidemiology of HIV infection in men who have sex with men. *Lancet* 2012;**380**:367–77.

43 Alam SJ, Meyer R, Norling E. A model for HIV spread in a South African village. *Multi-Agent-Based Simul IX* 2009;:33–45.

44 Baggaley RF, Ferguson NM, Garnett GP. The epidemiological impact of antiretroviral use predicted by mathematical models: a review. *Emerg Themes Epidemiol* 2005;**2**:9.

45 The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;**373**:795–807.

46 Kitahata MM, Gange SJ, Abraham AG, *et al.* Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009;**360**:1815–26.

47 Palella Jr FJ, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with

advanced human immunodeficiency virus infection. *N Engl J Med* 1998;**338**:853–60.

48 Wit FW, Blanckenberg DH, Brinkman K, *et al.* Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. *AIDS* 2005;**19**:345–8.

49 Maggiolo F, Ripamonti D, Gregis G, *et al.* Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. *AIDS* 2004;**18**:439–46.

50 Ortiz GM, Wellons M, Brancato J, *et al.* Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects. *Proc Natl Acad Sci* 2001;**98**:3288–13293.

51 El-Sadr WM, Lundgren JD, Neaton JD, *et al.* CD4+ count-guided interruption of antiretroviral treatment. *New Engl J Med* 2006;**355**:2283–96.

52 Clotet B, Feinberg J, Lunzen J van, *et al.* Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised. *Lancet* 2014;**383**:2222–31.

53 Hill T, Bansi L, Sabin C, *et al.* Data linkage reduces loss to follow-up in an observational HIV cohort study. *J Clin* 2010;**63**:1101–9.

54 Mocroft A, Kirk O, Aldins P, *et al.* Loss to follow-up in an international, multicentre observational study. *HIV Med* 2008;**9**:261–9.

55 Ndiaye B, Ould-Kaci K, Salleron J, *et al.* Characteristics of and outcomes in HIV-infected patients who return to care after loss to follow-up. *AIDS* 2009;**23**:1786–9.

56 Mills E, Nachega J, Buchan I, *et al.* Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *Jama* 2006;**296**:679–90.

57 Rana AI, Liu T, Gillani FS, *et al.* Multiple gaps in care common among newly diagnosed HIV patients. *AIDS Care* 2015;**27**:697–687.

58 Rosenberg ES, Millett GA, Sullivan PS, *et al.* Understanding the HIV disparities between black and white men who have sex with men in the USA using the HIV care continuum: a modelling study. *Lancet HIV* 2014;**1**:e112–8.

59 Maryland Department of Health and Mental Hygiene, MDHMH. 2012 Baltimore City Annual HIV Epidemiological Profile. Baltimore: 2012.

60 Virginia Department of Health. STD Surveillance Network Report. Published Online First: 2013.http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf (accessed 30 Jun2017).

61 Castro JG, Alcaide ML. High rates of STIs in HIV-infected patients attending an STI clinic. *South Med J* 2016;**109**:1–4.

62 Berry SA. Gonorrhoea and chlamydia screening in HIV clinics: time for new tools and targets. *Sex Transm Infect* 2014;**90**:574–5.

63 Hoover KW, Butler M, Workowski K, *et al.* STD screening of HIV-infected MSM in HIV clinics. *Sex Transm Dis* 2010;**37**:771–6.

64 CDC. PrEP for men who have sex with men. 2018.

https://prepmaryland.org/sites/default/files/download-resources/PrEP - MSM both sides March 2017.pdf

65 Koenig L, Lyles C, Smith D. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis. *Am J Prev* 2013;**44**:S91–8.

66 Jenness S, Goodreau S. Impact of the centers for disease control's HIV preexposure prophylaxis guidelines for men who have sex with men in the United States. *J Infect Dis* 2016;**14**:1800–7.

67 Vissers DCJ, Voeten HACM, Nagelkerke NJD, *et al.* The impact of pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: a simulation study. *PLoS One* 2008;**3**:e2077.

68 Bolu OO, Lindsey C, Kamb ML, *et al.* Is HIV/sexually transmitted disease prevention counseling effective among vulnerable populations? a subset analysis of data collected for a randomized, controlled trial evaluating counseling efficacy (Project RESPECT). *Sex Transm Dis* 2003;**31**:469–74.

69 Carter JW, Hart-Cooper GD, Butler MO, *et al.* Provider barriers prevent recommended sexually transmitted disease screening of HIV-infected men who have sex with men. *Sex Transm Dis* 2014;**41**:137–42.

70 Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States-2014: a clinical practice guideline. 2014.

71 Calabrese SK, Underhill K. How stigma surrounding the use of HIV preexposure prophylaxis undermines prevention and pleasure: a call to destigmatize 'Truvada Whores'. *Am J Public Health* 2015;**105**:1960–4.

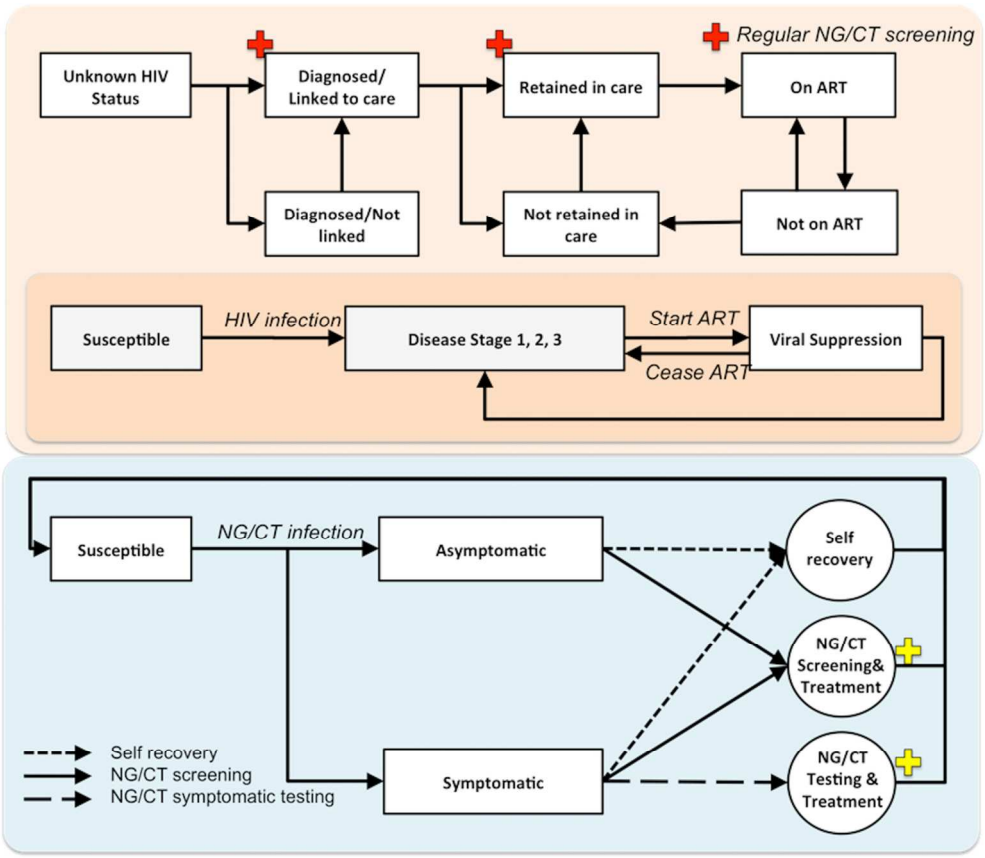
72 Highleyman L. PrEP use is rising fast in US, but large racial disparities remain. Aidsmap. 2016.http://www.aidsmap.com/PrEP-use-is-rising-fast-in-US-but-large-racial-disparities-remain/page/3065545/ (accessed 14 May2018).

Figure legends:

Figure 1: An agent-based model of gonorrhoea/chlamydia (NG/CT) and HIV co-transmission. The top panel represents the HIV care continuum and natural history: Upon infection with HIV, individuals serially progress through three disease stages over time; this progression can be halted by initiation of antiretroviral therapy (ART), which is assumed to result – if taken – in viral suppression within 4 to 24 weeks (see Table 1) [52]. We assume, for simplicity, that engagement in care involves initiation of ART (as episodes of care engagement not resulting in ART initiation do not affect HIV transmission in the model). HIV-positive individuals in care are assumed to undergo regular screening for NG/CT (marked in red) subject to patients presenting for scheduled visits and clinician decision to screen. The bottom panel represents the natural history of NG/CT: infection may be symptomatic or asymptomatic, individuals remain infectious until diagnosis and treatment (which can occur either through symptomatic presentation to care or routine screening of asymptomatic individuals) or spontaneous resolution. Upon diagnosis with incident NG/CT, we assume that individuals are also screened for HIV infection (marked in yellow); if HIV-negative, we consider the possibility of PrEP delivery in this analysis.

Figure 2: Impact of NG/CT-integrated PrEP, according to frequency of NG/CT screening/testing. Shown on the y-axes are the annual incidence of HIV (A), cumulative number of transmissions averted (B), (C) number of MSM on PrEP and (D) NG/CT prevalence. The green line depicts a scenario in which all MSM currently diagnosed with NG/CT are placed on PrEP with 60% uptake and adherence (NG/CT-integrated PrEP scenario in the main text), and the purple line shows a hypothetical scenario in which 50% of MSM are screened for NG/CT every year, with those testing positive for NG/CT also offered PrEP.

Figure 3: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in green, also corresponding to the green line in Figure 2), compared against PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. In the first set of experiments, the three strategies are compared under the assumption that the same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be screened for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenario (similar pattern in panels E through H).



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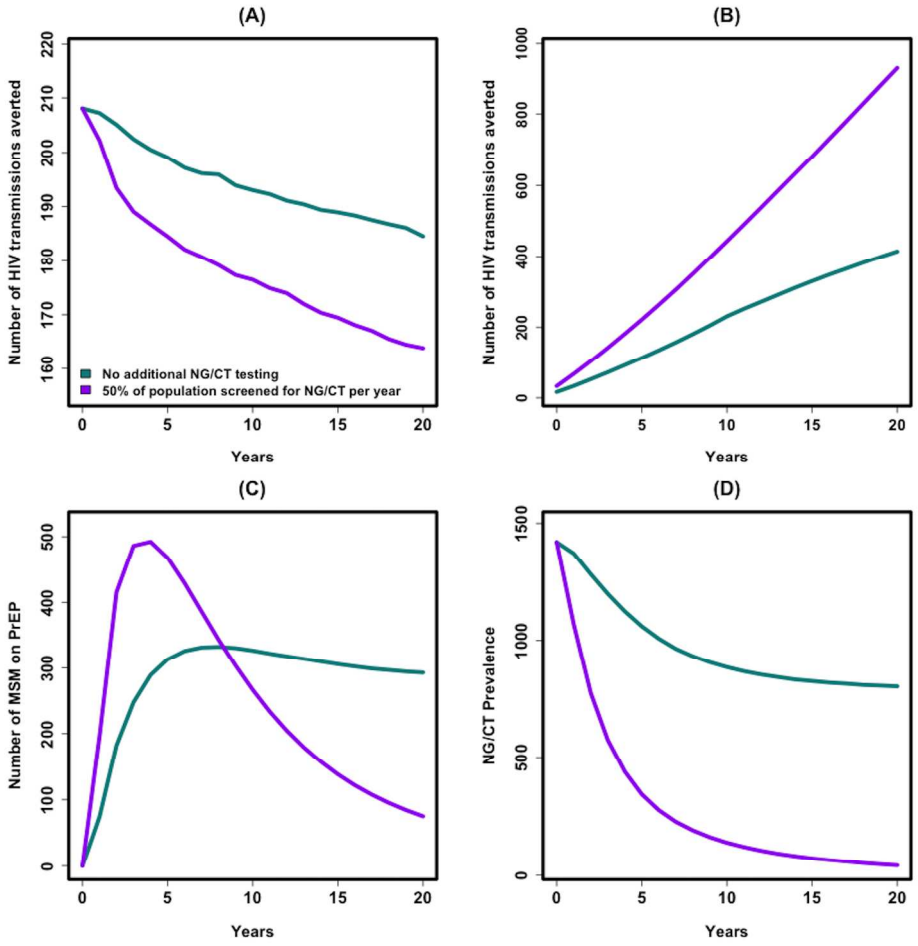

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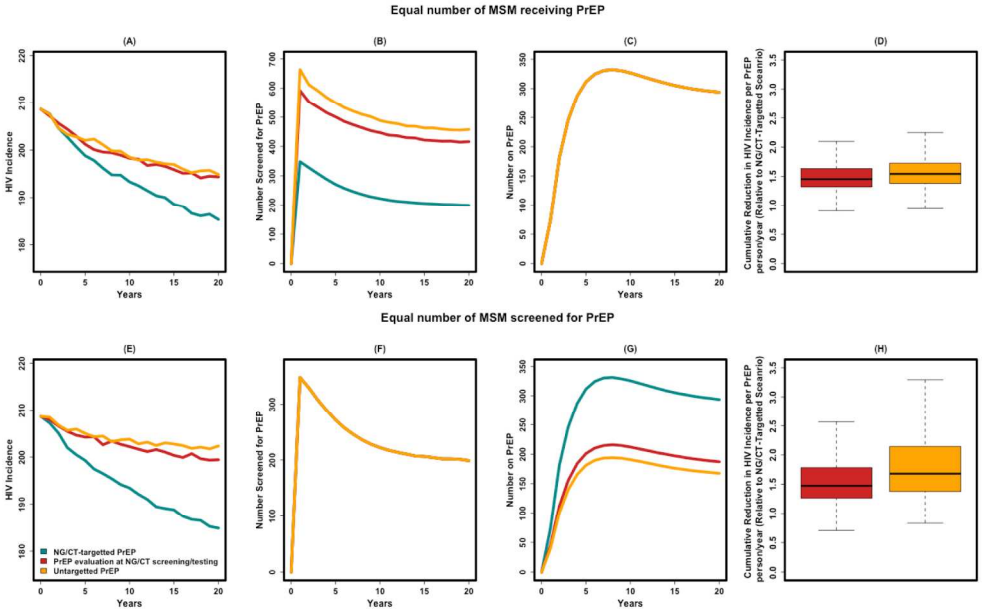

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SUPPLEMENTARY MATERIAL

Title: Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study

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1 HIV SIMULATION MODEL DESIGN

Overview

Our agent-based simulation model of the HIV epidemic among MSM in Baltimore City is structured as a collection of modules that govern population demographics, sexual partnerships, the epidemiological aspects of disease with regard to HIV natural history, cascade of care and transmission. Each "agent" represents a single MSM in Baltimore City, characterized by age, race, and place of residence, and the model is evaluated in a series of one-week time steps. The HIV natural history module characterizes the progression of HIV among infected individuals according to disease stage. Each stage is associated with a different per-act risk of HIV transmission, and disease progression from stage 2 to stage 3 can be prevented (and/or reversed) by provision of ART. The HIV cascade of care estimates probabilities of HIV testing, linkage to care, disengagement/re-engagement, and ART provision/viral suppression at each time step. The sexual network and transmission module create and modify the population's sexual networks (as a series of stable and casual partnerships) at each step, modeling HIV transmission as a per-act probability among serodiscordant partnerships according to frequency and safety of sex act, HIV stage of the infected partner, and ART/PrEP use. Sexual partnerships are modeled as assortative according to age, race, and location of residence. Finally, the population demographic module accounts for aging, death, and birth processes.

1.1 Population Demographic Module

This module characterizes the initial population structure and governs various procedures for aging, death, and birth at end of each simulated year. We model the population of MSM in Baltimore City between the ages of 15 to 75. The population is structured as a collection of population groups corresponding to Baltimore's Community Statistical Areas (CSA) [1]. CSAs are clusters of neighborhoods and are organized according to census tract boundaries, which are consistent statistical boundaries. In some cases, CSA boundaries may cross neighborhood boundaries. There are 55 CSAs in Baltimore City. Neighborhood lines often do not fall along CSA boundaries, but CSAs are representations of the conditions occurring within those particular neighborhoods. Simulated population groups are characterized with regard to their geographical location (CSA of residence) and racial structure (black and non-black). We do not model the spatial distribution of individuals within each CSA; rather geographical assignments are made at the CSA level by assigning the corresponding CSA-center coordinates to each MSM living in that CSA. The initial HIV distribution across CSAs is estimated according to publicly available data from Maryland's Department of Health and Mental Hygiene (MDHMH) [2].

Individuals age with the simulation clock (years) and exit the model according to an age-specific natural mortality rate [3], or by reaching the age of 75, or via an additional mortality rate associated with HIV infection. To maintain the initial population decomposition without disturbing the CSA structures, we model a natural birth process at the CSA level for replenishing the population size over time. The birth process is modeled via a non-stationary Poisson process tuned to maintain each CSA's population at a constant mean over time. Newborns enter the MSM population at age of 15 to 20 years old and follow the corresponding racial structure of the CSA of residence.

Using the current estimate of Baltimore City male population (approximately 287,000) who are 15 year or older in age (about 232,000), and estimated percentage of adult MSMs in each racial group (7.5% of non-black males and 5.8% of black males [4]), we estimate the size of Baltimore City's MSM population at approximately 15,000.

Forming CSA-groups: To determine groupings of similar CSAs, we first ranked the CSAs according to the median income level and racial makeup based on available information from Baltimore City census [1].

For simplicity, levels of income (Figure S1-left panel) and proportion of population that is Black/African-American (Figure S1-right panel) were coded into values from 1 to 5 (representative of various shades in Figure S1), and two values were assigned to each CSA. For example, CSA "Midtown" (T-shaped in the center of the map) was assigned a rank of 3 for median household income, and 2 for the proportion of population that is Black/African-American.

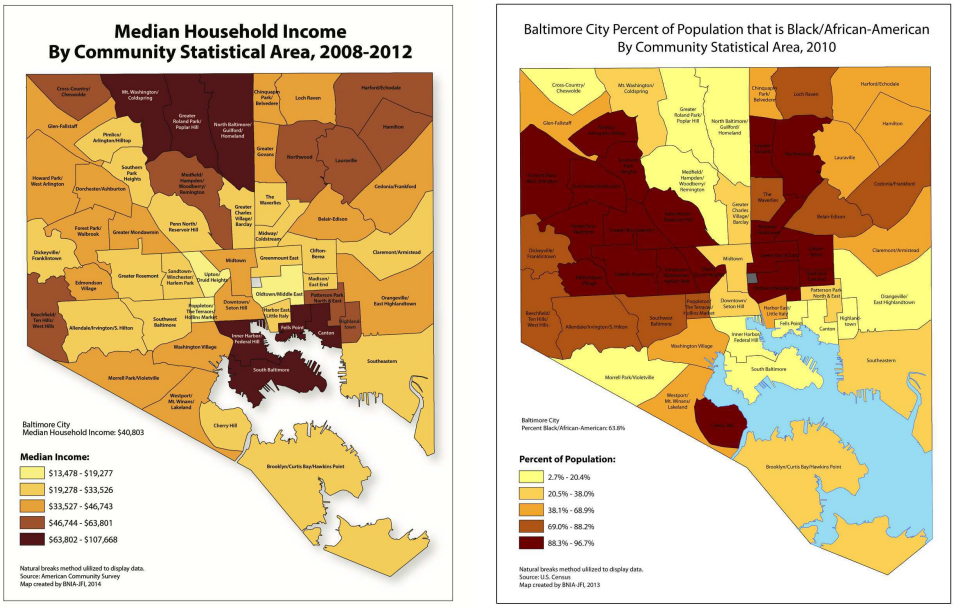

Figure S1: Baltimore City CSA ranking according to median income and racial structure [1].

We defined a CSA-group to include a number of neighboring CSAs (sharing a border) with at most a one-level difference in their ranked levels of income and racial makeup. To determine the CSA-groups throughout the city, we implemented a random search mechanism using a branch and bound logic. The search was started from a random CSA and branched through all neighboring CSAs to determine how many could belong to the same CSA-group. The search was bounded by those CSAs representing a difference of more than one level in ranked income and racial makeup but continued for those CSAs that belonged to the same group and branched further to test their other neighbors, until it was bounded in all directions. At the end of each iteration, a list of CSAs grouped by relative similarity across the whole city was generated. This search was repeated many times and the CSA groups that were most likely (i.e., high frequency) to form were identified. Overlapping CSA-groups were further checked for the possibility of combination into a single group. Finally, we had 16 CSA-groups across Baltimore City, representing geographically approximate neighborhoods with similar levels of income and racial makeup (Figure S2). Using CSA numbers as identifiers, a complete list of CSA groups is provided in Table S1.

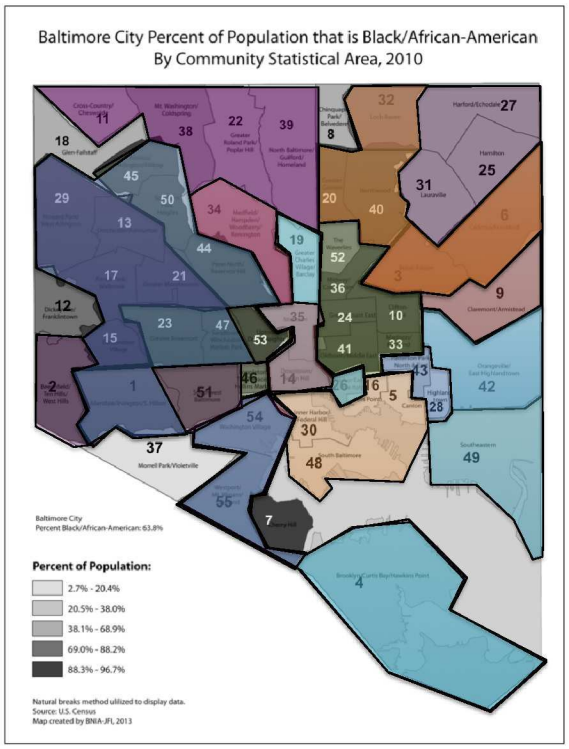

Figure S2: Baltimore City CSA ID's and CSA groups structure. Each CSA group is marked with a closed border in a different color. Some groups overlap such that some CSAs belong to more than one group. Some CSAs may not belong to any groups and are considered by themselves.

Table S1: List of CSA group and member CSAs

Group ID	CSA members
1	11 22 34 38 39
2	3 6 9
3	28 42 43
4	3 6 8 25 27 31 32
5	42 49
6	10 24 33 36 41 52
7	5 16 28 30 43 48
8	3 6 20 32 40
9	4 14 19 26 35 54 55
10	14 34 35
11	1 23 44 45 46 47 50 51 53
12	1 51 54 55
13	4 14 19 26 35 54 55
14	2 13 15 17 21 29
15	1 12 13 15 17 21 23 29 44 45 47 50 51
16	3 6 10 20 24 33 36 52

1.2 Sexual Partnership Module

This module governs the network of sexual partnerships and runs in discrete time steps, each representing a week. Following previous models of sexual contact networks [5–7], we conceptualize the network of sexual partnerships at an individual level (with regard to age, race, geography, sexual positioning, etc.) and calibrate the simulation parameters using local behavioral surveillance data available through the BESURE study, the Baltimore City branch of the National HIV Behavioral Surveillance System (NHBS) [8]. BESURE is a CDC funded project operated by the Maryland Department of Health and Mental Hygiene and the Johns Hopkins Bloomberg School of Public Health. Starting in 2004, BESURE has conducted four venue-based sampling surveys among Baltimore's MSM (Table S2). We use this data to extract information on several behavioral parameters at the individual level (e.g., preference toward using condoms in each type of partnerships) that will be directly implemented at the agent level, as well as population-level estimates for calibrating the unknown variables (e.g., frequency of the annual sexual partnerships). For those measures available across multiple BESURE waves, we use a pooled estimate of the reported values.

Table S2: Survey methods and sample characteristics, BESURE MSM 2004-2010

	Wave 1	Wave 2	Wave 3	Wave 4
Date	June 04-April 05	Jul-Oct 2008	Aug-Dec 2011	Jun-Dec 2014
Total MSM	645	448	404	455
HIV prevalence	37.7%	37.5%	42.6%	30.6%
Proportion of HIV that was unrecognized	58.4%	78.4%	67.3%	33.1%

1.3 Partnership types and formation

We model two types of partnerships representing long-term "stable" and short-term "casual" partnerships. Stable partnerships can last for several years [5], while casual partnerships will only last a single time step (one week) in the model. We assume that individuals can have multiple casual partnerships from one week to the next [9], but they can only engage in a maximum of one stable and one casual partnership at any time step. All partnerships are updated at the end of each simulation week, and those partnerships reaching their pre-specified duration will be dissolved. At the beginning of each following week, individuals' tendency to engage in a new partnership is evaluated and "eligible" individuals will select the geographical search domain for meeting their future partners based on their location of residence. Once the partnership domains are established for all eligible MSM, individuals will follow a search mechanism based on a combination of race- and age-dependent mixing patterns, as well as sexual role preference, to select their future partner from the pool of eligible people at the selected domain. This process is modeled in 3 steps:

Step 1. Evaluating an individual's probability of engaging in a new partnership

Each individual's likelihood of engaging in a new partnership is modeled as a function of his age, the level of sexual activity, and current partnership status.

In accordance with the heterogeneous frequency of reported partnerships by age, we define a partnership coefficient for modeling the likelihood of engaging in new partnerships as a function of individual's age ($c_{Part|Age}$) (assumed to be a fixed level for each age group).

Furthermore, we model the heterogeneous level of sexual activity among MSM by assuming three sexual activity classes, each corresponding to a lifetime level of engagement in casual partnerships. An individual's sexual activity class (c_{SA}) is determined at the time of birth (entry to population) and remains fixed throughout his life (though within each sexual activity class, the actual level of partnership formation changes with age – for example, partnership formation declines with older age in all three classes). This attribute represents a combination of factors determining an individual's tendency for engaging in casual partnerships, reflecting the diversity of sexual activity seen in real populations. For simplicity, we assume equal probability of membership to each sexual activity class at the population level, and we calibrate the corresponding level of sexual activities in each class to provide the reported frequency of annual partnerships from data.

Finally, we model each agent's tendency for engaging in casual and stable partnerships at any point of time via two additional parameters (p_{Csl} and p_{Stb}) at the agent-level, and also define the conditional likelihood of engaging in new casual partnerships concurrent to an existing stable partnership via a separate parameter ($p_{Csl|Stb}$).

With these definitions, an individual's likelihood of engaging in a new stable (P_{new_stb}) or casual (P_{new_csl}) partnership at each timestep can be estimated as follow:

$$P_{new\_stb} = p_{Stb} \times c_{Part|Age}$$

$$P_{new\_csl} = p_{Csl} \times p^{*}_{Csl|Stb} \times c_{Part|Age} \times c_{SA}$$

$$p^{*}_{Csl|Stb} = \begin{cases} p_{Csl|Stb} & number\ of\ stable\ partnerships > 0 \\ 1 & o.w. \end{cases}$$

At each time step, an individual's likelihood for engaging in a new partnership is evaluated and eligible individuals are added to the pool of available people at their CSA of residence to find their potential partners in the next steps.

Step 2. Choosing the partnership domain

The partnership domain is determined according to a discrete mixing structure at the CSA level (Figure S3). In order to model the spatial mixing patterns across the population and among various subgroups, we first define sets of "neighboring" CSA groups with regard to geographical proximity and similar socioeconomic status (income levels) and racial structure [1]. Upon seeking a new partnership, an individual's search scope (for choosing the new partner) is determined according to a discrete geographical mixing probability (*pGM*) for selecting one's own CSA (p_0), a random neighboring CSA in the same CSA group (p_1) or non-neighbor CSA (p_2). The geographical mixing probability (*pGM=*(p_0, p_1, p_2)) represents a measure of geographical/socioeconomic clustering in the network of partnerships, where *pGM*=(1,0,0) translates into an isolated mixing pattern for partnership only with individuals in one's CSA of residence, and *pGM*=(0.33,0.33,0.33) translates into a homogeneous mixing structure across the entire population. In our initial analysis, we calibrate the geographical mixing likelihoods at *pGM* = (0.5, 0.3, 0.2) according to available estimates from [10].

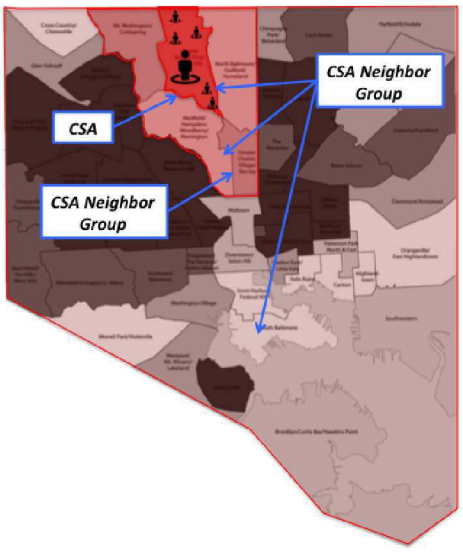

Figure S3: Partnership search domains. Individuals can choose their future partner from their own CSA or a random CSA within or outside their neighbor group.

Step 3. Modeling the search mechanism within the partnership domain

Once the partnership domain is established, individuals follow a search mechanism for finding their new partners from the pool of eligible members in the selected domain. The probability of partnership between two people is evaluated according to an age- and race-mixing structure, as well as sexual role preference. Assuming independent patterns of age- and race-specific mixing, the age-race mixing probability is computed as the product of age-mixing and race-mixing probabilities for each pair of potential partners. A random search mechanism is implemented to evaluate the probability of partnership with each potential partner in the selected domain until a successful match is found or the entire domain is searched. Potential partners are also checked for their compatibility with regard to sexual role and incompatible pairs (e.g., receptive-receptive or insertive-insertive) are dismissed. Upon a successful match, a new partnership is formed for both parties, who are then excluded from the pool of eligible partners for other individuals.

1.3.1 Age-Specific Mixing

Age-specific mixing is modeled based on absolute difference in the square root (ADSR) of men's ages [5]. The ADSR provides a closer fit to the observed age-mixing matrix than does age directly. This statistic also has the desirable property that the same absolute difference in age becomes less important over time. Using data on participant's age and their last male partner's age from BESURE, we estimate the reported ADSR level for main/casual partnerships ($ADSR_{partnership}$) as shown in Table S3. The probability of age-mixing between person p and q for each partnership type ($pAgeMixing$) is then computed as a function of partners' age and the target ADSR level for each type of partnerships. Figure S4-A and S4-B compare the simulated distribution of ADSR values among casual and stable partnerships in the baseline simulation model.

$$pAgeMixing = \text{Min}(ADSR_{p,q,2} \times ADSR_{partnership} - ADSR_{p,q}) / ADSR_{partnership}$$

where

$$ADSR_{p,q} = \left| \sqrt{p_{age}} - \sqrt{q_{age}} \right|$$

$$ADSR_{partnership} = (ADSR_{Stb}, ADSR_{Csl})$$

Table S3: Estimates of reported ADSR for Stable/Casual partnerships in BESURE. Estimates are made based on the participant's age and their last male partner's age.

BESURE Waves:	$ADSR_{Stb}$ (Number of reported partnerships)	$ADSR_{Csl}$ (Number of reported partnerships)
Wave 2	0.62 (66)	0.72 (75)
Wave 3	0.68 (71)	0.73 (87)
Wave 4	0.51 (62)	0.76 (77)
Average estimate	**0.6**	**0.74**

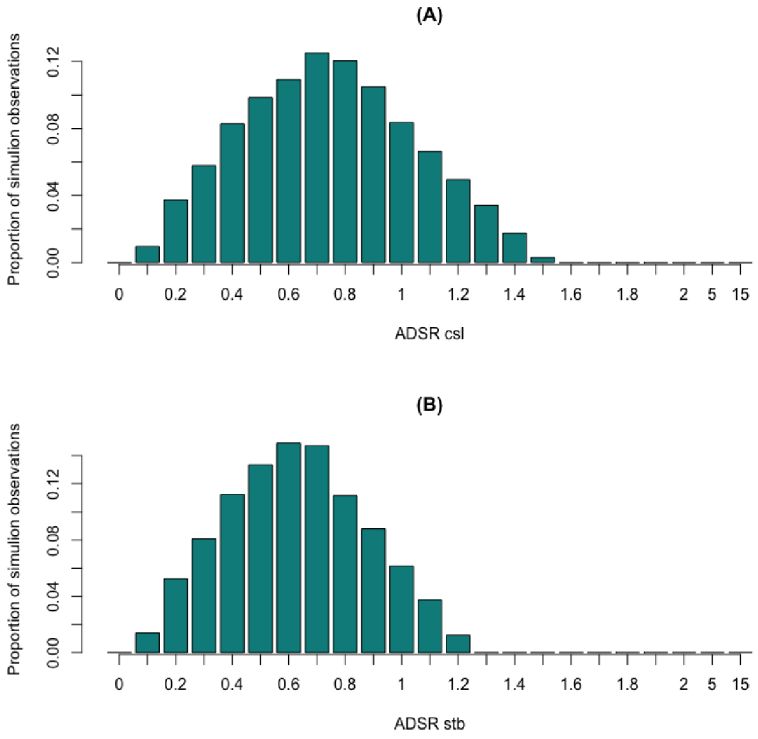

Figure S4: Distribution of ADSR in simulated casual (Panel A) and stable (Panel B) partnerships at the baseline model.

1.3.2 Race-Mixing

We model the probability of partnership between MSM of the same sex by estimating the reported ratio of same-sex partnerships for Black MSM at 90% and for White MSM at 75% through BESURE data.

1.3.3 Sexual Role Preference

Each MSM is assigned an individual sexual role preference (insertive only, receptive only, versatile) at the time of birth (entry to population). The sexual role preferences prohibit the partnerships between two men who are insertive only or those who are receptive only (allowing for 5 partnership configuration). The type of sexual act in partnerships between two versatile men is determined via uniform probability distribution between 0 and 1 (e.g., 50% chance of insertive/receptive act for each man) and will be updated at each time step for their active partnerships. Using data from BESURE, we estimate the proportions of population that fall within each category at 42% insertive-only, 26% receptive-only, and 32% versatile.

1.4 HIV Epidemiological Module

This module governs various aspects of HIV natural history and cascade of care, and it is updated at the end of each time step (week).

1.4.1 HIV Natural History

Upon a successful HIV transmission event, individuals experience a gradual increase in viral load (VL) and move through various stages of disease (Figure 1, main manuscript). We consider three disease stages in absence of ART, including stage 1 (CD4 count > 500 cells/ µL), stage 2 (CD4 count between 200-500 cells/ µL) and stage 3 (CD4 count <200 cells/ µL). Each disease stage is characterized with regard to duration of disease (as a crude measure of CD4 decline over time), mean VL level (determining the level of infectiousness) as well as the HIV mortality rate. In this model, we do not model the dynamics in the number of CD4 counts directly, but rather use the defined disease stages as surrogate marker of VL and mortality level for all HIV+ individuals.

1.4.2 HIV Cascade of Care

The continuum of care for infected individuals is modeled in five levels corresponding to those 1) unaware of their HIV infection, 2) diagnosed with HIV but not linked to care, 3) linked to care but not engaged in care, 4) engaged in care and on ART, and 5) engaged in care but not taking ART (Figure 1, main manuscript).

HIV-positive individuals are subject to a probability of screening for HIV at the beginning of each week. Upon diagnosis with HIV, individuals experience a fixed likelihood of linking to care over the following weeks. Once linked to care, individuals are assumed to engage in HIV care and start ART immediately. Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 24 weeks after ART initiation; rarely, in some patients it may take longer. Taking ART will further lower the disease mortality rate at each disease stage to a certain degree [11–13]. We assume that individuals starting ART through stage 3 (with CD4 count < 200 cells/ µL) will continue to experience the stage 3 mortality level (adjusted with ART reduction factor) for one year before reverting back to stage 2 (and experiencing stage 2 mortality level adjusted with ART reduction factor).

Those on ART can become non-adherent to treatment over time and/or become disengaged in care[1]. These individuals are subject to a weekly probability of reengagement in care and reinitiating ART in the future, but cannot reinitiate ART for 6 months after discontinuation [14]. Once off ART, individuals are assumed to lose viral suppression immediately and to experience a rapid decline in their CD4 counts. For simplicity, we assume that the effect of ART on CD4 count levels is maintained for one year following discontinuation (unless the agent was not previously on ART for a year, in which case the duration of ART is used) – and we also add this amount of time to the individual's "clock" of progression for HIV disease. Thus, for example, an individual starting ART in stage 2 and taking ART for 6 months before discontinuation will go back to stage 2, but the time until progression to stage 3 is prolonged by 6 additional months. We further assume that those starting ART in stage 1 will return to stage 2 if they discontinue treatment, and those beginning ART through stage 3 can revert to stage 2 or stage 3 depending on the duration of treatment.

1.5 HIV Transmission module

HIV transmission is evaluated for all active partnerships between HIV-positive individuals and susceptible partners at the end of each week. The probability of transmission is modeled as a function of an infected partner's infectiousness for transmitting HIV, the immunity of the negative partner toward transmission with HIV (through PrEP), potential protection through condom use, and an additional coefficient tuning the overall probability of transmission. HIV infectiousness is modeled as a function of an individual's VL corresponding to his disease stage and care status, as noted in Table 1 of the main manuscript. An individual's immunity to infection is modeled as a function of PrEP use and adherence, ranging from 0 (in absence of PrEP) to 1 (full adherence to PrEP). The probabilities of condom use in casual and stable partnerships are estimated based on reported levels through BESURE (Table S4). Finally, the transmission coefficient captures the baseline probability of HIV transmission per contact and is calibrated to reflect disease prevalence at equilibrium.

Table S4: Reported frequency of condom use in stable and casual partnerships from BESURE.

	Never	Part-time	The whole time
Stable partnership	0.45	0.55	0
Casual partnership	0.47	0.12	0.4

With these definitions, the weekly likelihood of HIV transmission through an active sexual contact is estimated as follow:

[1] At ART discontinuation, if the person has started ART during Chronic disease, they are assumed to return to stage 2 with the same level of infectiousness and will be subjected to the corresponding mortality level. The duration of stage 2 is assumed to be the lesser of the preceding duration of ART (before loss to follow-up) or one year. If the person had started ART during stage 3, they will can return to stage 2 or stage 3 depending on the duration of treatment:

- If duration of treatment is smaller than the time spent in stage 3, agents return to stage 3 with the same level of infectiousness and mortality. The duration of stage 3 is extended for the duration of treatment up to one year.
- If duration of treatment is greater than the time spent in stage 3, agents return to stage 2. The duration of stage 2 will be expanded for the duration of treatment minus time spent in stage 3.

$$Ptrans(\mathrm{X},\mathrm{Y},\mathrm{Q}) = C \times X_{Inf} \times Y_{sus} \times (1 - pCondumUse(Q) \times cCondomEffectiveness) \times Y_{sexualPositionCoef}$$

where

Ptrans(*X,Y,Q*): Per week probability of transmission from person *X* (infected) to *Y* (susceptible) in a partnership type Q (stable, casual)

C: Simulation coefficient

Y_{Inf}: Person Y's infectiousness

X_{Sus}: Person *X's susceptibility* toward infection

pCondomUse(*Q*): Probability of using condom in partnership type Q

cCondomEffectiveness: condom effectiveness in reducing the risk of transmission

$Y_{sexualPositionCoef}$: Person Y's increased probability of transmission based on sexual positioning

1.6 GC Epidemiological Module

We consider NG/CT as a 'SIS'-type disease; specifically, individuals become infectious after an initial infection and remain infectious until treatment or spontaneous resolution, at which time they become immediately susceptible to recurrent infection. We assume that NG/CT is spread through sexual (genital-genital, genital-rectal, genital-oral, or oral-rectal) contact, and that infection may be either symptomatic or asymptomatic. Symptomatic individuals experience a fixed probability of seeking care in each week. We include only those care-seeking episodes that would trigger a clinical decision to test for NG/CT at the appropriate site and would result in treatment if the test were positive; other care-seeking episodes (whether for unrelated conditions [e.g., upper respiratory infections] or for symptoms of NG/CT that are either not recognized or would not result in treatment even if the test were positive) are ignored. We assume that individuals remain infectious during the week of treatment and one week thereafter [15–17]. In addition to this symptomatic testing behavior, all MSM (whether infected with NG/CT or not) can further undergo regular screening for NG/CT (i.e., in the absence of symptoms) according to CDC recommended criteria for MSM based on their HIV status, PrEP status, and STI history [18]. The duration of untreated disease (*d*) is based on literature estimates, and the weekly probability of spontaneous resolution is set to inverse of this duration (1/*d*).

1.6.1 Site of infection

We differentiate three types of NG/CT infections based on the site of infection as Urethral, Rectal or Pharyngeal infections. Given the low degree of overlap for simultaneous infections in multiple sites, and the higher likelihood of symptomatic disease in urethral infections for those co-infected with rectal and pharyngeal infections, we only allow for a single-site NG/CT infection in each individual and will exclude the possibility of simultaneous infections in various sites (allowing for no reinfection while the original infection lasts). Each type of infection is further associated with a specific likelihood of developing symptomatic disease (Table 1 of the main manuscript). Among HIV- individuals, a rectal/urethral NG/CT

can increase the transmissibility of HIV to sexual contacts among HIV infected MSM and also increase the susceptibility for HIV acquisition among HIV uninfected MSM.

1.6.2 NG/CT Transmission dynamics

NG/CT-infected individuals can transmit the disease to other individuals through exiting network of sexual contacts (previously built and calibrated for the HIV model). Due to complications in conceptualizing all various pathways for transmission of disease from one site to another with regard to different types of sex acts, unknown level of individuals' preferences for each sexual role and the degree of versatility to change this role in each partnership, in addition to the lack of data informing the risk of NG/CT infection through each mode of transmission, we adopt a simplifying assumption to combine various modes of transmission for all types of infections through a single transmission event modeled over each active sexual contact between an infected and uninfected MSM at each time step. Upon transmission with NG/CT, the clinical site of the recipient infection is randomly assigned in such a way as to replicate the relative incidence of infection at each site as estimated from local surveillance report in Baltimore City (see Table 1 of the main manuscript).

1.6.3 Computing the probability of presenting to STI care

MSM may present to HIV/STI care providers (e.g., STD clinics, community health centers, HIV counseling programs) for a variety of reasons, and get tested for HIV and other STIs. We model visits for STI screening as a fixed weekly probability that reflects an individual's age-group (modeled in 12 classes for MSM age 15 to 75) and sexual activity level (modeled in 3 classes of sexual activity), such that younger MSM with higher propensity of partnerships experience a higher likelihood of visits [19,20].

We let *S* represent the individuals' sexual activity class (values ranging from 1 to 3 representing low-, medium- and high-activity classes) and we let A represent the individual's age-group (values ranging from 1 to 12 representing age groups of 5 years each: [15,19], [20-24], …, [70,75]). Finally, according to previous assumptions for lower level of access to HIV care among Black MSM compared to White MSM in the baseline simulation model, we modify the probability of accessing to STI care (*pAccessCare*) by race (R) set at 50% for Black MSM relative to White MSM [21]. Given these assumptions, an individual's probability of presenting to STI care (*PPSC*) at each week is computed as follow:

$$PPSC\ (\mathrm{S},\mathrm{A},\mathrm{R}) = {}^{(13-\mathrm{A})}/_{12} \times {}^{(\mathrm{S})}/_{3} \times pAccessCare(\mathrm{R}) \times C$$

where C is the fixed coefficient for fine-tuning the probability of presenting to STI care.

1.7 PrEP module

PrEP Eligibility criteria: Our primary outcome for the current analysis is the projected incidence of HIV after 20 years of delivering PrEP to MSM in Baltimore City. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the added benefit of targeting PrEP at individuals diagnosed with NG/CT. In all three scenarios, indication for PrEP use (eligibility) is considered in accordance with CDC recommendations [22] and Baltimore City's PrEP guidelines [23].

The CDC guidelines for PrEP use among MSM use the following criteria as indications for PrEP: sexually active HIV negative adult MSM who are not in a monogamous partnership with an HIV-negative male partner and who in the last 6 months: report any condomless anal sex, have any STI reported or diagnosed,

or report having an ongoing sex partner with HIV [22]. The PrEP guidelines in Baltimore City further suggest that all HIV negative MSM who 1) may not have access to condom or always ask a partner to use a condom, 2) are diagnosed with a STI in the last 6 months, 3) are in a serodiscordant relationship with a HIV-infected partner (who may or may not be on HIV treatment), 4) are unsure of HIV-status of their sexual partner, or 5) inject drugs or are in a sexual partnership with a person who inject drugs should consider PrEP. As such, we modelled the criteria for PrEP eligibility among MSM to include HIV-negative MSM who are diagnosed with NG/CT in the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual partnership in the last 6 months.

2 SIMULATION CALIBRATION

Individual-level parameters in our models fall into two categories: "fixed" parameters estimated based on available literature or data, and "variable" parameters that are unknown and will be calibrated based on epidemiological setting. Fixed (known) parameters include those associated with the natural history of HIV (such as viral load levels in each disease stage) and those defining behavioral characteristics (e.g., likelihood of condom use). Variable parameters include descriptors of HIV and NG/CT transmission and care that are defined at the individual-level and will be calibrated to provide the corresponding calibration targets (at the population-level) from Baltimore City (e.g., tuning the individual's probability of presenting to care for HIV screening to provide the target proportion of infected population diagnosed in Baltimore City). Table 1 in the main manuscript includes a list of main calibration targets for HIV and NG/CT modules.

2.1 Calibration Targets

2.1.1 HIV prevalence and continuum of care

Using the latest report of public HIV surveillance data from Baltimore City (year 2012) [2], we estimate the prevalence of HIV among MSM at a total of 3329 people, which corresponds to a prevalence of 22% in our simulated population. Furthermore, we estimate the reported proportion of HIV-infected MSM in each step of the cascade at 86% for those diagnosed but not linked to care, 62% for those linked to care but not engaged, 50% for those engaged but not on ART, 39% for those on ART but not virally suppressed and finally 27% for those virally suppressed.

2.1.2 NG/CT incidence

In this section, we provide details of our estimation procedure for NG/CT incidence using data made available to us through several sources including 1) the gonorrhoea Surveillance dataset, 2) STD Surveillance Network, and 3) BCHD facility dataset in Baltimore City.

Estimating the annual diagnosis of gonorrhoea infection in Baltimore City: The gonorrhoea Surveillance dataset includes all males residing in Baltimore City who were reported to the Baltimore City Health Department for infection with gonorrhoea at one or more anatomic site, regardless of sex partner gender, beginning with cases diagnosed on 1/1/09 and ending with cases reported through 5/31/16. Due to changes in testing technology, we only consider data from 2011 and later for estimating gonorrhoea diagnosis as that is when the STD clinics started using NAATs for extragenital swabs (due to the lab becoming validated for this) which is more in line with practices moving forward. We further restrict the data to the end of 2015, to cover the annual number of diagnosis in each full year (Table S5). We further

analyze this data by reported site of infection and estimate the range of reported gonorrhoea diagnosis in each body site (Table S6).

Table S5: Annual number of reported gonorrhoea diagnosis among men in Baltimore City.

	2011	2012	2013	2014	2015
Gonorrhoea diagnosis	1139	901	1052	1083	1297

Table S6: Annual gonorrhoea diagnosis among men by site of infection in Baltimore City.

Site of infection	Lower bound	Upper bound
Urethral	681	1026
Rectal	46	83
Pharyngeal	58	151

Adjusting for MSM risk group: The surveillance dataset does not include information on gender of sex partners for all persons diagnosed with gonorrhoea infection. This information is however available for a subset of population through STD Surveillance Network (SSuN). SSuN attendees are randomly selected from MSM diagnosed with gonorrhoea who will then agree to complete a SSuN interview. Within this group, 26% to 30% of all male patients identified themselves as MSM in Baltimore City.

Adjusting for non-overlapping Chlamydia infections: The BCHD facility dataset provides information on diagnosis of gonorrhoea or chlamydia infection among all male patients visiting the two STD clinics in Baltimore City. This data is further stratified for MSM by including men who reported male sex partners in the past 3 months OR self-identified as gay or bisexual. For patients who visited the clinic multiple times, if he was classified as MSM at any visit, we included all his clinic visits. The dataset provides information on all episodes of visit and diagnosis with gonorrhoea or chlamydia infection among these men. Based on the reported number of diagnosis, we estimate the proportion of diagnosed chlamydia infection that did not overlap with gonorrhoea infection relative to overall number of gonorrhoea diagnosis at 40%, and use this value to adjust the annual number of gonorrhoea diagnosis among MSM to include non-overlapping chlamydia infections as well. This estimate also agrees with the reported level of chlamydia infection relative gonorrhoea infection in Baltimore City through the STD Surveillance Network (SSuN) 2013 [24].

Adjusting for proportion of symptomatic cases not seeking care: In order to derive the true incidence of disease from the current estimates of the number diagnosis, we further adjust our estimate to account for the proportion of symptomatic cases not seeking care. Based on literature, we estimate that approximately 60% symptomatic population may not seek direct care for their disease (56% for Urethral infection, 60% for Rectal and 70% for Pharyngeal infection) [25], and inflate the number of symptomatic cases in our sample (approximately 78% of sample) by 250% to account for these cases.

Adjusting for the number of asymptomatic infection: Given the restrictions in capturing the underlying level of asymptomatic disease from the estimated of NG/CT diagnosis, we rely on our estimate of the symptomatic NG/CT incidence, and assume that each episode of NG/CT infection is associated with a 74% likelihood of symptomatic infection for urethral, 20% for Rectal, and 10% for Pharyngeal disease [25–27].

Based on this assumption, we derive the estimate for annual incidence of NG/CT among MSM by site of infection as follow:

- Incidence of urethral infection [725 – 1135] Person/year
- Incidence of rectal infection [144 – 259] Person/year
- Incidence of pharyngeal infection [327 – 852] Person/year

Challenges in interpreting local estimates: Despite general expectations, our estimated ratio of rectal/pharyngeal to urethral infections is very small. This pattern does not agree with the previously reported prevalence of extragenital relative to genital NG/CT in different populations that estimate the average prevalence ratio of rectal to urethral infections at 4.1 (ranging from 2.43 to 6.23) and pharyngeal to urethral infections at 1.5 (ranging from 1.35 to 1.71) [28–30]. In a previous analysis of SSuN data, researcher reported a similarly low proportion of extragenital to genital NG/CT infections among MSM attending STD clinics [31], and attributed it to low rate of extragenital NG/CT screening at STD clinics that results in missing those infections [32].

Given that our estimates of the genital and extragenital NG/CT infections based on local datasets from Baltimore City are more in line with the observed trends in the SSuN data, we believe that the same pattern of underestimation is evident for the true incidence of extragenital NG/CT infection in this population. In order to fix this problem, we chose to rely on the estimated incidence of genital (urethral) NG/CT infection from the surveillance dataset in Baltimore City (assuming appropriate level of genital-site testing/screening and reporting), and to estimate the incidence of rectal and pharyngeal infections by applying the reported prevalence ratio of each infection site relative to urethral infection.

Estimating the incidence of rectal and pharyngeal infection: We assume that diagnosed NG/CT will be treated very rapidly, such that the relative duration of disease is driven by the proportion of infections for which people are not treated - whether because they are asymptomatic, symptoms are not sufficient to drive care-seeking, or the clinical presentation (e.g., sore throat) does not prompt testing or treatment for NG/CT. Screening is assumed to have relatively little impact on the *relative* duration of infection (i.e., screening can occur, but it does not pick up so many more prevalent urethral infections than pharyngeal infections, for example, that it drives the ratio of disease duration in the population to a significant degree). We further assume that the asymptomatic disease is likely to go undetected and therefore 26% of urethral infections, as well as 80% of rectal and 90% of pharyngeal infections will go untreated [25–27].

Based on these assumptions, we derive the incidence ratios based on prevalence ratios as follow:

- Incidence ratio of rectal to urethral disease: 4.08 (prevalence ratio) * 0.26 /0.8 (proportion of untreated cases) = 1.33
- Incidence ratio of pharyngeal to urethral disease: 1.5 (prevalence ratio) * 0.26 /0.9 (proportion of untreated cases) = 0.43

Using the estimated incidence ratios, we estimate the incidence of rectal and pharyngeal NG/CT among MSM as follow:

- Incidence of urethral NG/CT among Baltimore's MSM: [735-1135] Person/year
- Incidence of rectal NG/CT among Baltimore's MSM: [998-1505] Person/year
- Incidence of pharyngeal NG/CT among Baltimore's MSM: [326-492] Person/year

2.2 Calibration procedure

Upon collection of all individual-level data and incorporation into the model (fixed parameters), we calibrated the model as a whole against population-level targets (above) to ensure that the model provides realistic outputs. This was done via a random search mechanism to find the best combination of parameter values that minimizes the observed difference between simulated outputs and the calibration targets.

2.2.1 Burn-in period

The model starts from a randomly generated population of MSM with no active partnership at time zero with a randomly assigned pattern of HIV infection (randomly according to age, race and location of residence). In order to create a realistic pattern of sexual partnerships with age, we allowed the original population to age and evolve for at least one generation before reaching a stable level of HIV incidence in the absence of PrEP – thus generating a full burn-in period of 100 years (a decision made on an a-priori basis).

2.3 Calibrating results

BESURE surveys (2004 – 2014) provide the main source of local information available on MSM network of partnerships in Baltimore. The data include aggregate information for the reported number of sexual partners (by age-group) and type of those partnerships in the last 12 months. Assuming a fixed mixing structure over time, we use this information to calibrate the individual-level likelihood of engaging in a stable or casual partnership at each simulated time step (week). We use the coefficients of sexual-activity to calibrate the right and left tail of the partnership frequency distribution (for those MSM reporting 0 or more than 5 partners in a given year). The partnership calibration results are summarized in Figure S5-A and S5-B.

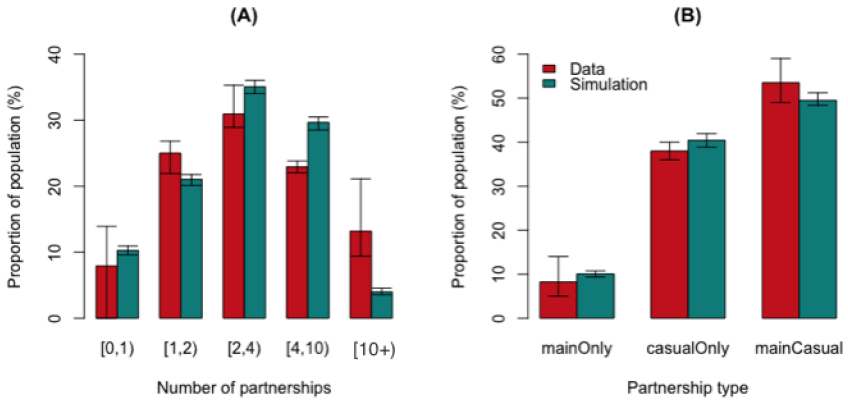

Figure S5: Model calibration to partnership data. Shown are the mean values of 200 simulations (in green) compared against empirical data (in red). The error bars around simulated values represent the 95% uncertainty range of observations around each simulated measure, and the error bars around the data represent the range of annual observations through the 4 BESURE surveys from 2004 to 2014.

Using the population-level targets for annual diagnosis and incidence of NG/CT as well as HIV prevalence and cascade of care (section 3.1), we calibrate the simulation model to provide these outcomes within an acceptable range (Figure S6 A through D).

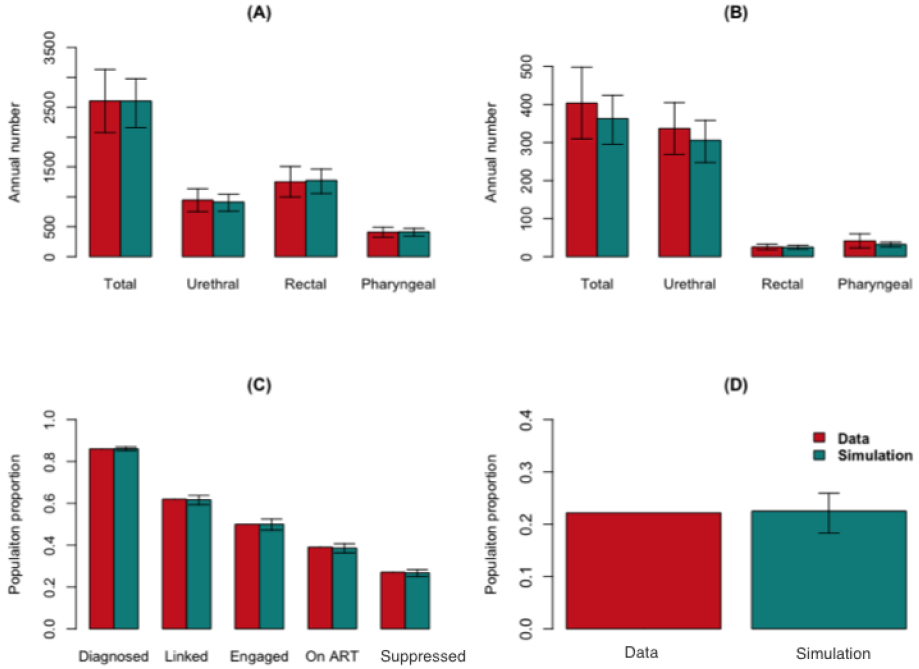

Figure S6: Model calibration to epidemiological data for (A) annual incidence of NG/CT, (B) annual diagnosis of NG/CT, (C) Cascade of HIV Care, and (D) HIV prevalence. Shown are the mean values of 200 simulations (in green) compared against empirical data (in red). The error bars around simulated values represent the 95% uncertainty range of observations around each simulated measure, and the error bars around the data in panel A&B represent the range of annual observations through the Baltimore City surveillance dataset (2011 – 2015). Data used for calibration in panel C&D is only available as point estimate in year 2012.

2.4 Complete list of model parameters

Table S7 provides a complete list of model parameters and values.

Table S7: Complete list of model parameters and values.

Parameter	Value	References
Partnerships		
Age Mixing (Absolute different in square root of ages)		
• Stable partnerships	0.6	[33]
• Casual partnerships	0.73	

Race mixing (Likelihood of mixing with a partner of the same race) - Black & Black - White & White	 0.9 0.75	[33]
Likelihood of condom use - Stable partnerships - Casual partnerships	[Never, Partially, Always] [0.45, 0.55, 0.00] [0.47, 0.12, 0.41]	[33]
Sexual position preference - Insertive only - Receptive only - Versatile	 0.42 0.26 0.32	[33]
Transmission coefficient for insertive relative to receptive sexual position	0.384	[34]
NG/CT		
Proportion of cases symptomatic - Urethral - Rectal - Pharyngeal	 74% 20% 10%	 [26] [25,35] [27,35]
Duration of infection in the absence of treatment	[3 – 12] months [2]	[15,36–49]
Duration of treatment	2 weeks	[15–17]
Regular GC screening intervals for HIV+ MSM on ART - All MSM - MSM with a history of NG/CT in the last 6 months	 12 months 6 months	[50]
Likelihood of compliance with CDC guideline for NG/CT screening	40%	[51–56]
Efficacy of condoms to prevent NG/CT transmission	70%	[15,57,58]
Increase in HIV transmissibility (from urethral or rectal infection)	[1.5 – 2] fold [3]	[59–63]
Increase in HIV susceptibility (from urethral or rectal infection)	[1 – 2.5] fold [3]	[15,27,63,64]
Coefficient of NG/CT transmission per act	0.294	Calibrated to provide the incidence of NG/CT
Proportion of NG/CT infections assigned to each site - Urethral - Rectal - Pharyngeal	 35% 49% 16%	Calibrated to provide the site-specific incidence of NG/CT
Weekly probability of symptomatic NG/CT testing - Urethral - Rectal - Pharyngeal	 0.009 0.001 0.04	Calibrated to provide the site-specific diagnosis of NG/CT
Weekly probability of screening high-risk (according to age and sexual activity class) MSM for HIV and NG/CT	0.014	Calibrated to provide the annual diagnosis of NG/CT and HIV
Probability that NG/CT screening only at urethral site	0.94	Calibrated to provide the relative diagnosis of extragenital to genital NG/CT

[2] Values are selected over uniform distributions across the ranges presented

Relative likelihood of NG/CT screening among Black MSM relative to White MSM	0.5	[21]
HIV		
Disease stage duration - Stage 1 (CD4 >500 cells/μL): Acute - Stage 2 (CD4 200-499 cells/μL): Chronic - Stage 3 (CD4 <200 cells/μL)[3]: Late stage	 [6 – 9] weeks [3] [8 – 10] years [1 – 3] years	[5,65,66] [5,67] [5,65,67]
Time from ART initiation to full viral suppression	[4-24] weeks [3]	[68]
Time from ART discontinuation to pre-ART CD4 nadir[4]	ART treatment duration up to one year	[69–72]
Mortality rate [3] - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART	 5 per 1000 person years 1/duration of stage 3 58%	[11–13]
Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART - Stage 3, no ART - On ART, partially suppressed - On ART, fully suppressed	 6.5 4.5 5 3.5 1.5	[5]
Efficacy of condoms to prevent HIV transmission	80%	[73,74]
Infectiousness per sexual contact	2.45 $^{(\log(VL)-4.5)}$	[5]
Individual's weekly likelihood of engagement in HIV care	0.00577	[75–77]
Weekly probability of ART discontinuation	0.0015	[78]
Gap in care after ART discontinuation	26 weeks	[14]
Weekly probability of - Screening for HIV only (not NG/CT) - Linkage to care (if HIV-positive and not linked) - Starting ART (if engaged)	 0.0065 0.0065 0.095	Calibrated to provide the HIV cascade of care
Relative likelihood of accessing HIV care among Black MSM	0.5	[21]

[3] Mortality rate in stage 3 is defined as 1/(duration of stage 3).

[4] Infectiousness assumed equal to that of stage 2

3 SENSITIVITY ANALYSIS

One-way sensitivity analysis of simulation results was performed with regard to all model parameters (listed in Table S7). For this purpose, we changed each parameter to +/- 25% of its original value, one at a time (keeping all others fixed at the original value) and evaluated the main simulation outputs after such variation. The primary output of interest for the sensitivity analysis was HIV incidence at 10 years without PrEP (baseline) and with PrEP (under each PrEP campaign). For this analysis, we assumed an uptake and adherence of 60% to PrEP. The tornado graphs (Figure S7) represent the results of the one-way sensitivity analysis. Figure S7-A presents the results for HIV incidence at year 10 in Baseline (absence of PrEP), and Figure S7-B through Figure S7-D present HIV incidence in year 10 of a PrEP campaign targeting MSM at the time of NG/CT-diagnosis (Figure S7-B), at the time of NG/CT screening (Figure S7-C) or through a community-wide campaign (Figure S7-D).

Assuming a threshold of 25% to detect significant changes, the projected HIV incidence at baseline and in absence of PrEP (Panel A) was sensitive to variation of parameters relating to 1) transmission of HIV including coefficient of HIV transmission (*cHivTrans*), viral load as a measure of infectiousness (*cHivVL*), and condom use and effectiveness (*pCondom_csl_never, cCondom_Eff*); 2) coefficient of NG/CT transmission (*cGCTrans*); and 3) parameters describing overall sexual activity including the probabilities of starting new partnerships (*cStartStbPart, cStartCslPart, cStartCasual_stb*) and the level of sexual activity in the most sexually active class (*cSaLevelHigh*). A similar behavior was observed in scenarios modeling the implementation of PrEP at NG/CT-diagnosis (Panel B), at the time of NG/CT screening (Panel C) or through a community-wide campaign (Panel D). None of the sensitivity analysis scenarios resulted in significant variation (>25%) of HIV incidence in PrEP scenarios compared to the baseline.

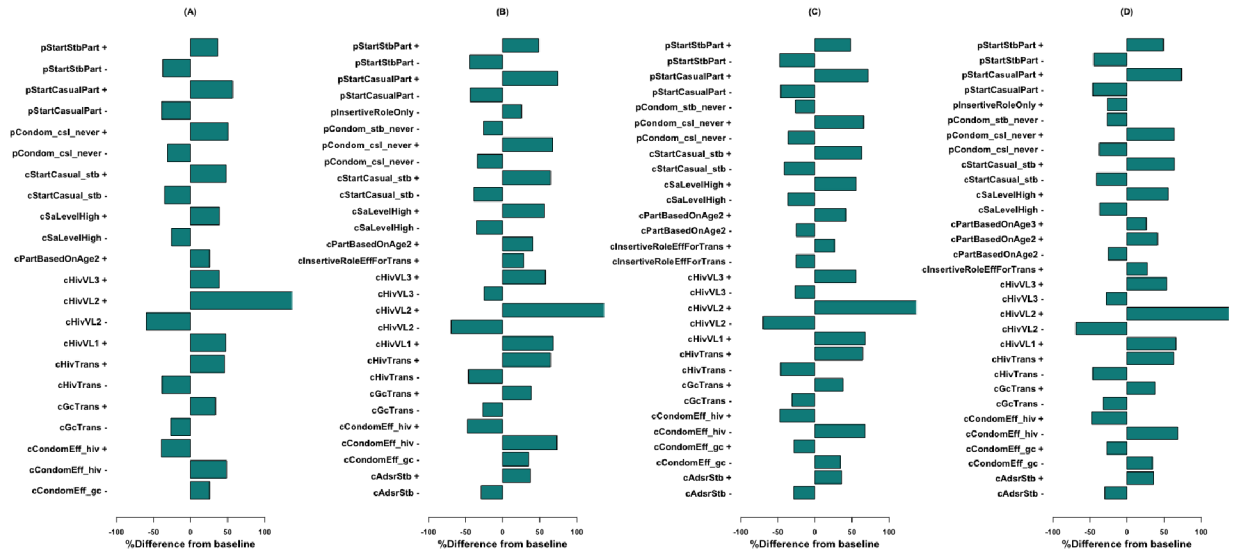

Figure S7: Sensitivity analysis of HIV incidence to variation of model parameters. Panel A presents the results for HIV incidence at year 10 in Baseline (absence of PrEP), and Panel B through D present HIV incidence in year 10 of a PrEP campaign targeting MSM at the time of NG/CT-diagnosis (Panel B), at the time of NG/CT screening (Panel C) or through a community-wide campaign (Panel D). Input parameters are listed on the left, +/- corresponding to 25% increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant.

3.1 Sensitivity analysis to impact of behavioral disinhibition

In the absence of strong data on existence of behaviour change for people on PrEP, we have elected to keep the model in the simplest format as possible. However, we acknowledge that this may limit the applicability of our findings to settings in which such behaviour may occur. To further study the impact of such assumption on our findings, we performed an additional sensitivity analysis of results to impact of behavioural disinhibition. For this purpose, we model behavioural disinhibition as %reduction in rate of condom use among MSM taking PrEP (reflected equally on rate of condom use in casual and stable partnerships), varied from 0% (no behavioural disinhibition) to 100% (no condom use).

Figure S8 compares the projected impact of NG/CT targeted PrEP at different rates of condom use reduction among PrEP users. The red line represents the baseline scenario in the model in absence of behavioral disinhibition. As expected, the projected impact of NG/CT-targeted PrEP on HIV incidence declines with reduced levels of condom use among PrEP users. For example, at baseline and in absence of behavioural disinhibition, the NG/CT targeted PrEP results in 12% [10.4% - 14.1%] reduction in HIV incidence over 20 years. Decreasing the condom use among PrEP users by 25% and 50% will consequently results in lower impact of PrEP at the population level, corresponding to 9.8% [7.7% - 11.9%] and 7.2% [5.1% - 9.4%] reductions in HIV incidence over 20-years. Reduction in rate of condom use among PrEP users can further reduce the potential impact of PrEP (through increased STI screening) on incidence and prevalence of NG/CT. At very high levels of behavioural disinhibition (light green line representing a 75% reduction in condom use among PrEP users), implementation of PrEP can in turn increase the rate of STI transmission and incidence over time.

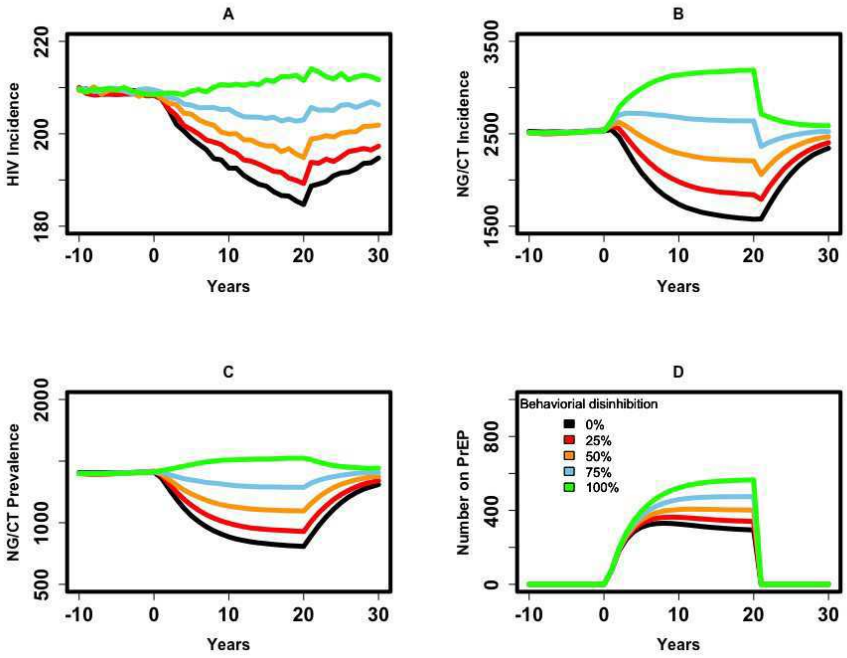

Figure S8: Sensitivity of the impact of NG/CT targeted PrEP to variation in rate of condom use among PrEP users. Shown on the y-axes are the annual incidence of HIV (A), incidence of NG/CT (B), prevalence of NG/CT (C) and number of MSM on PrEP and (D). Different colors represent PrEP scenarios at various levels of reduction in condom use among PrEP users, ranging from 0% (the baseline analysis in the main manuscript, shown in black) to 100% (no condom use among PrEP users, shown in light green).

Figure S9 further compares the impact of 3 PrEP scenarios that were discussed in the main text at various levels of behavioural disinhibition. Despite sensitivity of PrEP outcomes to variation in rate of condom use reduction in each scenario, the relative impact of NG/CT targeted PrEP scenario on HIV incidence compared to the other two scenarios (PrEP evaluation at NG/CT screening/testing and Untargeted PrEP) shows little sensitivity to underlying assumptions regarding behavioural disinhibition (Panel D in each set of graphs), and only begins to decline at very high levels of condom use reduction (last set of graphs for 75% reduction in condom use).

These results further characterize the impact of behavioural disinhibition on population-level impact of PrEP on incidence of HIV and other STIs as proposed by previous studies. This further highlight the need for additional behavioural surveillance data characterizing the changes in level of condom use and risky behaviours among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis for increased efficacy of PrEP implementation through a NG/CT targeted approach remains robust to variation in rate of condom use reduction.

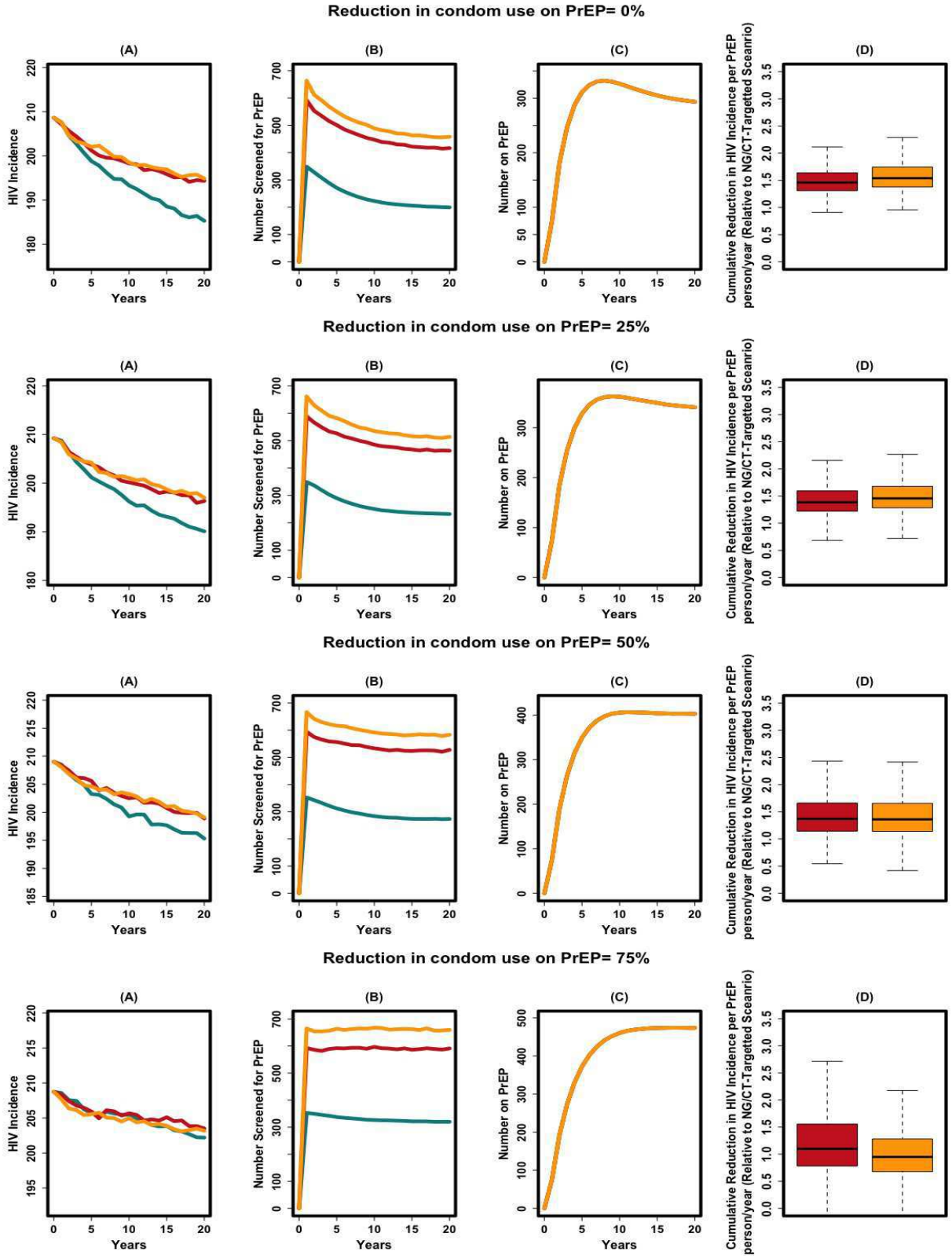

Figure S9: Sensitivity of the impact of all PrEP scenarios to variation in rate of condom use among PrEP users. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in green) compared against

PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. The three strategies are compared under the assumption that the same number of MSM would receive PrEP, at various levels of reduction in condom use among PrEP users. Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenario.

REFERENCES

1. Alliance BNI. Vital Signs 12 [Internet]. 2012. Available: http://bniajfi.org/vital_signs/
2. Maryland Department of Health and Mental Hygiene, MDHMH. 2012 Baltimore City Annual HIV Epidemiological Profile. Baltimore; 2012.
3. World Health Organization. Life tables by country United States of America. In: Global Health Observatory Data Repository [Internet]. 2013. Available: http://apps.who.int/gho/data/view.main.61780?lang=en
4. Lieb S, Fallon SJ, Friedman SR, Thompson DR, Gates GJ, Liberti TM, et al. Statewide Estimation of Racial/Ethnic Populations of Men Who Have Sex with Men in the U.S. Public Health Rep. 2011;126: 60–72.
5. Beyrer C, Baral SD, van Griensven F, Goodreau SM, Chariyalertsak S, Wirtz AL, et al. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012;380: 367–77.
6. Marshall BD, Paczkowski MM, Seemann L, Tempalski B, Pouget ER, Galea S, et al. A complex systems approach to evaluate HIV prevention in metropolitan areas: preliminary implications for combination intervention strategies. PLoS One. 2012;7: e44833.
7. Escobar E, Durgham R, Dammann O, Stopka T. Agent-based computational model of the prevalence of gonococcal infections after the implementation of HIV pre-exposure prophylaxis guidelines. Online Journal of Public Health Informatics. 2015. doi:10.5210/ojphi.v7i3.6104
8. German D. BESURE Study: National HIV Behavioral Surveillance Study in Baltimore [Internet]. Available: http://www.jhsph.edu/faculty/research/map/US/1413/8192
9. Vieira IT, Senna V de, Pereira. HB de B. A small world model for the spread of HIV infection. Pesqui Operacional. 2011;31: 373–389.
10. Egan JE, Frye V, Kurtz SP, Latkin C, Chen M, Tobin K, et al. Migration, neighborhoods, and networks: approaches to understanding how urban environmental conditions affect syndemic adverse health outcomes among gay, bisexual and other men who have sex with men. AIDS Behav. 2011;15: 35–50.
11. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373: 795–807.
12. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009;360: 1815–1826.
13. Palella Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med. 1998;338: 853–860.
14. Rana AI, Liu T, Gillani FS, Reece R, Kojic EM, Zlotnick C, et al. Multiple gaps in care common among newly diagnosed HIV patients. AIDS Care. 2015;27: 697–687.
15. Beck EEC, Birkett M, Armbruster B, Mustanski B. A data-driven simulation of HIV spread among young men who Hhave sex with men: role of age and race mixing and STIs. JAIDS J Acquir Immune Defic Syndr. 2015;70: 186–194.
16. Vriend HJ, Lugnér AK, Xiridou M, Schim van der Loeff MF, Prins M, de Vries HJC, et al. Sexually transmitted infections screening at HIV treatment centers for MSM can be cost-effective. AIDS. 2013;27: 2281–90. doi:10.1097/QAD.0b013e32836281ee

17. Chen MI, Ghani AC, Edmunds WJ. A metapopulation modelling framework for gonorrhoea and other sexually transmitted infections in heterosexual populations. J R Soc Interface. 2009;6: 775–91. doi:10.1098/rsif.2008.0394

18. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. MMWR recomm. 2015.

19. Virginia Department of Health. STD Surveillance Network Report. 2013; Available: http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf

20. Castro JG, Alcaide ML. High rates of STIs in HIV-infected patients attending an STI clinic. South Med J. 2016;109: 1–4.

21. Sullivan PS, Peterson J, Rosenberg ES, Kelley CF, Cooper H, Vaughan A, et al. Understanding racial HIV/STI disparities in black and white men who have sex with men: a multilevel approach. PLoS One. 2014;9: e90514.

22. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States-2014: a clinical practice guideline. 2014.

23. CDC. PrEP for men who have sex with men [Internet]. 2018. Available: https://prepmaryland.org/sites/default/files/download-resources/PrEP - MSM both sides March 2017.pdf

24. Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TP, Prevention D of S. Sexually transmitted disease surveillance 2013. 2014.

25. Lister N, Smith A, Tabrizi S, Hayes P. Screening for neisseria gonorrhoeae and chlamydia trachomatis in men who have sex with men at male-only saunas. Sex Transm Dis. 2003;30: 886–889.

26. Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis. 2005;41: 67–74.

27. Morris SR, Klausner JD, Buchbinder SP, Wheeler SL, Koblin B, Coates T, et al. Prevalence and incidence of pharyngeal gonorrhea in a longitudinal sample of men who have sex with men: the EXPLORE study. Clin Infect Dis. 2006;43: 1284–1289.

28. Soni S, White J. Self-screening for Neisseria gonorrhoeae and Chlamydia trachomatis in the human immunodeficiency virus clinic—high yields and high acceptability. Sex Transm Dis. 2011; Available: http://journals.lww.com/stdjournal/Abstract/2011/12000/Self_Screening_for_Neisseria_gonorrhoeae_and.6.aspx

29. Heiligenberg M, Rijnders B. High prevalence of sexually transmitted infections in HIV-infected men during routine outpatient visits in the Netherlands. Sex Transm. 2012; Available: http://journals.lww.com/stdjournal/Abstract/2012/01000/High_Prevalence_of_Sexually_Transmitted_Infections.2.aspx

30. Rieg G, Lewis R, Miller L, Witt M. Asymptomatic sexually transmitted infections in HIV-infected men who have sex with men: prevalence, incidence, predictors, and screening strategies. AIDS Patient Care. 2008; Available: http://online.liebertpub.com/doi/abs/10.1089/apc.2007.0240

31. Patton ME, Kidd S, Llata E, Stenger M, Braxton J, Asbel L, et al. Extragenital gonorrhea and chlamydia testing and infection among men who have sex with men--STD Surveillance Network, United States, 2010-2012. Clin Infect Dis. 2014;58: 1564–70.

32. Chamberlain N, Crosby RA, Mena L, Chan PA, Mayer KH. Is Patient-Reported Exposure a Reliable Indicator for Anogenital Gonorrhea and Chlamydia Screening in Young Black Men Who Have Sex With Men? Sex Transm Dis. 2017;44: 390–392. doi:10.1097/OLQ.0000000000000619

33. Maryland Department of Health and Mental Hygiene. BESURE Study 2004-2014: Baltimore site of National HIV Behavioral Surveillance (NHBS) [Internet]. 2015.

34. Jenness S, Goodreau S. Impact of the centers for disease control's HIV preexposure prophylaxis guidelines for men who have sex with men in the United States. J Infect Dis. 2016;14: 1800–1807.

35. Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. Genitourin Med. 1996;72: 422–6.

36. Kretzschmar M, Duynhoven Y van. Modeling prevention strategies for gonorrhea and chlamydia using stochastic network simulations. Am J Epidemiol. 1996;144: 306–317.

37. Korenromp EL, Sudaryo MK, de Vlas SJ, Gray RH, Sewankambo NK, Serwadda D, et al. What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? Int J STD AIDS. 2002;13: 91–101.

38. Althaus CL, Heijne JCM, Roellin A, Low N. Transmission dynamics of chlamydia trachomatis affect the impact of screening programmes. Epidemics. 2010;2: 123–131.

39. Price MJ, Ades AE, Angelis D De, Welton NJ, Macleod J, Soldan K, et al. Mixture-of-exponentials models to explain heterogeneity in studies of the duration of Chlamydia trachomatis infection. Stat Med. 2013;32: 1547–1560.

40. Turner KM, Adams EJ, Gay N, Ghani AC, Mercer C, Edmunds WJ. Developing a realistic sexual network model of chlamydia transmission in Britain. Theor Biol Med Model. 2006;3: 3.

41. Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. J Acquir Immune Defic Syndr. 2000;24: 48–56.

42. Chesson HW, Bernstein KT, Gift TL, Marcus JL, Pipkin S, Kent CK. The cost-effectiveness of screening men who have sex with men for rectal chlamydial and gonococcal infection to prevent HIV Infection. Sex Transm Dis. 2013;40: 366–71.

43. Tuite A, Jayaraman G, Allen V. Estimation of the burden of disease and costs of genital Chlamydia trachomatis infection in Canada. Sex Transm Dis. 2012;39: 260–267.

44. Vries R De, Bergen J Van. Systematic screening for Chlamydia trachomatis: estimating cost-effectiveness using dynamic modeling and Dutch data. Value in. 2006;9: 1–1.

45. Adams EJ, Turner KME, Edmunds WJ. The cost effectiveness of opportunistic chlamydia screening in England. Sex Transm Infect. 2007;83: 267-74–5.

46. Andersen B, Gundgaard J, Kretzschmar M. Prediction of costs, effectiveness, and disease control of a population-based program using home sampling for diagnosis of urogenital Chlamydia trachomatis. Sex Transm Dis. 2006;33: 407–415.

47. Gillespie P, O'Neill C, Adams E, Turner K. The cost and cost-effectiveness of opportunistic screening for Chlamydia trachomatis in Ireland. Sex Transm Dis. 2012;88: 222–228.

48. Roberts T, Robinson S, Barton P, Bryan S. Cost effectiveness of home based population screening for Chlamydia trachomatis in the UK: economic evaluation of chlamydia screening studies (ClaSS) project. Bmj. 2007;335: 291.

49. Welte R, Kretzschmar M, Leidl R, Hoek A Van Den, Jager JC, Postma MJ. Cost-effectiveness of screening programs for Chlamydia trachomatis: a population-based dynamic approach. Sex Transm Dis. 2000;27: 518–529.

50. Sexually transmitted diseases treatment guidelines, 2006. MMWR recomm. 2006; Available: http://origin.glb.cdc.gov/mmWR/preview/mmwrhtml/rr5511a1.htm

51. Berry SA. Gonorrhoea and chlamydia screening in HIV clinics: time for new tools and targets. Sex Transm Infect. 2014;90: 574–575.

52. Berry SA, Ghanem KG, Page KR, Gange SJ, Thio CL, Moore RD, et al. Increased gonorrhoea and chlamydia testing did not increase case detection in an HIV clinical cohort 1999-2007. Sex Transm Infect. NIH Public Access; 2011;87: 469–475.

53. Hutchinson J, Goold P, Wilson H, Jones K, Estcourt C. Sexual health care of HIV-positive patients: an audit of a local service. Int J STD AIDS. 2003;14: 493–496.

54. Hamlyn E, Barrett S, Kelsey J, Lockyer S, Welz T, Poulton M. Improvement in screening for sexually transmitted infections in HIV-positive patients following implementation of a nurse-led clinic. Int J STD AIDS. 2007;18: 424–426. Available: http://www.ncbi.nlm.nih.gov/pubmed/17609038

55. Hoover KW, Butler M, Workowski K, Carpio F, Follansbee S, Gratzer B, et al. STD screening of HIV-infected MSM in HIV clinics. Sex Transm Dis. 2010;37: 771–776.

56. Teague R, Mijch A, Fairley CK, Sidat M, Watson K, Boyd K, et al. Testing rates for sexually transmitted infections among HIV-infected men who have sex with men attending two different HIV services. Int J STD AIDS. 2008;19: 200–2.

57. Joesoef MR, Linnan M, Barakbah Y, Idajadi a, Kambodji a, Schulz K. Patterns of sexually transmitted diseases in female sex workers in Surabaya, Indonesia. Int J STD AIDS. 1997;8: 576–80. doi:10.1258/0956462971920811

58. Darrow WW. Condom Use and Use-Effectiveness in High-Risk Populations. SexTransmDis. 1989;16: 157–160.

59. Cohen M. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. Lancet. 1998;351: S5–S7.

60. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect. 1999;75: 3–17.

61. Winter AJ, Taylor S, Workman J, White D, Ross JD, Swan A V, et al. Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. Sex Transm Infect. 1999;75: 261–263.

62. Cohen MS, Hoffman IF, Royce RA, Kazembe P, Dyer JR, Daly CC, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. Lancet. 1997;349: 1868–1873.

63. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV. Sex Transm Dis. 2001;28: 579–597.

64. Jin F, Prestage GP, Imrie J, Kippax SC, Donovan B, Templeton DJ, et al. Anal sexually transmitted infections and risk of HIV infection in homosexual men. J Acquir Immune Defic Syndr. 2010;53: 144–149.

65. Baggaley RF, Ferguson NM, Garnett GP. The epidemiological impact of antiretroviral use predicted by

mathematical models: a review. Emerg Themes Epidemiol. 2005;2: 9.

66. Salomon JA, Hogan DR, Stover J, Stanecki KA, Walker N, Ghys PD, et al. Integrating HIV prevention and treatment: from slogans to impact. PLoS Med. 2005;2: e16.

67. Alam SJ, Meyer R, Norling E. A model for HIV spread in a South African village. Multi-Agent-Based Simul IX. 2009; 33–45.

68. Clotet B, Feinberg J, Lunzen J van, Khuong-Josses M. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised. Lancet. 2014;383: 2222–2231.

69. Wit FW, Blanckenberg DH, Brinkman K, Prins JM, Ende ME van der, Schneider MM, et al. Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. AIDS. 2005;19: 345–348.

70. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callegaro A, Suter F. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. AIDS. 2004;18: 439–446.

71. Ortiz GM, Wellons M, Brancato J, Vo HT, Zinn RL, Clarkson DE, et al. Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects. Proc Natl Acad Sci. 2001;98: 3288–13293.

72. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. New Engl J Med. 2006;355: 2283–2296.

73. Sc W, Davis-Beaty. Condom effectiveness in reducing heterosexual HIV transmission (Review). Available: http://www.thecochranelibrary.com

74. Holmes KK, Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. Bull World Health Organ. 2004;82: 454–461.

75. Hill T, Bansi L, Sabin C, Phillips A, Dunn D. Data linkage reduces loss to follow-up in an observational HIV cohort study. J Clin. 2010;63: 1101–1109.

76. Mocroft A, Kirk O, Aldins P, Chies A, Blaxhult A. Loss to follow-up in an international, multicentre observational study. HIV Med. 2008;9: 261–269.

77. Ndiaye B, Ould-Kaci K, Salleron J, Bataille P. Characteristics of and outcomes in HIV-infected patients who return to care after loss to follow-up. AIDS. 2009;23: 1786–1789.

78. Mills E, Nachega J, Buchan I, Orbinski J. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. Jama. 2006;296: 679–690.

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Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study

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Key messages:

- Several barriers exist to the successful implementation of PrEP in local settings, and optimizing the efficiency of PrEP delivery is a public health priority
- Targeting MSM infected with *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* increases the efficiency and effectiveness of PrEP delivery
- Expanding levels of STI screening among MSM can significantly improve the impact of PrEP (with PrEP offered to those testing positive)

ABSTRACT

Objectives: *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) increase the risk of HIV transmission among men who have sex with men (MSM). Diagnosis of NG/CT may provide an efficient entry point for prevention of HIV through delivery of pre-exposure prophylaxis (PrEP).

Methods: To quantify the added value of targeting PrEP to those diagnosed with NG/CT, we simulated the co-epidemic of NG/CT and HIV among MSM in Baltimore City, and compared various strategies for implementation of PrEP in this population.

Results: Assuming 60% uptake and 60% adherence, targeting PrEP to MSM diagnosed with NG/CT could reduce HIV incidence among MSM in Baltimore City by 12.4% [95% uncertainty range (UR): 10.3 – 14.4%] in 20 years, relative to no PrEP. Expanding the coverage of NG/CT screening (such that individuals experience a 50% annual probability of NG/CT screening and evaluation for PrEP upon NG/CT diagnosis), can further increase the impact of targeted PrEP to generate a 22.0% [95% UR 20.1 – 23.9%] reduction in HIV incidence within 20 years. When compared to alternative implementation scenarios, PrEP evaluation at NG/CT diagnosis increased impact of PrEP on HIV incidence by 1.7 [95% UR 1.0 – 2.6] relative to a scenario in which PrEP evaluation happened at the time of NG/CT screening/testing, and by 1.9 [95% UR 1.1 – 3.4] relative to evaluating random MSM from the community.

Conclusions: Targeting MSM infected with NG/CT increases the efficiency and effectiveness of PrEP delivery. If high levels of STI screening can be achieved at the community level, NG/CT diagnosis may be a highly effective entry point for PrEP initialization.

Strengths and limitations of this study

- Given the epidemiologic link between *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT) infection and HIV among men who have sex with (MSM), new NG/CT diagnoses may serve as a useful means to identify high-risk MSM for PrEP evaluation and delivery. At present, the impact of such a strategy is not clear. Using surveillance data from Baltimore City, Maryland, this study applies a modeling framework to evaluate the added value of targeting PrEP to MSM diagnosed with NG/CT, in terms of population-level impact on disease incidence over time.
- We base our depiction of HIV on a published agent-based model of HIV transmission among MSM in Baltimore City, and we extend this model to include coinfection of HIV with NG and CT infections modeled at the individual level.
- Our simulation model is calibrated against aggregate estimates of HIV and NG/CT incidence and prevalence, as well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City Health Department as part of the STD Surveillance Network Project.
- Our findings are limited by simplifying assumptions including (but not limited to) exclusion of other STIs such as syphilis, simplified representation of NG/CT natural history, simplification of sexual networks for NG/CT and HIV transmission, exclusion of HIV transmission through injection drugs or heterosexual sex, and exclusion of transgender and bisexual individuals from the simulated population.
- Given the controversies on existence of behavior change among MSM taking PrEP and lack of supporting data from our local population of MSM in Baltimore City, we excluded behavioral disinhibition from this analysis. Future studies can extend this analysis by evaluating changes in population-level impact of PrEP for HIV and STI control under potential levels of behavioral disinhibition for those on PrEP.

Keywords: HIV Infections; Gonorrhoea; Chlamydia; Pre-Exposure Prophylaxis; Homosexuality, Computer Simulation

BACKGROUND

Infection with *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT) may impact HIV transmission in multiple ways, particularly among men who have sex with men (MSM). From a biological standpoint, NG/CT infection may increase one's susceptibility to HIV acquisition: rectal infection in particular has been linked to an increased risk of HIV acquisition [1,2]. HIV and NG/CT also share many risk factors at the individual level (e.g., condomless sex) and network level (e.g., having sex within a high-prevalence network), such that the three conditions are often epidemiologically linked [3]. Additionally, HIV-negative men have an increased risk of HIV acquisition when in partnership with a HIV-positive partner who is also co-infected with NG/CT [4,5]. As a result, better diagnosis and treatment of NG/CT can potentially reduce HIV incidence [6], and help to identify individuals at high risk of future HIV infection.

Pre-Exposure Prophylaxis (PrEP) is part of comprehensive HIV prevention services in which HIV-negative people take daily antiretroviral medication to lower risk of HIV transmission upon exposure. The U.S. Centers for Disease Control and Prevention (CDC) has recommended PrEP for HIV-negative individuals at substantial risk of infection [7]. Among MSM, this includes HIV-negative men who are either diagnosed with a sexually transmitted infection (STI) in the last 6 months, are in a HIV discordant partnership, or report a condomless sex act in the last 6 months. Despite this broad recommendation, the potential population-level impact of PrEP remains uncertain. Several barriers exist to the successful implementation of PrEP, including providers' perceived inability to deliver PrEP in primary care settings [8], individuals' limited knowledge of PrEP effectiveness [9], low self-perceived risk for HIV infection [10], patients' difficulty in maintaining adherence [11], and high costs (at over $10,000 per person-year for those without insurance or access to a medication assistance plan) [12,13].

Given these challenges, optimizing the efficiency of PrEP delivery is a public health priority. Specifically, it is important to tailor PrEP delivery to those who stand to gain the most from its preventive efficacy. Given the epidemiologic link between NG/CT infection and HIV among MSM, new NG/CT diagnoses may serve as a useful means to identify high-risk MSM for PrEP evaluation and delivery [7]. At present, the impact of such a strategy—in terms of reducing HIV and NG/CT incidence at a population level—is not clear. To address this question, we used surveillance data from Baltimore City, Maryland, to construct an agent-based simulation model of the co-transmission of HIV and NG/CT among MSM, [14] and applied this model to study the added value of targeting PrEP to MSM diagnosed with NG/CT, in terms of population-level impact on HIV incidence over time.

METHODS

We base our depiction of HIV on a published agent-based model of HIV transmission among MSM in Baltimore City [14] (Figure 1-top panel), and we extend this model to include coinfection of HIV with NG and CT infections (see section 1 of the Supplementary Material).

NG/CT infection: NG and CT share similarities in natural history, including their acute nature, symptomatology, frequent co-diagnosis, and co-treatment [15]. Given these similarities, and for simplicity of modeling, we model NG/CT as a single biological entity. We assume that NG/CT infection may occur at the urethral, rectal or pharyngeal site – each with different probabilities of symptomatic presentation, diagnosis and treatment, and effects on HIV transmission, as shown in Table 1. We include both asymptomatic and symptomatic infection and fit the model to the annual number of diagnoses at each clinical site (urethral, rectal, or pharyngeal) among MSM in Baltimore City (see section 2 of the Supplementary Material).

Table 1: List of selected simulation parameters and calibration targets.

Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT) Parameters	Value	Reference
Proportion of cases symptomatic[1]		
• **Urethral**	74%	[16]
• **Rectal**	20%	[17,18]
• **Pharyngeal**	10%	[18,19]
Duration of infection (at each site) in the absence of treatment	[3 – 12] months[2]	[4,20–33]
Coefficient of NG/CT transmission per week	0.294	Calibrated to provide the incidence of NG/CT
Proportion of NG/CT infections assigned to each site		
• **Urethral**	0.35	Calibrated to provide the site-specific incidence of NG/CT
• **Rectal**	0.49	
• **Pharyngeal**	0.16	
Increase in HIV transmissibility (for those with urethral or rectal infection)	[1.5 – 2] fold [1]	[34–38]
Increase in HIV susceptibility (for those with urethral or rectal infection)	[1 – 2.5] fold [1]	[19,20,38,39]
NG/CT Calibration Targets	**Mean**[3] **[Range]**	
Annual diagnosis of NG/CT among MSM in Baltimore City		Values estimated from local data on gonorrhea surveillance and STI clinic visitis in Baltimore City (See section 2 in the Supplementary Material)
• **Urethral**	337 [269 – 405]	
• **Rectal**	25 [18 – 33]	
• **Pharyngeal**	42 [23 – 60]	
Site specific annual incidence of NG/CT among MSM in Baltimore City		
• **Urethral**	944 [753 – 1135]	
• **Rectal**	1251 [998 – 1505]	
• **Pharyngeal**	409 [326 – 492]	
HIV Parameters		
Disease duration		
• **Acute**	[6 – 9] weeks[1]	[40,41]
• **Chronic**	[8 –10] years[1]	[42,43]
• **Late stage** [4]	[1 –3] years[1]	[42–44]
Mortality rate[3]		
• **Acute & Chronic, no ART**	5 per 1000 person years	[45–47]
• **Late stage, no ART**	1/duration of late stage	
Reduction in mortality due to ART	0.58	
Time from ART discontinuation to pre-ART CD4 nadir[5]	ART treatment duration up to one year	[48–51]
Time from ART initiation to full viral suppression	[4 – 24] weeks[1]	[52]

[1] Values represent a pooled estimate of the reported measures for NG and CT infections

[2] Values are selected over uniform distributions across the ranges presented.

[3] Values represent the reported levels of NG/CT diagnosis among Baltimore City's MSM, and they are likely to underestimate the proportion of ongoing rectal and pharyngeal infections. We therefore consider such potential underestimation in estimating the annual incidence of NG/CT (see section 2 of the Supplementary Material) and have calibrated the model to represent realistic levels of prevalence (see the section on population overview in the main text).

[4] Mortality rate in late stage is defined as 1/(duration of late stage disease).

[5] Infectiousness assumed equal to that of the chronic disease.

Average viral load (log10 copies/mL)		[42]
• **Acute, no ART**	6.5	
• **Chronic, no ART**	4.5	
• **Late stage, no ART**	5	
• **On ART, partially suppressed**	3.5	
• **On ART, fully suppressed**	1.5	
Infectiousness per sexual contact	$2.45^{(\log(VL)-4.5)}$	[42]
Weekly probability of engagement in HIV care	0.006	[53–55]
Weekly probability of ART discontinuation	0.015	[56]
Gap in care after ART discontinuation	26 weeks	[57]
Relative probability of accessing HIV care among black MSM compared to white MSM	0.5	[58]
HIV calibration targets		
HIV prevalence	0.22 per 100,000 person/year	[59]
HIV continuum of care: Proportion of cases		[59]
• **Diagnosed**	0.86	
• **Linked to care**	0.62	
• **Engaged in care**	0.5	
• **On ART**	0.39	
• **Virally suppressed**	0.27	

STI Screening: In addition to testing of symptomatic NG/CT diagnosis, we also assume screening of asymptomatic individuals as follows (Figure 1- bottom panel):

- **Guidelines-based screening for HIV and NG/CT:** MSM may present to HIV/STI care providers (e.g., STI clinics, community health centers, HIV counseling programs) for a variety of reasons, and get tested for HIV and other STIs. We model visits for STI screening as a fixed weekly probability that reflects an individual's age-group and sexual activity such that younger MSM with higher propensity of partnerships experience a higher likelihood of visits [60,61]. We further assume that NG/CT is always screened at the urethral site, and a proportion of patients are also screened at the rectal and pharyngeal sites (calibrated to match the reported level of NG/CT infections diagnosis at each site among MSM in Baltimore City, as shown in Table 1).

- **NG/CT screening for HIV-positive MSM in care:** Based on CDC recommendations, most MSM who are continuously engaged in HIV care should undergo repeated NG/CT screening at least annually [15]. More frequent screening, such as screening every 3-6 months, is recommended for high-risk MSM, including those with an NG/CT diagnosis in the last year. Based on data from Baltimore City and a conservative estimate, we assume 40% adherence to these guidelines [62,63].

HIV Testing: In addition to combined HIV/STI testing that takes place as part of STI screening, we assume that all MSM experience an additional probability of HIV testing (in excess of testing though the STI program) can calibrate this probability to match the reported level of HIV diagnosis among MSM in Baltimore City.

Calibration: The model was calibrated against aggregate estimates of HIV and NG/CT incidence and prevalence, as well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City Health Department as part of the STD Surveillance Network Project (see section 2 of the Supplementary Material).

PrEP: Our primary outcome for this analysis is the projected incidence of HIV after 20 years of delivering PrEP to MSM. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the added benefit of targeting PrEP at individuals diagnosed with NG/CT. In all three scenarios, indication for PrEP use (eligibility) is considered in accordance with CDC recommendations and Baltimore City PrEP guidelines [64] (See

section 1 of the Supplementary Material) and includes HIV-negative individuals who are diagnosed with NG/CT in the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual partnership in the last 6 months. The three scenarios are thus:

- **PrEP delivery at NG/CT diagnosis** ("targeted" strategy & primary analysis)**:** all MSM diagnosed with NG/CT are offered PrEP at the time of diagnosis
- **PrEP evaluation at NG/CT screening/testing** ("at-testing")**:** PrEP eligibility is evaluated at the time of screening/testing for NG/CT, and all eligible individuals are offered PrEP
- **Untargeted PrEP:** PrEP eligibility is evaluated at random, and all eligible MSM are offered PrEP

All else being equal, increasing the number of MSM on PrEP will result in larger effects on HIV incidence (as more people are protected from HIV transmission). However, for a given number of MSM screened – or a given number of MSM on PrEP (e.g., if resource constraints are such that not all MSM meeting the criteria for PrEP can be placed/maintained on PrEP) – targeting PrEP to those screened for/diagnosed with NG/CT may be more efficient. Our primary aim was to quantify the extent of this gain in efficiency; thus, we compared scenarios in which the same number of MSM would be evaluated for PrEP, or alternatively the same number of MSM would be maintained on PrEP. Furthermore, to illustrate the potential impact of reaching highly ambitious targets for improved STI screening, we considered a hypothetical scenario for improving the underlying level of NG/CT screening (such that individual MSM not on PrEP experience a 50% annual probability of NG/CT screening and evaluation for PrEP upon NG/CT diagnosis), and studied the additional gain in effectiveness of NG/CT-targeted PrEP under this assumption.

In all scenarios, we assume that PrEP eligibility is reassessed every 3 months among patients receiving PrEP, and those who remain eligible for PrEP continue to receive it over time. Furthermore, we assume that in each scenario, a given proportion of eligible MSM who are offered PrEP will initiate prophylaxis (PrEP uptake ranging [0%-100%]) and adhere to it (PrEP adherence ranging [0%-100%]), with adherence defined as taking a sufficient number of doses to provide 60% protection against HIV transmission [65]. As a criterion for initiation of PrEP, all eligible MSM are also screened and treated for NG/CT infection before starting PrEP.

Sensitivity Analysis: A variety of sensitivity analyses were performed with the model. Using the HIV incidence at 10 years in absence and presence of PrEP (via all 3 scenarios) as the main output of interest, one-way sensitivity analyses were performed to variation of all model parameters to +/- 25% of their original value. We also varied condom usage among MSM on PrEP to model behavioral disinhibition (section 3 of the Supplementary Material).

Patient and Public Involvement: Patients and/or public were not involved in this study.

RESULTS

Population overview

The simulation models a population of 15,000 MSM in Baltimore City, projecting an average of 215 [95% UR: 181 – 251] incident HIV cases per year. Within this population, the co-epidemic of NG/CT is calibrated to 2598 [2204 – 2996] incident cases annually among which 35.0% [33.4 – 36.5%] of cases appear with urethral infection, 49.0% [47.4 – 50.6%] with non-urethral/rectal infection and 16.0% [14.8 – 17.2%] with pharyngeal-only infection. Point prevalence of NG/CT infection is estimated as 9.9% [8.4 – 11.5%], with 68.0% [63.5 – 72.5%] of infections occurring among black MSM (accounting for 58% of the MSM population) and 56.0% [54 – 58.2%] among MSM younger than 30 years old (accounting for 28% of the MSM population). Overall, 81.5% [81.0 – 82.1%] of MSM diagnosed with NG/CT in the model were tested on the basis of symptomatic presentation (rather than asymptomatic screening), and 20% [18.0 – 22.0%] of incident NG/CT cases were coinfected with HIV.

Epidemiological impact of PrEP at NG/CT diagnosis

At baseline, and in the absence of PrEP (steady-state equilibrium), 361 [95% UR: 298 – 427] MSM were annually diagnosed and treated for NG/CT infection (calibrated). If 60% of MSM diagnosed with NG/CT could be started on PrEP (i.e., uptake = 60%) and maintained at a degree to which 60% of subsequent HIV infections were averted (i.e., adherence = 60%), HIV incidence was estimated to decline by 12.4% [10.3 – 14.4%] over 20 years (Figure 2A). This corresponds to averting 318 [253 – 385] potential HIV transmissions through 5808 [5730 – 5886] person-years of PrEP delivered, or 5479 [4330 – 6632] infections averted per 100,000 person-years of PrEP (Figure 2B). Under the current level of NG/CT diagnosis, the number of MSM receiving PrEP is projected to increase through the first 8 years of the program (reaching a total of 332 [327 – 338] MSM on PrEP) and to fall afterward with declining incidence of NG/CT (Figure 2C). Due to the increased level of NG/CT screening/treatment among those on PrEP (through reassessment every 3 months), the prevalence of NG/CT was estimated to decline by 43.3% [41.6 – 44.9%] over 20 years of PrEP implementation (Figure 2D).

The impact of PrEP on HIV incidence can be further increased by expanding the coverage of NG/CT screening at the community level. In our baseline model, 25.0% [95% UR: 24.0 – 26.0%] of MSM undergo NG/CT screening/testing at least once annually (CDC recommendation). In an expanded-screening scenario in which all MSM experienced a 50% probability of screening for NG/CT annually, we projected a 180% increase in the baseline estimate of 4033 [3883 – 4182] annual NG/CT testing/screening events. Offering PrEP to those testing positive for NG/CT subsequently provided a 22.0% [20.1 – 23.9%] decline in HIV incidence over 20 years, corresponding to 648 [589 – 710] potential HIV transmissions averted. For further information on levels of uncertainty in these results, see section 4 of the Supplementary Material.

Relative impact of targeted versus untargeted PrEP

NG/CT-integrated PrEP increased efficiency of PrEP delivery in at least two ways (Figure 3A). First, a higher percentage of MSM were eligible for PrEP among those evaluated for PrEP (Figure 3B and 3C). In our model, 71.1% [95% UR: 65.0 – 77.2%] of all MSM diagnosed with NG/CT were eligible to receive PrEP (as 29% of this population is HIV-positive), compared to 45.2% [43.2 – 48.2%] of MSM screened for NG/CT, and 41.3% [39.1 – 43.5%] of randomly selected MSM. Second, providing PrEP to MSM diagnosed with NG/CT targets individuals at higher risk of potential HIV infection (due to both biological factors and high-risk behavior), such that – under the baseline assumption of equal numbers of people receiving PrEP—impact of NG/CT-targeted PrEP on HIV incidence was greater than the other two scenarios (Figure 3D). Specifically, over 20 years of implementation, targeting PrEP to MSM diagnosed with NG/CT infection increased impact of PrEP by 1.5 [1.1 – 1.9] relative to PrEP evaluation at NG/CT screening/testing, and by 1.6 [1.2 – 2.2] relative to untargeted PrEP. In another comparison, if the same number of individuals were evaluated for PrEP, the efficacy of NG/CT-integrated PrEP was increased even further relative to other scenarios (Figure 3E through 3H).

In one-way sensitivity analyses, the projected HIV incidence at 10 years in the absence of PrEP was sensitive to parameters relating to HIV and NG/CT transmission (including level of HIV viral load, condom use, and condom effectiveness) and parameters describing overall sexual activity (including the probabilities of starting new partnerships and the level of sexual activity in the most sexually active class). A similar variation in HIV incidence was observed in scenarios modeling PrEP evaluation at the time of NG/CT diagnosis, NG/CT screening or at random. Impact of PrEP in terms of reduction in HIV incidence in all scenarios relative to baseline was robust to reasonable variation of most model parameters (section 3 of the Supplementary Material).

DISCUSSION

This agent-based simulation of HIV transmission among MSM suggests that screening for NG/CT may be an important and efficient entry point for PrEP evaluation and delivery. Specifically, if all MSM who currently test positive for NG/CT could be offered PrEP – assuming 60% uptake and sufficient adherence to maintain 60%

protection – HIV incidence could be reduced by approximately 12%, averting one HIV infection annually per 1,000 MSM population, with fewer than 20 per 1,000 taking PrEP every year. On the basis of infections averted per PrEP dose delivered, providing PrEP to MSM with NG/CT diagnosis is nearly twice as efficient as providing PrEP randomly among eligible MSM. Thus, use of NG/CT diagnosis as an entry point is a highly efficient and feasible mechanism for PrEP delivery. If NG/CT screening could be expanded to 50% of MSM every year (with PrEP offered only to those testing positive), this impact could be more than doubled. Given this substantial potential impact, it will be important to assess willingness and uptake and identify best practices to support PrEP uptake and adherence among MSM diagnosed with NG/CT.

These findings are consistent with other studies of PrEP delivery among MSM [66,67]. Previous studies have shown that the population-level impact of PrEP depends strongly on PrEP uptake and adherence [14,66], as suggested in our study as well. Importantly, NG/CT diagnosis may be useful in this regard, as MSM who have recently been diagnosed with an STI may be more aware of their HIV risk and more likely to accept and initiate PrEP. Past research has shown that HIV interventions may be more effective when they are conducted or initiated at the time of an STI diagnosis [68]. Initiation of PrEP simultaneously with NG/CT diagnosis may also be a clinically feasible approach – as an STI diagnosis is already likely to prompt an HIV test (if not already performed), and MSM who are diagnosed with NG/CT have at least some level of health care access. Unlike performing detailed sexual histories, offering PrEP to all HIV-negative MSM diagnosed with NG/CT is a simple guideline that is easy for most clinicians to follow [69,70]. Further research is needed to assess the feasibility of this approach in the field, especially in ascertaining the degree to which the continuum of PrEP care (including linkage to care and longer-term maintenance on PrEP) can be maintained in this population. Furthermore, the potential tradeoff between the positive impact of PrEP on STI prevalence through enhanced screening and its negative impact through behavioral disinhibition (if MSM on PrEP adopt riskier sexual behaviors) merits further investigation. Additional implementation research is also needed to identify effective mechanisms for improving adherence to CDC PrEP guidelines and overcoming barriers to acceptance and uptake of PrEP such as lack of awareness, lack of access, financial strain, and stigma [11,71].

As with any modeling analysis, our findings are limited by necessary simplifying assumptions. Given the overlap in clinical practice for treating NG and CT and the substantial uncertainty regarding the natural history of the two infections (e.g., duration of infectiousness, propensity toward asymptomatic infection), we have combined these infections as a single entity (NG/CT) and have used composite parameter values to describe the natural history of both diseases. However, there are still important differences between NG and CT, and to the extent that the natural history of each disease may differ, our findings may over- or under-estimate the impact of PrEP targeted at these STIs. For example, an infection with a shorter infectious period and a higher transmission probability per sex act will concentrate more strongly in high risk networks and may provide a more effective entry point for HIV PrEP. Further research can extend our analysis by considering the impact of each disease separately on HIV transmission dynamics. Furthermore, due to limited data on site-specific transmission dynamics (e.g., relative frequency of oral-only versus oral-plus-anal versus anal-only sex among MSM in Baltimore), we adopted a simplified approach that does not fully capture the complete transmission dynamics but should result in the appropriate distributions of NG/CT infections at each anatomical site. Additional simplifying assumptions used in the underlying HIV simulation model include applying the same sexual network for NG/CT and HIV transmission; simplification of sexual networks as comprising only stable and casual partnerships; simplified definition of sexual activity classes as a lifetime attribute among MSM; exclusion of serosorting on HIV, sexual activity class or PrEP; exclusion of HIV transmission through injection drugs or heterosexual sex; and exclusion of transgender individuals from the simulated population. To the extent that these dynamics result in higher concentration of NG/CT among MSM at high-risk for HIV infection, our model may underestimate the impact of STI-targeted PrEP.

We excluded the potential existence of behavioral disinhibition for MSM on PrEP in the main analysis and applied a simplified approach for modeling the combined role of PrEP uptake/adherence for HIV protection. In additional

sensitivity analyses, we studied the impact of decreased condom use among MSM on PrEP on the outcome of NG/CT-targeted PrEP, and the relative efficacy of STI-targeted scenario compared to the other comparators (See section 3 of the Supplementary Material) . As expected, the projected impact of NG/CT-targeted PrEP on incidence of HIV and NG/CT declined with reduced levels of condom use among PrEP users. This further highlights the need for additional behavioural surveillance data characterizing changes in level of condom use and risky behaviours among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis (increased effectiveness of PrEP implementation through an NG/CT targeted approach) remained robust to variation in the rate of condom use reduction.

There are strong racial disparities in HIV incidence and healthcare access in the US, such that the highest risk populations may be the ones least likely to have access to PrEP [72]; these disparities were not included in our simplified cascade of PrEP. Our model calibration was limited to the scope of local surveillance data, and available literature for values lacking direct empiric estimates from Baltimore City (e.g., probability of symptomatic infection). We also assumed a future trajectory of HIV infection in the future that represents continuation of current trends; this trajectory is unlikely to remain constant for the next 20 years but may help to provide a useful conceptual construct for present-day decision-making, which is the ultimate goal of this analysis. Our results are further limited by exclusion of syphilis infection, another STI that is often transmitted in the same populations and may affect transmission and acquisition of HIV. Finally, we did not incorporate cost or other resource constraints into the present model; future analyses could evaluate the efficiency of NG/CT-targeted PrEP delivery from a cost-effectiveness or budget impact perspective.

In summary, this stochastic agent-based model representing the co-dynamics of NG/CT and HIV transmission among MSM suggests that NG/CT diagnosis may serve as an efficient and effective entry point for PrEP. If linkage between STI and HIV control programs can be effectively developed, further investment in NG/CT screening (followed by PrEP initiation) can have major impact, not only on the incidence and prevalence of NG/CT, but also on transmission of HIV – potentially averting up to 20% of all HIV infections through NG/CT-targeted PrEP alone. Future analyses could evaluate whether such approaches could even be cost-saving in the long term. Ultimately, ending the HIV epidemic in MSM populations will require a combination of multiple activities, including strengthening the continuum of HIV care, ensuring continued access to clinical services, and prevention through both behavioral approaches (e.g., condom use) and PrEP. Using NG/CT diagnosis as an entry point for PrEP initiation may serve as an important component of such a combined prevention approach.

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Contributions

Designed the study [PK and DWD]; Wrote the model code [PK]; Provided data [CS,JJ,ST,DG], Analyzed the data [PK]; supervised the analyses [DWD]; reviewed results [MS,SB, KH, TG, HC]; wrote the first draft of the manuscript [PK]; revised the manuscript and contributed intellectual content [PK, SB, MS, ER, KH, TG, HC]; All authors saw and approved the final manuscript.

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All authors report no potential conflicts of interest.

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Data sharing statement:

Additional data are presented in the online Supplementary Material.

REFERENCES

1 Katz D, Dombrowski J, Bell T. HIV incidence among men who have sex with men after diagnosis with sexually transmitted infections. *Sex Transm Dis* 2016;**43**:249–54.

2 Pathela P, Braunstein S, Blank S. HIV incidence among men with and without sexually transmitted rectal infections: estimates from matching against an HIV case registry. *Clin Infect Dis* 2013;**57**:1203–9.

3 Ward H, Rönn M. Contribution of sexually transmitted infections to the sexual transmission of HIV. *Curr Opin HIV AIDS* 2010;**5**:305–10.

4 Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. *J Acquir Immune Defic Syndr* 2000;**24**:48–56.

5 Fleming DTDT, Wasserheit JNJN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;**75**:3–17.

6 Grosskurth H, Mosha F, Todd J, *et al.* Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530–6.

7 Centers for Disease Control Prevention. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline. 2014.

8 Krakower D, Ware N, Mitty JA, *et al.* HIV providers' perceived barriers and facilitators to implementing pre-exposure prophylaxis in care Settings: a qualitative study. *AIDS Behav* 2014;**18**:1712–21.

9 Eaton L, Driffin D, Bauermeister J. Minimal awareness and stalled uptake of pre-exposure prophylaxis (PrEP) among at risk, HIV-negative, black men who have sex with men. *AIDS Patient Care STDS* 2015;**29**:423–9.

10 Galindo G, Ja'Nina J. Community member perspectives from transgender women and men who have sex with men on pre-exposure prophylaxis as an HIV prevention strategy: implications for implementation. *Implement Sci* 2012;**7**:116.

11 Golub SA, Gamarel KE, Rendina HJ, *et al.* From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among MSM and transgender women in New York City. *AIDS Patient Care STDS* 2013;**27**:248–54.

12 Juusola JL, Brandeau ML, Owens DK, *et al.* The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Ann Intern Med* 2012;**156**:541–50.

13 Koppenhaver RRT, Sorensen SSW, Farnham PG, *et al.* The cost-effectiveness of pre-exposure prophylaxis in men who have sex with men in the United States: an epidemic model. *AIDS J Acquir Immune Defic Syndr* 2011;**58**:e51–2.

14 Kasaie P, Pennington J, Berry SA, *et al.* The impact of pre-exposure prophylaxis among men who have

sex Withmen in Baltimore City: an agent-based simulation. *JAIDS J Acquir Immune Defic Syndr* 2017;**75**:175–83.

15 Workowski KA, Bolan GA. Sexually Transmitted Diseases Treatment Guidelines, 2015. *Morb Mortal Wkly Rep* 2015;**64(RR3)**:1–137.

16 Kent CK, Chaw JK, Wong W, *et al.* Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. *Clin Infect Dis* 2005;**41**:67–74.

17 Lister N, Smith A, Tabrizi S, *et al.* Screening for neisseria gonorrhoeae and chlamydia trachomatis in men who have sex with men at male-only saunas. *Sex Transm Dis* 2003;**30**:886–9.

18 Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. *Genitourin Med* 1996;**72**:422–6.

19 Morris SR, Klausner JD, Buchbinder SP, *et al.* Prevalence and incidence of pharyngeal gonorrhea in a longitudinal sample of men who have sex with men: the EXPLORE study. *Clin Infect Dis* 2006;**43**:1284–9.

20 Beck EEC, Birkett M, Armbruster B, *et al.* A data-driven simulation of HIV spread among young men who Hhave sex with men: role of age and race mixing and STIs. *JAIDS J Acquir Immune Defic Syndr* 2015;**70**:186–94.

21 Kretzschmar M, Duynhoven Y van. Modeling prevention strategies for gonorrhea and chlamydia using stochastic network simulations. *Am J Epidemiol* 1996;**144**:306–17.

22 Korenromp EL, Sudaryo MK, de Vlas SJ, *et al.* What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *Int J STD AIDS* 2002;**13**:91–101.

23 Althaus CL, Heijne JCM, Roellin A, *et al.* Transmission dynamics of chlamydia trachomatis affect the impact of screening programmes. *Epidemics* 2010;**2**:123–31.

24 Price MJ, Ades AE, Angelis D De, *et al.* Mixture-of-exponentials models to explain heterogeneity in studies of the duration of Chlamydia trachomatis infection. *Stat Med* 2013;**32**:1547–60.

25 Turner KM, Adams EJ, Gay N, *et al.* Developing a realistic sexual network model of chlamydia transmission in Britain. *Theor Biol Med Model* 2006;**3**:3.

26 Chesson HW, Bernstein KT, Gift TL, *et al.* The cost-effectiveness of screening men who have sex with men for rectal chlamydial and gonococcal infection to prevent HIV Infection. *Sex Transm Dis* 2013;**40**:366–71.

27 Tuite A, Jayaraman G, Allen V. Estimation of the burden of disease and costs of genital Chlamydia trachomatis infection in Canada. *Sex Transm Dis* 2012;**39**:260–7.

28 Vries R De, Bergen J Van. Systematic screening for Chlamydia trachomatis: estimating cost-effectiveness using dynamic modeling and Dutch data. *Value in* 2006;**9**:1–1.

29 Adams EJ, Turner KME, Edmunds WJ. The cost effectiveness of opportunistic chlamydia screening in England. *Sex Transm Infect* 2007;**83**:267-74-5.

30 Andersen B, Gundgaard J, Kretzschmar M. Prediction of costs, effectiveness, and disease control of a

population-based program using home sampling for diagnosis of urogenital Chlamydia trachomatis. *Sex Transm Dis* 2006;**33**:407–15.

31 Gillespie P, O'Neill C, Adams E, *et al.* The cost and cost-effectiveness of opportunistic screening for Chlamydia trachomatis in Ireland. *Sex Transm Dis* 2012;**88**:222–8.

32 Roberts T, Robinson S, Barton P, *et al.* Cost effectiveness of home based population screening for Chlamydia trachomatis in the UK: economic evaluation of chlamydia screening studies (ClaSS) project. *Bmj* 2007;**335**:291.

33 Welte R, Kretzschmar M, Leidl R, *et al.* Cost-effectiveness of screening programs for Chlamydia trachomatis: a population-based dynamic approach. *Sex Transm Dis* 2000;**27**:518–29.

34 Cohen M. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. *Lancet* 1998;**351**:S5–7.

35 Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;**75**:3–17.

36 Winter AJ, Taylor S, Workman J, *et al.* Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. *Sex Transm Infect* 1999;**75**:261–3.

37 Cohen MS, Hoffman IF, Royce RA, *et al.* Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet* 1997;**349**:1868–73.

38 Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV. *Sex Transm Dis* 2001;**28**:579–97.

39 Jin F, Prestage GP, Imrie J, *et al.* Anal sexually transmitted infections and risk of HIV infection in homosexual men. *J Acquir Immune Defic Syndr* 2010;**53**:144–9.

40 Little SJ, McLean AR, Spina CA, *et al.* Viral dynamics of acute HIV-1 infection. *J Exp Med 1* 1999;**90**:841–50.

41 Leynaert B n d., Downs AM, de Vincenzi I. Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. *Am J Epidemiol* 1998;**148**:88–96.

42 Beyrer C, Baral SD, van Griensven F, *et al.* Global epidemiology of HIV infection in men who have sex with men. *Lancet* 2012;**380**:367–77.

43 Alam SJ, Meyer R, Norling E. A model for HIV spread in a South African village. *Multi-Agent-Based Simul IX* 2009;:33–45.

44 Baggaley RF, Ferguson NM, Garnett GP. The epidemiological impact of antiretroviral use predicted by mathematical models: a review. *Emerg Themes Epidemiol* 2005;**2**:9.

45 The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;**373**:795–807.

46 Kitahata MM, Gange SJ, Abraham AG, *et al.* Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009;**360**:1815–26.

47 Palella Jr FJ, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;**338**:853–60.

48 Wit FW, Blanckenberg DH, Brinkman K, *et al.* Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. *AIDS* 2005;**19**:345–8.

49 Maggiolo F, Ripamonti D, Gregis G, *et al.* Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. *AIDS* 2004;**18**:439–46.

50 Ortiz GM, Wellons M, Brancato J, *et al.* Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects. *Proc Natl Acad Sci* 2001;**98**:3288–13293.

51 El-Sadr WM, Lundgren JD, Neaton JD, *et al.* CD4+ count-guided interruption of antiretroviral treatment. *New Engl J Med* 2006;**355**:2283–96.

52 Clotet B, Feinberg J, Lunzen J van, *et al.* Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised. *Lancet* 2014;**383**:2222–31.

53 Hill T, Bansi L, Sabin C, *et al.* Data linkage reduces loss to follow-up in an observational HIV cohort study. *J Clin* 2010;**63**:1101–9.

54 Mocroft A, Kirk O, Aldins P, *et al.* Loss to follow-up in an international, multicentre observational study. *HIV Med* 2008;**9**:261–9.

55 Ndiaye B, Ould-Kaci K, Salleron J, *et al.* Characteristics of and outcomes in HIV-infected patients who return to care after loss to follow-up. *AIDS* 2009;**23**:1786–9.

56 Mills E, Nachega J, Buchan I, *et al.* Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *Jama* 2006;**296**:679–90.

57 Rana AI, Liu T, Gillani FS, *et al.* Multiple gaps in care common among newly diagnosed HIV patients. *AIDS Care* 2015;**27**:697–687.

58 Rosenberg ES, Millett GA, Sullivan PS, *et al.* Understanding the HIV disparities between black and white men who have sex with men in the USA using the HIV care continuum: a modelling study. *Lancet HIV* 2014;**1**:e112–8.

59 Maryland Department of Health and Mental Hygiene, MDHMH. 2012 Baltimore City Annual HIV Epidemiological Profile. Baltimore: 2012.

60 Virginia Department of Health. STD Surveillance Network Report. Published Online First: 2013.http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf (accessed 30 Jun2017).

61 Castro JG, Alcaide ML. High rates of STIs in HIV-infected patients attending an STI clinic. *South Med J* 2016;**109**:1–4.

62 Berry SA. Gonorrhoea and chlamydia screening in HIV clinics: time for new tools and targets. *Sex Transm Infect* 2014;**90**:574–5.

63 Hoover KW, Butler M, Workowski K, *et al.* STD screening of HIV-infected MSM in HIV clinics. *Sex Transm Dis* 2010;**37**:771–6.

64 CDC. PrEP for men who have sex with men. 2018. https://prepmaryland.org/sites/default/files/download-resources/PrEP - MSM both sides March 2017.pdf

65 Koenig L, Lyles C, Smith D. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis. *Am J Prev* 2013;**44**:S91–8.

66 Jenness S, Goodreau S. Impact of the centers for disease control's HIV preexposure prophylaxis guidelines for men who have sex with men in the United States. *J Infect Dis* 2016;**14**:1800–7.

67 Vissers DCJ, Voeten HACM, Nagelkerke NJD, *et al.* The impact of pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: a simulation study. *PLoS One* 2008;**3**:e2077.

68 Bolu OO, Lindsey C, Kamb ML, *et al.* Is HIV/sexually transmitted disease prevention counseling effective among vulnerable populations? a subset analysis of data collected for a randomized, controlled trial evaluating counseling efficacy (Project RESPECT). *Sex Transm Dis* 2003;**31**:469–74.

69 Carter JW, Hart-Cooper GD, Butler MO, *et al.* Provider barriers prevent recommended sexually transmitted disease screening of HIV-infected men who have sex with men. *Sex Transm Dis* 2014;**41**:137–42.

70 Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States-2014: a clinical practice guideline. 2014.

71 Calabrese SK, Underhill K. How stigma surrounding the use of HIV preexposure prophylaxis undermines prevention and pleasure: a call to destigmatize 'Truvada Whores'. *Am J Public Health* 2015;**105**:1960–4.

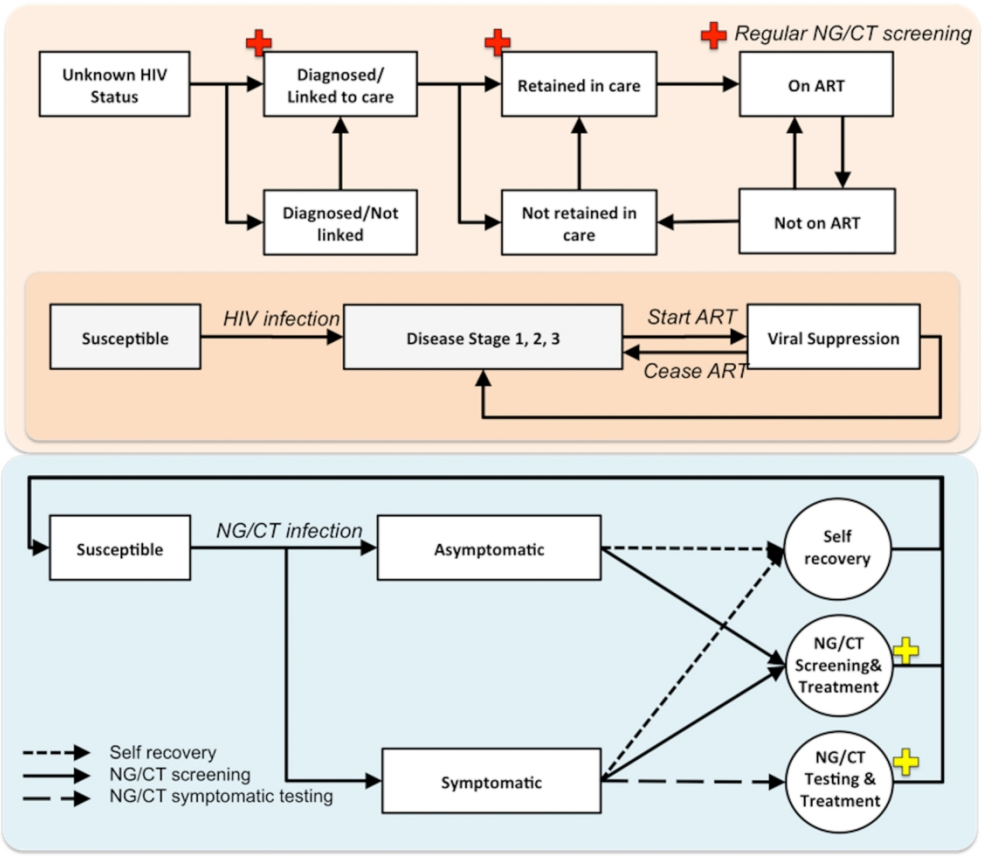
72 Highleyman L. PrEP use is rising fast in US, but large racial disparities remain. Aidsmap. 2016.http://www.aidsmap.com/PrEP-use-is-rising-fast-in-US-but-large-racial-disparities-remain/page/3065545/ (accessed 14 May2018).

Figure legends:

Figure 1: An agent-based model of gonorrhoea/chlamydia (NG/CT) and HIV co-transmission. The top panel represents the HIV care continuum and natural history: Upon infection with HIV, individuals serially progress through three disease stages over time; this progression can be halted by initiation of antiretroviral therapy (ART), which is assumed to result – if taken – in viral suppression within 4 to 24 weeks (see Table 1) [52]. We assume, for simplicity, that engagement in care involves initiation of ART (as episodes of care engagement not resulting in ART initiation do not affect HIV transmission in the model). HIV-positive individuals in care are assumed to undergo regular screening for NG/CT (marked in red) subject to patients presenting for scheduled visits and clinician decision to screen. The bottom panel represents the natural history of NG/CT: infection may be symptomatic or asymptomatic, individuals remain infectious until diagnosis and treatment (which can occur either through symptomatic presentation to care or routine screening of asymptomatic individuals) or spontaneous resolution. Upon diagnosis with incident NG/CT, we assume that individuals are also screened for HIV infection (marked in yellow); if HIV-negative, we consider the possibility of PrEP delivery in this analysis.

Figure 2: Impact of NG/CT-integrated PrEP, according to frequency of NG/CT screening/testing. Shown on the y-axes are the annual incidence of HIV (A), cumulative number of transmissions averted (B), number of MSM on PrEP (C) and NG/CT prevalence (D). The green line depicts a scenario in which all MSM currently diagnosed with NG/CT are placed on PrEP with 60% uptake and adherence (NG/CT-integrated PrEP scenario in the main text), and the purple line shows a hypothetical scenario in which 50% of MSM are screened for NG/CT every year, with those testing positive for NG/CT also offered PrEP.

Figure 3: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in green, also corresponding to the green line in Figure 2), compared against PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. In the first set of experiments, the three strategies are compared under the assumption that the same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be screened for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenario (similar pattern in panels E through H).



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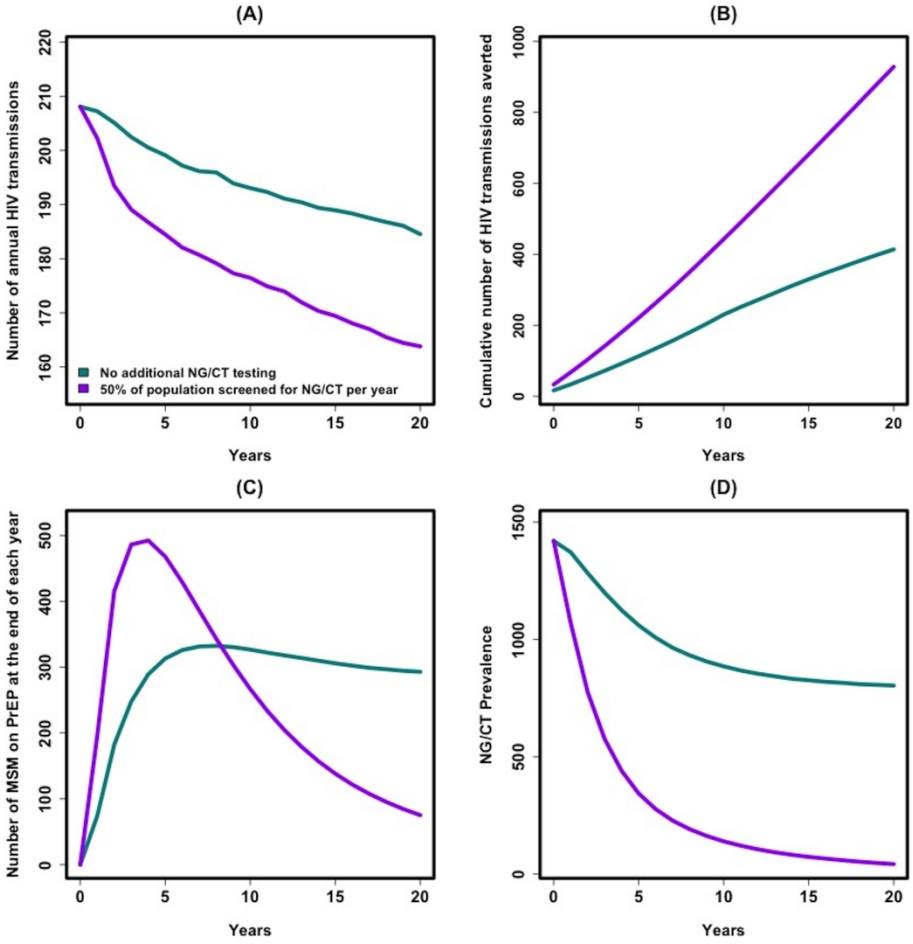

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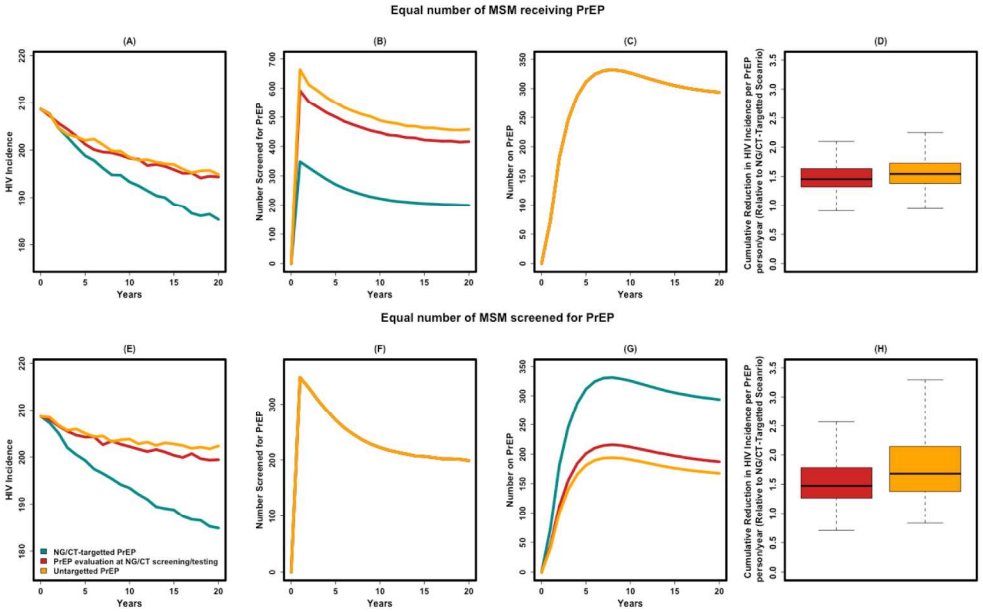

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SUPPLEMENTARY MATERIAL

Title: Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study

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1 HIV SIMULATION MODEL DESIGN

Overview

Our agent-based simulation model of the HIV epidemic among MSM in Baltimore City is structured as a collection of modules that govern population demographics, sexual partnerships, the epidemiological aspects of disease with regard to HIV natural history, cascade of care and transmission. Each "agent" represents a single MSM in Baltimore City, characterized by age, race, and place of residence, and the model is evaluated in a series of one-week time steps. The HIV natural history module characterizes the progression of HIV among infected individuals according to disease stage. Each stage is associated with a different per-act risk of HIV transmission, and disease progression from stage 2 to stage 3 can be prevented (and/or reversed) by provision of ART. The HIV cascade of care estimates probabilities of HIV testing, linkage to care, disengagement/re-engagement, and ART provision/viral suppression at each time step. The sexual network and transmission module create and modify the population's sexual networks (as a series of stable and casual partnerships) at each step, modeling HIV transmission as a per-act probability among serodiscordant partnerships according to frequency and safety of sex act, HIV stage of the infected partner, and ART/PrEP use. Sexual partnerships are modeled as assortative according to age, race, and location of residence. Finally, the population demographic module accounts for aging, death, and birth processes.

1.1 Population Demographic Module

This module characterizes the initial population structure and governs various procedures for aging, death, and birth at end of each simulated year. We model the population of MSM in Baltimore City between the ages of 15 to 75. The population is structured as a collection of population groups corresponding to Baltimore's Community Statistical Areas (CSA) [1]. CSAs are clusters of neighborhoods and are organized according to census tract boundaries, which are consistent statistical boundaries. In some cases, CSA boundaries may cross neighborhood boundaries. There are 55 CSAs in Baltimore City. Neighborhood lines often do not fall along CSA boundaries, but CSAs are representations of the conditions occurring within those particular neighborhoods. Simulated population groups are characterized with regard to their geographical location (CSA of residence) and racial structure (black and non-black). We do not model the spatial distribution of individuals within each CSA; rather geographical assignments are made at the CSA level by assigning the corresponding CSA-center coordinates to each MSM living in that CSA. The initial HIV distribution across CSAs is estimated according to publicly available data from Maryland's Department of Health and Mental Hygiene (MDHMH) [2].

Individuals age with the simulation clock (years) and exit the model according to an age-specific natural mortality rate [3], or by reaching the age of 75, or via an additional mortality rate associated with HIV infection. To maintain the initial population decomposition without disturbing the CSA structures, we model a natural birth process at the CSA level for replenishing the population size over time. The birth process is modeled via a non-stationary Poisson process tuned to maintain each CSA's population at a constant mean over time. Newborns enter the MSM population at age of 15 to 20 years old and follow the corresponding racial structure of the CSA of residence.

Using the current estimate of Baltimore City male population (approximately 287,000) who are 15 year or older in age (about 232,000), and estimated percentage of adult MSMs in each racial group (7.5% of non-black males and 5.8% of black males [4]), we estimate the size of Baltimore City's MSM population at approximately 15,000.

Forming CSA-groups: To determine groupings of similar CSAs, we first ranked the CSAs according to the median income level and racial makeup based on available information from Baltimore City census [1].

For simplicity, levels of income (Figure S1-left panel) and proportion of population that is Black/African-American (Figure S1-right panel) were coded into values from 1 to 5 (representative of various shades in Figure S1), and two values were assigned to each CSA. For example, CSA "Midtown" (T-shaped in the center of the map) was assigned a rank of 3 for median household income, and 2 for the proportion of population that is Black/African-American.

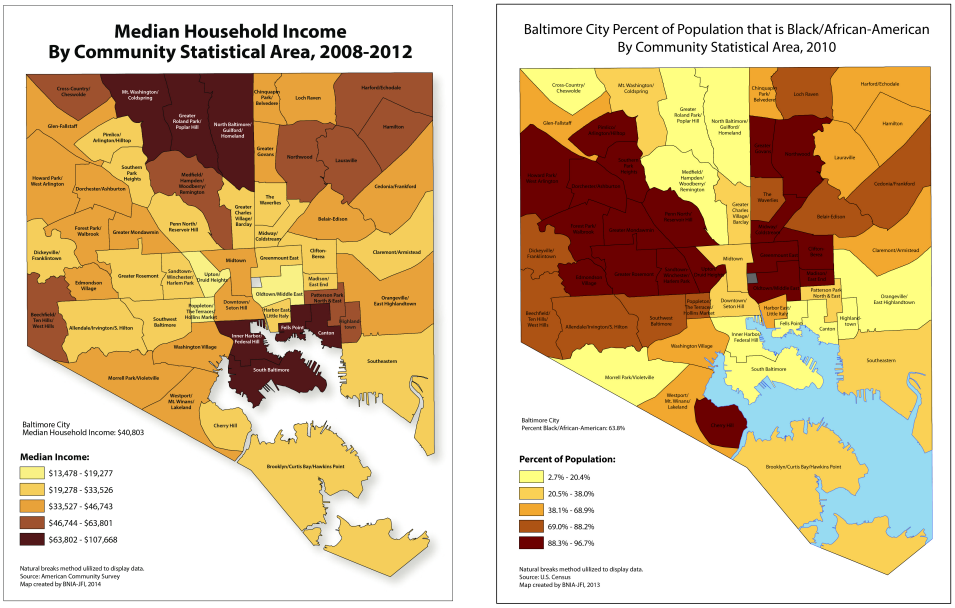

Figure S1: Baltimore City CSA ranking according to median income and racial structure [1].

We defined a CSA-group to include a number of neighboring CSAs (sharing a border) with at most a one-level difference in their ranked levels of income and racial makeup. To determine the CSA-groups throughout the city, we implemented a random search mechanism using a branch and bound logic. The search was started from a random CSA and branched through all neighboring CSAs to determine how many could belong to the same CSA-group. The search was bounded by those CSAs representing a difference of more than one level in ranked income and racial makeup but continued for those CSAs that belonged to the same group and branched further to test their other neighbors, until it was bounded in all directions. At the end of each iteration, a list of CSAs grouped by relative similarity across the whole city was generated. This search was repeated many times and the CSA groups that were most likely (i.e., high frequency) to form were identified. Overlapping CSA-groups were further checked for the possibility of combination into a single group. Finally, we had 16 CSA-groups across Baltimore City, representing geographically approximate neighborhoods with similar levels of income and racial makeup (Figure S2). Using CSA numbers as identifiers, a complete list of CSA groups is provided in Table S1.

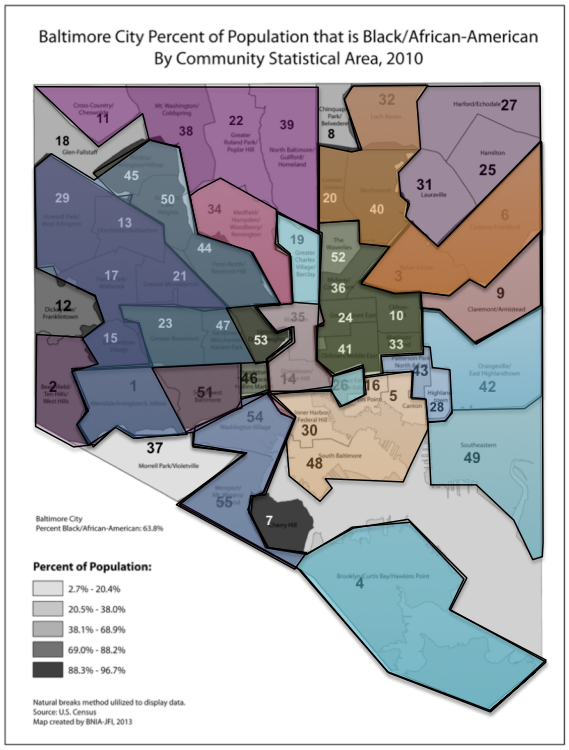

Figure S2: Baltimore City CSA ID's and CSA groups structure. Each CSA group is marked with a closed border in a different color. Some groups overlap such that some CSAs belong to more than one group. Some CSAs may not belong to any groups and are considered by themselves.

Table S1: List of CSA group and member CSAs

Group ID	CSA members
1	11 22 34 38 39
2	3 6 9
3	28 42 43
4	3 6 8 25 27 31 32
5	42 49
6	10 24 33 36 41 52
7	5 16 28 30 43 48
8	3 6 20 32 40
9	4 14 19 26 35 54 55
10	14 34 35
11	1 23 44 45 46 47 50 51 53
12	1 51 54 55
13	4 14 19 26 35 54 55
14	2 13 15 17 21 29
15	1 12 13 15 17 21 23 29 44 45 47 50 51
16	3 6 10 20 24 33 36 52

1.2 Sexual Partnership Module

This module governs the network of sexual partnerships and runs in discrete time steps, each representing a week. Following previous models of sexual contact networks [5–7], we conceptualize the network of sexual partnerships at an individual level (with regard to age, race, geography, sexual positioning, etc.) and calibrate the simulation parameters using local behavioral surveillance data available through the BESURE study, the Baltimore City branch of the National HIV Behavioral Surveillance System (NHBS) [8]. BESURE is a CDC funded project operated by the Maryland Department of Health and Mental Hygiene and the Johns Hopkins Bloomberg School of Public Health. Starting in 2004, BESURE has conducted four venue-based sampling surveys among Baltimore's MSM (Table S2). We use this data to extract information on several behavioral parameters at the individual level (e.g., preference toward using condoms in each type of partnerships) that will be directly implemented at the agent level, as well as population-level estimates for calibrating the unknown variables (e.g., frequency of the annual sexual partnerships). For those measures available across multiple BESURE waves, we use a pooled estimate of the reported values.

Table S2: Survey methods and sample characteristics, BESURE MSM 2004-2010

	Wave 1	Wave 2	Wave 3	Wave 4
Date	June 04-April 05	Jul-Oct 2008	Aug-Dec 2011	Jun-Dec 2014
Total MSM	645	448	404	455
HIV prevalence	37.7%	37.5%	42.6%	30.6%
Proportion of HIV that was unrecognized	58.4%	78.4%	67.3%	33.1%

1.3 Partnership types and formation

We model two types of partnerships representing long-term "stable" and short-term "casual" partnerships. Stable partnerships can last for several years [5], while casual partnerships will only last a single time step (one week) in the model. We assume that individuals can have multiple casual partnerships from one week to the next [9], but they can only engage in a maximum of one stable and one casual partnership at any time step. All partnerships are updated at the end of each simulation week, and those partnerships reaching their pre-specified duration will be dissolved. At the beginning of each following week, individuals' tendency to engage in a new partnership is evaluated and "eligible" individuals will select the geographical search domain for meeting their future partners based on their location of residence. Once the partnership domains are established for all eligible MSM, individuals will follow a search mechanism based on a combination of race- and age-dependent mixing patterns, as well as sexual role preference, to select their future partner from the pool of eligible people at the selected domain. This process is modeled in 3 steps:

1.3.1 Step 1. Evaluating an individual's probability of engaging in a new partnership

Each individual's likelihood of engaging in a new partnership is modeled as a function of his age, the level of sexual activity, and current partnership status.

In accordance with the heterogeneous frequency of reported partnerships by age, we define a partnership coefficient for modeling the likelihood of engaging in new partnerships as a function of individual's age ($c_{Part|Age}$) (assumed to be a fixed level for each age group).

Sexual activity class: In order to represent the heterogeneous level of sexual activity among MSM, we defined three sexual activity classes ("low", "medium" and "high"), each corresponding to a lifetime level of engagement in casual partnerships. An individual's sexual activity class (c_{SA}) is determined at the time of birth (entry to population) and remains fixed throughout his life (though within each sexual activity class, the actual level of partnership formation changes with age – for example, partnership formation declines with older age in all three classes). This attribute represents a combination of factors determining an individual's tendency for engaging in casual partnerships, reflecting the diversity of sexual activity seen in real populations. As described in a previously published modeling construct [10], we implement the simplified definition of the 3 sexual activity classes in order to more accurately represent "tails" in the observed distribution of (self-reported) sexual activity in data from Baltimore City. Individuals with particularly high sexual frequency are potentially important drivers of STI transmission dynamics but are not easily represented assuming a simple Poisson process of sexual partnership formation. We therefore arbitrarily assign equal numbers of individuals to these three sexual activity classes, and then calibrate the relative frequency of casual partnership formation in each of these classes to most closely fit the observed distribution among MSM in Baltimore City.

Finally, we model each agent's tendency for engaging in casual and stable partnerships at any point of time via two additional parameters (p_{Csl} and p_{Stb}) at the agent-level, and also define the conditional likelihood of engaging in new casual partnerships concurrent to an existing stable partnership via a separate parameter ($p_{Csl|Stb}$).

With these definitions, an individual's likelihood of engaging in a new stable (P_{new_stb}) or casual (P_{new_csl}) partnership at each timestep can be estimated as follow:

$$P_{new\_stb} = p_{Stb} \times c_{Part|Age}$$

$$P_{new\_csl} = p_{Csl} \times p^{*}_{Csl|Stb} \times c_{Part|Age} \times c_{SA}$$

$$p^{*}_{Csl|Stb} = \begin{cases} p_{Csl|Stb} & number\ of\ stable\ partnerships > 0 \\ 1 & o.w. \end{cases}$$

At each time step, an individual's likelihood for engaging in a new partnership is evaluated and eligible individuals are added to the pool of available people at their CSA of residence to find their potential partners in the next steps.

1.3.2 Step 2. Choosing the partnership domain

The partnership domain is determined according to a discrete mixing structure at the CSA level (Figure S3). In order to model the spatial mixing patterns across the population and among various subgroups, we first define sets of "neighboring" CSA groups with regard to geographical proximity and similar socioeconomic status (income levels) and racial structure [1]. Upon seeking a new partnership, an individual's search scope (for choosing the new partner) is determined according to a discrete geographical mixing probability (*pGM*) for selecting one's own CSA (p_0), a random neighboring CSA in the same CSA group (p_1) or non-neighbor CSA (p_2). The geographical mixing probability ($pGM=(p_0, p_1, p_2)$)

represents a measure of geographical/socioeconomic clustering in the network of partnerships, where *pGM*=(1,0,0) translates into an isolated mixing pattern for partnership only with individuals in one's CSA of residence, and *pGM*=(0.33,0.33,0.33) translates into a homogeneous mixing structure across the entire population. In our initial analysis, we calibrate the geographical mixing likelihoods at *pGM* = (0.5, 0.3, 0.2) according to available estimates from [11].

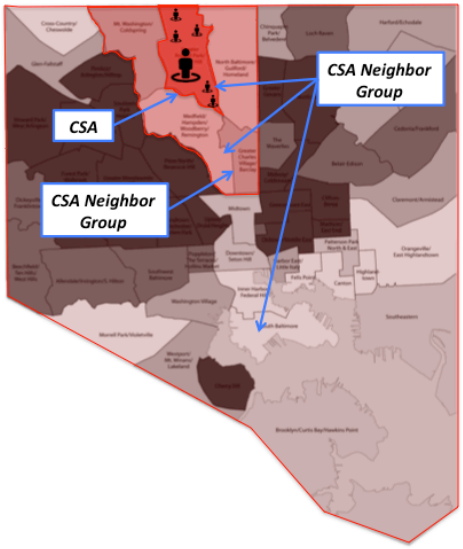

Figure S3: Partnership search domains. Individuals can choose their future partner from their own CSA or a random CSA within or outside their neighbor group.

1.3.3 Step 3. Modeling the search mechanism within the partnership domain

Once the partnership domain is established, individuals follow a search mechanism for finding their new partners from the pool of eligible members in the selected domain. The probability of partnership between two people is evaluated according to an age- and race-mixing structure, as well as sexual role preference. Assuming independent patterns of age- and race-specific mixing, the age-race mixing probability is computed as the product of age-mixing and race-mixing probabilities for each pair of potential partners. A random search mechanism is implemented to evaluate the probability of partnership with each potential partner in the selected domain until a successful match is found or the entire domain is searched. Potential partners are also checked for their compatibility with regard to sexual role and incompatible pairs (e.g., receptive-receptive or insertive-insertive) are dismissed. Upon a successful match, a new partnership is formed for both parties, who are then excluded from the pool of eligible partners for other individuals.

1.3.4 Age-Specific Mixing

Age-specific mixing is modeled based on absolute difference in the square root (ADSR) of men's ages [5]. The ADSR provides a closer fit to the observed age-mixing matrix than does age directly. This statistic also has the desirable property that the same absolute difference in age becomes less important over time. Using data on participant's age and their last male partner's age from BESURE, we estimate the reported ADSR level for main/casual partnerships ($ADSR_{partnership}$) as shown in Table S3. The probability of age-mixing between person *p* and *q* for each partnership type (*pAgeMixing*) is then computed as a function of

partners' age and the target ADSR level for each type of partnerships. Figure S4-A and S4-B compare the simulated distribution of ADSR values among casual and stable partnerships in the baseline simulation model.

$$pAgeMixing = \text{Min}(ADSR_{p,q,2} \times ADSR_{partnership} - ADSR_{p,q}) / ADSR_{partnership}$$

where

$$ADSR_{p,q} = \left| \sqrt{p_{age}} - \sqrt{q_{age}} \right|$$

$$ADSR_{partnership} = (ADSR_{Stb}, ADSR_{Csl})$$

Table S3: Estimates of reported ADSR for Stable/Casual partnerships in BESURE. Estimates are made based on the participant's age and their last male partner's age.

BESURE Waves:	$ADSR_{Stb}$ (Number of reported partnerships)	$ADSR_{Csl}$ (Number of reported partnerships)
Wave 2	0.62 (66)	0.72 (75)
Wave 3	0.68 (71)	0.73 (87)
Wave 4	0.51 (62)	0.76 (77)
Average estimate	**0.6**	**0.74**

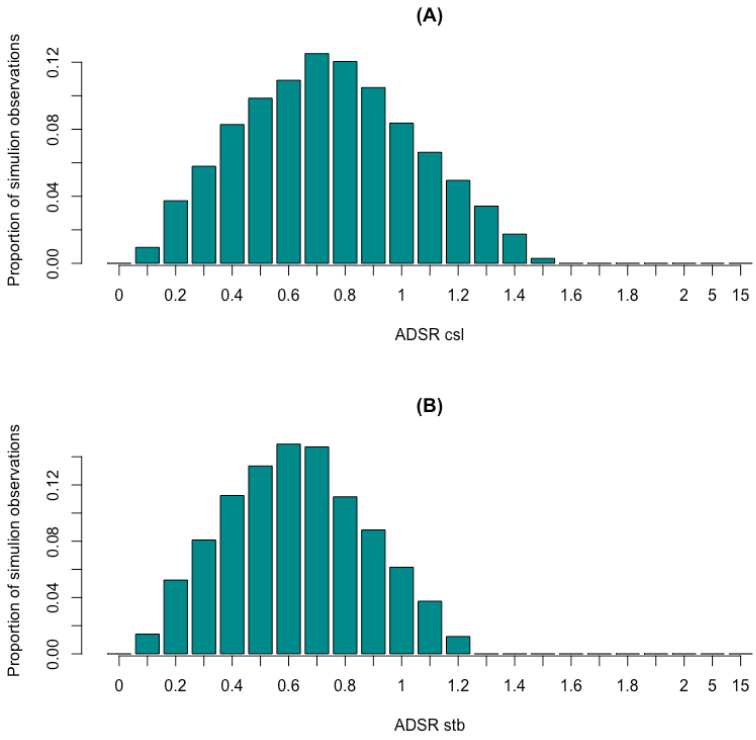

Figure S4: Distribution of ADSR in simulated casual (Panel A) and stable (Panel B) partnerships at the baseline model.

1.3.5 Race-Mixing

We model the probability of partnership between MSM of the same sex by estimating the reported ratio of same-sex partnerships for Black MSM at 90% and for White MSM at 75% through BESURE data.

1.3.6 Sexual Role Preference

Each MSM is assigned an individual sexual role preference (insertive only, receptive only, versatile) at the time of birth (entry to population). The sexual role preferences prohibit the partnerships between two men who are insertive only or those who are receptive only (allowing for 5 partnership configuration). The type of sexual act in partnerships between two versatile men is determined via uniform probability distribution between 0 and 1 (e.g., 50% chance of insertive/receptive act for each man) and will be updated at each time step for their active partnerships. Using data from BESURE, we estimate the proportions of population that fall within each category at 42% insertive-only, 26% receptive-only, and 32% versatile.

1.4 HIV Epidemiological Module

This module governs various aspects of HIV natural history and cascade of care, and it is updated at the end of each time step (week).

1.4.1 HIV Natural History

Upon a successful HIV transmission event, individuals experience a gradual increase in viral load (VL) and move through various stages of disease (Figure 1, main manuscript). We consider three disease stages in absence of ART, including stage 1 (CD4 count > 500 cells/ μL), stage 2 (CD4 count between 200-500 cells/ μL) and stage 3 (CD4 count <200 cells/ μL). Each disease stage is characterized with regard to duration of disease (as a crude measure of CD4 decline over time), mean VL level (determining the level of infectiousness) as well as the HIV mortality rate. In this model, we do not model the dynamics in the number of CD4 counts directly, but rather use the defined disease stages as surrogate marker of VL and mortality level for all HIV+ individuals.

1.4.2 HIV Cascade of Care

The continuum of care for infected individuals is modeled in five levels corresponding to those 1) unaware of their HIV infection, 2) diagnosed with HIV but not linked to care, 3) linked to care but not engaged in care, 4) engaged in care and on ART, and 5) engaged in care but not taking ART (Figure 1, main manuscript).

HIV-positive individuals are subject to a probability of screening for HIV at the beginning of each week. Upon diagnosis with HIV, individuals experience a fixed likelihood of linking to care over the following weeks. Once linked to care, individuals are assumed to engage in HIV care and start ART immediately. Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 24 weeks after ART initiation; rarely, in some patients it may take longer. Taking ART will further lower the disease mortality rate at each disease stage to a certain degree [12–14]. We assume that individuals starting ART through stage 3 (with CD4 count < 200 cells/ μL) will continue to experience the stage 3 mortality level (adjusted with ART reduction factor) for one year before reverting back to stage 2 (and experiencing stage 2 mortality level adjusted with ART reduction factor).

Those on ART can become non-adherent to treatment over time and/or become disengaged in care[1]. These individuals are subject to a weekly probability of reengagement in care and reinitiating ART in the future, but cannot reinitiate ART for 6 months after discontinuation [15]. Once off ART, individuals are assumed to lose viral suppression immediately and to experience a rapid decline in their CD4 counts. For simplicity, we assume that the effect of ART on CD4 count levels is maintained for one year following discontinuation (unless the agent was not previously on ART for a year, in which case the duration of ART is used) – and we also add this amount of time to the individual's "clock" of progression for HIV disease. Thus, for example, an individual starting ART in stage 2 and taking ART for 6 months before discontinuation will go back to stage 2, but the time until progression to stage 3 is prolonged by 6 additional months. We further assume that those starting ART in stage 1 will return to stage 2 if they discontinue treatment, and

[1] At ART discontinuation, if the person has started ART during Chronic disease, they are assumed to return to stage 2 with the same level of infectiousness and will be subjected to the corresponding mortality level. The duration of stage 2 is assumed to be the lesser of the preceding duration of ART (before loss to follow-up) or one year. If the person had started ART during stage 3, they will can return to stage 2 or stage 3 depending on the duration of treatment:

- If duration of treatment is smaller than the time spent in stage 3, agents return to stage 3 with the same level of infectiousness and mortality. The duration of stage 3 is extended for the duration of treatment up to one year.
- If duration of treatment is greater than the time spent in stage 3, agents return to stage 2. The duration of stage 2 will be expanded for the duration of treatment minus time spent in stage 3.

those beginning ART through stage 3 can revert to stage 2 or stage 3 depending on the duration of treatment.

1.5 HIV Transmission module

HIV transmission is evaluated for all active partnerships between HIV-positive individuals and susceptible partners at the end of each week. The probability of transmission is modeled as a function of an infected partner's infectiousness for transmitting HIV, the immunity of the negative partner toward transmission with HIV (through PrEP), potential protection through condom use, and an additional coefficient tuning the overall probability of transmission. HIV infectiousness is modeled as a function of an individual's VL corresponding to his disease stage and care status, as noted in Table 1 of the main manuscript. An individual's immunity to infection is modeled as a function of PrEP use and adherence, ranging from 0 (in absence of PrEP) to 1 (full adherence to PrEP). The probabilities of condom use in casual and stable partnerships are estimated based on reported levels through BESURE (Table S4). Finally, the transmission coefficient captures the baseline probability of HIV transmission per contact and is calibrated to reflect disease prevalence at equilibrium.

Table S4: Reported frequency of condom use in stable and casual partnerships from BESURE.

	Never	Part-time	The whole time
Stable partnership	0.45	0.55	0
Casual partnership	0.47	0.12	0.4

With these definitions, the weekly likelihood of HIV transmission through an active sexual contact is estimated as follow:

$$Ptrans(\mathrm{X},\mathrm{Y},\mathrm{Q}) = C \times X_{Inf} \times Y_{sus} \times (1 - pCondumUse(Q) \times cCondomEffectiveness) \times Y_{sexualPositionCoef}$$

where

Ptrans(*X,Y,Q*): Per week probability of transmission from person *X* (infected) to *Y* (susceptible) in a partnership type Q (stable, casual)

C: Simulation coefficient

Y_{Inf}: Person Y's infectiousness

X_{Sus}: Person *X's susceptibility* toward infection

pCondomUse(*Q*): Probability of using condom in partnership type Q

cCondomEffectiveness: condom effectiveness in reducing the risk of transmission

$Y_{sexualPositionCoef}$: Person Y's increased probability of transmission based on sexual positioning

1.6 GC Epidemiological Module

We consider NG/CT as a 'SIS'-type disease; specifically, individuals become infectious after an initial infection and remain infectious until treatment or spontaneous resolution, at which time they become immediately susceptible to recurrent infection. We assume that NG/CT is spread through sexual (genital-genital, genital-rectal, genital-oral, or oral-rectal) contact, and that infection may be either symptomatic or asymptomatic. Symptomatic individuals experience a fixed probability of seeking care in each week. We include only those care-seeking episodes that would trigger a clinical decision to test for NG/CT at the appropriate site and would result in treatment if the test were positive; other care-seeking episodes (whether for unrelated conditions [e.g., upper respiratory infections] or for symptoms of NG/CT that are either not recognized or would not result in treatment even if the test were positive) are ignored. We assume that individuals remain infectious during the week of treatment and one week thereafter [16–18]. In addition to this symptomatic testing behavior, all MSM (whether infected with NG/CT or not) can further undergo regular screening for NG/CT (i.e., in the absence of symptoms) according to CDC recommended criteria for MSM based on their HIV status, PrEP status, and STI history [19]. The duration of untreated disease (d) is based on literature estimates, and the weekly probability of spontaneous resolution is set to inverse of this duration ($1/d$).

1.6.1 Site of infection

We differentiate three types of NG/CT infections based on the site of infection as Urethral, Rectal or Pharyngeal infections. Given the low degree of overlap for simultaneous infections in multiple sites, and the higher likelihood of symptomatic disease in urethral infections for those co-infected with rectal and pharyngeal infections, we only allow for a single-site NG/CT infection in each individual and will exclude the possibility of simultaneous infections in various sites (allowing for no reinfection while the original infection lasts). Each type of infection is further associated with a specific likelihood of developing symptomatic disease (Table 1 of the main manuscript). Among HIV- individuals, a rectal/urethral NG/CT can increase the transmissibility of HIV to sexual contacts among HIV infected MSM and also increase the susceptibility for HIV acquisition among HIV uninfected MSM.

1.6.2 NG/CT Transmission dynamics

NG/CT-infected individuals can transmit the disease to other individuals through exiting network of sexual contacts (previously built and calibrated for the HIV model). Due to complications in conceptualizing all various pathways for transmission of disease from one site to another with regard to different types of sex acts, unknown level of individuals' preferences for each sexual role and the degree of versatility to change this role in each partnership, in addition to the lack of data informing the risk of NG/CT infection through each mode of transmission, we adopt a simplifying assumption to combine various modes of transmission for all types of infections through a single transmission event modeled over each active sexual contact between an infected and uninfected MSM at each time step. Upon transmission with NG/CT, the clinical site of the recipient infection is randomly assigned in such a way as to replicate the relative incidence of infection at each site as estimated from local surveillance report in Baltimore City (see Table 1 of the main manuscript).

1.6.3 Computing the probability of presenting to STI care

MSM may present to HIV/STI care providers (e.g., STD clinics, community health centers, HIV counseling programs) for a variety of reasons, and get tested for HIV and other STIs. We model visits for STI screening as a fixed weekly probability that reflects an individual's age-group (modeled in 12 classes for MSM age 15 to 75) and sexual activity level (modeled in 3 classes of sexual activity), such that younger MSM with higher propensity of partnerships experience a higher likelihood of visits [20,21].

We let *S* represent the individuals' sexual activity class (values ranging from 1 to 3 representing low-, medium- and high-activity classes) and we let A represent the individual's age-group (values ranging from 1 to 12 representing age groups of 5 years each: [15,19], [20-24], …, [70,75]). Finally, according to previous assumptions for lower level of access to HIV care among Black MSM compared to White MSM in the baseline simulation model, we modify the probability of accessing to STI care (*pAccessCare*) by race (R) set at 50% for Black MSM relative to White MSM [22]. Given these assumptions, an individual's probability of presenting to STI care (*PPSC*) at each week is computed as follow:

$$PPSC\ (\mathrm{S},\mathrm{A},\mathrm{R}) = {}^{(13-\mathrm{A})}/_{12} \times {}^{(\mathrm{S})}/_{3} \times pAccessCare(\mathrm{R}) \times C$$

where C is the fixed coefficient for fine-tuning the probability of presenting to STI care.

1.7 PrEP module

PrEP Eligibility criteria: Our primary outcome for the current analysis is the projected incidence of HIV after 20 years of delivering PrEP to MSM in Baltimore City. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the added benefit of targeting PrEP at individuals diagnosed with NG/CT. In all three scenarios, indication for PrEP use (eligibility) is considered in accordance with CDC recommendations [23] and Baltimore City's PrEP guidelines [24].

The CDC guidelines for PrEP use among MSM use the following criteria as indications for PrEP: sexually active HIV negative adult MSM who are not in a monogamous partnership with an HIV-negative male partner and who in the last 6 months: report any condomless anal sex, have any STI reported or diagnosed, or report having an ongoing sex partner with HIV [23]. The PrEP guidelines in Baltimore City further suggest that all HIV negative MSM who 1) may not have access to condom or always ask a partner to use a condom, 2) are diagnosed with a STI in the last 6 months, 3) are in a serodiscordant relationship with a HIV-infected partner (who may or may not be on HIV treatment), 4) are unsure of HIV-status of their sexual partner, or 5) inject drugs or are in a sexual partnership with a person who inject drugs should consider PrEP. As such, we modelled the criteria for PrEP eligibility among MSM to include HIV-negative MSM who are diagnosed with NG/CT in the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual partnership in the last 6 months.

2 SIMULATION CALIBRATION

Individual-level parameters in our models fall into two categories: "fixed" parameters estimated based on available literature or data, and "variable" parameters that are unknown and will be calibrated based on epidemiological setting. Fixed (known) parameters include those associated with the natural history of HIV (such as viral load levels in each disease stage) and those defining behavioral characteristics (e.g., likelihood of condom use). Variable parameters include descriptors of HIV and NG/CT transmission and

care that are defined at the individual-level and will be calibrated to provide the corresponding calibration targets (at the population-level) from Baltimore City (e.g., tuning the individual's probability of presenting to care for HIV screening to provide the target proportion of infected population diagnosed in Baltimore City). Table 1 in the main manuscript includes a list of main calibration targets for HIV and NG/CT modules.

2.1 Calibration Targets

2.1.1 HIV prevalence and continuum of care

Using the latest report of public HIV surveillance data from Baltimore City (year 2012) [2], we estimate the prevalence of HIV among MSM at a total of 3329 people, which corresponds to a prevalence of 22% in our simulated population. Furthermore, we estimate the reported proportion of HIV-infected MSM in each step of the cascade at 86% for those diagnosed but not linked to care, 62% for those linked to care but not engaged, 50% for those engaged but not on ART, 39% for those on ART but not virally suppressed and finally 27% for those virally suppressed.

2.1.2 NG/CT incidence

In this section, we provide details of our estimation procedure for NG/CT incidence using data made available to us through several sources including 1) the gonorrhoea Surveillance dataset, 2) STD Surveillance Network, and 3) BCHD facility dataset in Baltimore City.

Estimating the annual diagnosis of gonorrhoea infection in Baltimore City: The gonorrhoea Surveillance dataset includes all males residing in Baltimore City who were reported to the Baltimore City Health Department for infection with gonorrhoea at one or more anatomic site, regardless of sex partner gender, beginning with cases diagnosed on 1/1/09 and ending with cases reported through 5/31/16. Due to changes in testing technology, we only consider data from 2011 and later for estimating gonorrhoea diagnosis as that is when the STD clinics started using NAATs for extragenital swabs (due to the lab becoming validated for this) which is more in line with practices moving forward. We further restrict the data to the end of 2015, to cover the annual number of diagnosis in each full year (Table S5). We further analyze this data by reported site of infection and estimate the range of reported gonorrhoea diagnosis in each body site (Table S6).

Table S5: Annual number of reported gonorrhoea diagnosis among men in Baltimore City.

	2011	2012	2013	2014	2015
Gonorrhoea diagnosis	1139	901	1052	1083	1297

Table S6: Annual gonorrhoea diagnosis among men by site of infection in Baltimore City.

Site of infection	Lower bound	Upper bound
Urethral	681	1026
Rectal	46	83
Pharyngeal	58	151

Adjusting for MSM risk group: The surveillance dataset does not include information on gender of sex partners for all persons diagnosed with gonorrhoea infection. This information is however available for a

subset of population through STD Surveillance Network (SSuN). SSuN attendees are randomly selected from MSM diagnosed with gonorrhoea who will then agree to complete a SSuN interview. Within this group, 26% to 30% of all male patients identified themselves as MSM in Baltimore City.

Adjusting for non-overlapping Chlamydia infections: The BCHD facility dataset provides information on diagnosis of gonorrhoea or chlamydia infection among all male patients visiting the two STD clinics in Baltimore City. This data is further stratified for MSM by including men who reported male sex partners in the past 3 months OR self-identified as gay or bisexual. For patients who visited the clinic multiple times, if he was classified as MSM at any visit, we included all his clinic visits. The dataset provides information on all episodes of visit and diagnosis with gonorrhoea or chlamydia infection among these men. Based on the reported number of diagnosis, we estimate the proportion of diagnosed chlamydia infection that did not overlap with gonorrhoea infection relative to overall number of gonorrhoea diagnosis at 40%, and use this value to adjust the annual number of gonorrhoea diagnosis among MSM to include non-overlapping chlamydia infections as well. This estimate also agrees with the reported level of chlamydia infection relative gonorrhoea infection in Baltimore City through the STD Surveillance Network (SSuN) 2013 [25].

Adjusting for proportion of symptomatic cases not seeking care: In order to derive the true incidence of disease from the current estimates of the number diagnosis, we further adjust our estimate to account for the proportion of symptomatic cases not seeking care. Based on literature, we estimate that approximately 60% symptomatic population may not seek direct care for their disease (56% for Urethral infection, 60% for Rectal and 70% for Pharyngeal infection) [26], and inflate the number of symptomatic cases in our sample (approximately 78% of sample) by 250% to account for these cases.

Adjusting for the number of asymptomatic infection: Given the restrictions in capturing the underlying level of asymptomatic disease from the estimated of NG/CT diagnosis, we rely on our estimate of the symptomatic NG/CT incidence, and assume that each episode of NG/CT infection is associated with a 74% likelihood of symptomatic infection for urethral, 20% for Rectal, and 10% for Pharyngeal disease [26–28]. Based on this assumption, we derive the estimate for annual incidence of NG/CT among MSM by site of infection as follow:

- Incidence of urethral infection [725 – 1135] Person/year
- Incidence of rectal infection [144 – 259] Person/year
- Incidence of pharyngeal infection [327 – 852] Person/year

Challenges in interpreting local estimates: Despite general expectations, our estimated ratio of rectal/pharyngeal to urethral infections is very small. This pattern does not agree with the previously reported prevalence of extragenital relative to genital NG/CT in different populations that estimate the average prevalence ratio of rectal to urethral infections at 4.1 (ranging from 2.43 to 6.23) and pharyngeal to urethral infections at 1.5 (ranging from 1.35 to 1.71) [29–31]. In a previous analysis of SSuN data, researcher reported a similarly low proportion of extragenital to genital NG/CT infections among MSM attending STD clinics [32], and attributed it to low rate of extragenital NG/CT screening at STD clinics that results in missing those infections [33].

Given that our estimates of the genital and extragenital NG/CT infections based on local datasets from Baltimore City are more in line with the observed trends in the SSuN data, we believe that the same pattern of underestimation is evident for the true incidence of extragenital NG/CT infection in this population. In order to fix this problem, we chose to rely on the estimated incidence of genital (urethral)

NG/CT infection from the surveillance dataset in Baltimore City (assuming appropriate level of genital-site testing/screening and reporting), and to estimate the incidence of rectal and pharyngeal infections by applying the reported prevalence ratio of each infection site relative to urethral infection.

Estimating the incidence of rectal and pharyngeal infection: We assume that diagnosed NG/CT will be treated very rapidly, such that the relative duration of disease is driven by the proportion of infections for which people are not treated - whether because they are asymptomatic, symptoms are not sufficient to drive care-seeking, or the clinical presentation (e.g., sore throat) does not prompt testing or treatment for NG/CT. Screening is assumed to have relatively little impact on the *relative* duration of infection (i.e., screening can occur, but it does not pick up so many more prevalent urethral infections than pharyngeal infections, for example, that it drives the ratio of disease duration in the population to a significant degree). We further assume that the asymptomatic disease is likely to go undetected and therefore 26% of urethral infections, as well as 80% of rectal and 90% of pharyngeal infections will go untreated [26–28].

Based on these assumptions, we derive the incidence ratios based on prevalence ratios as follow:

- Incidence ratio of rectal to urethral disease: 4.08 (prevalence ratio) * 0.26 /0.8 (proportion of untreated cases) = 1.33
- Incidence ratio of pharyngeal to urethral disease: 1.5 (prevalence ratio) * 0.26 /0.9 (proportion of untreated cases) = 0.43

Using the estimated incidence ratios, we estimate the incidence of rectal and pharyngeal NG/CT among MSM as follow:

- Incidence of urethral NG/CT among Baltimore's MSM: [735-1135] Person/year
- Incidence of rectal NG/CT among Baltimore's MSM: [998-1505] Person/year
- Incidence of pharyngeal NG/CT among Baltimore's MSM: [326-492] Person/year

2.2 Calibration procedure

Upon collection of all individual-level data and incorporation into the model (fixed parameters), we calibrated the model as a whole against population-level targets (above) to ensure that the model provides realistic outputs. This was done via a random search mechanism to find the best combination of parameter values that minimizes the observed difference between simulated outputs and the calibration targets.

Burn-in Period: The model starts from a randomly generated population of MSM with no active partnership at time zero with a randomly assigned pattern of HIV infection (randomly according to age, race and location of residence). In order to create a realistic pattern of sexual partnerships with age, we allowed the original population to age and evolve for at least one generation before reaching a stable level of HIV incidence in the absence of PrEP – thus generating a full burn-in period of 100 years (a decision made on an a-priori basis).

2.3 Calibrating partnerships

BESURE surveys (2004 – 2014) provided the main source of local information available on the network of MSM partnerships in Baltimore. The data included aggregate information on the reported number of sexual partners (by age group) and type of those partnerships in the last 12 months. Assuming a fixed mixing structure over time, we used this information to calibrate the individual-level likelihood of engaging in a stable or casual partnership at each simulated time step (week). We further used the coefficients of sexual activity to calibrate the right and left tail of the partnership frequency distribution

(for those MSM reporting 0 or more than 5 partners in a given year). The partnership calibration results are summarized in Figure S5.

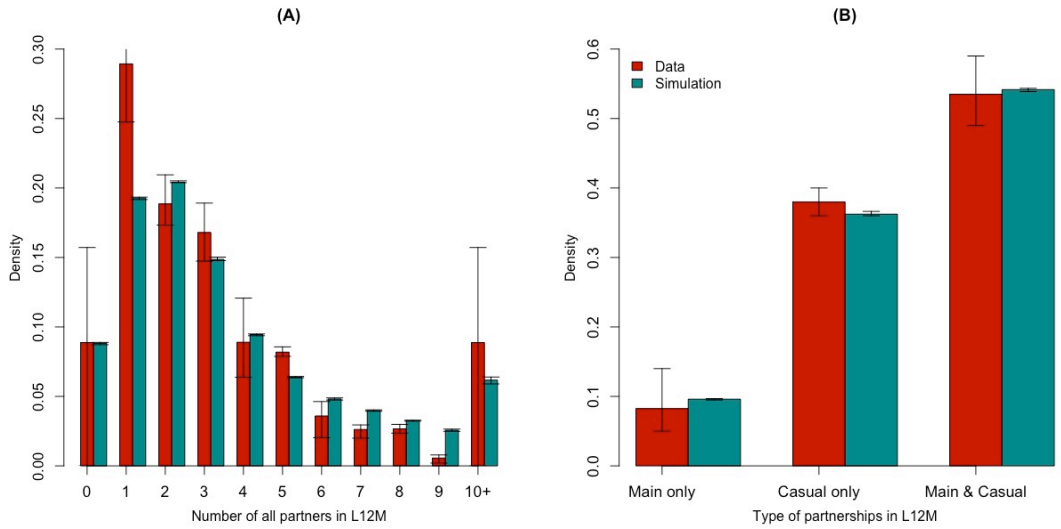

Figure S5: Model calibration to partnership data. Shown are the mean values of simulations (in green) compared against empirical data (in red). The error bars around simulated values represent the 95% uncertainty range of observations around each simulated measure, and the error bars around the data represent the range of annual observations through the 4 BESURE surveys from 2004 to 2014.

2.3.1 Frequency of partnerships by age and sexual activity

The age-dependent coefficients of partnerships in each sexual activity class were calibrated to accurately portray the right and left tails of the partnership frequency distribution for all MSM and in each age group. The calibration results are summarized in Figure S6.

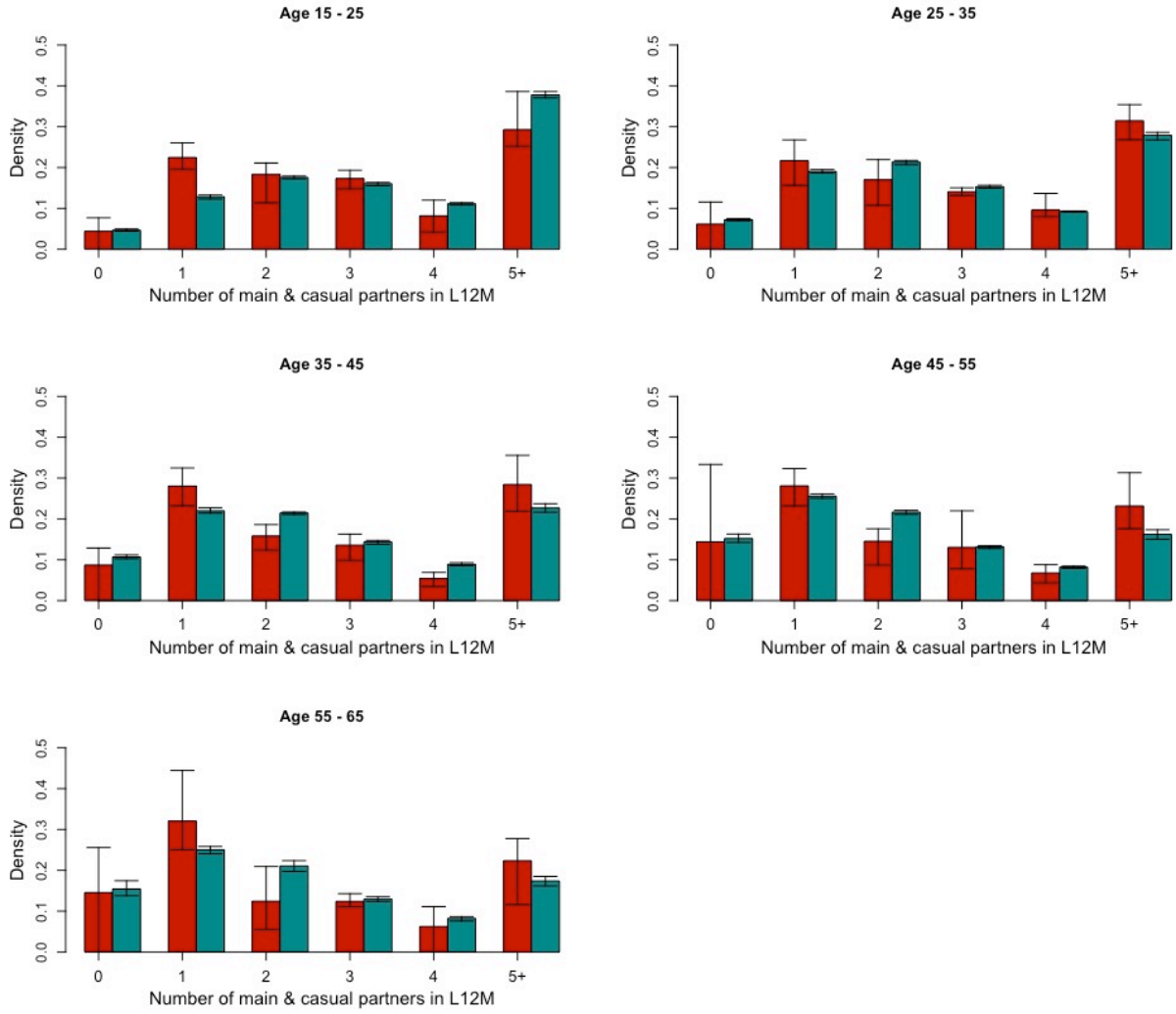

Figure S6: Frequency of reported partnerships in each age group in the last 12 months (L12M), comparing model results to the data against which the model was calibrated. Shown are the mean values across all simulations (in green) compared against empirical data (in red). The error bars around simulated bars represent the 95% uncertainty range of simulated values and the error bars around the data represent the range of annual observations through the 4 BESURE surveys from 2004 to 2014.

There were conceptual challenges with the use of BESURE data as the main data source for calibrating the network of sexual partnerships. Specifically, BESURE applies a venue-based sampling method, which is more likely to capture a representative sample of young (as opposed to older) MSM. Based on discussions with the BESURE investigators, we felt that the general population of older MSM was likely to have lower numbers of sex partners than reported in BESURE and therefore allowed for a lower frequency of partnerships among older MSM.

Furthermore, given the strong bimodal distribution of partnerships among young adults, we were not able to replicate these empirical distributions precisely and thus chose to minimize the estimation error at the tails of this distribution. To further assist the calibration of tails, we defined sexual activity classes

according to the mean number of casual partnerships to represent natural heterogeneity in in individual-level partnerships. Addition of high versus low/medium sexual activity classes allowed us to calibrate the overall frequency of partnerships in each age group with more precision. Figure S7 represents model projections of the frequency of partnerships in each sexual activity class. This figure illustrates that, after calibration to BESURE data, the low and medium sexual activity classes behave very similarly (and may likely be represented equally well as a single class). Given the lack of representative data against which to explicitly calibrate these distributions, this presumed distribution of sexual partnerships is an assumption/limitation of the current model.

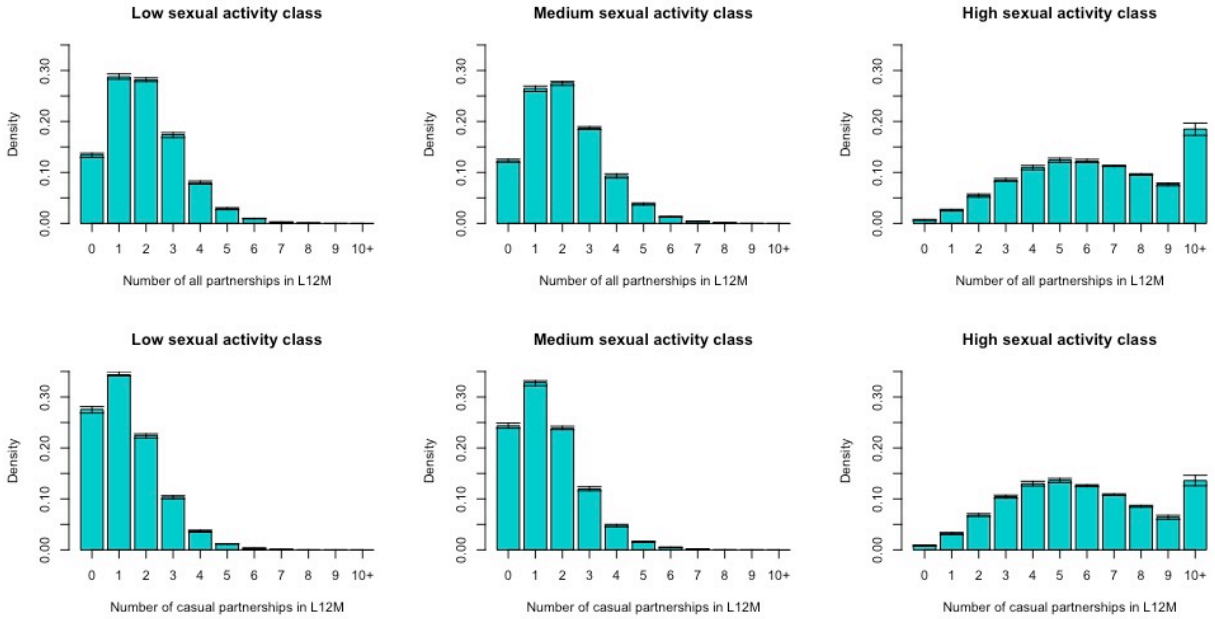

Figure S7: Model projections of the frequency of partnerships in the last 12 months (L12M) in each sexual activity class. Panels represent the distribution of all (top row) and casual (bottom row) partnerships in low, medium and high sexual activity classes. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

2.4 Calibrating HIV and NG/CT epidemiology

Using the population-level targets for annual diagnosis and incidence of NG/CT as well as HIV prevalence and cascade of care (section 3.1), we calibrate the simulation model to provide these outcomes within an acceptable range (Figure S8 A through D).

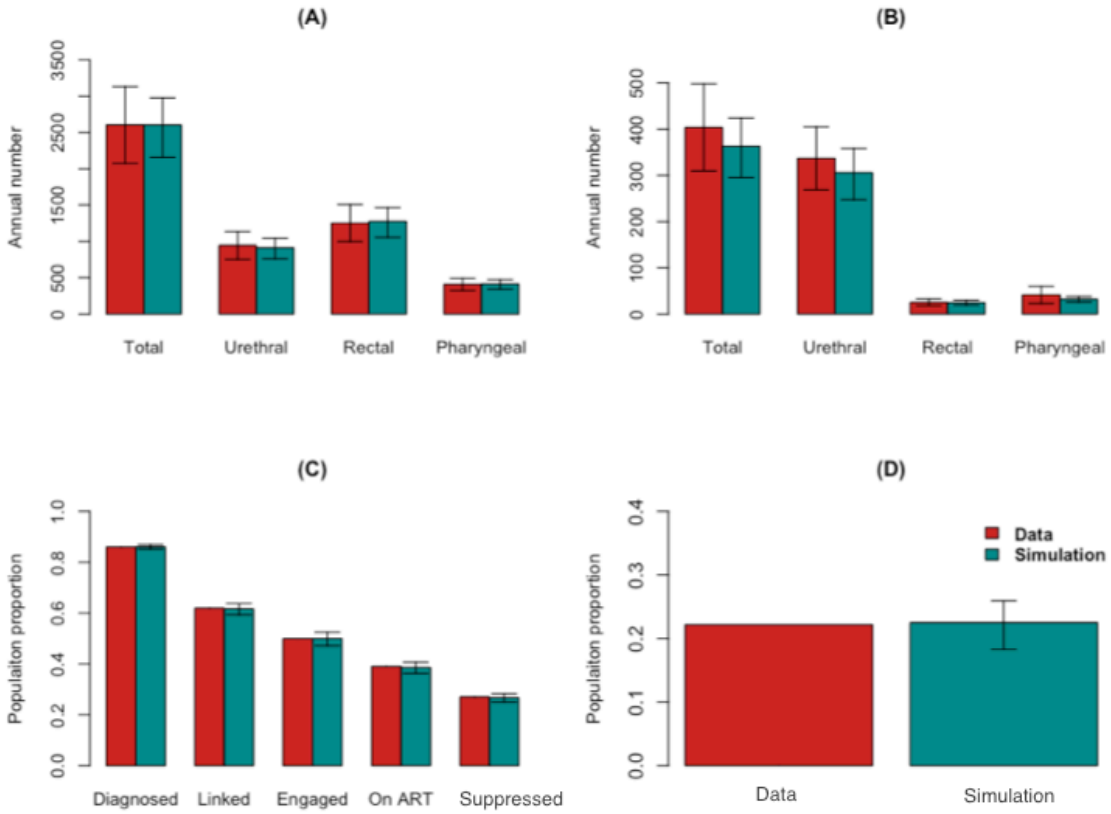

Figure S8: Closeness of model fit to epidemiological data for (A) annual incidence of NG/CT, (B) annual diagnosis of NG/CT, (C) Cascade of HIV Care, and (D) HIV prevalence. These graphs illustrate the effectiveness of the calibration procedure and are not a validation of the underlying data or the model itself. Shown are the mean values of 200 simulations (in green) compared against empirical data (in red). The error bars around simulated values represent the 95% uncertainty range of observations around each simulated measure, and the error bars around the data in panel A&B represent the range of annual observations through the Baltimore City surveillance dataset (2011 – 2015). Data used for calibration in panel C&D is only available as point estimate in year 2012.

Given the lack of data regarding the anatomical site of infection and the relative frequency of oral-only versus oral-plus-anal versus anal-only sex to model site-specific transmission dynamics for NG/CT, we adopted a simplified approach that does not fully capture the complete transmission dynamics but should result in the appropriate distributions of NG/CT infection at each anatomical site. For this purpose, we combined various modes of transmission for all types of infections through a single transmission event modeled over each active sexual contact between an infected and uninfected MSM at each time step. Upon transmission with NG/CT, the clinical site of the recipient infection was randomly assigned in such a way as to replicate the relative incidence of infection at each site as estimated from local surveillance report in Baltimore City (see Table 1). The final calibration results in a probability of 35% for urethral, 49% for rectal and 16% for pharyngeal infections modeled upon each successful transmission event. Since the goal of this model is not to comprehensively represent the dynamics of NG/CT transmission but rather to estimate the impact of PrEP strategies for HIV that incorporate NG/CT screening and treatment, we

adopted this simplified approach (which may have some inaccuracies regarding the specific transmission dynamics but should result in the appropriate marginal distributions of infection by each anatomical site), rather than incorporating data-free assumptions about the relative frequency of oral-only versus oral-plus-genital sex and the relative transmissibility of NG/CT from each anatomical site to the other.

2.4.1 HIV and NG/CT co-infection:

As described above, our calibration targets were limited to the marginal distributions of HIV and NG/CT infections among MSM, and excluded the co-infection rates due to data unavailability. Unpublished results from analysis of STD Surveillance Network (SSuN) data [34] from 2008 to 2013 in 12 jurisdictions suggest that 8% of patients diagnosed with NG had a previous HIV diagnosis, and among the remaining individuals diagnosed with NG, 69% received an HIV test within 30 days of their STI diagnosis. However, the proportion of patients diagnosed with HIV coinfection on that test is not recorded. We therefore took a conservative approach, assuming that the only correlations between HIV and NG/CT would be induced by age- and race-specific assortative mixing, plus differentiation of individuals into three different sexual activity classes. Figure S9A represents the projected levels of HIV and NG/CT prevalence at the end of each year in the model, corresponding to 22% of MSM infected with HIV (calibration target), 10% infected with NG/CT (calibration target) and 2.5% infected with HIV and NG/CT (a cross survey estimate). Figure S9B represents the proportion of incident cases who were co-infected with NG/CT and HIV at the time of HIV or STI infection. For example, this figure suggests that 20% of incident HIV cases are co-infected with NG/CT at the time of disease transmission. These results suggest that our underlying sexual activity assumptions do not impose a high rate of correlation between the two diseases; as a result, our estimates of the impact of STI-based PrEP may be conservative. To the extent that HIV and NG/CT co-locate among similar populations beyond age, race, and tertiles of sexual activity, one would expect that NG/CT-targeted PrEP strategies would have even greater impact than projected in this model.

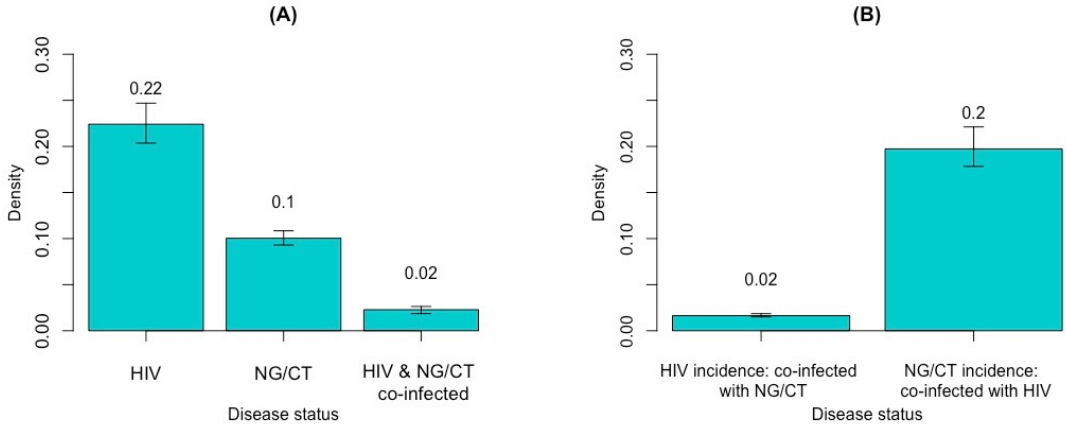

Figure S9: Model projections of the distribution of HIV, NG/CT, and coinfection among MSM (Panel A) and the proportion of HIV and NG/CT incident cases coinfected at the time of transmission (Panel B). Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

2.4.2 Distribution of HIV and NG/CT by age and sexual activity

Figure S10 represents the distribution of HIV infections (panels A & C) and NG/CT infections (Panels B&D) by age (first row) and tertile of sexual activity (second row).

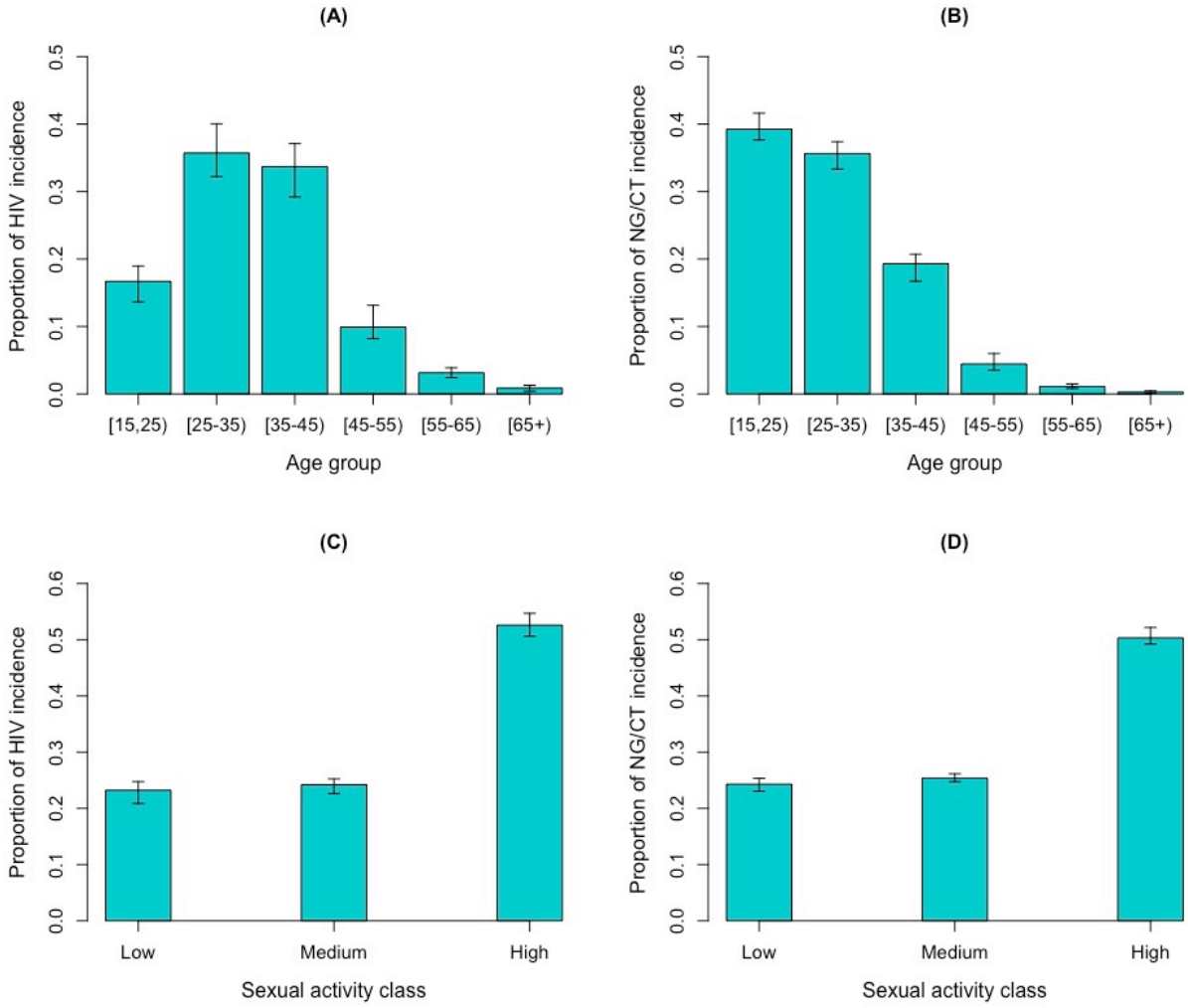

Figure S10: Model projections of the distribution of HIV (A, C) and NG/CT (B,D) incidence by age and sexual activity class. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

2.5 Complete list of model parameters

Table S7 provides a complete list of model parameters and values.

Table S7: Complete list of model parameters and values.

Parameter	Value	References
Partnerships		
Proportion of population in each sexual activity (SA) **class**	0.33	
Rate of casual partnership formation in each sexual activity class relative to the medium sexual activity class	Low sexual activity class 0.85 High sexual activity class 5.0	
Rate of casual partnership by age group	[15-25): 0.5 [25-45): 0.3 [45-55): 0.25 [55-75+): 0.3	
Age Mixing (Absolute different in square root of ages) • Stable partnerships • Casual partnerships	 0.6 0.73	 [35]
Race mixing (Likelihood of mixing with a partner of the same race) - Black & Black - White & White	 0.9 0.75	[35]
Likelihood of condom use - Stable partnerships - Casual partnerships	[Never, Partially, Always] [0.45, 0.55, 0.00] [0.47, 0.12, 0.41]	 [35]
Sexual position preference - Insertive only - Receptive only - Versatile	 0.42 0.26 0.32	 [35]
Transmission coefficient for insertive relative to receptive sexual position	0.384	[36]
NG/CT		
Proportion of cases symptomatic - Urethral - Rectal - Pharyngeal	 74% 20% 10%	 [27] [26,37] [28,37]
Duration of infection in the absence of treatment	[3 – 12] months [2]	[16,38,47–51,39–46]
Duration of treatment	2 weeks	[16–18]
Regular GC screening intervals for HIV+ MSM on ART - All MSM - MSM with a history of NG/CT in the last 6 months	 12 months 6 months	 [52]
Likelihood of compliance with CDC guideline for NG/CT screening	40%	[53–58]
Efficacy of condoms to prevent NG/CT transmission	70%	[16,59,60]
Increase in HIV transmissibility (from urethral or rectal infection)	[1.5 – 2] fold [3]	[61–65]
Increase in HIV susceptibility (from urethral or rectal infection)	[1 – 2.5] fold [3]	[16,28,65,66]

[2] Values are selected over uniform distributions across the ranges presented

Probability of NG/CT transmission per act	0.294	Calibrated to provide the incidence of NG/CT
Proportion of NG/CT infections assigned to each site - Urethral - Rectal - Pharyngeal	 35% 49% 16%	Calibrated to provide the site-specific incidence of NG/CT
Weekly probability of symptomatic NG/CT testing - Urethral - Rectal - Pharyngeal	 0.009 0.001 0.04	Calibrated to provide the site-specific diagnosis of NG/CT
Weekly probability of screening high-risk (according to age and sexual activity class) MSM for HIV and NG/CT	0.014	Calibrated to provide the annual diagnosis of NG/CT and HIV
Probability that NG/CT screening only at urethral site	0.94	Calibrated to provide the relative diagnosis of extragenital to genital NG/CT
Relative likelihood of NG/CT screening among Black MSM relative to White MSM	0.5	[22]
HIV		
Disease stage duration - Stage 1 (CD4 >500 cells/µL): Acute - Stage 2 (CD4 200-499 cells/µL): Chronic - Stage 3 (CD4 <200 cells/µL)[3]: Late stage	 [6 – 9] weeks [3] [8 – 10] years [1 – 3] years	[5,67,68] [5,69] [5,67,69]
Time from ART initiation to full viral suppression	[4-24] weeks [3]	[70]
Time from ART discontinuation to pre-ART CD4 nadir[4]	ART treatment duration up to one year	[71–74]
Mortality rate [3] - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART	 5 per 1000 person years 1/duration of stage 3 58%	[12–14]
Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART - Stage 3, no ART - On ART, partially suppressed - On ART, fully suppressed	 6.5 4.5 5 3.5 1.5	[5]
Efficacy of condoms to prevent HIV transmission	80%	[75,76]
Infectiousness per sexual contact	2.45 $^{(\log(VL)-4.5)}$	[5]
Individual's weekly likelihood of engagement in HIV care	0.00577	[77–79]
Weekly probability of ART discontinuation	0.0015	[80]

[3] Mortality rate in stage 3 is defined as 1/(duration of stage 3).

[4] Infectiousness assumed equal to that of stage 2

Gap in care after ART discontinuation	26 weeks	[15]
Weekly probability of - Screening for HIV only (not NG/CT) - Linkage to care (if HIV-positive and not linked) - Starting ART (if engaged)	 0.0065 0.0065 0.095	 Calibrated to provide the HIV cascade of care
Relative likelihood of accessing HIV care among Black MSM	0.5	[22]

2.6 Additional analysis

Since sexual activity class is a modeling construct rather than a measurable feature of an individual (see section 1.3.1), there are no data to describe assortative mixing by activity class per se. Similarly, lacking data on serosorting among primary and casual partnerships, we did not explicitly incorporate this into the model. In order to further elucidate model dynamics, we have generated additional figures to report the simulated frequency of sexual partnerships by sexual activity classes (e.g., High-High, High-Med, etc.) and also HIV serostatus (Figure S11 and S12). Note that, since sexual activity class was assumed to reflect casual partnerships only, the frequency of stable partnerships is similar and randomly distributed across all classes (with partnerships across classes being twice as likely as partnerships within classes, reflecting the laws of probability with random assortment).

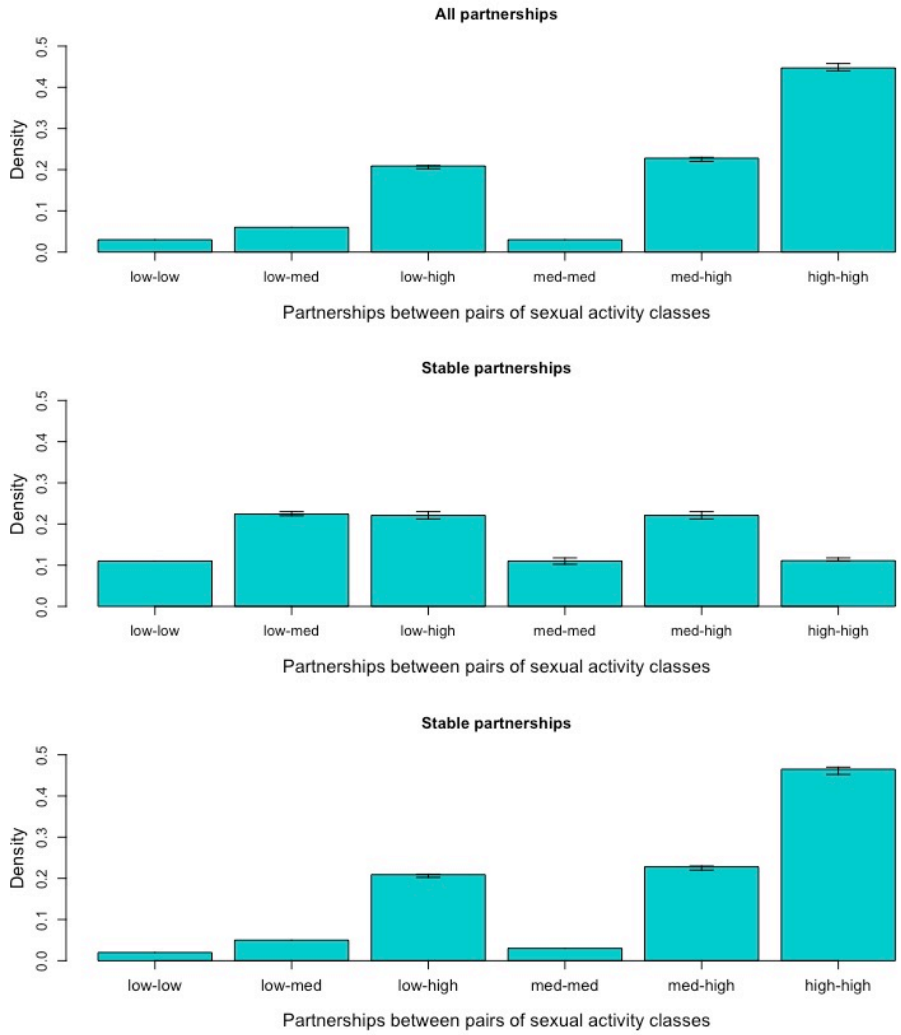

Figure S11: Model projections of the distribution of partnerships among MSM by sexual activity class. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

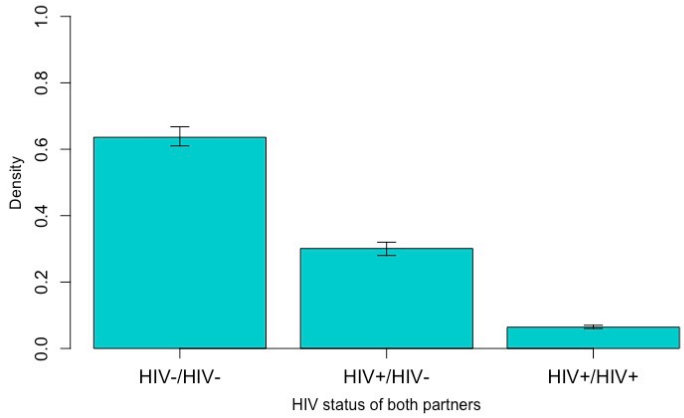

Figure S12: Model projections of the distribution of partnerships by HIV status. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

In order to better illustrate the implications of these modeling assumptions on impact of STI targeted PrEP, we also checked the distribution of MSM receiving PrEP in the model by sexual activity class an age (Figure S13). As expected, targeting PrEP at MSM diagnosed with STIs provides an efficient approach for providing PrEP to high-risk individuals in the high sexual activity class and younger age groups (Figure S13-Panels A & D)

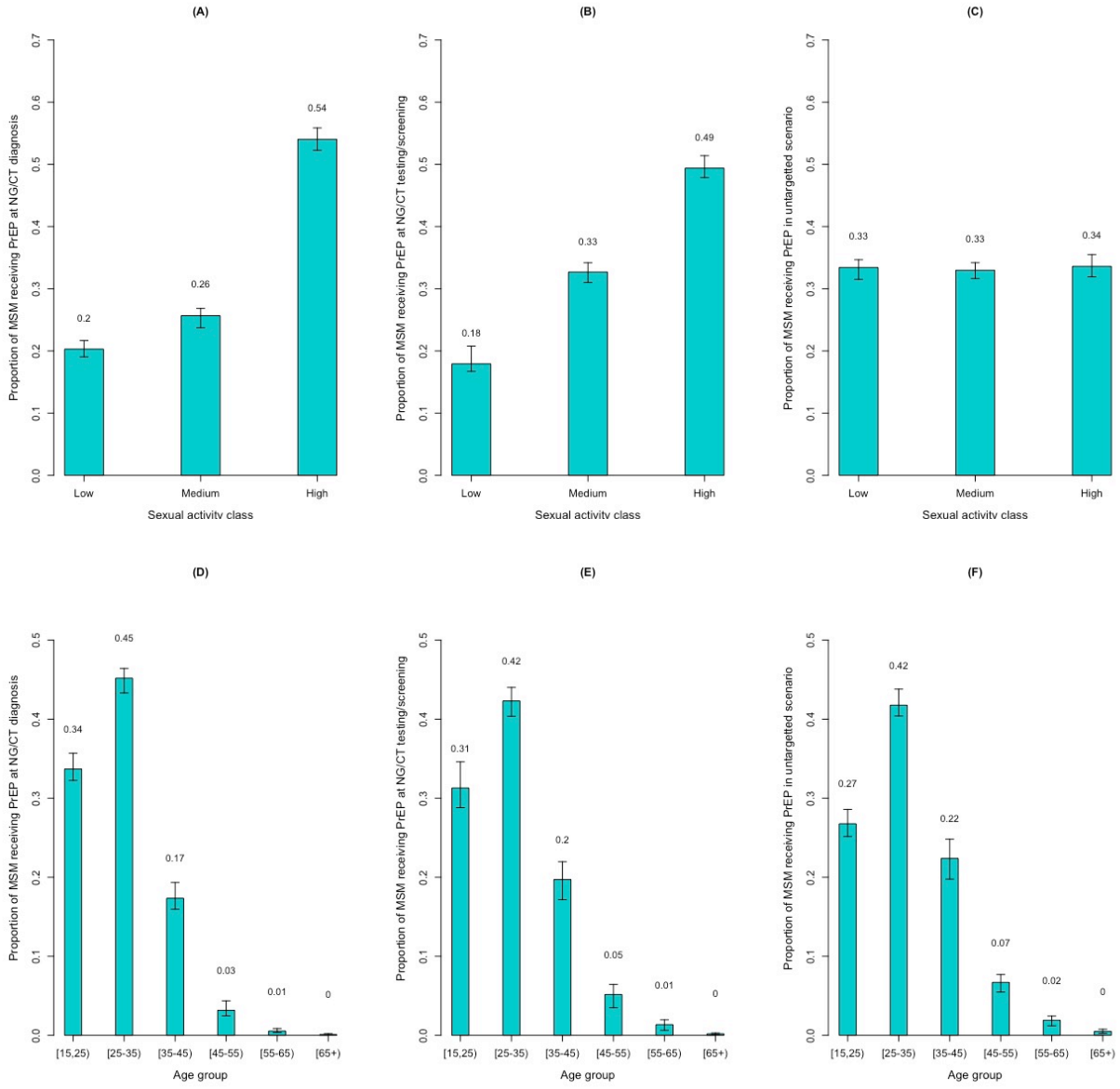

Figure S13: Model projections of the distribution of MSM receiving PrEP in each sexual activity class (top row) and each age group (bottom row) in each PrEP scenario. Panels A and D depict this distribution under NG/CT-targeted PREP; panels B and E illustrate PrEP evaluation at NG/CT screening and testing; and panels C and F represent untargeted PrEP. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

3 SENSITIVITY ANALYSIS

One-way sensitivity analysis of simulation results was performed with regard to all model parameters (listed in Table S7). For this purpose, we changed each parameter to +/- 25% of its original value, one at a

time (keeping all others fixed at the original value) and evaluated the main simulation outputs after such variation. The primary output of interest for the sensitivity analysis was HIV incidence at 10 years without PrEP (baseline) and with PrEP (under each PrEP campaign). For this analysis, we assumed an uptake and adherence of 60% to PrEP. The tornado graphs (Figure S14 to S17) represent the results of the one-way sensitivity analysis. Figure S14 presents the results for HIV incidence at year 10 in Baseline (absence of PrEP), and Figure S15 through Figure S17 present HIV incidence in year 10 of a PrEP campaign targeting MSM at the time of NG/CT-diagnosis (Figure S15), at the time of NG/CT screening (Figure S16) or through a community-wide campaign (Figure S17).

Assuming a threshold of 25% to detect significant changes, the projected HIV incidence at baseline and in absence of PrEP (Figure S14) was sensitive to variation of parameters relating to 1) transmission of HIV including the coefficient of HIV transmission, viral load as a measure of infectiousness, and condom use and effectiveness; 2) the coefficient of NG/CT transmission; and 3) parameters describing overall sexual activity including the probabilities of starting new partnerships, and the level of sexual activity in the most sexually active class. Similar behavior was observed in scenarios modeling the implementation of PrEP at NG/CT diagnosis (Figure S15), at the time of NG/CT screening (Figure S16) or through a community-wide campaign (Figure S17). None of the sensitivity analysis scenarios resulted in significant variation (>25%) of HIV incidence in PrEP scenarios compared to the baseline.

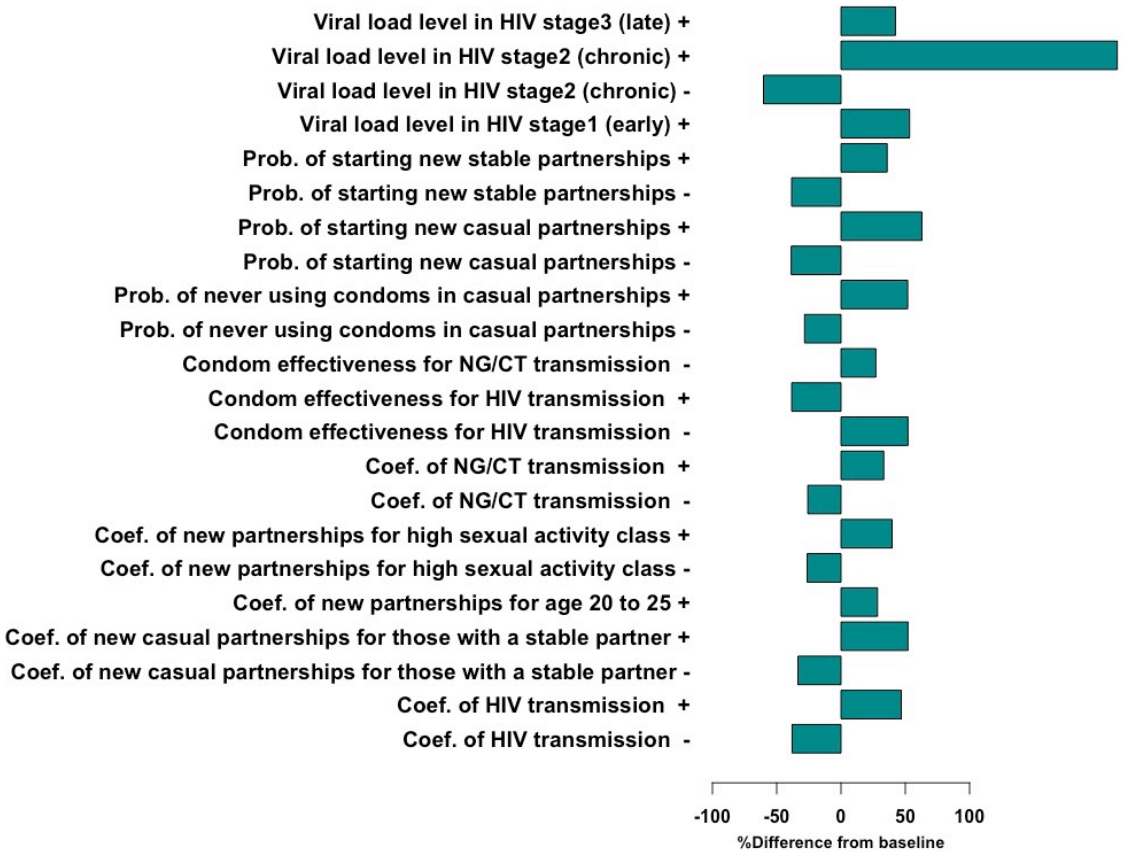

Figure S14: Sensitivity analysis of HIV incidence at year 10 to variation of model parameters in the Baseline (absence of PrEP) scenario. Input parameters are listed on the left, +/- corresponding to 25%

increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant.

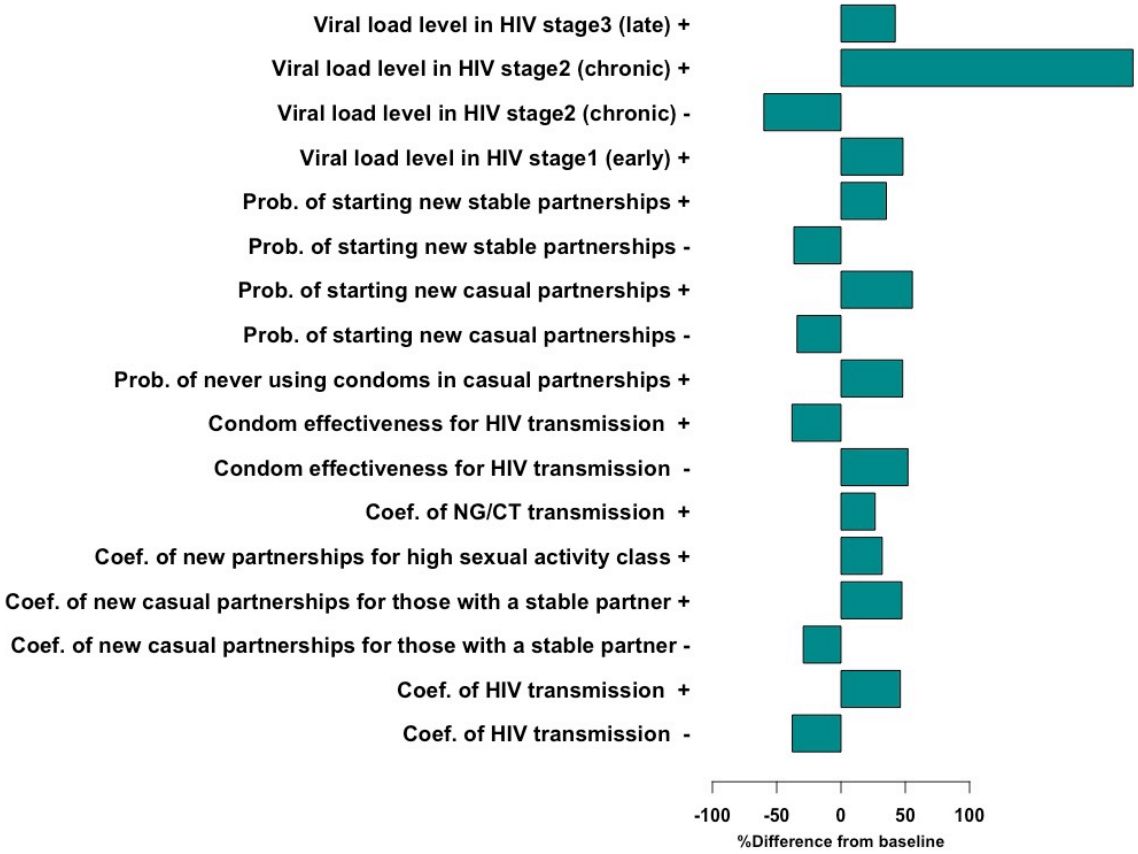

Figure S15: Sensitivity analysis of HIV incidence in year 10 to variation of model parameters in the scenario of a PrEP campaign targeting MSM at the time of NG/CT-diagnosis. Input parameters are listed on the left, +/- corresponding to 25% increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant

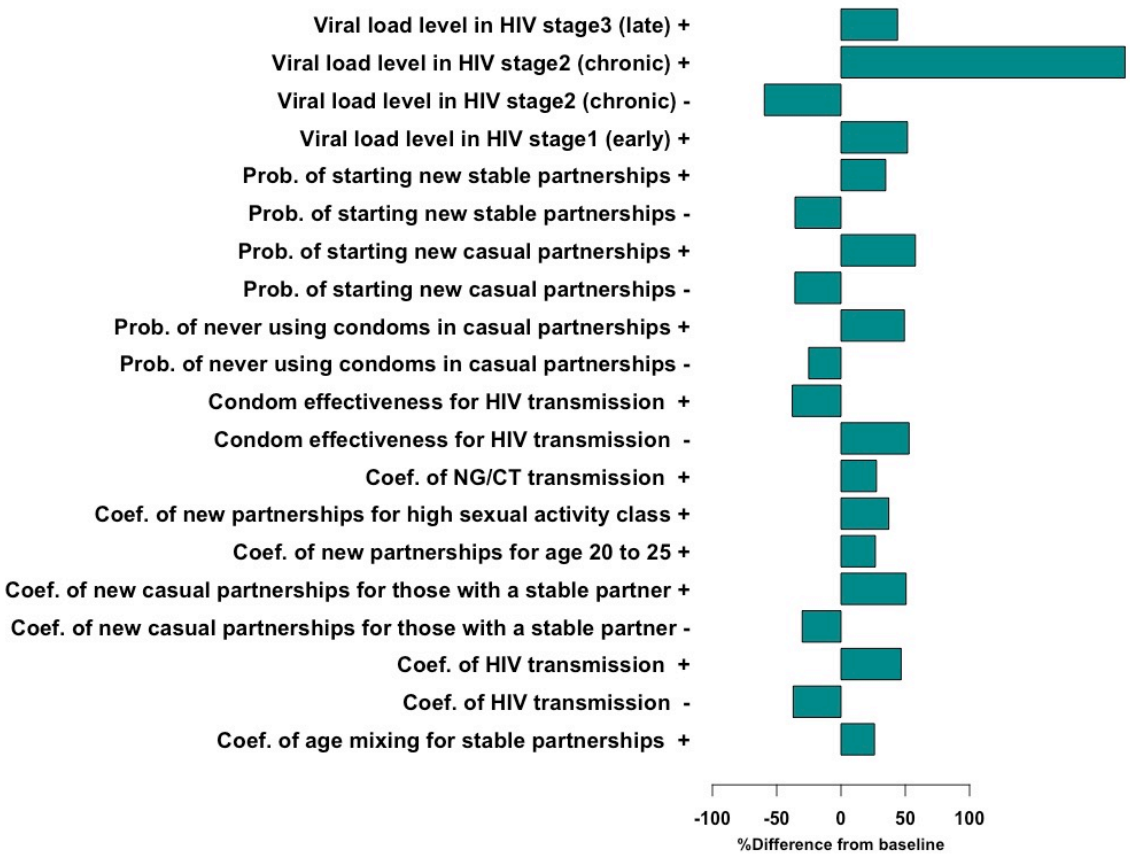

Figure S16: Sensitivity analysis of HIV incidence in year 10 to variation in model parameters in the scenario of a PrEP campaign targeting MSM at the time of NG/CT screening. Input parameters are listed on the left, +/- corresponding to 25% increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant

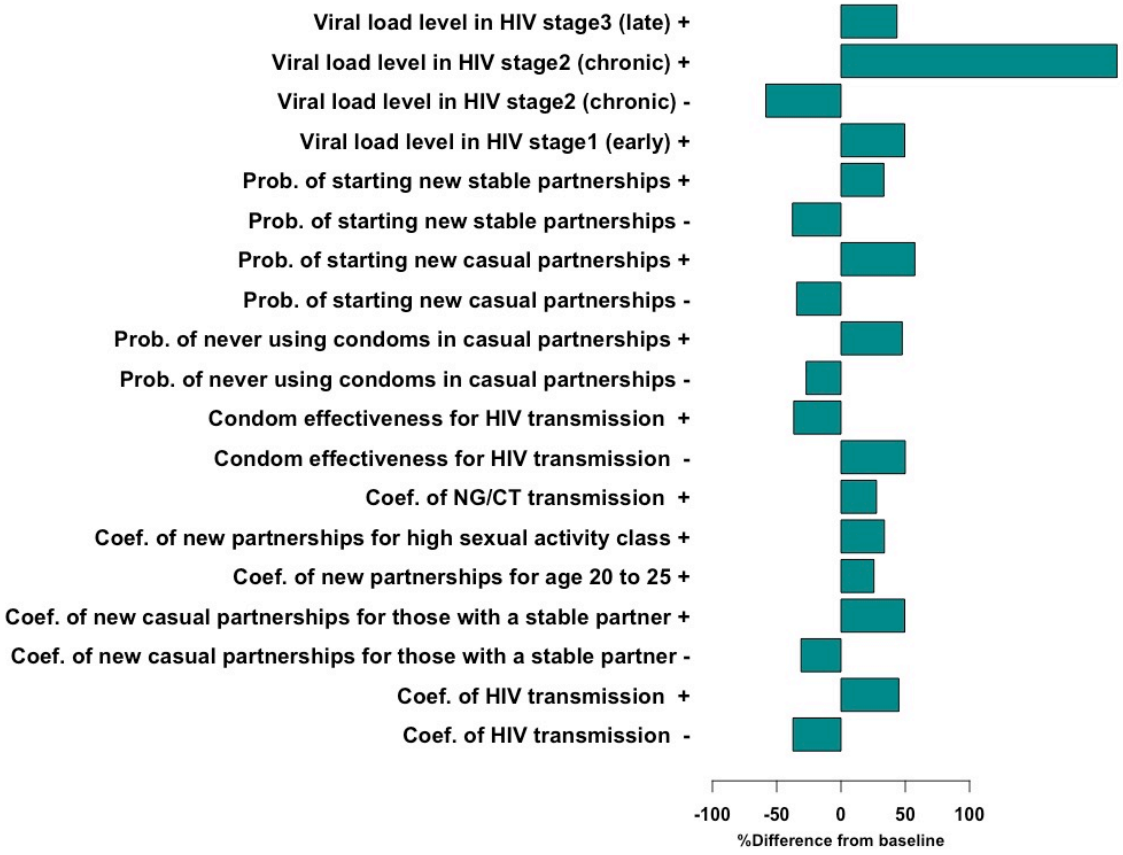

Figure S17: Sensitivity analysis of HIV incidence in year 10 to variation in model parameters in the scenario of a PrEP campaign targeting MSM through a community-wide campaign. Input parameters are listed on the left, +/- corresponding to 25% increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant.

3.1 Sensitivity analysis to impact of behavioral disinhibition

In the absence of strong data on existence of behaviour change for people on PrEP, we have elected to keep the model in the simplest format as possible. However, we acknowledge that this may limit the applicability of our findings to settings in which such behaviour may occur. To further study the impact of such assumption on our findings, we performed an additional sensitivity analysis of results to impact of behavioural disinhibition. For this purpose, we model behavioural disinhibition as %reduction in rate of condom use among MSM taking PrEP (reflected equally on rate of condom use in casual and stable partnerships), varied from 0% (no behavioural disinhibition) to 100% (no condom use).

Figure S18 compares the projected impact of NG/CT targeted PrEP at different rates of condom use reduction among PrEP users. The red line represents the baseline scenario in the model in absence of behavioral disinhibition. As expected, the projected impact of NG/CT-targeted PrEP on HIV incidence declines with reduced levels of condom use among PrEP users. For example, at baseline and in absence

of behavioural disinhibition, the NG/CT targeted PrEP results in 12% [10.4% - 14.1%] reduction in HIV incidence over 20 years. Decreasing the condom use among PrEP users by 25% and 50% will consequently results in lower impact of PrEP at the population level, corresponding to 9.8% [7.7% - 11.9%] and 7.2% [5.1% - 9.4%] reductions in HIV incidence over 20-years. Reduction in rate of condom use among PrEP users can further reduce the potential impact of PrEP (through increased STI screening) on incidence and prevalence of NG/CT. At very high levels of behavioural disinhibition (light green line representing a 75% reduction in condom use among PrEP users), implementation of PrEP can in turn increase the rate of STI transmission and incidence over time.

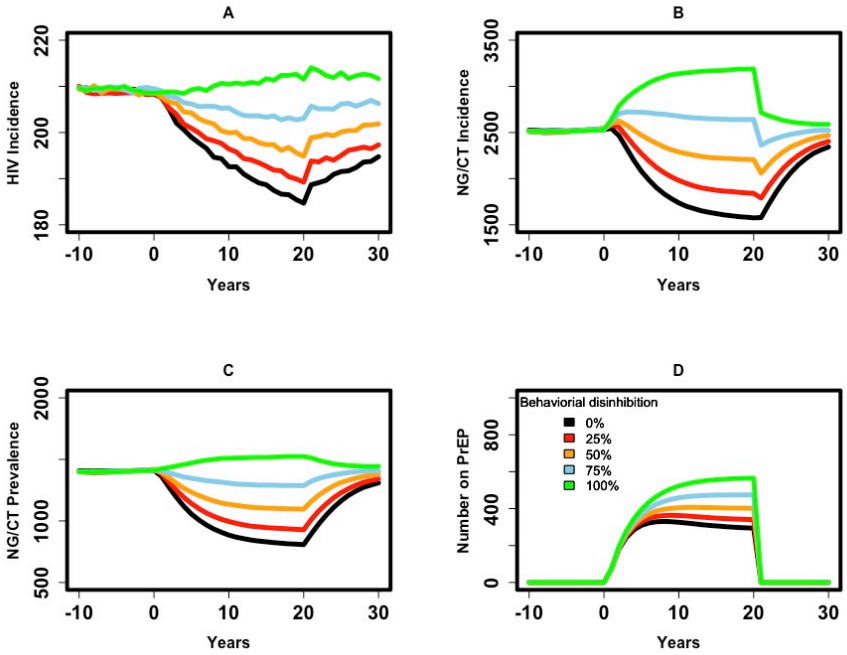

Figure S18: Sensitivity of the impact of NG/CT targeted PrEP to variation in rate of condom use among PrEP users. Shown on the y-axes are the annual incidence of HIV (A), incidence of NG/CT (B), prevalence of NG/CT (C) and number of MSM on PrEP and (D). Different colors represent PrEP scenarios at various levels of reduction in condom use among PrEP users, ranging from 0% (the baseline analysis in the main manuscript, shown in black) to 100% (no condom use among PrEP users, shown in light green).

Figure S19 further compares the impact of 3 PrEP scenarios that were discussed in the main text at various levels of behavioural disinhibition. Despite sensitivity of PrEP outcomes to variation in rate of condom use reduction in each scenario, the relative impact of NG/CT targeted PrEP scenario on HIV incidence compared to the other two scenarios (PrEP evaluation at NG/CT screening/testing and Untargeted PrEP) shows little sensitivity to underlying assumptions regarding behavioural disinhibition (Panel D in each set of graphs), and only begins to decline at very high levels of condom use reduction (last set of graphs for 75% reduction in condom use).

These results further characterize the impact of behavioural disinhibition on population-level impact of PrEP on incidence of HIV and other STIs as proposed by previous studies. This further highlight the need for additional behavioural surveillance data characterizing the changes in level of condom use and risky behaviours among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis

for increased efficacy of PrEP implementation through a NG/CT targeted approach remains robust to variation in rate of condom use reduction.

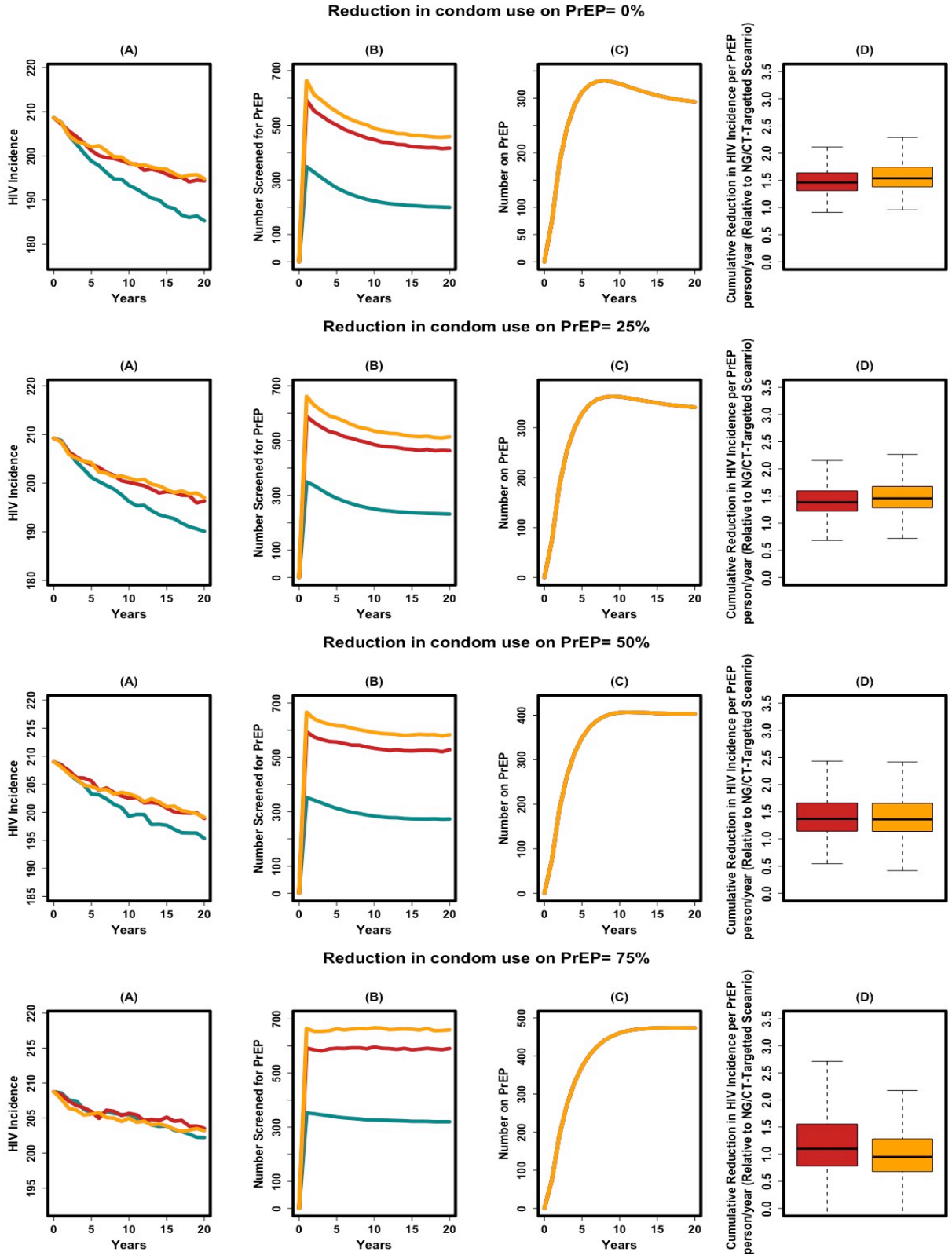

Figure S19: Sensitivity of the impact of all PrEP scenarios to variation in rate of condom use among PrEP users. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in green) compared against

PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. The three strategies are compared under the assumption that the same number of MSM would receive PrEP, at various levels of reduction in condom use among PrEP users. Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenario.

4 ADDITIONAL FIGURES

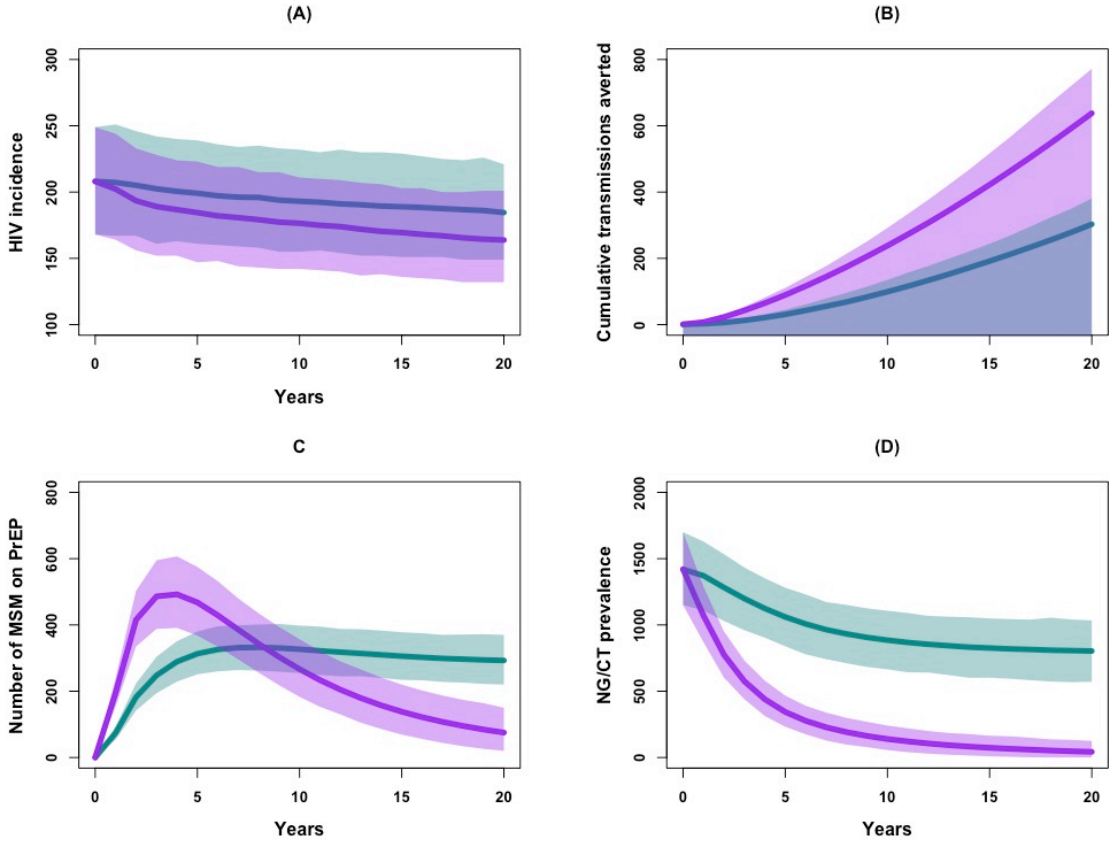

Figure S20: Impact of NG/CT-integrated PrEP, according to frequency of NG/CT screening/testing, with uncertainty ranges shown. Shown on the y-axes are the annual incidence of HIV (A), cumulative number of transmissions averted (B), (C) number of MSM on PrEP and (D) NG/CT prevalence. The green line depicts a scenario in which all MSM currently diagnosed with NG/CT are placed on PrEP with 60% uptake and adherence (NG/CT-integrated PrEP scenario in the main text), and the purple line shows a hypothetical scenario in which 50% of MSM are screened for NG/CT every year, with those testing positive for NG/CT also offered PrEP. Shaded areas represent the 95% uncertainty ranges of simulated data. This figure corresponds to Figure 2 in the main manuscript, but with uncertainty ranges given.

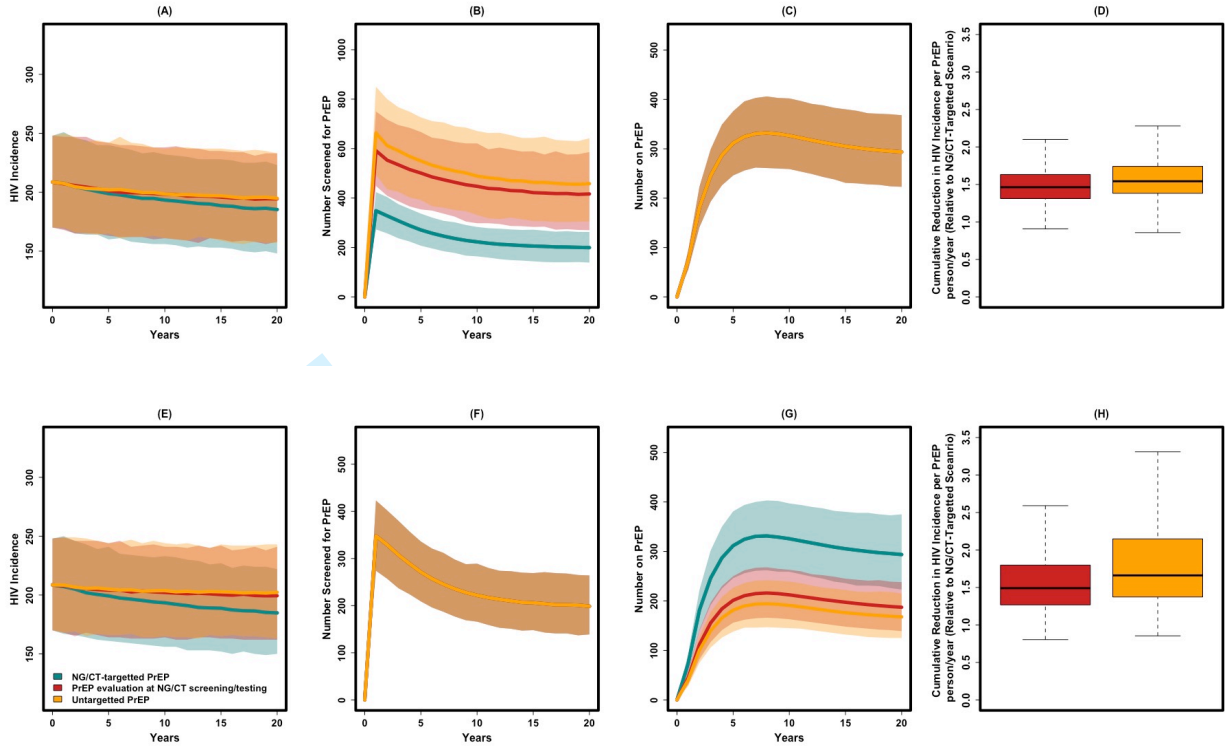

Figure S21: Relative impact of NG/CT-integrated PrEP with uncertainty ranges. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in green, also corresponding to the green line in Figure 2), compared against PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. In the first set of experiments, the three strategies are compared under the assumption that the same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be screened for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenarios (similar pattern in panels E through H). This figure corresponds to Figure 3 in the main manuscript, but with uncertainty ranges given.

REFERENCES

1. Alliance BNI. Vital Signs 12 [Internet]. 2012. Available: http://bniajfi.org/vital_signs/
2. Maryland Department of Health and Mental Hygiene, MDHMH. 2012 Baltimore City Annual HIV Epidemiological Profile. Baltimore; 2012.
3. World Health Organization. Life tables by country United States of America. In: Global Health Observatory Data Repository [Internet]. 2013. Available: http://apps.who.int/gho/data/view.main.61780?lang=en
4. Lieb S, Fallon SJ, Friedman SR, Thompson DR, Gates GJ, Liberti TM, et al. Statewide Estimation of Racial/Ethnic Populations of Men Who Have Sex with Men in the U.S. Public Health Rep. 2011;126: 60–72.
5. Beyrer C, Baral SD, van Griensven F, Goodreau SM, Chariyalertsak S, Wirtz AL, et al. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012;380: 367–77.
6. Marshall BD, Paczkowski MM, Seemann L, Tempalski B, Pouget ER, Galea S, et al. A complex systems approach to evaluate HIV prevention in metropolitan areas: preliminary implications for combination intervention strategies. PLoS One. 2012;7: e44833.
7. Escobar E, Durgham R, Dammann O, Stopka T. Agent-based computational model of the prevalence of gonococcal infections after the implementation of HIV pre-exposure prophylaxis guidelines. Online Journal of Public Health Informatics. 2015. doi:10.5210/ojphi.v7i3.6104
8. German D. BESURE Study: National HIV Behavioral Surveillance Study in Baltimore [Internet]. Available: http://www.jhsph.edu/faculty/research/map/US/1413/8192
9. Vieira IT, Senna V de, Pereira. HB de B. A small world model for the spread of HIV infection. Pesqui Operacional. 2011;31: 373–389.
10. Kasaie P, Pennington J, Berry SA, Shah MS, German D, Flynn CP, et al. The impact of pre-exposure prophylaxis among men who have sex Withmen in Baltimore City: an agent-based simulation. JAIDS J Acquir Immune Defic Syndr. 2017;75: 175–183.
11. Egan JE, Frye V, Kurtz SP, Latkin C, Chen M, Tobin K, et al. Migration, neighborhoods, and networks: approaches to understanding how urban environmental conditions affect syndemic adverse health outcomes among gay, bisexual and other men who have sex with men. AIDS Behav. 2011;15: 35–50.
12. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373: 795–807.
13. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009;360: 1815–1826.
14. Palella Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med. 1998;338: 853–860.
15. Rana AI, Liu T, Gillani FS, Reece R, Kojic EM, Zlotnick C, et al. Multiple gaps in care common among newly diagnosed HIV patients. AIDS Care. 2015;27: 697–687.
16. Beck EEC, Birkett M, Armbruster B, Mustanski B. A data-driven simulation of HIV spread among young men who Hhave sex with men: role of age and race mixing and STIs. JAIDS J Acquir Immune Defic Syndr. 2015;70: 186–194.

17. Vriend HJ, Lugnér AK, Xiridou M, Schim van der Loeff MF, Prins M, de Vries HJC, et al. Sexually transmitted infections screening at HIV treatment centers for MSM can be cost-effective. AIDS. 2013;27: 2281–90. doi:10.1097/QAD.0b013e32836281ee

18. Chen MI, Ghani AC, Edmunds WJ. A metapopulation modelling framework for gonorrhoea and other sexually transmitted infections in heterosexual populations. J R Soc Interface. 2009;6: 775–91. doi:10.1098/rsif.2008.0394

19. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. MMWR recomm. 2015.

20. Virginia Department of Health. STD Surveillance Network Report. 2013; Available: http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf

21. Castro JG, Alcaide ML. High rates of STIs in HIV-infected patients attending an STI clinic. South Med J. 2016;109: 1–4.

22. Sullivan PS, Peterson J, Rosenberg ES, Kelley CF, Cooper H, Vaughan A, et al. Understanding racial HIV/STI disparities in black and white men who have sex with men: a multilevel approach. PLoS One. 2014;9: e90514.

23. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States-2014: a clinical practice guideline. 2014.

24. Centers for Disease Control and Prevention. PrEP for men who have sex with men [Internet]. 2018. Available: https://prepmaryland.org/sites/default/files/download-resources/PrEP - MSM both sides March 2017.pdf

25. Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TP, Prevention D of S. Sexually transmitted disease surveillance 2013. 2014.

26. Lister N, Smith A, Tabrizi S, Hayes P. Screening for neisseria gonorrhoeae and chlamydia trachomatis in men who have sex with men at male-only saunas. Sex Transm Dis. 2003;30: 886–889.

27. Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis. 2005;41: 67–74.

28. Morris SR, Klausner JD, Buchbinder SP, Wheeler SL, Koblin B, Coates T, et al. Prevalence and incidence of pharyngeal gonorrhea in a longitudinal sample of men who have sex with men: the EXPLORE study. Clin Infect Dis. 2006;43: 1284–1289.

29. Soni S, White J. Self-screening for Neisseria gonorrhoeae and Chlamydia trachomatis in the human immunodeficiency virus clinic—high yields and high acceptability. Sex Transm Dis. 2011; Available: http://journals.lww.com/stdjournal/Abstract/2011/12000/Self_Screening_for_Neisseria_gonorrhoeae_and.6.aspx

30. Heiligenberg M, Rijnders B. High prevalence of sexually transmitted infections in HIV-infected men during routine outpatient visits in the Netherlands. Sex Transm. 2012; Available: http://journals.lww.com/stdjournal/Abstract/2012/01000/High_Prevalence_of_Sexually_Transmitted_Infections.2.aspx

31. Rieg G, Lewis R, Miller L, Witt M. Asymptomatic sexually transmitted infections in HIV-infected men who have sex with men: prevalence, incidence, predictors, and screening strategies. AIDS Patient Care. 2008; Available: http://online.liebertpub.com/doi/abs/10.1089/apc.2007.0240

32. Patton ME, Kidd S, Llata E, Stenger M, Braxton J, Asbel L, et al. Extragenital gonorrhea and chlamydia testing and infection among men who have sex with men--STD Surveillance Network, United States, 2010-2012. Clin Infect Dis. 2014;58: 1564–70. doi:10.1093/cid/ciu184

33. Chamberlain N, Crosby RA, Mena L, Chan PA, Mayer KH. Is Patient-Reported Exposure a Reliable Indicator for Anogenital Gonorrhea and Chlamydia Screening in Young Black Men Who Have Sex With Men? Sex Transm Dis. 2017;44: 390–392. doi:10.1097/OLQ.0000000000000619

34. Health VD of. STD Surveillance Network Report. 2013; Available: http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf

35. Maryland Department of Health and Mental Hygiene. BESURE Study 2004-2014: Baltimore site of National HIV Behavioral Surveillance (NHBS) [Internet]. 2015.

36. Jenness S, Goodreau S. Impact of the centers for disease control's HIV preexposure prophylaxis guidelines for men who have sex with men in the United States. J Infect Dis. 2016;14: 1800–1807.

37. Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. Genitourin Med. 1996;72: 422–6.

38. Kretzschmar M, Duynhoven Y van. Modeling prevention strategies for gonorrhea and chlamydia using stochastic network simulations. Am J Epidemiol. 1996;144: 306–317.

39. Korenromp EL, Sudaryo MK, de Vlas SJ, Gray RH, Sewankambo NK, Serwadda D, et al. What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? Int J STD AIDS. 2002;13: 91–101.

40. Althaus CL, Heijne JCM, Roellin A, Low N. Transmission dynamics of chlamydia trachomatis affect the impact of screening programmes. Epidemics. 2010;2: 123–131.

41. Price MJ, Ades AE, Angelis D De, Welton NJ, Macleod J, Soldan K, et al. Mixture-of-exponentials models to explain heterogeneity in studies of the duration of Chlamydia trachomatis infection. Stat Med. 2013;32: 1547–1560.

42. Turner KM, Adams EJ, Gay N, Ghani AC, Mercer C, Edmunds WJ. Developing a realistic sexual network model of chlamydia transmission in Britain. Theor Biol Med Model. 2006;3: 3.

43. Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. J Acquir Immune Defic Syndr. 2000;24: 48–56.

44. Chesson HW, Bernstein KT, Gift TL, Marcus JL, Pipkin S, Kent CK. The cost-effectiveness of screening men who have sex with men for rectal chlamydial and gonococcal infection to prevent HIV Infection. Sex Transm Dis. 2013;40: 366–71.

45. Tuite A, Jayaraman G, Allen V. Estimation of the burden of disease and costs of genital Chlamydia trachomatis infection in Canada. Sex Transm Dis. 2012;39: 260–267.

46. Vries R De, Bergen J Van. Systematic screening for Chlamydia trachomatis: estimating cost-effectiveness using dynamic modeling and Dutch data. Value in. 2006;9: 1–1.

47. Adams EJ, Turner KME, Edmunds WJ. The cost effectiveness of opportunistic chlamydia screening in England. Sex Transm Infect. 2007;83: 267-74; discussion 274–5.

48. Andersen B, Gundgaard J, Kretzschmar M. Prediction of costs, effectiveness, and disease control of a population-based program using home sampling for diagnosis of urogenital Chlamydia trachomatis. Sex Transm Dis. 2006;33: 407–415.

49. Gillespie P, O'Neill C, Adams E, Turner K. The cost and cost-effectiveness of opportunistic screening for Chlamydia trachomatis in Ireland. Sex Transm Dis. 2012;88: 222–228.

50. Roberts T, Robinson S, Barton P, Bryan S. Cost effectiveness of home based population screening for Chlamydia trachomatis in the UK: economic evaluation of chlamydia screening studies (ClaSS) project. Bmj. 2007;335: 291.

51. Welte R, Kretzschmar M, Leidl R, Hoek A Van Den, Jager JC, Postma MJ. Cost-effectiveness of screening programs for Chlamydia trachomatis: a population-based dynamic approach. Sex Transm Dis. 2000;27: 518–529.

52. Sexually transmitted diseases treatment guidelines, 2006. MMWR recomm. 2006; Available: http://origin.glb.cdc.gov/mmWR/preview/mmwrhtml/rr5511a1.htm

53. Berry SA. Gonorrhoea and chlamydia screening in HIV clinics: time for new tools and targets. Sex Transm Infect. 2014;90: 574–575.

54. Berry SA, Ghanem KG, Page KR, Gange SJ, Thio CL, Moore RD, et al. Increased gonorrhoea and chlamydia testing did not increase case detection in an HIV clinical cohort 1999-2007. Sex Transm Infect. NIH Public Access; 2011;87: 469–475.

55. Hutchinson J, Goold P, Wilson H, Jones K, Estcourt C. Sexual health care of HIV-positive patients: an audit of a local service. Int J STD AIDS. 2003;14: 493–496.

56. Hamlyn E, Barrett S, Kelsey J, Lockyer S, Welz T, Poulton M. Improvement in screening for sexually transmitted infections in HIV-positive patients following implementation of a nurse-led clinic. Int J STD AIDS. 2007;18: 424–426. Available: http://www.ncbi.nlm.nih.gov/pubmed/17609038

57. Hoover KW, Butler M, Workowski K, Carpio F, Follansbee S, Gratzer B, et al. STD screening of HIV-infected MSM in HIV clinics. Sex Transm Dis. 2010;37: 771–776.

58. Teague R, Mijch A, Fairley CK, Sidat M, Watson K, Boyd K, et al. Testing rates for sexually transmitted infections among HIV-infected men who have sex with men attending two different HIV services. Int J STD AIDS. 2008;19: 200–2.

59. Joesoef MR, Linnan M, Barakbah Y, Idajadi a, Kambodji a, Schulz K. Patterns of sexually transmitted diseases in female sex workers in Surabaya, Indonesia. Int J STD AIDS. 1997;8: 576–80. doi:10.1258/0956462971920811

60. Darrow WW. Condom Use and Use-Effectiveness in High-Risk Populations. SexTransmDis. 1989;16: 157–160.

61. Cohen M. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. Lancet. 1998;351: S5–S7.

62. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect. 1999;75: 3–17.

63. Winter AJ, Taylor S, Workman J, White D, Ross JD, Swan A V, et al. Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. Sex Transm Infect. 1999;75: 261–263.

64. Cohen MS, Hoffman IF, Royce RA, Kazembe P, Dyer JR, Daly CC, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. Lancet. 1997;349: 1868–1873.

65. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions

between classic sexually transmitted diseases and HIV. Sex Transm Dis. 2001;28: 579–597.

66. Jin F, Prestage GP, Imrie J, Kippax SC, Donovan B, Templeton DJ, et al. Anal sexually transmitted infections and risk of HIV infection in homosexual men. J Acquir Immune Defic Syndr. 2010;53: 144–149.

67. Baggaley RF, Ferguson NM, Garnett GP. The epidemiological impact of antiretroviral use predicted by mathematical models: a review. Emerg Themes Epidemiol. 2005;2: 9.

68. Salomon JA, Hogan DR, Stover J, Stanecki KA, Walker N, Ghys PD, et al. Integrating HIV prevention and treatment: from slogans to impact. PLoS Med. 2005;2: e16.

69. Alam SJ, Meyer R, Norling E. A model for HIV spread in a South African village. Multi-Agent-Based Simul IX. 2009; 33–45.

70. Clotet B, Feinberg J, Lunzen J van, Khuong-Josses M. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised. Lancet. 2014;383: 2222–2231.

71. Wit FW, Blanckenberg DH, Brinkman K, Prins JM, Ende ME van der, Schneider MM, et al. Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. AIDS. 2005;19: 345–348.

72. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callegaro A, Suter F. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. AIDS. 2004;18: 439–446.

73. Ortiz GM, Wellons M, Brancato J, Vo HT, Zinn RL, Clarkson DE, et al. Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects. Proc Natl Acad Sci. 2001;98: 3288–13293.

74. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. New Engl J Med. 2006;355: 2283–2296.

75. Sc W, Davis-Beaty. Condom effectiveness in reducing heterosexual HIV transmission (Review). Available: http://www.thecochranelibrary.com

76. Holmes KK, Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. Bull World Health Organ. 2004;82: 454–461.

77. Hill T, Bansi L, Sabin C, Phillips A, Dunn D. Data linkage reduces loss to follow-up in an observational HIV cohort study. J Clin. 2010;63: 1101–1109.

78. Mocroft A, Kirk O, Aldins P, Chies A, Blaxhult A. Loss to follow-up in an international, multicentre observational study. HIV Med. 2008;9: 261–269.

79. Ndiaye B, Ould-Kaci K, Salleron J, Bataille P. Characteristics of and outcomes in HIV-infected patients who return to care after loss to follow-up. AIDS. 2009;23: 1786–1789.

80. Mills E, Nachega J, Buchan I, Orbinski J. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. Jama. 2006;296: 679–690.

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Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study

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Title: Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study

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Key messages:

- Several barriers exist to the successful implementation of PrEP in local settings, and optimizing the efficiency of PrEP delivery is a public health priority
- Targeting MSM infected with *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* increases the efficiency and effectiveness of PrEP delivery
- Expanding levels of STI screening among MSM can significantly improve the impact of PrEP (with PrEP offered to those testing positive)

ABSTRACT

Objectives: *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) increase the risk of HIV transmission among men who have sex with men (MSM). Diagnosis of NG/CT may provide an efficient entry point for prevention of HIV through delivery of pre-exposure prophylaxis (PrEP).

Methods: To quantify the added value of targeting PrEP to those diagnosed with NG/CT, we simulated the co-epidemic of NG/CT and HIV among MSM in Baltimore City, and compared various strategies for implementation of PrEP in this population.

Results: Assuming 60% uptake and 60% adherence, targeting PrEP to MSM diagnosed with NG/CT could reduce HIV incidence among MSM in Baltimore City by 12.4% [95% uncertainty range (UR): 10.3 – 14.4%] in 20 years, relative to no PrEP. Expanding the coverage of NG/CT screening (such that individuals experience a 50% annual probability of NG/CT screening and evaluation for PrEP upon NG/CT diagnosis), can further increase the impact of targeted PrEP to generate a 22.0% [95% UR 20.1 – 23.9%] reduction in HIV incidence within 20 years. When compared to alternative implementation scenarios, PrEP evaluation at NG/CT diagnosis increased impact of PrEP on HIV incidence by 1.7 [95% UR 1.0 – 2.6] relative to a scenario in which PrEP evaluation happened at the time of NG/CT screening/testing, and by 1.9 [95% UR 1.1 – 3.4] relative to evaluating random MSM from the community.

Conclusions: Targeting MSM infected with NG/CT increases the efficiency and effectiveness of PrEP delivery. If high levels of STI screening can be achieved at the community level, NG/CT diagnosis may be a highly effective entry point for PrEP initialization.

Strengths and limitations of this study

- Given the epidemiologic link between *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT) infection and HIV among men who have sex with (MSM), new NG/CT diagnoses may serve as a useful means to identify high-risk MSM for PrEP evaluation and delivery. At present, the impact of such a strategy is not clear. Using surveillance data from Baltimore City, Maryland, this study applies a modeling framework to evaluate the added value of targeting PrEP to MSM diagnosed with NG/CT, in terms of population-level impact on disease incidence over time.
- We base our depiction of HIV on a published agent-based model of HIV transmission among MSM in Baltimore City, and we extend this model to include coinfection of HIV with NG and CT infections modeled at the individual level.
- Our simulation model is calibrated against aggregate estimates of HIV and NG/CT incidence and prevalence, as well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City Health Department as part of the STD Surveillance Network Project.
- Our findings are limited by simplifying assumptions including (but not limited to) exclusion of other STIs such as syphilis, simplified representation of NG/CT natural history, simplification of sexual networks for NG/CT and HIV transmission, exclusion of HIV transmission through injection drugs or heterosexual sex, and exclusion of transgender and bisexual individuals from the simulated population.
- Given the controversies on existence of behavior change among MSM taking PrEP and lack of supporting data from our local population of MSM in Baltimore City, we excluded behavioral disinhibition from this analysis. Future studies can extend this analysis by evaluating changes in population-level impact of PrEP for HIV and STI control under potential levels of behavioral disinhibition for those on PrEP.

Keywords: HIV Infections; Gonorrhoea; Chlamydia; Pre-Exposure Prophylaxis; Homosexuality, Computer Simulation

BACKGROUND

Infection with *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT) may impact HIV transmission in multiple ways, particularly among men who have sex with men (MSM). From a biological standpoint, NG/CT infection may increase one's susceptibility to HIV acquisition: rectal infection in particular has been linked to an increased risk of HIV acquisition [1,2]. HIV and NG/CT also share many risk factors at the individual level (e.g., condomless sex) and network level (e.g., having sex within a high-prevalence network), such that the three conditions are often epidemiologically linked [3]. Additionally, HIV-negative men have an increased risk of HIV acquisition when in partnership with a HIV-positive partner who is also co-infected with NG/CT [4,5]. As a result, better diagnosis and treatment of NG/CT can potentially reduce HIV incidence [6], and help to identify individuals at high risk of future HIV infection.

Pre-Exposure Prophylaxis (PrEP) is part of comprehensive HIV prevention services in which HIV-negative people take daily antiretroviral medication to lower risk of HIV transmission upon exposure. The U.S. Centers for Disease Control and Prevention (CDC) has recommended PrEP for HIV-negative individuals at substantial risk of infection [7]. Among MSM, this includes HIV-negative men who are either diagnosed with a sexually transmitted infection (STI) in the last 6 months, are in a HIV discordant partnership, or report a condomless sex act in the last 6 months. Despite this broad recommendation, the potential population-level impact of PrEP remains uncertain. Several barriers exist to the successful implementation of PrEP, including providers' perceived inability to deliver PrEP in primary care settings [8], individuals' limited knowledge of PrEP effectiveness [9], low self-perceived risk for HIV infection [10], patients' difficulty in maintaining adherence [11], and high costs (at over $10,000 per person-year for those without insurance or access to a medication assistance plan) [12,13].

Given these challenges, optimizing the efficiency of PrEP delivery is a public health priority. Specifically, it is important to tailor PrEP delivery to those who stand to gain the most from its preventive efficacy. Given the epidemiologic link between NG/CT infection and HIV among MSM, new NG/CT diagnoses may serve as a useful means to identify high-risk MSM for PrEP evaluation and delivery [7]. At present, the impact of such a strategy—in terms of reducing HIV and NG/CT incidence at a population level—is not clear. To address this question, we used surveillance data from Baltimore City, Maryland, to construct an agent-based simulation model of the co-transmission of HIV and NG/CT among MSM, [14] and applied this model to study the added value of targeting PrEP to MSM diagnosed with NG/CT, in terms of population-level impact on HIV incidence over time.

METHODS

We base our depiction of HIV on a published agent-based model of HIV transmission among MSM in Baltimore City [14] (Figure 1-top panel), and we extend this model to include coinfection of HIV with NG and CT infections (see section 1 of the Supplementary Material).

NG/CT infection: NG and CT share similarities in natural history, including their acute nature, symptomatology, frequent co-diagnosis, and co-treatment [15]. Given these similarities, and for simplicity of modeling, we model NG/CT as a single biological entity. We assume that NG/CT infection may occur at the urethral, rectal or pharyngeal site – each with different probabilities of symptomatic presentation, diagnosis and treatment, and effects on HIV transmission, as shown in Table 1. We include both asymptomatic and symptomatic infection and fit the model to the annual number of diagnoses at each clinical site (urethral, rectal, or pharyngeal) among MSM in Baltimore City (see section 2 of the Supplementary Material).

Table 1: List of selected simulation parameters and calibration targets.

Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT) Parameters	Value	Reference
Proportion of cases symptomatic[1]		
• **Urethral**	74%	[16]
• **Rectal**	20%	[17,18]
• **Pharyngeal**	10%	[18,19]
Duration of infection (at each site) in the absence of treatment	[3 – 12] months[2]	[4,20–33]
Coefficient of NG/CT transmission per week	0.294	Calibrated to provide the incidence of NG/CT
Proportion of NG/CT infections assigned to each site		
• **Urethral**	0.35	Calibrated to provide the site-specific incidence of NG/CT
• **Rectal**	0.49	
• **Pharyngeal**	0.16	
Increase in HIV transmissibility (for those with urethral or rectal infection)	[1.5 – 2] fold [1]	[34–38]
Increase in HIV susceptibility (for those with urethral or rectal infection)	[1 – 2.5] fold [1]	[19,20,38,39]
NG/CT Calibration Targets	**Mean[3] [Range]**	
Annual diagnosis of NG/CT among MSM in Baltimore City		Values estimated from local data on gonorrhea surveillance and STI clinic visitis in Baltimore City (See section 2 in the Supplementary Material)
• **Urethral**	337 [269 – 405]	
• **Rectal**	25 [18 – 33]	
• **Pharyngeal**	42 [23 – 60]	
Site specific annual incidence of NG/CT among MSM in Baltimore City		
• **Urethral**	944 [753 – 1135]	
• **Rectal**	1251 [998 – 1505]	
• **Pharyngeal**	409 [326 – 492]	
HIV Parameters		
Disease duration		
• **Acute**	[6 – 9] weeks[1]	[40,41]
• **Chronic**	[8 –10] years[1]	[42,43]
• **Late stage** [4]	[1 –3] years[1]	[42–44]
Mortality rate[3]		
• **Acute & Chronic, no ART**	5 per 1000 person years	[45–47]
• **Late stage, no ART**	1/duration of late stage	
Reduction in mortality due to ART	0.58	
Time from ART discontinuation to pre-ART CD4 nadir[5]	ART treatment duration up to one year	[48–51]
Time from ART initiation to full viral suppression	[4 – 24] weeks[1]	[52]

[1] Values represent a pooled estimate of the reported measures for NG and CT infections

[2] Values are selected over uniform distributions across the ranges presented.

[3] Values represent the reported levels of NG/CT diagnosis among Baltimore City's MSM, and they are likely to underestimate the proportion of ongoing rectal and pharyngeal infections. We therefore consider such potential underestimation in estimating the annual incidence of NG/CT (see section 2 of the Supplementary Material) and have calibrated the model to represent realistic levels of prevalence (see the section on population overview in the main text).

[4] Mortality rate in late stage is defined as 1/(duration of late stage disease).

[5] Infectiousness assumed equal to that of the chronic disease.

Average viral load (log10 copies/mL)		[42]
• **Acute, no ART**	6.5	
• **Chronic, no ART**	4.5	
• **Late stage, no ART**	5	
• **On ART, partially suppressed**	3.5	
• **On ART, fully suppressed**	1.5	
Infectiousness per sexual contact	$2.45^{(\log(VL)-4.5)}$	[42]
Weekly probability of engagement in HIV care	0.006	[53–55]
Weekly probability of ART discontinuation	0.015	[56]
Gap in care after ART discontinuation	26 weeks	[57]
Relative probability of accessing HIV care among black MSM compared to white MSM	0.5	[58]
HIV calibration targets		
HIV prevalence	0.22 per 100,000 person/year	[59]
HIV continuum of care: Proportion of cases		[59]
• **Diagnosed**	0.86	
• **Linked to care**	0.62	
• **Engaged in care**	0.5	
• **On ART**	0.39	
• **Virally suppressed**	0.27	

STI Screening: In addition to testing of symptomatic NG/CT diagnosis, we also assume screening of asymptomatic individuals as follows (Figure 1- bottom panel):

- **Guidelines-based screening for HIV and NG/CT:** MSM may present to HIV/STI care providers (e.g., STI clinics, community health centers, HIV counseling programs) for a variety of reasons, and get tested for HIV and other STIs. We model visits for STI screening as a fixed weekly probability that reflects an individual's age-group and sexual activity such that younger MSM with higher propensity of partnerships experience a higher likelihood of visits [60,61]. We further assume that NG/CT is always screened at the urethral site, and a proportion of patients are also screened at the rectal and pharyngeal sites (calibrated to match the reported level of NG/CT infections diagnosis at each site among MSM in Baltimore City, as shown in Table 1).

- **NG/CT screening for HIV-positive MSM in care:** Based on CDC recommendations, most MSM who are continuously engaged in HIV care should undergo repeated NG/CT screening at least annually [15]. More frequent screening, such as screening every 3-6 months, is recommended for high-risk MSM, including those with an NG/CT diagnosis in the last year. Based on data from Baltimore City and a conservative estimate, we assume 40% adherence to these guidelines [62,63].

HIV Testing: In addition to combined HIV/STI testing that takes place as part of STI screening, we assume that all MSM experience an additional probability of HIV testing (in excess of testing though the STI program) can calibrate this probability to match the reported level of HIV diagnosis among MSM in Baltimore City.

Calibration: The model was calibrated against aggregate estimates of HIV and NG/CT incidence and prevalence, as well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City Health Department as part of the STD Surveillance Network Project (see section 2 of the Supplementary Material).

PrEP: Our primary outcome for this analysis is the projected incidence of HIV after 20 years of delivering PrEP to MSM. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the added benefit of targeting PrEP at individuals diagnosed with NG/CT. In all three scenarios, indication for PrEP use (eligibility) is considered in accordance with CDC recommendations and Baltimore City PrEP guidelines [64] (See

section 1 of the Supplementary Material) and includes HIV-negative individuals who are diagnosed with NG/CT in the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual partnership in the last 6 months. The three scenarios are thus:

- **PrEP delivery at NG/CT diagnosis** ("targeted" strategy & primary analysis)**:** all MSM diagnosed with NG/CT are offered PrEP at the time of diagnosis
- **PrEP evaluation at NG/CT screening/testing** ("at-testing")**:** PrEP eligibility is evaluated at the time of screening/testing for NG/CT, and all eligible individuals are offered PrEP
- **Untargeted PrEP:** PrEP eligibility is evaluated at random, and all eligible MSM are offered PrEP

All else being equal, increasing the number of MSM on PrEP will result in larger effects on HIV incidence (as more people are protected from HIV transmission). However, for a given number of MSM screened – or a given number of MSM on PrEP (e.g., if resource constraints are such that not all MSM meeting the criteria for PrEP can be placed/maintained on PrEP) – targeting PrEP to those screened for/diagnosed with NG/CT may be more efficient. Our primary aim was to quantify the extent of this gain in efficiency; thus, we compared scenarios in which the same number of MSM would be evaluated for PrEP, or alternatively the same number of MSM would be maintained on PrEP. Furthermore, to illustrate the potential impact of reaching highly ambitious targets for improved STI screening, we considered a hypothetical scenario for improving the underlying level of NG/CT screening (such that individual MSM not on PrEP experience a 50% annual probability of NG/CT screening and evaluation for PrEP upon NG/CT diagnosis), and studied the additional gain in effectiveness of NG/CT-targeted PrEP under this assumption.

In all scenarios, we assume that PrEP eligibility is reassessed every 3 months among patients receiving PrEP, and those who remain eligible for PrEP continue to receive it over time. Furthermore, we assume that in each scenario, a given proportion of eligible MSM who are offered PrEP will initiate prophylaxis (PrEP uptake ranging [0%-100%]) and adhere to it (PrEP adherence ranging [0%-100%]), with adherence defined as taking a sufficient number of doses to provide 60% protection against HIV transmission [65]. As a criterion for initiation of PrEP, all eligible MSM are also screened and treated for NG/CT infection before starting PrEP.

Sensitivity Analysis: A variety of sensitivity analyses were performed with the model. Using the HIV incidence at 10 years in absence and presence of PrEP (via all 3 scenarios) as the main output of interest, one-way sensitivity analyses were performed to variation of all model parameters to +/- 25% of their original value. We also varied condom usage among MSM on PrEP to model behavioral disinhibition (section 3 of the Supplementary Material).

Patient and Public Involvement: Patients and/or public were not involved in this study.

RESULTS

Population overview

The simulation models a population of 15,000 MSM in Baltimore City, projecting an average of 215 [95% UR: 181 – 251] incident HIV cases per year. Within this population, the co-epidemic of NG/CT was calibrated to 2598 [2204 – 2996] incident cases annually among which 35.0% [33.4 – 36.5%] of cases appear with urethral infection, 49.0% [47.4 – 50.6%] with non-urethral/rectal infection and 16.0% [14.8 – 17.2%] with pharyngeal-only infection. Point prevalence of NG/CT infection was estimated as 9.9% [8.4 – 11.5%], with 68.0% [63.5 – 72.5%] of infections occurring among black MSM (accounting for 58% of the MSM population). New infections occurred primarily in younger individuals, with 74% [72 – 78%] of new NG/CT infections occurring in MSM younger than 35 years old, and 69% [66 – 72%] of new HIV infections occurring among MSM between the ages of 25 and 45 (Figure 2A and 2B). Over half of new HIV and NG/CT infections occurred among MSM in the high sexual activity class, which accounted for 33% of the simulated population (Figure 2C and 2D). Overall, 81.5% [81.0 – 82.1%] of MSM

diagnosed with NG/CT in the model were tested on the basis of symptomatic presentation (rather than asymptomatic screening), and 20% [18.0 – 22.0%] of incident NG/CT cases were coinfected with HIV.

Epidemiological impact of PrEP at NG/CT diagnosis

At baseline, and in the absence of PrEP (steady-state equilibrium), 361 [95% UR: 298 – 427] MSM were annually diagnosed and treated for NG/CT infection (calibrated). If 60% of MSM diagnosed with NG/CT could be started on PrEP (i.e., uptake = 60%) and maintained at a degree to which 60% of subsequent HIV infections were averted (i.e., adherence = 60%), HIV incidence was estimated to decline by 12.4% [10.3 – 14.4%] over 20 years (Figure 3A). This corresponds to averting 318 [253 – 385] potential HIV transmissions through 5808 [5730 – 5886] person-years of PrEP delivered, or 5479 [4330 – 6632] infections averted per 100,000 person-years of PrEP (Figure 3B). Under the current level of NG/CT diagnosis, the number of MSM receiving PrEP is projected to increase through the first 8 years of the program (reaching a total of 332 [327 – 338] MSM on PrEP) and to fall afterward with declining incidence of NG/CT (Figure 3C). Due to the increased level of NG/CT screening/treatment among those on PrEP (through reassessment every 3 months), the prevalence of NG/CT was estimated to decline by 43.3% [41.6 – 44.9%] over 20 years of PrEP implementation (Figure 3D).

The impact of PrEP on HIV incidence can be further increased by expanding the coverage of NG/CT screening at the community level. In our baseline model, 25.0% [95% UR: 24.0 – 26.0%] of MSM undergo NG/CT screening/testing at least once annually (CDC recommendation). In an expanded-screening scenario in which all MSM experienced a 50% probability of screening for NG/CT annually, we projected a 180% increase in the baseline estimate of 4033 [3883 – 4182] annual NG/CT testing/screening events. Offering PrEP to those testing positive for NG/CT subsequently provided a 22.0% [20.1 – 23.9%] decline in HIV incidence over 20 years, corresponding to 648 [589 – 710] potential HIV transmissions averted. For further information on levels of uncertainty in these results, see section 4 of the Supplementary Material.

Relative impact of targeted versus untargeted PrEP

NG/CT-integrated PrEP increased efficiency of PrEP delivery in at least two ways (Figure 4A). First, a higher percentage of MSM were eligible for PrEP among those evaluated for PrEP (Figure 4B and 4C). In our model, 71.1% [95% UR: 65.0 – 77.2%] of all MSM diagnosed with NG/CT were eligible to receive PrEP (as 29% of this population is HIV-positive), compared to 45.2% [43.2 – 48.2%] of MSM screened for NG/CT, and 41.3% [39.1 – 43.5%] of randomly selected MSM. Second, providing PrEP to MSM diagnosed with NG/CT targets individuals at higher risk of potential HIV infection (due to both biological factors and high-risk behavior), such that – under the baseline assumption of equal numbers of people receiving PrEP—impact of NG/CT-targeted PrEP on HIV incidence was greater than the other two scenarios (Figure 4D). Specifically, over 20 years of implementation, targeting PrEP to MSM diagnosed with NG/CT infection increased impact of PrEP by 1.5 [1.1 – 1.9] relative to PrEP evaluation at NG/CT screening/testing, and by 1.6 [1.2 – 2.2] relative to untargeted PrEP. In another comparison, if the same number of individuals were evaluated for PrEP, the efficacy of NG/CT-integrated PrEP was increased even further relative to other scenarios (Figure 4E through 4H).

In one-way sensitivity analyses, the projected HIV incidence at 10 years in the absence of PrEP was sensitive to parameters relating to HIV and NG/CT transmission (including level of HIV viral load, condom use, and condom effectiveness) and parameters describing overall sexual activity (including the probabilities of starting new partnerships and the level of sexual activity in the most sexually active class). A similar variation in HIV incidence was observed in scenarios modeling PrEP evaluation at the time of NG/CT diagnosis, NG/CT screening or at random. Impact of PrEP in terms of reduction in HIV incidence in all scenarios relative to baseline was robust to reasonable variation of most model parameters (section 3 of the Supplementary Material).

DISCUSSION

This agent-based simulation of HIV transmission among MSM suggests that screening for NG/CT may be an important and efficient entry point for PrEP evaluation and delivery. Specifically, if all MSM who currently test positive for NG/CT could be offered PrEP – assuming 60% uptake and sufficient adherence to maintain 60% protection – HIV incidence could be reduced by approximately 12%, averting one HIV infection annually per 1,000 MSM population, with fewer than 20 per 1,000 taking PrEP every year. On the basis of infections averted per PrEP dose delivered, providing PrEP to MSM with NG/CT diagnosis is nearly twice as efficient as providing PrEP randomly among eligible MSM. Thus, use of NG/CT diagnosis as an entry point is a highly efficient and feasible mechanism for PrEP delivery. If NG/CT screening could be expanded to 50% of MSM every year (with PrEP offered only to those testing positive), this impact could be more than doubled. Given this substantial potential impact, it will be important to assess willingness and uptake and identify best practices to support PrEP uptake and adherence among MSM diagnosed with NG/CT.

These findings are consistent with other studies of PrEP delivery among MSM [66,67]. Previous studies have shown that the population-level impact of PrEP depends strongly on PrEP uptake and adherence [14,66], as suggested in our study as well. Importantly, NG/CT diagnosis may be useful in this regard, as MSM who have recently been diagnosed with an STI may be more aware of their HIV risk and more likely to accept and initiate PrEP. Past research has shown that HIV interventions may be more effective when they are conducted or initiated at the time of an STI diagnosis [68]. Initiation of PrEP simultaneously with NG/CT diagnosis may also be a clinically feasible approach – as an STI diagnosis is already likely to prompt an HIV test (if not already performed), and MSM who are diagnosed with NG/CT have at least some level of health care access. Unlike performing detailed sexual histories, offering PrEP to all HIV-negative MSM diagnosed with NG/CT is a simple guideline that is easy for most clinicians to follow [69,70]. Further research is needed to assess the feasibility of this approach in the field, especially in ascertaining the degree to which the continuum of PrEP care (including linkage to care and longer-term maintenance on PrEP) can be maintained in this population. Furthermore, the potential tradeoff between the positive impact of PrEP on STI prevalence through enhanced screening and its negative impact through behavioral disinhibition (if MSM on PrEP adopt riskier sexual behaviors) merits further investigation. Additional implementation research is also needed to identify effective mechanisms for improving adherence to CDC PrEP guidelines and overcoming barriers to acceptance and uptake of PrEP such as lack of awareness, lack of access, financial strain, and stigma [11,71].

As with any modeling analysis, our findings are limited by necessary simplifying assumptions. Given the overlap in clinical practice for treating NG and CT and the substantial uncertainty regarding the natural history of the two infections (e.g., duration of infectiousness, propensity toward asymptomatic infection), we have combined these infections as a single entity (NG/CT) and have used composite parameter values to describe the natural history of both diseases. However, there are still important differences between NG and CT, and to the extent that the natural history of each disease may differ, our findings may over- or under-estimate the impact of PrEP targeted at these STIs. For example, an infection with a shorter infectious period and a higher transmission probability per sex act will concentrate more strongly in high risk networks and may provide a more effective entry point for HIV PrEP. Further research can extend our analysis by considering the impact of each disease separately on HIV transmission dynamics. Furthermore, due to limited data on site-specific transmission dynamics (e.g., relative frequency of oral-only versus oral-plus-anal versus anal-only sex among MSM in Baltimore), we adopted a simplified approach that does not fully capture the complete transmission dynamics but should result in the appropriate distributions of NG/CT infections at each anatomical site. Additional simplifying assumptions used in the underlying HIV simulation model include applying the same sexual network for NG/CT and HIV transmission; simplification of sexual networks as comprising only stable and casual partnerships; simplified definition of sexual activity classes as a lifetime attribute among MSM; exclusion of serosorting on HIV, sexual activity class or PrEP; exclusion of HIV transmission through injection drugs or heterosexual sex; and exclusion of transgender individuals from the simulated population. To the extent

that these dynamics result in higher concentration of NG/CT among MSM at high-risk for HIV infection, our model may underestimate the impact of STI-targeted PrEP.

We excluded the potential existence of behavioral disinhibition for MSM on PrEP in the main analysis and applied a simplified approach for modeling the combined role of PrEP uptake/adherence for HIV protection. In additional sensitivity analyses, we studied the impact of decreased condom use among MSM on PrEP on the outcome of NG/CT-targeted PrEP, and the relative efficacy of STI-targeted scenario compared to the other comparators (See section 3 of the Supplementary Material) . As expected, the projected impact of NG/CT-targeted PrEP on incidence of HIV and NG/CT declined with reduced levels of condom use among PrEP users. This further highlights the need for additional behavioural surveillance data characterizing changes in level of condom use and risky behaviours among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis (increased effectiveness of PrEP implementation through an NG/CT targeted approach) remained robust to variation in the rate of condom use reduction.

There are strong racial disparities in HIV incidence and healthcare access in the US, such that the highest risk populations may be the ones least likely to have access to PrEP [72]; these disparities were not included in our simplified cascade of PrEP. Our model calibration was limited to the scope of local surveillance data, and available literature for values lacking direct empiric estimates from Baltimore City (e.g., probability of symptomatic infection). We also assumed a future trajectory of HIV infection in the future that represents continuation of current trends; this trajectory is unlikely to remain constant for the next 20 years but may help to provide a useful conceptual construct for present-day decision-making, which is the ultimate goal of this analysis. Our results are further limited by exclusion of syphilis infection, another STI that is often transmitted in the same populations and may affect transmission and acquisition of HIV. Finally, we did not incorporate cost or other resource constraints into the present model; future analyses could evaluate the efficiency of NG/CT-targeted PrEP delivery from a cost-effectiveness or budget impact perspective.

In summary, this stochastic agent-based model representing the co-dynamics of NG/CT and HIV transmission among MSM suggests that NG/CT diagnosis may serve as an efficient and effective entry point for PrEP. If linkage between STI and HIV control programs can be effectively developed, further investment in NG/CT screening (followed by PrEP initiation) can have major impact, not only on the incidence and prevalence of NG/CT, but also on transmission of HIV – potentially averting up to 20% of all HIV infections through NG/CT-targeted PrEP alone. Future analyses could evaluate whether such approaches could even be cost-saving in the long term. Ultimately, ending the HIV epidemic in MSM populations will require a combination of multiple activities, including strengthening the continuum of HIV care, ensuring continued access to clinical services, and prevention through both behavioral approaches (e.g., condom use) and PrEP. Using NG/CT diagnosis as an entry point for PrEP initiation may serve as an important component of such a combined prevention approach.

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Contributions

Designed the study [PK and DWD]; Wrote the model code [PK]; Provided data [CS,JJ,ST,DG], Analyzed the data [PK]; supervised the analyses [DWD]; reviewed results [MS,SB, KH, TG, HC]; wrote the first draft of the manuscript [PK]; revised the manuscript and contributed intellectual content [PK, SB, MS, ER, KH, TG, HC]; All authors saw and approved the final manuscript.

Conflict of interest:

All authors report no potential conflicts of interest.

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Data sharing statement:

Additional data are presented in the online Supplementary Material.

REFERENCES

1 Katz D, Dombrowski J, Bell T. HIV incidence among men who have sex with men after diagnosis with sexually transmitted infections. *Sex Transm Dis* 2016;**43**:249–54.

2 Pathela P, Braunstein S, Blank S. HIV incidence among men with and without sexually transmitted rectal infections: estimates from matching against an HIV case registry. *Clin Infect Dis* 2013;**57**:1203–9.

3 Ward H, Rönn M. Contribution of sexually transmitted infections to the sexual transmission of HIV. *Curr Opin HIV AIDS* 2010;**5**:305–10.

4 Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. *J Acquir Immune Defic Syndr* 2000;**24**:48–56.

5 Fleming DTDT, Wasserheit JNJN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;**75**:3–17.

6 Grosskurth H, Mosha F, Todd J, *et al.* Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530–6.

7 Centers for Disease Control Prevention. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline. 2014.

8 Krakower D, Ware N, Mitty JA, *et al.* HIV providers' perceived barriers and facilitators to implementing pre-exposure prophylaxis in care Settings: a qualitative study. *AIDS Behav* 2014;**18**:1712–21.

9 Eaton L, Driffin D, Bauermeister J. Minimal awareness and stalled uptake of pre-exposure prophylaxis (PrEP) among at risk, HIV-negative, black men who have sex with men. *AIDS Patient Care STDS* 2015;**29**:423–9.

10 Galindo G, Ja'Nina J. Community member perspectives from transgender women and men who have sex with men on pre-exposure prophylaxis as an HIV prevention strategy: implications for implementation. *Implement Sci* 2012;**7**:116.

11 Golub SA, Gamarel KE, Rendina HJ, *et al.* From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among MSM and transgender women in New York City. *AIDS Patient Care STDS* 2013;**27**:248–54.

12 Juusola JL, Brandeau ML, Owens DK, *et al.* The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Ann Intern Med* 2012;**156**:541–50.

13 Koppenhaver RRT, Sorensen SSW, Farnham PG, *et al.* The cost-effectiveness of pre-exposure prophylaxis in men who have sex with men in the United States: an epidemic model. *AIDS J Acquir Immune Defic Syndr* 2011;**58**:e51–2.

14 Kasaie P, Pennington J, Berry SA, *et al.* The impact of pre-exposure prophylaxis among men who have sex Withmen in Baltimore City: an agent-based simulation. *JAIDS J Acquir Immune Defic Syndr* 2017;**75**:175–83.

15 Workowski KA, Bolan GA. Sexually Transmitted Diseases Treatment Guidelines, 2015. *Morb Mortal*

Wkly Rep 2015;**64(RR3)**:1–137.

16 Kent CK, Chaw JK, Wong W, *et al.* Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. *Clin Infect Dis* 2005;**41**:67–74.

17 Lister N, Smith A, Tabrizi S, *et al.* Screening for neisseria gonorrhoeae and chlamydia trachomatis in men who have sex with men at male-only saunas. *Sex Transm Dis* 2003;**30**:886–9.

18 Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. *Genitourin Med* 1996;**72**:422–6.

19 Morris SR, Klausner JD, Buchbinder SP, *et al.* Prevalence and incidence of pharyngeal gonorrhea in a longitudinal sample of men who have sex with men: the EXPLORE study. *Clin Infect Dis* 2006;**43**:1284–9.

20 Beck EEC, Birkett M, Armbruster B, *et al.* A data-driven simulation of HIV spread among young men who Hhave sex with men: role of age and race mixing and STIs. *JAIDS J Acquir Immune Defic Syndr* 2015;**70**:186–94.

21 Kretzschmar M, Duynhoven Y van. Modeling prevention strategies for gonorrhea and chlamydia using stochastic network simulations. *Am J Epidemiol* 1996;**144**:306–17.

22 Korenromp EL, Sudaryo MK, de Vlas SJ, *et al.* What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *Int J STD AIDS* 2002;**13**:91–101.

23 Althaus CL, Heijne JCM, Roellin A, *et al.* Transmission dynamics of chlamydia trachomatis affect the impact of screening programmes. *Epidemics* 2010;**2**:123–31.

24 Price MJ, Ades AE, Angelis D De, *et al.* Mixture-of-exponentials models to explain heterogeneity in studies of the duration of Chlamydia trachomatis infection. *Stat Med* 2013;**32**:1547–60.

25 Turner KM, Adams EJ, Gay N, *et al.* Developing a realistic sexual network model of chlamydia transmission in Britain. *Theor Biol Med Model* 2006;**3**:3.

26 Chesson HW, Bernstein KT, Gift TL, *et al.* The cost-effectiveness of screening men who have sex with men for rectal chlamydial and gonococcal infection to prevent HIV Infection. *Sex Transm Dis* 2013;**40**:366–71.

27 Tuite A, Jayaraman G, Allen V. Estimation of the burden of disease and costs of genital Chlamydia trachomatis infection in Canada. *Sex Transm Dis* 2012;**39**:260–7.

28 Vries R De, Bergen J Van. Systematic screening for Chlamydia trachomatis: estimating cost-effectiveness using dynamic modeling and Dutch data. *Value in* 2006;**9**:1–1.

29 Adams EJ, Turner KME, Edmunds WJ. The cost effectiveness of opportunistic chlamydia screening in England. *Sex Transm Infect* 2007;**83**:267-74-5.

30 Andersen B, Gundgaard J, Kretzschmar M. Prediction of costs, effectiveness, and disease control of a population-based program using home sampling for diagnosis of urogenital Chlamydia trachomatis. *Sex Transm Dis* 2006;**33**:407–15.

31 Gillespie P, O'Neill C, Adams E, *et al.* The cost and cost-effectiveness of opportunistic screening for

Chlamydia trachomatis in Ireland. *Sex Transm Dis* 2012;**88**:222–8.

32 Roberts T, Robinson S, Barton P, *et al.* Cost effectiveness of home based population screening for Chlamydia trachomatis in the UK: economic evaluation of chlamydia screening studies (ClaSS) project. *Bmj* 2007;**335**:291.

33 Welte R, Kretzschmar M, Leidl R, *et al.* Cost-effectiveness of screening programs for Chlamydia trachomatis: a population-based dynamic approach. *Sex Transm Dis* 2000;**27**:518–29.

34 Cohen M. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. *Lancet* 1998;**351**:S5–7.

35 Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;**75**:3–17.

36 Winter AJ, Taylor S, Workman J, *et al.* Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. *Sex Transm Infect* 1999;**75**:261–3.

37 Cohen MS, Hoffman IF, Royce RA, *et al.* Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet* 1997;**349**:1868–73.

38 Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV. *Sex Transm Dis* 2001;**28**:579–97.

39 Jin F, Prestage GP, Imrie J, *et al.* Anal sexually transmitted infections and risk of HIV infection in homosexual men. *J Acquir Immune Defic Syndr* 2010;**53**:144–9.

40 Little SJ, McLean AR, Spina CA, *et al.* Viral dynamics of acute HIV-1 infection. *J Exp Med 1* 1999;**90**:841–50.

41 Leynaert B n d., Downs AM, de Vincenzi I. Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. *Am J Epidemiol* 1998;**148**:88–96.

42 Beyrer C, Baral SD, van Griensven F, *et al.* Global epidemiology of HIV infection in men who have sex with men. *Lancet* 2012;**380**:367–77.

43 Alam SJ, Meyer R, Norling E. A model for HIV spread in a South African village. *Multi-Agent-Based Simul IX* 2009;:33–45.

44 Baggaley RF, Ferguson NM, Garnett GP. The epidemiological impact of antiretroviral use predicted by mathematical models: a review. *Emerg Themes Epidemiol* 2005;**2**:9.

45 The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;**373**:795–807.

46 Kitahata MM, Gange SJ, Abraham AG, *et al.* Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009;**360**:1815–26.

47 Palella Jr FJ, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;**338**:853–60.

48 Wit FW, Blanckenberg DH, Brinkman K, *et al.* Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. *AIDS* 2005;**19**:345–8.

49 Maggiolo F, Ripamonti D, Gregis G, *et al.* Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. *AIDS* 2004;**18**:439–46.

50 Ortiz GM, Wellons M, Brancato J, *et al.* Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects. *Proc Natl Acad Sci* 2001;**98**:3288–13293.

51 El-Sadr WM, Lundgren JD, Neaton JD, *et al.* CD4+ count-guided interruption of antiretroviral treatment. *New Engl J Med* 2006;**355**:2283–96.

52 Clotet B, Feinberg J, Lunzen J van, *et al.* Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised. *Lancet* 2014;**383**:2222–31.

53 Hill T, Bansi L, Sabin C, *et al.* Data linkage reduces loss to follow-up in an observational HIV cohort study. *J Clin* 2010;**63**:1101–9.

54 Mocroft A, Kirk O, Aldins P, *et al.* Loss to follow-up in an international, multicentre observational study. *HIV Med* 2008;**9**:261–9.

55 Ndiaye B, Ould-Kaci K, Salleron J, *et al.* Characteristics of and outcomes in HIV-infected patients who return to care after loss to follow-up. *AIDS* 2009;**23**:1786–9.

56 Mills E, Nachega J, Buchan I, *et al.* Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *Jama* 2006;**296**:679–90.

57 Rana AI, Liu T, Gillani FS, *et al.* Multiple gaps in care common among newly diagnosed HIV patients. *AIDS Care* 2015;**27**:697–687.

58 Rosenberg ES, Millett GA, Sullivan PS, *et al.* Understanding the HIV disparities between black and white men who have sex with men in the USA using the HIV care continuum: a modelling study. *Lancet HIV* 2014;**1**:e112–8.

59 Maryland Department of Health and Mental Hygiene, MDHMH. 2012 Baltimore City Annual HIV Epidemiological Profile. Baltimore: 2012.

60 Virginia Department of Health. STD Surveillance Network Report. Published Online First: 2013.http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf (accessed 30 Jun2017).

61 Castro JG, Alcaide ML. High rates of STIs in HIV-infected patients attending an STI clinic. *South Med J* 2016;**109**:1–4.

62 Berry SA. Gonorrhoea and chlamydia screening in HIV clinics: time for new tools and targets. *Sex Transm Infect* 2014;**90**:574–5.

63 Hoover KW, Butler M, Workowski K, *et al.* STD screening of HIV-infected MSM in HIV clinics. *Sex Transm Dis* 2010;**37**:771–6.

64 CDC. PrEP for men who have sex with men. 2018. https://prepmaryland.org/sites/default/files/download-resources/PrEP - MSM both sides March 2017.pdf

65 Koenig L, Lyles C, Smith D. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis.

Am J Prev 2013;**44**:S91–8.

66 Jenness S, Goodreau S. Impact of the centers for disease control's HIV preexposure prophylaxis guidelines for men who have sex with men in the United States. *J Infect Dis* 2016;**14**:1800–7.

67 Vissers DCJ, Voeten HACM, Nagelkerke NJD, *et al.* The impact of pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: a simulation study. *PLoS One* 2008;**3**:e2077.

68 Bolu OO, Lindsey C, Kamb ML, *et al.* Is HIV/sexually transmitted disease prevention counseling effective among vulnerable populations? a subset analysis of data collected for a randomized, controlled trial evaluating counseling efficacy (Project RESPECT). *Sex Transm Dis* 2003;**31**:469–74.

69 Carter JW, Hart-Cooper GD, Butler MO, *et al.* Provider barriers prevent recommended sexually transmitted disease screening of HIV-infected men who have sex with men. *Sex Transm Dis* 2014;**41**:137–42.

70 Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States-2014: a clinical practice guideline. 2014.

71 Calabrese SK, Underhill K. How stigma surrounding the use of HIV preexposure prophylaxis undermines prevention and pleasure: a call to destigmatize 'Truvada Whores'. *Am J Public Health* 2015;**105**:1960–4.

72 Highleyman L. PrEP use is rising fast in US, but large racial disparities remain. Aidsmap. 2016.http://www.aidsmap.com/PrEP-use-is-rising-fast-in-US-but-large-racial-disparities-remain/page/3065545/ (accessed 14 May2018).

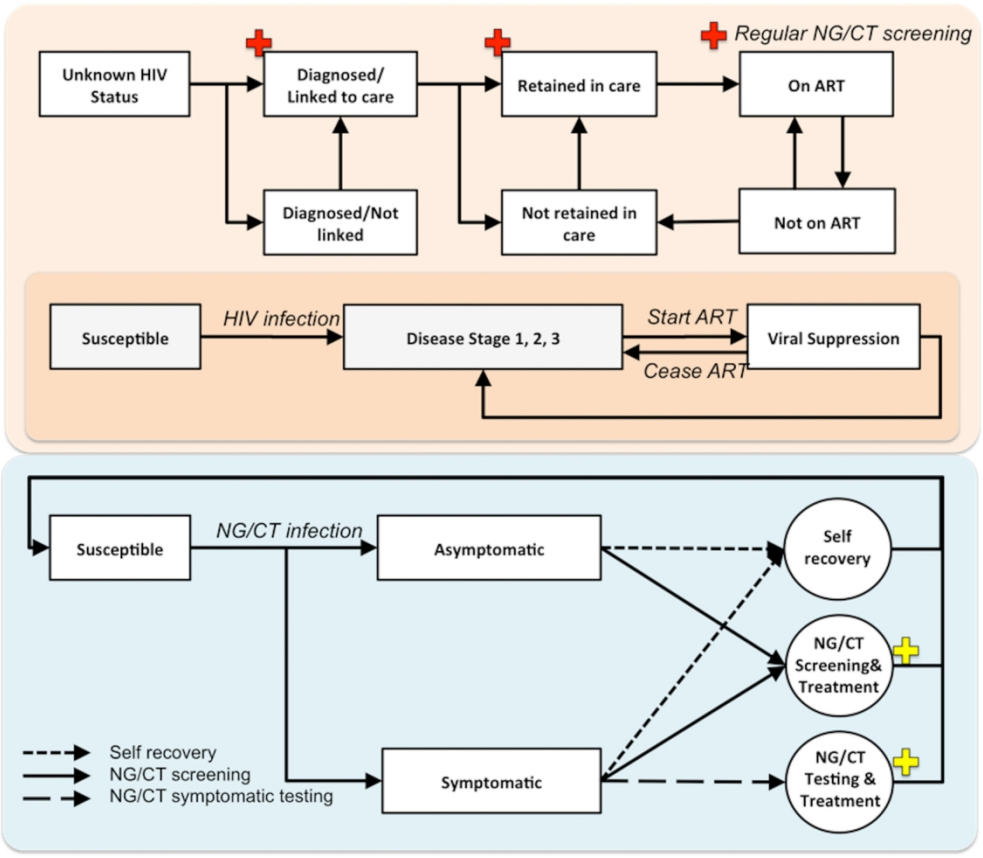
Figure legends:

Figure 1: An agent-based model of gonorrhoea/chlamydia (NG/CT) and HIV co-transmission. The top panel represents the HIV care continuum and natural history: Upon infection with HIV, individuals serially progress through three disease stages over time; this progression can be halted by initiation of antiretroviral therapy (ART), which is assumed to result – if taken – in viral suppression within 4 to 24 weeks (see Table 1) [52]. We assume, for simplicity, that engagement in care involves initiation of ART (as episodes of care engagement not resulting in ART initiation do not affect HIV transmission in the model). HIV-positive individuals in care are assumed to undergo regular screening for NG/CT (marked in red) subject to patients presenting for scheduled visits and clinician decision to screen. The bottom panel represents the natural history of NG/CT: infection may be symptomatic or asymptomatic, individuals remain infectious until diagnosis and treatment (which can occur either through symptomatic presentation to care or routine screening of asymptomatic individuals) or spontaneous resolution. Upon diagnosis with incident NG/CT, we assume that individuals are also screened for HIV infection (marked in yellow); if HIV-negative, we consider the possibility of PrEP delivery in this analysis.

Figure 2: Model projections of the distribution of new infections by age and sexual activity level. Shown on the y-axes are the distribution of HIV (A) and NG/CT (B) incidence by age-group and the distribution of HIV (C) and NG/CT (D) incidence by the sexual activity level. Bars represent the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

Figure 3: Impact of NG/CT-integrated PrEP, according to frequency of NG/CT screening/testing. Shown on the y-axes are the annual incidence of HIV (A), cumulative number of transmissions averted (B), number of MSM on PrEP (C) and NG/CT prevalence (D). The red line depicts a scenario in which all MSM currently diagnosed with NG/CT are placed on PrEP with 60% uptake and adherence (NG/CT-integrated PrEP scenario in the main text), and the blue line shows a hypothetical scenario in which 50% of MSM are screened for NG/CT every year, with those testing positive for NG/CT also offered PrEP.

Figure 4: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in red, also corresponding to the red line in Figure 3), compared against PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. In the first set of experiments, the three strategies are compared under the assumption that the same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be screened for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenario (similar pattern in panels E through H).



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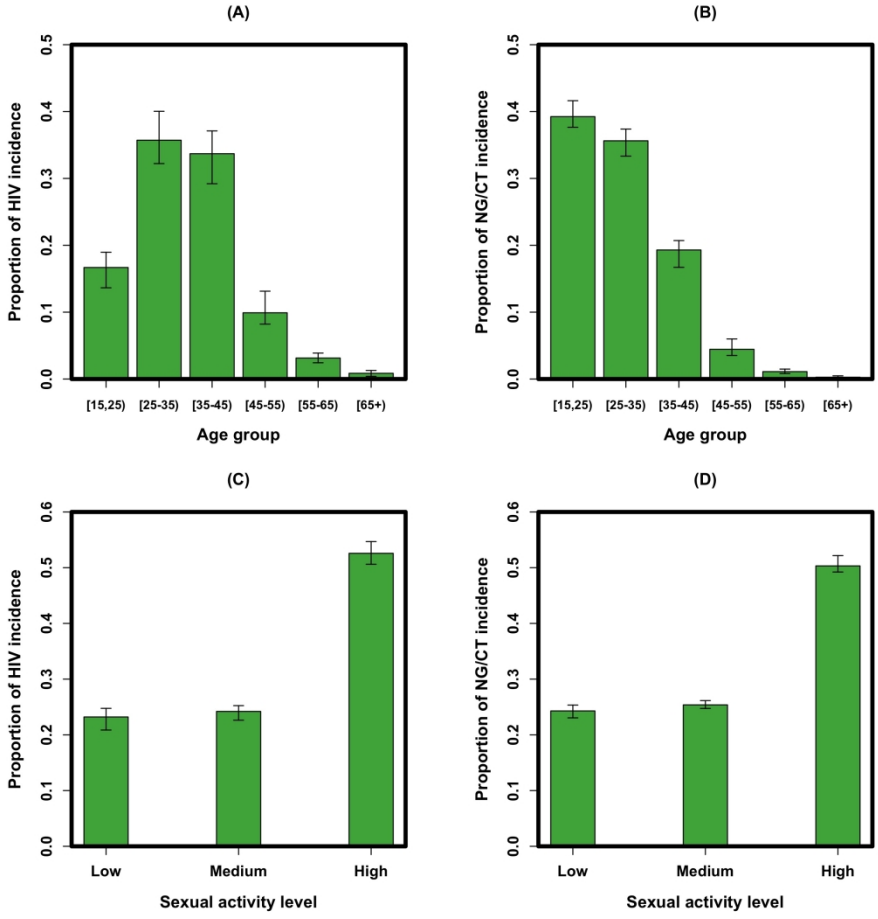

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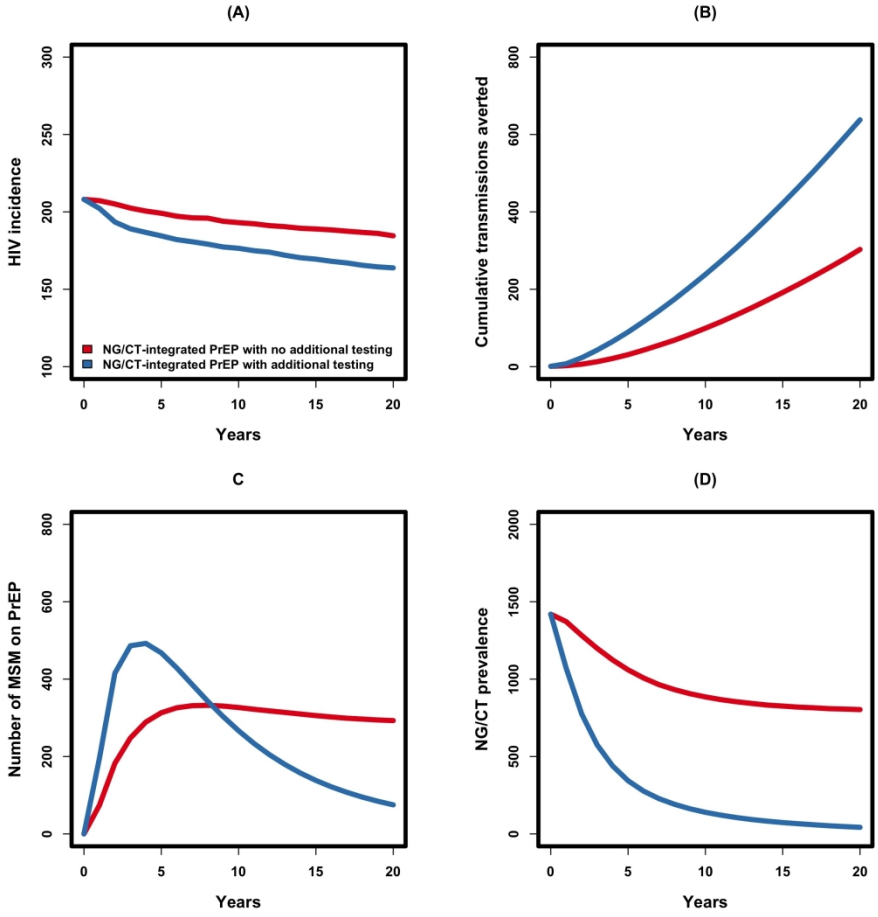

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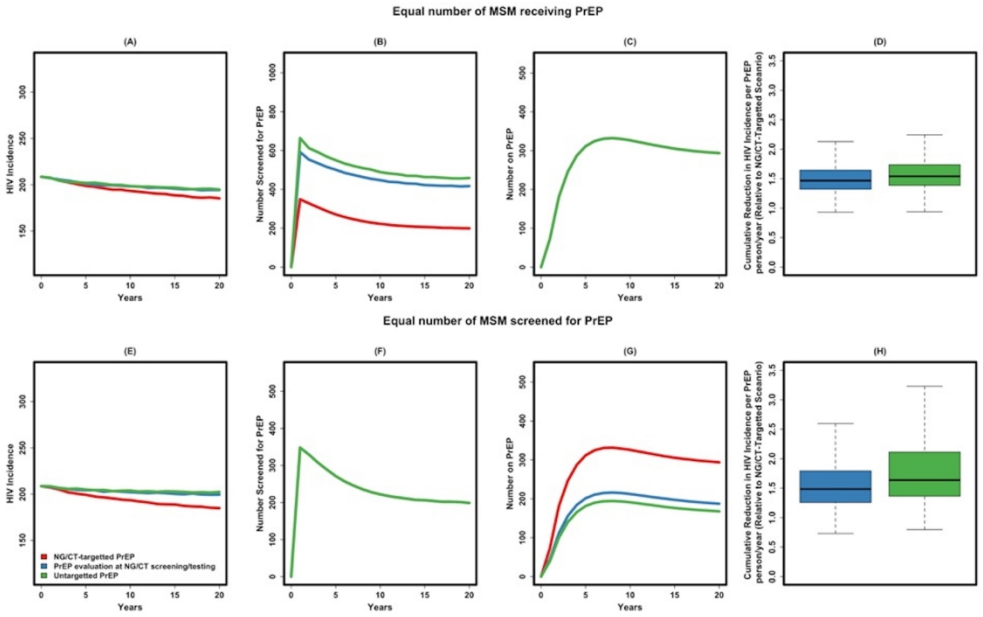

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SUPPLEMENTARY MATERIAL

Title: Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study

Authors: Parastu Kasaie[1], Christina M. Schumacher[2], Jacky M. Jennings[2], Stephen A. Berry[2], Susan A. Tuddenham[2], Maunank S. Shah[2], Eli S. Rosenberg[3], Karen W. Hoover[4], Thomas L. Gift[5], Harrell Chesson[5], Danielle German[1], and David W. Dowdy[1]

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1 HIV SIMULATION MODEL DESIGN

Overview

Our agent-based simulation model of the HIV epidemic among MSM in Baltimore City is structured as a collection of modules that govern population demographics, sexual partnerships, the epidemiological aspects of disease with regard to HIV natural history, cascade of care and transmission. Each "agent" represents a single MSM in Baltimore City, characterized by age, race, and place of residence, and the model is evaluated in a series of one-week time steps. The HIV natural history module characterizes the progression of HIV among infected individuals according to disease stage. Each stage is associated with a different per-act risk of HIV transmission, and disease progression from stage 2 to stage 3 can be prevented (and/or reversed) by provision of ART. The HIV cascade of care estimates probabilities of HIV testing, linkage to care, disengagement/re-engagement, and ART provision/viral suppression at each time step. The sexual network and transmission module create and modify the population's sexual networks (as a series of stable and casual partnerships) at each step, modeling HIV transmission as a per-act probability among serodiscordant partnerships according to frequency and safety of sex act, HIV stage of the infected partner, and ART/PrEP use. Sexual partnerships are modeled as assortative according to age, race, and location of residence. Finally, the population demographic module accounts for aging, death, and birth processes.

1.1 Population Demographic Module

This module characterizes the initial population structure and governs various procedures for aging, death, and birth at end of each simulated year. We model the population of MSM in Baltimore City between the ages of 15 to 75. The population is structured as a collection of population groups corresponding to Baltimore's Community Statistical Areas (CSA) [1]. CSAs are clusters of neighborhoods and are organized according to census tract boundaries, which are consistent statistical boundaries. In some cases, CSA boundaries may cross neighborhood boundaries. There are 55 CSAs in Baltimore City. Neighborhood lines often do not fall along CSA boundaries, but CSAs are representations of the conditions occurring within those particular neighborhoods. Simulated population groups are characterized with regard to their geographical location (CSA of residence) and racial structure (black and non-black). We do not model the spatial distribution of individuals within each CSA; rather geographical assignments are made at the CSA level by assigning the corresponding CSA-center coordinates to each MSM living in that CSA. The initial HIV distribution across CSAs is estimated according to publicly available data from Maryland's Department of Health and Mental Hygiene (MDHMH) [2].

Individuals age with the simulation clock (years) and exit the model according to an age-specific natural mortality rate [3], or by reaching the age of 75, or via an additional mortality rate associated with HIV infection. To maintain the initial population decomposition without disturbing the CSA structures, we model a natural birth process at the CSA level for replenishing the population size over time. The birth process is modeled via a non-stationary Poisson process tuned to maintain each CSA's population at a constant mean over time. Newborns enter the MSM population at age of 15 to 20 years old and follow the corresponding racial structure of the CSA of residence.

Using the current estimate of Baltimore City male population (approximately 287,000) who are 15 year or older in age (about 232,000), and estimated percentage of adult MSMs in each racial group (7.5% of non-black males and 5.8% of black males [4]), we estimate the size of Baltimore City's MSM population at approximately 15,000.

Forming CSA-groups: To determine groupings of similar CSAs, we first ranked the CSAs according to the median income level and racial makeup based on available information from Baltimore City census [1].

For simplicity, levels of income (Figure S1-left panel) and proportion of population that is Black/African-American (Figure S1-right panel) were coded into values from 1 to 5 (representative of various shades in Figure S1), and two values were assigned to each CSA. For example, CSA "Midtown" (T-shaped in the center of the map) was assigned a rank of 3 for median household income, and 2 for the proportion of population that is Black/African-American.

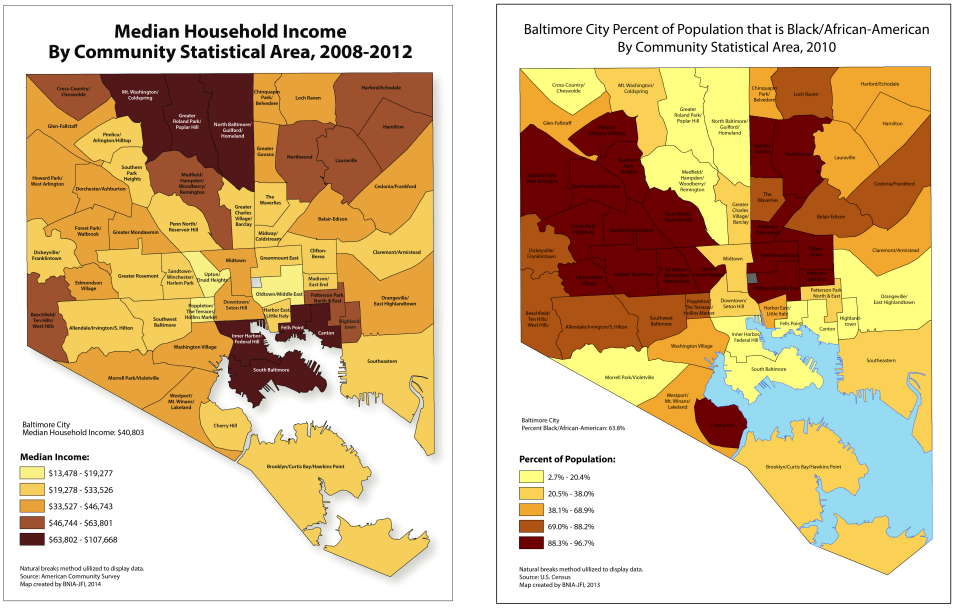

Figure S1: Baltimore City CSA ranking according to median income and racial structure [1].

We defined a CSA-group to include a number of neighboring CSAs (sharing a border) with at most a one-level difference in their ranked levels of income and racial makeup. To determine the CSA-groups throughout the city, we implemented a random search mechanism using a branch and bound logic. The search was started from a random CSA and branched through all neighboring CSAs to determine how many could belong to the same CSA-group. The search was bounded by those CSAs representing a difference of more than one level in ranked income and racial makeup but continued for those CSAs that belonged to the same group and branched further to test their other neighbors, until it was bounded in all directions. At the end of each iteration, a list of CSAs grouped by relative similarity across the whole city was generated. This search was repeated many times and the CSA groups that were most likely (i.e., high frequency) to form were identified. Overlapping CSA-groups were further checked for the possibility of combination into a single group. Finally, we had 16 CSA-groups across Baltimore City, representing geographically approximate neighborhoods with similar levels of income and racial makeup (Figure S2). Using CSA numbers as identifiers, a complete list of CSA groups is provided in Table S1.

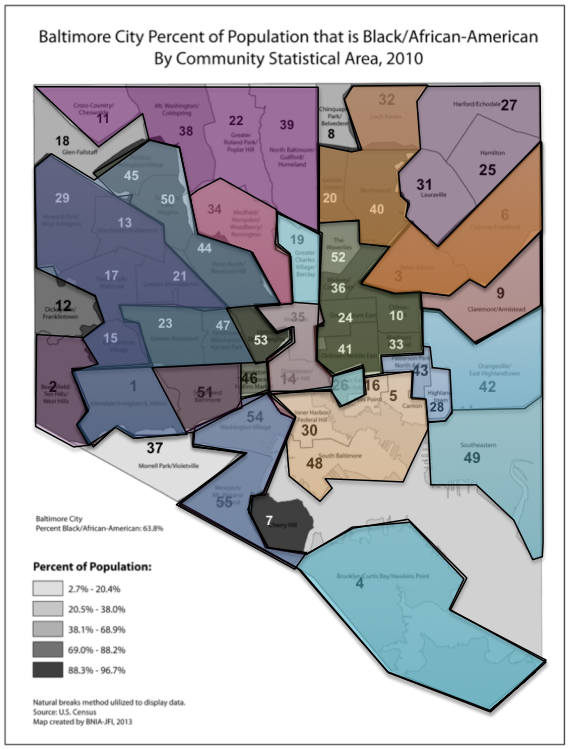

Figure S2: Baltimore City CSA ID's and CSA groups structure. Each CSA group is marked with a closed border in a different color. Some groups overlap such that some CSAs belong to more than one group. Some CSAs may not belong to any groups and are considered by themselves.

Table S1: List of CSA group and member CSAs

Group ID	CSA members
1	11 22 34 38 39
2	3 6 9
3	28 42 43
4	3 6 8 25 27 31 32
5	42 49
6	10 24 33 36 41 52
7	5 16 28 30 43 48
8	3 6 20 32 40
9	4 14 19 26 35 54 55
10	14 34 35
11	1 23 44 45 46 47 50 51 53
12	1 51 54 55
13	4 14 19 26 35 54 55
14	2 13 15 17 21 29
15	1 12 13 15 17 21 23 29 44 45 47 50 51
16	3 6 10 20 24 33 36 52

1.2 Sexual Partnership Module

This module governs the network of sexual partnerships and runs in discrete time steps, each representing a week. Following previous models of sexual contact networks [5–7], we conceptualize the network of sexual partnerships at an individual level (with regard to age, race, geography, sexual positioning, etc.) and calibrate the simulation parameters using local behavioral surveillance data available through the BESURE study, the Baltimore City branch of the National HIV Behavioral Surveillance System (NHBS) [8]. BESURE is a CDC funded project operated by the Maryland Department of Health and Mental Hygiene and the Johns Hopkins Bloomberg School of Public Health. Starting in 2004, BESURE has conducted four venue-based sampling surveys among Baltimore's MSM (Table S2). We use this data to extract information on several behavioral parameters at the individual level (e.g., preference toward using condoms in each type of partnerships) that will be directly implemented at the agent level, as well as population-level estimates for calibrating the unknown variables (e.g., frequency of the annual sexual partnerships). For those measures available across multiple BESURE waves, we use a pooled estimate of the reported values.

Table S2: Survey methods and sample characteristics, BESURE MSM 2004-2010

	Wave 1	Wave 2	Wave 3	Wave 4
Date	June 04-April 05	Jul-Oct 2008	Aug-Dec 2011	Jun-Dec 2014
Total MSM	645	448	404	455
HIV prevalence	37.7%	37.5%	42.6%	30.6%
Proportion of HIV that was unrecognized	58.4%	78.4%	67.3%	33.1%

1.3 Partnership types and formation

We model two types of partnerships representing long-term "stable" and short-term "casual" partnerships. Stable partnerships can last for several years [5], while casual partnerships will only last a single time step (one week) in the model. We assume that individuals can have multiple casual partnerships from one week to the next [9], but they can only engage in a maximum of one stable and one casual partnership at any time step. All partnerships are updated at the end of each simulation week, and those partnerships reaching their pre-specified duration will be dissolved. At the beginning of each following week, individuals' tendency to engage in a new partnership is evaluated and "eligible" individuals will select the geographical search domain for meeting their future partners based on their location of residence. Once the partnership domains are established for all eligible MSM, individuals will follow a search mechanism based on a combination of race- and age-dependent mixing patterns, as well as sexual role preference, to select their future partner from the pool of eligible people at the selected domain. This process is modeled in 3 steps:

1.3.1 Step 1. Evaluating an individual's probability of engaging in a new partnership

Each individual's likelihood of engaging in a new partnership is modeled as a function of his age, the level of sexual activity, and current partnership status.

In accordance with the heterogeneous frequency of reported partnerships by age, we define a partnership coefficient for modeling the likelihood of engaging in new partnerships as a function of individual's age ($c_{Part|Age}$) (assumed to be a fixed level for each age group).

Sexual activity class: In order to represent the heterogeneous level of sexual activity among MSM, we defined three sexual activity classes ("low", "medium" and "high"), each corresponding to a lifetime level of engagement in casual partnerships. An individual's sexual activity class (c_{SA}) is determined at the time of birth (entry to population) and remains fixed throughout his life (though within each sexual activity class, the actual level of partnership formation changes with age – for example, partnership formation declines with older age in all three classes). This attribute represents a combination of factors determining an individual's tendency for engaging in casual partnerships, reflecting the diversity of sexual activity seen in real populations. As described in a previously published modeling construct [10], we implement the simplified definition of the 3 sexual activity classes in order to more accurately represent "tails" in the observed distribution of (self-reported) sexual activity in data from Baltimore City. Individuals with particularly high sexual frequency are potentially important drivers of STI transmission dynamics but are not easily represented assuming a simple Poisson process of sexual partnership formation. We therefore arbitrarily assign equal numbers of individuals to these three sexual activity classes, and then calibrate the relative frequency of casual partnership formation in each of these classes to most closely fit the observed distribution among MSM in Baltimore City.

Finally, we model each agent's tendency for engaging in casual and stable partnerships at any point of time via two additional parameters (p_{Csl} and p_{Stb}) at the agent-level, and also define the conditional likelihood of engaging in new casual partnerships concurrent to an existing stable partnership via a separate parameter ($p_{Csl|Stb}$).

With these definitions, an individual's likelihood of engaging in a new stable (P_{new_stb}) or casual (P_{new_csl}) partnership at each timestep can be estimated as follow:

$$P_{new\_stb} = p_{Stb} \times c_{Part|Age}$$

$$P_{new\_csl} = p_{Csl} \times p^{*}_{Csl|Stb} \times c_{Part|Age} \times c_{SA}$$

$$p^{*}_{Csl|Stb} = \begin{cases} p_{Csl|Stb} & number\ of\ stable\ partnerships > 0 \\ 1 & o.w. \end{cases}$$

At each time step, an individual's likelihood for engaging in a new partnership is evaluated and eligible individuals are added to the pool of available people at their CSA of residence to find their potential partners in the next steps.

1.3.2 Step 2. Choosing the partnership domain

The partnership domain is determined according to a discrete mixing structure at the CSA level (Figure S3). In order to model the spatial mixing patterns across the population and among various subgroups, we first define sets of "neighboring" CSA groups with regard to geographical proximity and similar socioeconomic status (income levels) and racial structure [1]. Upon seeking a new partnership, an individual's search scope (for choosing the new partner) is determined according to a discrete geographical mixing probability (*pGM*) for selecting one's own CSA (p_0), a random neighboring CSA in the same CSA group (p_1) or non-neighbor CSA (p_2). The geographical mixing probability ($pGM=(p_0, p_1, p_2)$)

represents a measure of geographical/socioeconomic clustering in the network of partnerships, where *pGM*=(1,0,0) translates into an isolated mixing pattern for partnership only with individuals in one's CSA of residence, and *pGM*=(0.33,0.33,0.33) translates into a homogeneous mixing structure across the entire population. In our initial analysis, we calibrate the geographical mixing likelihoods at *pGM* = (0.5, 0.3, 0.2) according to available estimates from [11].

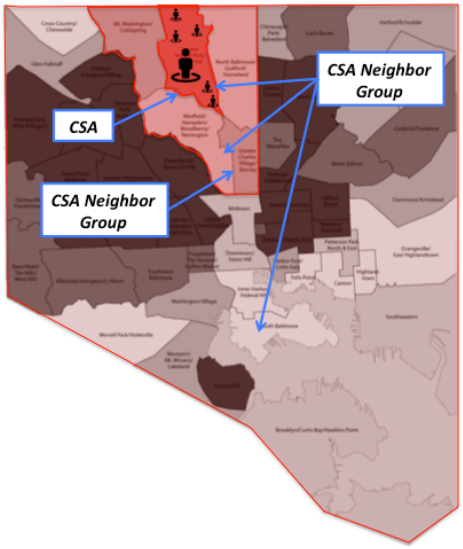

Figure S3: Partnership search domains. Individuals can choose their future partner from their own CSA or a random CSA within or outside their neighbor group.

1.3.3 Step 3. Modeling the search mechanism within the partnership domain

Once the partnership domain is established, individuals follow a search mechanism for finding their new partners from the pool of eligible members in the selected domain. The probability of partnership between two people is evaluated according to an age- and race-mixing structure, as well as sexual role preference. Assuming independent patterns of age- and race-specific mixing, the age-race mixing probability is computed as the product of age-mixing and race-mixing probabilities for each pair of potential partners. A random search mechanism is implemented to evaluate the probability of partnership with each potential partner in the selected domain until a successful match is found or the entire domain is searched. Potential partners are also checked for their compatibility with regard to sexual role and incompatible pairs (e.g., receptive-receptive or insertive-insertive) are dismissed. Upon a successful match, a new partnership is formed for both parties, who are then excluded from the pool of eligible partners for other individuals.

1.3.4 Age-Specific Mixing

Age-specific mixing is modeled based on absolute difference in the square root (ADSR) of men's ages [5]. The ADSR provides a closer fit to the observed age-mixing matrix than does age directly. This statistic also has the desirable property that the same absolute difference in age becomes less important over time. Using data on participant's age and their last male partner's age from BESURE, we estimate the reported ADSR level for main/casual partnerships ($ADSR_{partnership}$) as shown in Table S3. The probability of age-mixing between person *p* and *q* for each partnership type (*pAgeMixing*) is then computed as a function of

partners' age and the target ADSR level for each type of partnerships. Figure S4-A and S4-B compare the simulated distribution of ADSR values among casual and stable partnerships in the baseline simulation model.

$$pAgeMixing = \text{Min}(ADSR_{p,q,2} \times ADSR_{partnership} - ADSR_{p,q}) / ADSR_{partnership}$$

where

$$ADSR_{p,q} = \left| \sqrt{p_{age}} - \sqrt{q_{age}} \right|$$

$$ADSR_{partnership} = (ADSR_{Stb}, ADSR_{Csl})$$

Table S3: Estimates of reported ADSR for Stable/Casual partnerships in BESURE. Estimates are made based on the participant's age and their last male partner's age.

BESURE Waves:	$ADSR_{Stb}$ (Number of reported partnerships)	$ADSR_{Csl}$ (Number of reported partnerships)
Wave 2	0.62 (66)	0.72 (75)
Wave 3	0.68 (71)	0.73 (87)
Wave 4	0.51 (62)	0.76 (77)
Average estimate	**0.6**	**0.74**

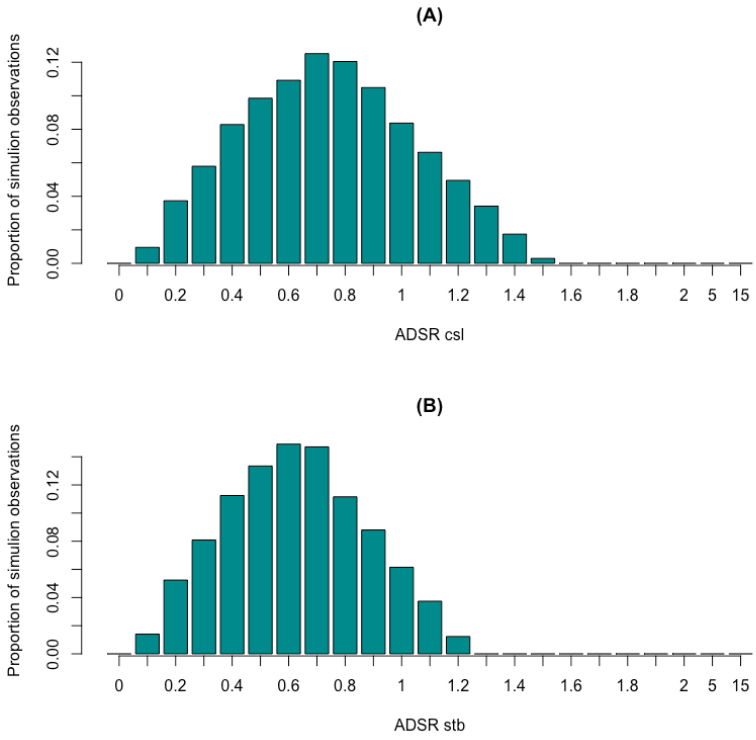

Figure S4: Distribution of ADSR in simulated casual (Panel A) and stable (Panel B) partnerships at the baseline model.

1.3.5 Race-Mixing

We model the probability of partnership between MSM of the same sex by estimating the reported ratio of same-sex partnerships for Black MSM at 90% and for White MSM at 75% through BESURE data.

1.3.6 Sexual Role Preference

Each MSM is assigned an individual sexual role preference (insertive only, receptive only, versatile) at the time of birth (entry to population). The sexual role preferences prohibit the partnerships between two men who are insertive only or those who are receptive only (allowing for 5 partnership configuration). The type of sexual act in partnerships between two versatile men is determined via uniform probability distribution between 0 and 1 (e.g., 50% chance of insertive/receptive act for each man) and will be updated at each time step for their active partnerships. Using data from BESURE, we estimate the proportions of population that fall within each category at 42% insertive-only, 26% receptive-only, and 32% versatile.

1.4 HIV Epidemiological Module

This module governs various aspects of HIV natural history and cascade of care, and it is updated at the end of each time step (week).

1.4.1 HIV Natural History

Upon a successful HIV transmission event, individuals experience a gradual increase in viral load (VL) and move through various stages of disease (Figure 1, main manuscript). We consider three disease stages in absence of ART, including stage 1 (CD4 count > 500 cells/ μL), stage 2 (CD4 count between 200-500 cells/ μL) and stage 3 (CD4 count <200 cells/ μL). Each disease stage is characterized with regard to duration of disease (as a crude measure of CD4 decline over time), mean VL level (determining the level of infectiousness) as well as the HIV mortality rate. In this model, we do not model the dynamics in the number of CD4 counts directly, but rather use the defined disease stages as surrogate marker of VL and mortality level for all HIV+ individuals.

1.4.2 HIV Cascade of Care

The continuum of care for infected individuals is modeled in five levels corresponding to those 1) unaware of their HIV infection, 2) diagnosed with HIV but not linked to care, 3) linked to care but not engaged in care, 4) engaged in care and on ART, and 5) engaged in care but not taking ART (Figure 1, main manuscript).

HIV-positive individuals are subject to a probability of screening for HIV at the beginning of each week. Upon diagnosis with HIV, individuals experience a fixed likelihood of linking to care over the following weeks. Once linked to care, individuals are assumed to engage in HIV care and start ART immediately. Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 24 weeks after ART initiation; rarely, in some patients it may take longer. Taking ART will further lower the disease mortality rate at each disease stage to a certain degree [12–14]. We assume that individuals starting ART through stage 3 (with CD4 count < 200 cells/ μL) will continue to experience the stage 3 mortality level (adjusted with ART reduction factor) for one year before reverting back to stage 2 (and experiencing stage 2 mortality level adjusted with ART reduction factor).

Those on ART can become non-adherent to treatment over time and/or become disengaged in care[1]. These individuals are subject to a weekly probability of reengagement in care and reinitiating ART in the future, but cannot reinitiate ART for 6 months after discontinuation [15]. Once off ART, individuals are assumed to lose viral suppression immediately and to experience a rapid decline in their CD4 counts. For simplicity, we assume that the effect of ART on CD4 count levels is maintained for one year following discontinuation (unless the agent was not previously on ART for a year, in which case the duration of ART is used) – and we also add this amount of time to the individual's "clock" of progression for HIV disease. Thus, for example, an individual starting ART in stage 2 and taking ART for 6 months before discontinuation will go back to stage 2, but the time until progression to stage 3 is prolonged by 6 additional months. We further assume that those starting ART in stage 1 will return to stage 2 if they discontinue treatment, and

[1] At ART discontinuation, if the person has started ART during Chronic disease, they are assumed to return to stage 2 with the same level of infectiousness and will be subjected to the corresponding mortality level. The duration of stage 2 is assumed to be the lesser of the preceding duration of ART (before loss to follow-up) or one year. If the person had started ART during stage 3, they will can return to stage 2 or stage 3 depending on the duration of treatment:

- If duration of treatment is smaller than the time spent in stage 3, agents return to stage 3 with the same level of infectiousness and mortality. The duration of stage 3 is extended for the duration of treatment up to one year.
- If duration of treatment is greater than the time spent in stage 3, agents return to stage 2. The duration of stage 2 will be expanded for the duration of treatment minus time spent in stage 3.

those beginning ART through stage 3 can revert to stage 2 or stage 3 depending on the duration of treatment.

1.5 HIV Transmission module

HIV transmission is evaluated for all active partnerships between HIV-positive individuals and susceptible partners at the end of each week. The probability of transmission is modeled as a function of an infected partner's infectiousness for transmitting HIV, the immunity of the negative partner toward transmission with HIV (through PrEP), potential protection through condom use, and an additional coefficient tuning the overall probability of transmission. HIV infectiousness is modeled as a function of an individual's VL corresponding to his disease stage and care status, as noted in Table 1 of the main manuscript. An individual's immunity to infection is modeled as a function of PrEP use and adherence, ranging from 0 (in absence of PrEP) to 1 (full adherence to PrEP). The probabilities of condom use in casual and stable partnerships are estimated based on reported levels through BESURE (Table S4). Finally, the transmission coefficient captures the baseline probability of HIV transmission per contact and is calibrated to reflect disease prevalence at equilibrium.

Table S4: Reported frequency of condom use in stable and casual partnerships from BESURE.

	Never	Part-time	The whole time
Stable partnership	0.45	0.55	0
Casual partnership	0.47	0.12	0.4

With these definitions, the weekly likelihood of HIV transmission through an active sexual contact is estimated as follow:

$$Ptrans(\mathrm{X},\mathrm{Y},\mathrm{Q}) = C \times X_{Inf} \times Y_{sus} \times (1 - pCondumUse(Q) \times cCondomEffectiveness) \times Y_{sexualPositionCoef}$$

where

Ptrans(*X,Y,Q*): Per week probability of transmission from person *X* (infected) to *Y* (susceptible) in a partnership type Q (stable, casual)

C: Simulation coefficient

Y_{Inf}: Person Y's infectiousness

X_{Sus}: Person *X's susceptibility* toward infection

pCondomUse(*Q*): Probability of using condom in partnership type Q

cCondomEffectiveness: condom effectiveness in reducing the risk of transmission

$Y_{sexualPositionCoef}$: Person Y's increased probability of transmission based on sexual positioning

1.6 GC Epidemiological Module

We consider NG/CT as a 'SIS'-type disease; specifically, individuals become infectious after an initial infection and remain infectious until treatment or spontaneous resolution, at which time they become immediately susceptible to recurrent infection. We assume that NG/CT is spread through sexual (genital-genital, genital-rectal, genital-oral, or oral-rectal) contact, and that infection may be either symptomatic or asymptomatic. Symptomatic individuals experience a fixed probability of seeking care in each week. We include only those care-seeking episodes that would trigger a clinical decision to test for NG/CT at the appropriate site and would result in treatment if the test were positive; other care-seeking episodes (whether for unrelated conditions [e.g., upper respiratory infections] or for symptoms of NG/CT that are either not recognized or would not result in treatment even if the test were positive) are ignored. We assume that individuals remain infectious during the week of treatment and one week thereafter [16–18]. In addition to this symptomatic testing behavior, all MSM (whether infected with NG/CT or not) can further undergo regular screening for NG/CT (i.e., in the absence of symptoms) according to CDC recommended criteria for MSM based on their HIV status, PrEP status, and STI history [19]. The duration of untreated disease (d) is based on literature estimates, and the weekly probability of spontaneous resolution is set to inverse of this duration ($1/d$).

1.6.1 Site of infection

We differentiate three types of NG/CT infections based on the site of infection as Urethral, Rectal or Pharyngeal infections. Given the low degree of overlap for simultaneous infections in multiple sites, and the higher likelihood of symptomatic disease in urethral infections for those co-infected with rectal and pharyngeal infections, we only allow for a single-site NG/CT infection in each individual and will exclude the possibility of simultaneous infections in various sites (allowing for no reinfection while the original infection lasts). Each type of infection is further associated with a specific likelihood of developing symptomatic disease (Table 1 of the main manuscript). Among HIV- individuals, a rectal/urethral NG/CT can increase the transmissibility of HIV to sexual contacts among HIV infected MSM and also increase the susceptibility for HIV acquisition among HIV uninfected MSM.

1.6.2 NG/CT Transmission dynamics

NG/CT-infected individuals can transmit the disease to other individuals through exiting network of sexual contacts (previously built and calibrated for the HIV model). Due to complications in conceptualizing all various pathways for transmission of disease from one site to another with regard to different types of sex acts, unknown level of individuals' preferences for each sexual role and the degree of versatility to change this role in each partnership, in addition to the lack of data informing the risk of NG/CT infection through each mode of transmission, we adopt a simplifying assumption to combine various modes of transmission for all types of infections through a single transmission event modeled over each active sexual contact between an infected and uninfected MSM at each time step. Upon transmission with NG/CT, the clinical site of the recipient infection is randomly assigned in such a way as to replicate the relative incidence of infection at each site as estimated from local surveillance report in Baltimore City (see Table 1 of the main manuscript).

1.6.3 Computing the probability of presenting to STI care

MSM may present to HIV/STI care providers (e.g., STD clinics, community health centers, HIV counseling programs) for a variety of reasons, and get tested for HIV and other STIs. We model visits for STI screening as a fixed weekly probability that reflects an individual's age-group (modeled in 12 classes for MSM age 15 to 75) and sexual activity level (modeled in 3 classes of sexual activity), such that younger MSM with higher propensity of partnerships experience a higher likelihood of visits [20,21].

We let *S* represent the individuals' sexual activity class (values ranging from 1 to 3 representing low-, medium- and high-activity classes) and we let A represent the individual's age-group (values ranging from 1 to 12 representing age groups of 5 years each: [15,19], [20-24], …, [70,75]). Finally, according to previous assumptions for lower level of access to HIV care among Black MSM compared to White MSM in the baseline simulation model, we modify the probability of accessing to STI care (*pAccessCare*) by race (R) set at 50% for Black MSM relative to White MSM [22]. Given these assumptions, an individual's probability of presenting to STI care (*PPSC*) at each week is computed as follow:

$$PPSC\ (\mathrm{S},\mathrm{A},\mathrm{R}) = {}^{(13-\mathrm{A})}/_{12} \times {}^{(\mathrm{S})}/_{3} \times pAccessCare(\mathrm{R}) \times C$$

where C is the fixed coefficient for fine-tuning the probability of presenting to STI care.

1.7 PrEP module

PrEP Eligibility criteria: Our primary outcome for the current analysis is the projected incidence of HIV after 20 years of delivering PrEP to MSM in Baltimore City. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the added benefit of targeting PrEP at individuals diagnosed with NG/CT. In all three scenarios, indication for PrEP use (eligibility) is considered in accordance with CDC recommendations [23] and Baltimore City's PrEP guidelines [24].

The CDC guidelines for PrEP use among MSM use the following criteria as indications for PrEP: sexually active HIV negative adult MSM who are not in a monogamous partnership with an HIV-negative male partner and who in the last 6 months: report any condomless anal sex, have any STI reported or diagnosed, or report having an ongoing sex partner with HIV [23]. The PrEP guidelines in Baltimore City further suggest that all HIV negative MSM who 1) may not have access to condom or always ask a partner to use a condom, 2) are diagnosed with a STI in the last 6 months, 3) are in a serodiscordant relationship with a HIV-infected partner (who may or may not be on HIV treatment), 4) are unsure of HIV-status of their sexual partner, or 5) inject drugs or are in a sexual partnership with a person who inject drugs should consider PrEP. As such, we modelled the criteria for PrEP eligibility among MSM to include HIV-negative MSM who are diagnosed with NG/CT in the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual partnership in the last 6 months.

2 SIMULATION CALIBRATION

Individual-level parameters in our models fall into two categories: "fixed" parameters estimated based on available literature or data, and "variable" parameters that are unknown and will be calibrated based on epidemiological setting. Fixed (known) parameters include those associated with the natural history of HIV (such as viral load levels in each disease stage) and those defining behavioral characteristics (e.g., likelihood of condom use). Variable parameters include descriptors of HIV and NG/CT transmission and

care that are defined at the individual-level and will be calibrated to provide the corresponding calibration targets (at the population-level) from Baltimore City (e.g., tuning the individual's probability of presenting to care for HIV screening to provide the target proportion of infected population diagnosed in Baltimore City). Table 1 in the main manuscript includes a list of main calibration targets for HIV and NG/CT modules.

2.1 Calibration Targets

2.1.1 HIV prevalence and continuum of care

Using the latest report of public HIV surveillance data from Baltimore City (year 2012) [2], we estimate the prevalence of HIV among MSM at a total of 3329 people, which corresponds to a prevalence of 22% in our simulated population. Furthermore, we estimate the reported proportion of HIV-infected MSM in each step of the cascade at 86% for those diagnosed but not linked to care, 62% for those linked to care but not engaged, 50% for those engaged but not on ART, 39% for those on ART but not virally suppressed and finally 27% for those virally suppressed.

2.1.2 NG/CT incidence

In this section, we provide details of our estimation procedure for NG/CT incidence using data made available to us through several sources including 1) the gonorrhoea Surveillance dataset, 2) STD Surveillance Network, and 3) BCHD facility dataset in Baltimore City.

Estimating the annual diagnosis of gonorrhoea infection in Baltimore City: The gonorrhoea Surveillance dataset includes all males residing in Baltimore City who were reported to the Baltimore City Health Department for infection with gonorrhoea at one or more anatomic site, regardless of sex partner gender, beginning with cases diagnosed on 1/1/09 and ending with cases reported through 5/31/16. Due to changes in testing technology, we only consider data from 2011 and later for estimating gonorrhoea diagnosis as that is when the STD clinics started using NAATs for extragenital swabs (due to the lab becoming validated for this) which is more in line with practices moving forward. We further restrict the data to the end of 2015, to cover the annual number of diagnosis in each full year (Table S5). We further analyze this data by reported site of infection and estimate the range of reported gonorrhoea diagnosis in each body site (Table S6).

Table S5: Annual number of reported gonorrhoea diagnosis among men in Baltimore City.

	2011	2012	2013	2014	2015
Gonorrhoea diagnosis	1139	901	1052	1083	1297

Table S6: Annual gonorrhoea diagnosis among men by site of infection in Baltimore City.

Site of infection	Lower bound	Upper bound
Urethral	681	1026
Rectal	46	83
Pharyngeal	58	151

Adjusting for MSM risk group: The surveillance dataset does not include information on gender of sex partners for all persons diagnosed with gonorrhoea infection. This information is however available for a

subset of population through STD Surveillance Network (SSuN). SSuN attendees are randomly selected from MSM diagnosed with gonorrhoea who will then agree to complete a SSuN interview. Within this group, 26% to 30% of all male patients identified themselves as MSM in Baltimore City.

Adjusting for non-overlapping Chlamydia infections: The BCHD facility dataset provides information on diagnosis of gonorrhoea or chlamydia infection among all male patients visiting the two STD clinics in Baltimore City. This data is further stratified for MSM by including men who reported male sex partners in the past 3 months OR self-identified as gay or bisexual. For patients who visited the clinic multiple times, if he was classified as MSM at any visit, we included all his clinic visits. The dataset provides information on all episodes of visit and diagnosis with gonorrhoea or chlamydia infection among these men. Based on the reported number of diagnosis, we estimate the proportion of diagnosed chlamydia infection that did not overlap with gonorrhoea infection relative to overall number of gonorrhoea diagnosis at 40%, and use this value to adjust the annual number of gonorrhoea diagnosis among MSM to include non-overlapping chlamydia infections as well. This estimate also agrees with the reported level of chlamydia infection relative gonorrhoea infection in Baltimore City through the STD Surveillance Network (SSuN) 2013 [25].

Adjusting for proportion of symptomatic cases not seeking care: In order to derive the true incidence of disease from the current estimates of the number diagnosis, we further adjust our estimate to account for the proportion of symptomatic cases not seeking care. Based on literature, we estimate that approximately 60% symptomatic population may not seek direct care for their disease (56% for Urethral infection, 60% for Rectal and 70% for Pharyngeal infection) [26], and inflate the number of symptomatic cases in our sample (approximately 78% of sample) by 250% to account for these cases.

Adjusting for the number of asymptomatic infection: Given the restrictions in capturing the underlying level of asymptomatic disease from the estimated of NG/CT diagnosis, we rely on our estimate of the symptomatic NG/CT incidence, and assume that each episode of NG/CT infection is associated with a 74% likelihood of symptomatic infection for urethral, 20% for Rectal, and 10% for Pharyngeal disease [26–28]. Based on this assumption, we derive the estimate for annual incidence of NG/CT among MSM by site of infection as follow:

- Incidence of urethral infection [725 – 1135] Person/year
- Incidence of rectal infection [144 – 259] Person/year
- Incidence of pharyngeal infection [327 – 852] Person/year

Challenges in interpreting local estimates: Despite general expectations, our estimated ratio of rectal/pharyngeal to urethral infections is very small. This pattern does not agree with the previously reported prevalence of extragenital relative to genital NG/CT in different populations that estimate the average prevalence ratio of rectal to urethral infections at 4.1 (ranging from 2.43 to 6.23) and pharyngeal to urethral infections at 1.5 (ranging from 1.35 to 1.71) [29–31]. In a previous analysis of SSuN data, researcher reported a similarly low proportion of extragenital to genital NG/CT infections among MSM attending STD clinics [32], and attributed it to low rate of extragenital NG/CT screening at STD clinics that results in missing those infections [33].

Given that our estimates of the genital and extragenital NG/CT infections based on local datasets from Baltimore City are more in line with the observed trends in the SSuN data, we believe that the same pattern of underestimation is evident for the true incidence of extragenital NG/CT infection in this population. In order to fix this problem, we chose to rely on the estimated incidence of genital (urethral)

NG/CT infection from the surveillance dataset in Baltimore City (assuming appropriate level of genital-site testing/screening and reporting), and to estimate the incidence of rectal and pharyngeal infections by applying the reported prevalence ratio of each infection site relative to urethral infection.

Estimating the incidence of rectal and pharyngeal infection: We assume that diagnosed NG/CT will be treated very rapidly, such that the relative duration of disease is driven by the proportion of infections for which people are not treated - whether because they are asymptomatic, symptoms are not sufficient to drive care-seeking, or the clinical presentation (e.g., sore throat) does not prompt testing or treatment for NG/CT. Screening is assumed to have relatively little impact on the *relative* duration of infection (i.e., screening can occur, but it does not pick up so many more prevalent urethral infections than pharyngeal infections, for example, that it drives the ratio of disease duration in the population to a significant degree). We further assume that the asymptomatic disease is likely to go undetected and therefore 26% of urethral infections, as well as 80% of rectal and 90% of pharyngeal infections will go untreated [26–28].

Based on these assumptions, we derive the incidence ratios based on prevalence ratios as follow:

- Incidence ratio of rectal to urethral disease: 4.08 (prevalence ratio) * 0.26 /0.8 (proportion of untreated cases) = 1.33
- Incidence ratio of pharyngeal to urethral disease: 1.5 (prevalence ratio) * 0.26 /0.9 (proportion of untreated cases) = 0.43

Using the estimated incidence ratios, we estimate the incidence of rectal and pharyngeal NG/CT among MSM as follow:

- Incidence of urethral NG/CT among Baltimore's MSM: [735-1135] Person/year
- Incidence of rectal NG/CT among Baltimore's MSM: [998-1505] Person/year
- Incidence of pharyngeal NG/CT among Baltimore's MSM: [326-492] Person/year

2.2 Calibration procedure

Upon collection of all individual-level data and incorporation into the model (fixed parameters), we calibrated the model as a whole against population-level targets (above) to ensure that the model provides realistic outputs. This was done via a random search mechanism to find the best combination of parameter values that minimizes the observed difference between simulated outputs and the calibration targets.

Burn-in Period: The model starts from a randomly generated population of MSM with no active partnership at time zero with a randomly assigned pattern of HIV infection (randomly according to age, race and location of residence). In order to create a realistic pattern of sexual partnerships with age, we allowed the original population to age and evolve for at least one generation before reaching a stable level of HIV incidence in the absence of PrEP – thus generating a full burn-in period of 100 years (a decision made on an a-priori basis).

2.3 Calibrating partnerships

BESURE surveys (2004 – 2014) provided the main source of local information available on the network of MSM partnerships in Baltimore. The data included aggregate information on the reported number of sexual partners (by age group) and type of those partnerships in the last 12 months. Assuming a fixed mixing structure over time, we used this information to calibrate the individual-level likelihood of engaging in a stable or casual partnership at each simulated time step (week). We further used the coefficients of sexual activity to calibrate the right and left tail of the partnership frequency distribution

(for those MSM reporting 0 or more than 5 partners in a given year). The partnership calibration results are summarized in Figure S5.

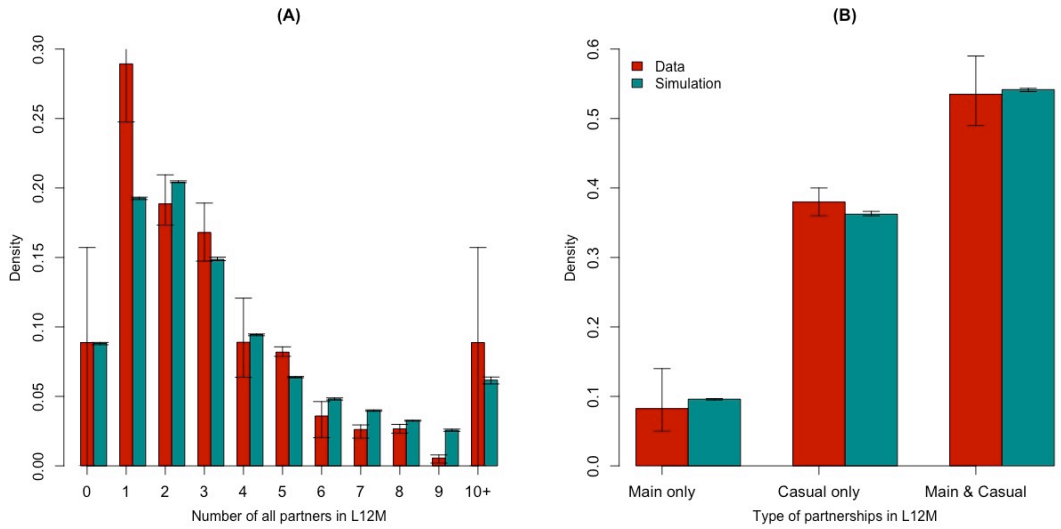

Figure S5: Model calibration to partnership data. Shown are the mean values of simulations (in green) compared against empirical data (in red). The error bars around simulated values represent the 95% uncertainty range of observations around each simulated measure, and the error bars around the data represent the range of annual observations through the 4 BESURE surveys from 2004 to 2014.

2.3.1 Frequency of partnerships by age and sexual activity

The age-dependent coefficients of partnerships in each sexual activity class were calibrated to accurately portray the right and left tails of the partnership frequency distribution for all MSM and in each age group. The calibration results are summarized in Figure S6.

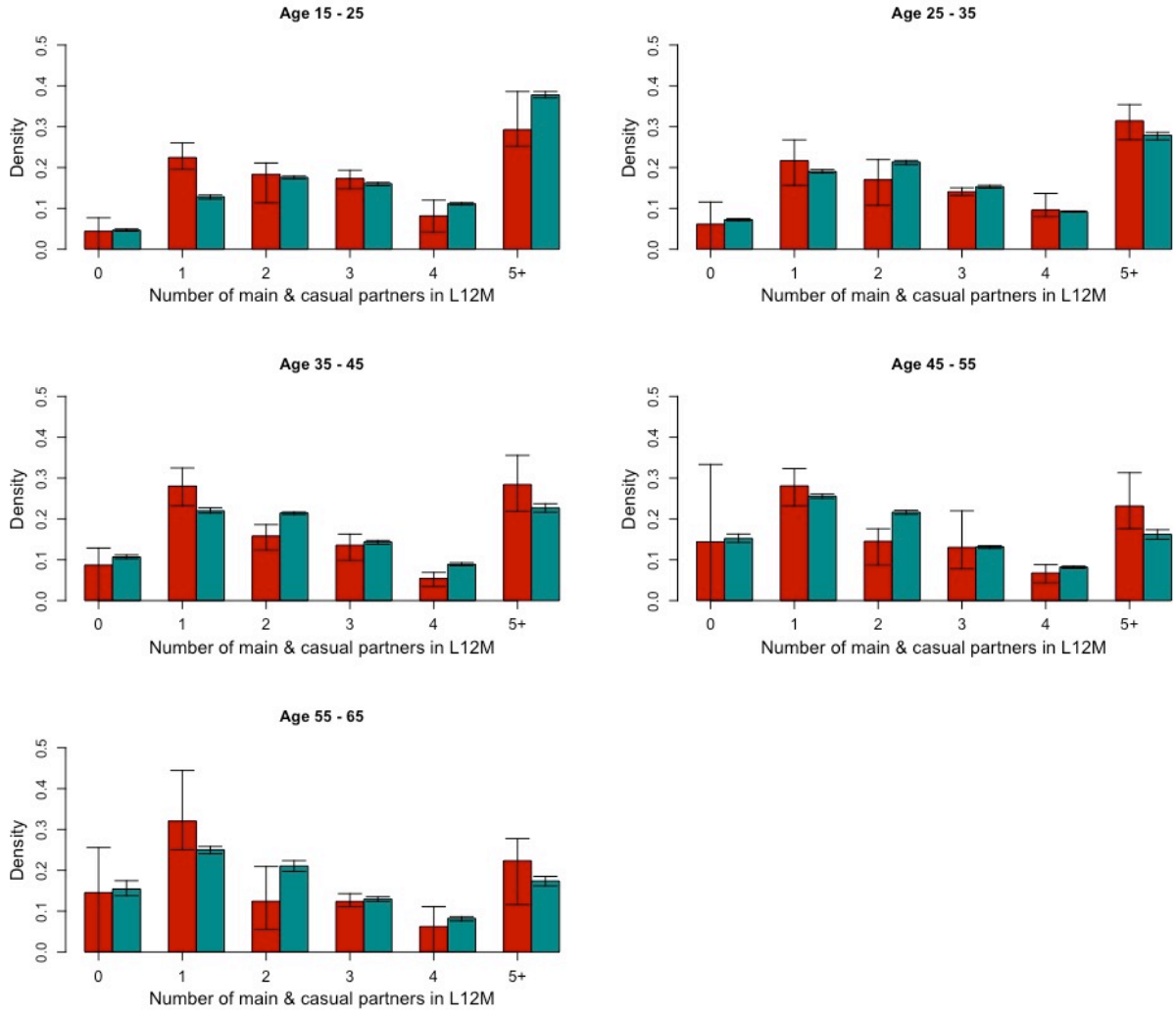

Figure S6: Frequency of reported partnerships in each age group in the last 12 months (L12M), comparing model results to the data against which the model was calibrated. Shown are the mean values across all simulations (in green) compared against empirical data (in red). The error bars around simulated bars represent the 95% uncertainty range of simulated values and the error bars around the data represent the range of annual observations through the 4 BESURE surveys from 2004 to 2014.

There were conceptual challenges with the use of BESURE data as the main data source for calibrating the network of sexual partnerships. Specifically, BESURE applies a venue-based sampling method, which is more likely to capture a representative sample of young (as opposed to older) MSM. Based on discussions with the BESURE investigators, we felt that the general population of older MSM was likely to have lower numbers of sex partners than reported in BESURE and therefore allowed for a lower frequency of partnerships among older MSM.

Furthermore, given the strong bimodal distribution of partnerships among young adults, we were not able to replicate these empirical distributions precisely and thus chose to minimize the estimation error at the tails of this distribution. To further assist the calibration of tails, we defined sexual activity classes

according to the mean number of casual partnerships to represent natural heterogeneity in in individual-level partnerships. Addition of high versus low/medium sexual activity classes allowed us to calibrate the overall frequency of partnerships in each age group with more precision. Figure S7 represents model projections of the frequency of partnerships in each sexual activity class. This figure illustrates that, after calibration to BESURE data, the low and medium sexual activity classes behave very similarly (and may likely be represented equally well as a single class). Given the lack of representative data against which to explicitly calibrate these distributions, this presumed distribution of sexual partnerships is an assumption/limitation of the current model.

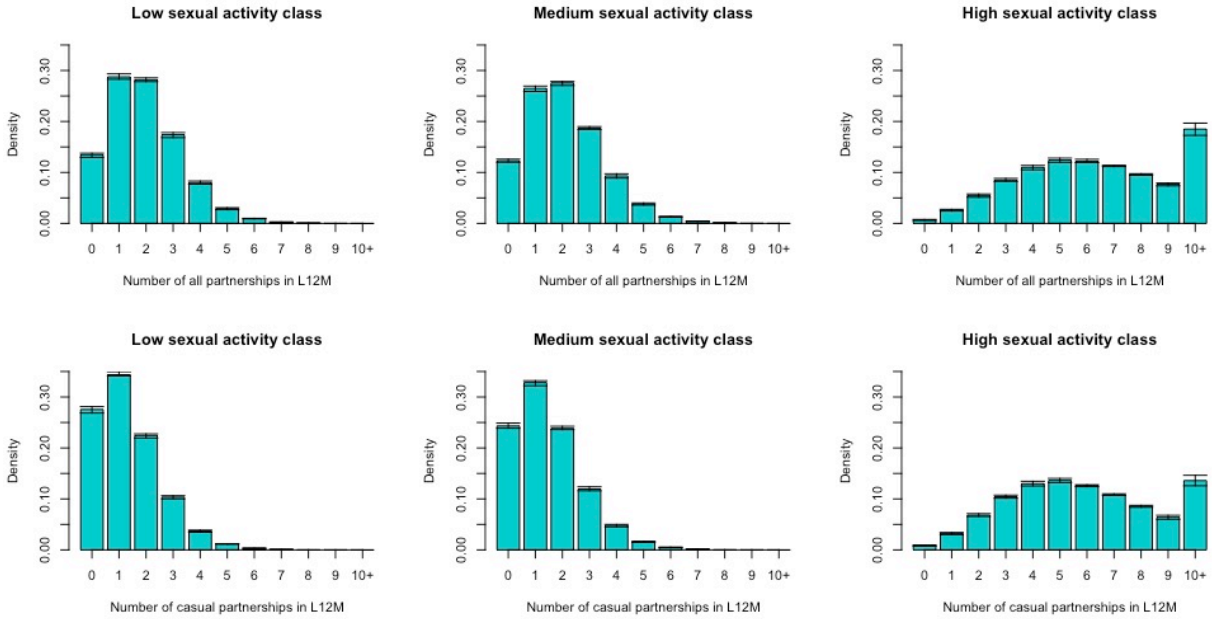

Figure S7: Model projections of the frequency of partnerships in the last 12 months (L12M) in each sexual activity class. Panels represent the distribution of all (top row) and casual (bottom row) partnerships in low, medium and high sexual activity classes. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

2.4 Calibrating HIV and NG/CT epidemiology

Using the population-level targets for annual diagnosis and incidence of NG/CT as well as HIV prevalence and cascade of care (section 3.1), we calibrate the simulation model to provide these outcomes within an acceptable range (Figure S8 A through D).

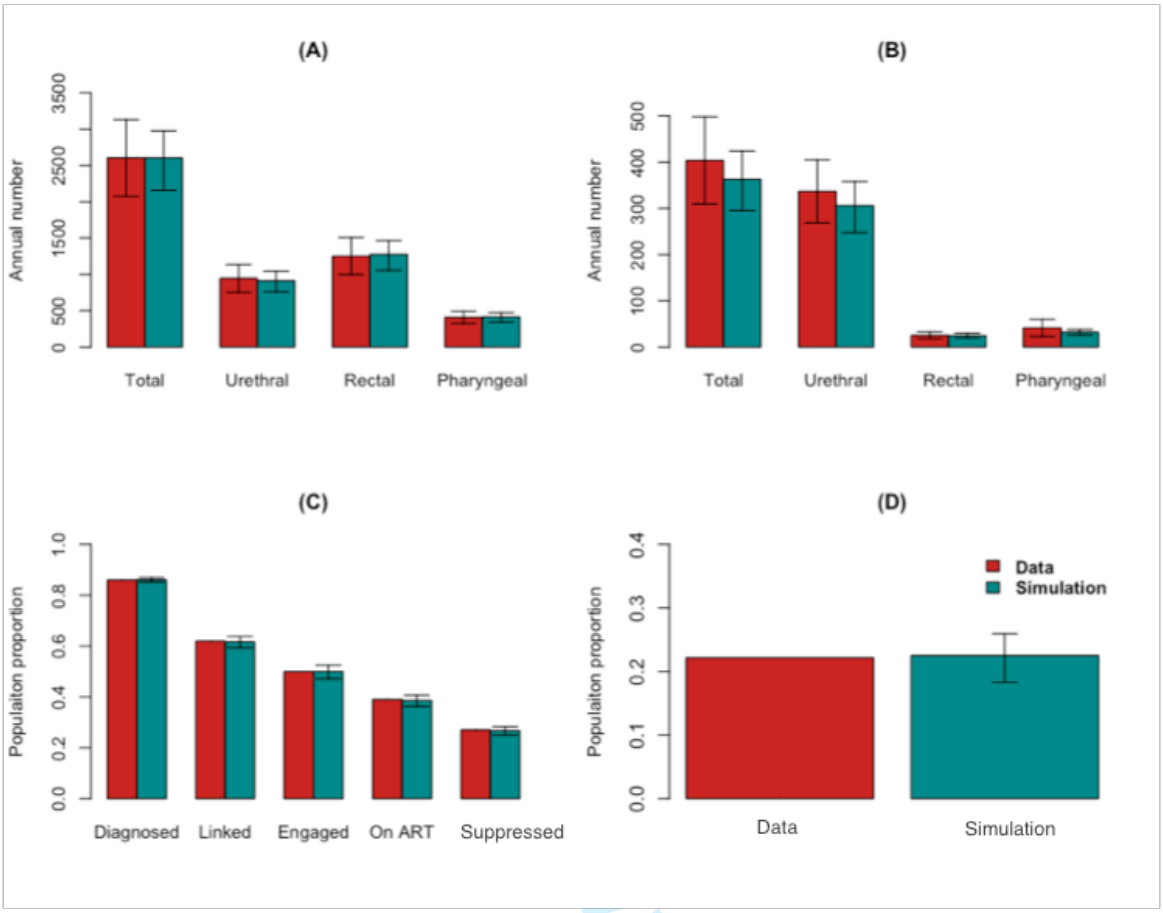

Figure S8: Closeness of model fit to epidemiological data for (A) annual incidence of NG/CT, (B) annual diagnosis of NG/CT, (C) Cascade of HIV Care, and (D) HIV prevalence. These graphs illustrate the effectiveness of the calibration procedure and are not a validation of the underlying data or the model itself. Shown are the mean values of 200 simulations (in green) compared against empirical data (in red). The error bars around simulated values represent the 95% uncertainty range of observations around each simulated measure, and the error bars around the data in panel A&B represent the range of annual observations through the Baltimore City surveillance dataset (2011 – 2015). Data used for calibration in panel C&D is only available as point estimate in year 2012.

Given the lack of data regarding the anatomical site of infection and the relative frequency of oral-only versus oral-plus-anal versus anal-only sex to model site-specific transmission dynamics for NG/CT, we adopted a simplified approach that does not fully capture the complete transmission dynamics but should result in the appropriate distributions of NG/CT infection at each anatomical site. For this purpose, we combined various modes of transmission for all types of infections through a single transmission event modeled over each active sexual contact between an infected and uninfected MSM at each time step. Upon transmission with NG/CT, the clinical site of the recipient infection was randomly assigned in such a way as to replicate the relative incidence of infection at each site as estimated from local surveillance report in Baltimore City (see Table 1). The final calibration results in a probability of 35% for urethral, 49% for rectal and 16% for pharyngeal infections modeled upon each successful transmission event. Since the goal of this model is not to comprehensively represent the dynamics of NG/CT transmission but rather to estimate the impact of PrEP strategies for HIV that incorporate NG/CT screening and treatment, we

adopted this simplified approach (which may have some inaccuracies regarding the specific transmission dynamics but should result in the appropriate marginal distributions of infection by each anatomical site), rather than incorporating data-free assumptions about the relative frequency of oral-only versus oral-plus-genital sex and the relative transmissibility of NG/CT from each anatomical site to the other.

2.4.1 HIV and NG/CT co-infection:

As described above, our calibration targets were limited to the marginal distributions of HIV and NG/CT infections among MSM, and excluded the co-infection rates due to data unavailability. Unpublished results from analysis of STD Surveillance Network (SSuN) data [34] from 2008 to 2013 in 12 jurisdictions suggest that 8% of patients diagnosed with NG had a previous HIV diagnosis, and among the remaining individuals diagnosed with NG, 69% received an HIV test within 30 days of their STI diagnosis. However, the proportion of patients diagnosed with HIV coinfection on that test is not recorded. We therefore took a conservative approach, assuming that the only correlations between HIV and NG/CT would be induced by age- and race-specific assortative mixing, plus differentiation of individuals into three different sexual activity classes. Figure S9A represents the projected levels of HIV and NG/CT prevalence at the end of each year in the model, corresponding to 22% of MSM infected with HIV (calibration target), 10% infected with NG/CT (calibration target) and 2.5% infected with HIV and NG/CT (a cross survey estimate). Figure S9B represents the proportion of incident cases who were co-infected with NG/CT and HIV at the time of HIV or STI infection. For example, this figure suggests that 20% of incident HIV cases are co-infected with NG/CT at the time of disease transmission. These results suggest that our underlying sexual activity assumptions do not impose a high rate of correlation between the two diseases; as a result, our estimates of the impact of STI-based PrEP may be conservative. To the extent that HIV and NG/CT co-locate among similar populations beyond age, race, and tertiles of sexual activity, one would expect that NG/CT-targeted PrEP strategies would have even greater impact than projected in this model.

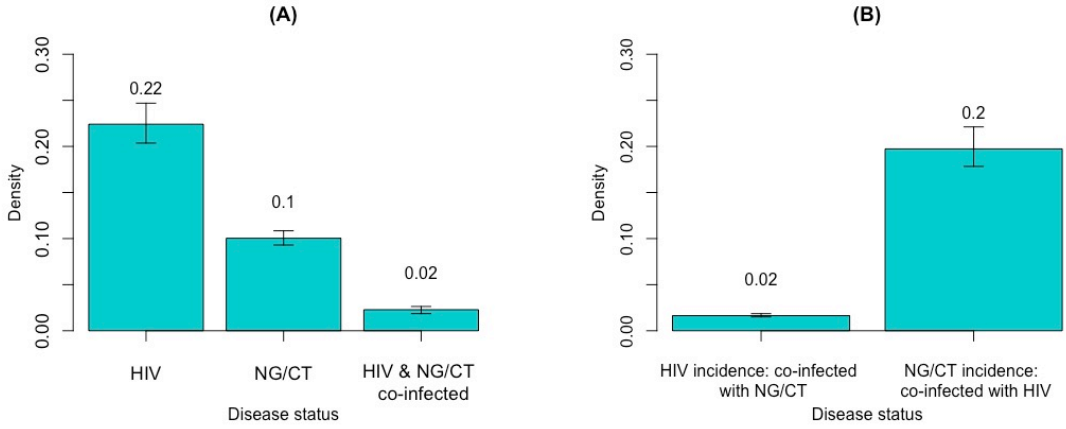

Figure S9: Model projections of the distribution of HIV, NG/CT, and coinfection among MSM (Panel A) and the proportion of HIV and NG/CT incident cases coinfected at the time of transmission (Panel B). Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

2.5 Complete list of model parameters

Table S7 provides a complete list of model parameters and values.

Table S7: Complete list of model parameters and values.

Parameter	Value	References
Partnerships		
Proportion of population in each sexual activity (SA) **class**	0.33	
Rate of casual partnership formation in each sexual activity class relative to the medium sexual activity class	Low sexual activity class 0.85 High sexual activity class 5.0	
Rate of casual partnership by age group	[15-25): 0.5 [25-45): 0.3 [45-55): 0.25 [55-75+): 0.3	
Age Mixing (Absolute different in square root of ages) • Stable partnerships • Casual partnerships	 0.6 0.73	 [35]
Race mixing (Likelihood of mixing with a partner of the same race) - Black & Black - White & White	 0.9 0.75	[35]
Likelihood of condom use - Stable partnerships - Casual partnerships	[Never, Partially, Always] [0.45, 0.55, 0.00] [0.47, 0.12, 0.41]	 [35]
Sexual position preference - Insertive only - Receptive only - Versatile	 0.42 0.26 0.32	[35]
Transmission coefficient for insertive relative to receptive sexual position	0.384	[36]
NG/CT		
Proportion of cases symptomatic - Urethral - Rectal - Pharyngeal	 74% 20% 10%	 [27] [26,37] [28,37]
Duration of infection in the absence of treatment	[3 – 12] months [2]	[16,38,47–51,39–46]
Duration of treatment	2 weeks	[16–18]
Regular GC screening intervals for HIV+ MSM on ART - All MSM - MSM with a history of NG/CT in the last 6 months	 12 months 6 months	 [52]
Likelihood of compliance with CDC guideline for NG/CT screening	40%	[53–58]
Efficacy of condoms to prevent NG/CT transmission	70%	[16,59,60]

[2] Values are selected over uniform distributions across the ranges presented

Increase in HIV transmissibility (from urethral or rectal infection)	[1.5 – 2] fold [3]	[61–65]
Increase in HIV susceptibility (from urethral or rectal infection)	[1 – 2.5] fold [3]	[16,28,65,66]
Probability of NG/CT transmission per act	0.294	Calibrated to provide the incidence of NG/CT
Proportion of NG/CT infections assigned to each site - Urethral - Rectal - Pharyngeal	 35% 49% 16%	Calibrated to provide the site-specific incidence of NG/CT
Weekly probability of symptomatic NG/CT testing - Urethral - Rectal - Pharyngeal	 0.009 0.001 0.04	Calibrated to provide the site-specific diagnosis of NG/CT
Weekly probability of screening high-risk (according to age and sexual activity class) MSM for HIV and NG/CT	0.014	Calibrated to provide the annual diagnosis of NG/CT and HIV
Probability that NG/CT screening only at urethral site	0.94	Calibrated to provide the relative diagnosis of extragenital to genital NG/CT
Relative likelihood of NG/CT screening among Black MSM relative to White MSM	0.5	[22]
HIV		
Disease stage duration - Stage 1 (CD4 >500 cells/µL): Acute - Stage 2 (CD4 200-499 cells/µL): Chronic - Stage 3 (CD4 <200 cells/µL)[3]: Late stage	 [6 – 9] weeks [3] [8 – 10] years [1 – 3] years	[5,67,68] [5,69] [5,67,69]
Time from ART initiation to full viral suppression	[4-24] weeks [3]	[70]
Time from ART discontinuation to pre-ART CD4 nadir[4]	ART treatment duration up to one year	[71–74]
Mortality rate [3] - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART	 5 per 1000 person years 1/duration of stage 3 58%	[12–14]
Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART - Stage 3, no ART - On ART, partially suppressed - On ART, fully suppressed	 6.5 4.5 5 3.5 1.5	[5]
Efficacy of condoms to prevent HIV transmission	80%	[75,76]
Infectiousness per sexual contact	$2.45^{(\log(VL)-4.5)}$	[5]

[3] Mortality rate in stage 3 is defined as 1/(duration of stage 3).

[4] Infectiousness assumed equal to that of stage 2

Individual's weekly likelihood of engagement in HIV care	0.00577	[77–79]
Weekly probability of ART discontinuation	0.0015	[80]
Gap in care after ART discontinuation	26 weeks	[15]
Weekly probability of - Screening for HIV only (not NG/CT) - Linkage to care (if HIV-positive and not linked) - Starting ART (if engaged)	 0.0065 0.0065 0.095	 Calibrated to provide the HIV cascade of care
Relative likelihood of accessing HIV care among Black MSM	0.5	[22]

2.6 Additional analysis

Since sexual activity class is a modeling construct rather than a measurable feature of an individual (see section 1.3.1), there are no data to describe assortative mixing by activity class per se. Similarly, lacking data on serosorting among primary and casual partnerships, we did not explicitly incorporate this into the model. In order to further elucidate model dynamics, we have generated additional figures to report the simulated frequency of sexual partnerships by sexual activity classes (e.g., High-High, High-Med, etc.) and also HIV serostatus (Figure S10 and S11). Note that, since sexual activity class was assumed to reflect casual partnerships only, the frequency of stable partnerships is similar and randomly distributed across all classes (with partnerships across classes being twice as likely as partnerships within classes, reflecting the laws of probability with random assortment).

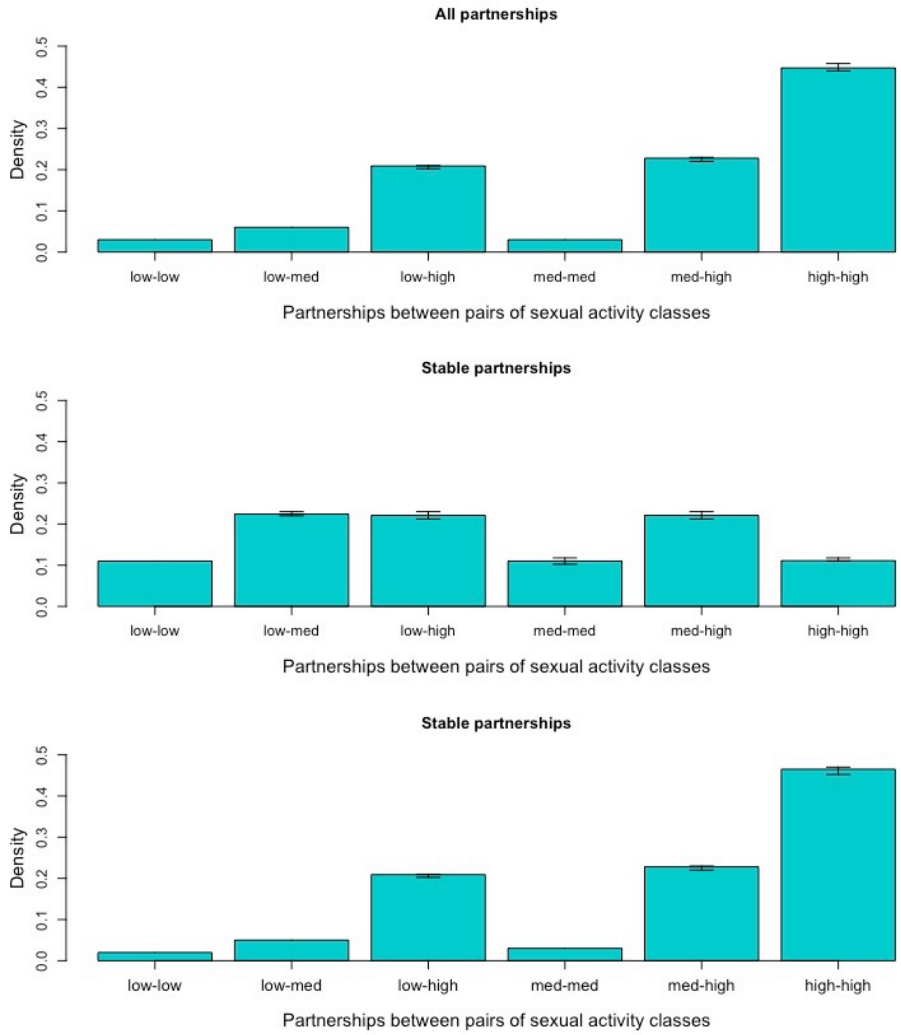

Figure S10: Model projections of the distribution of partnerships among MSM by sexual activity class. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

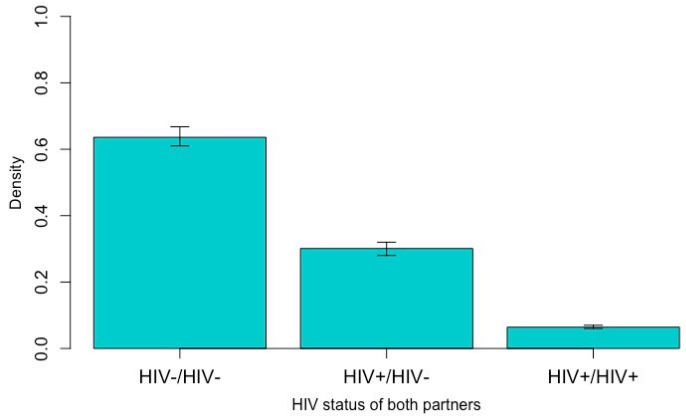

Figure S11: Model projections of the distribution of partnerships by HIV status. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

In order to better illustrate the implications of these modeling assumptions on impact of STI targeted PrEP, we also checked the distribution of MSM receiving PrEP in the model by sexual activity class an age (Figure S12). As expected, targeting PrEP at MSM diagnosed with STIs provides an efficient approach for providing PrEP to high-risk individuals in the high sexual activity class and younger age groups (Figure S12-Panels A & D)

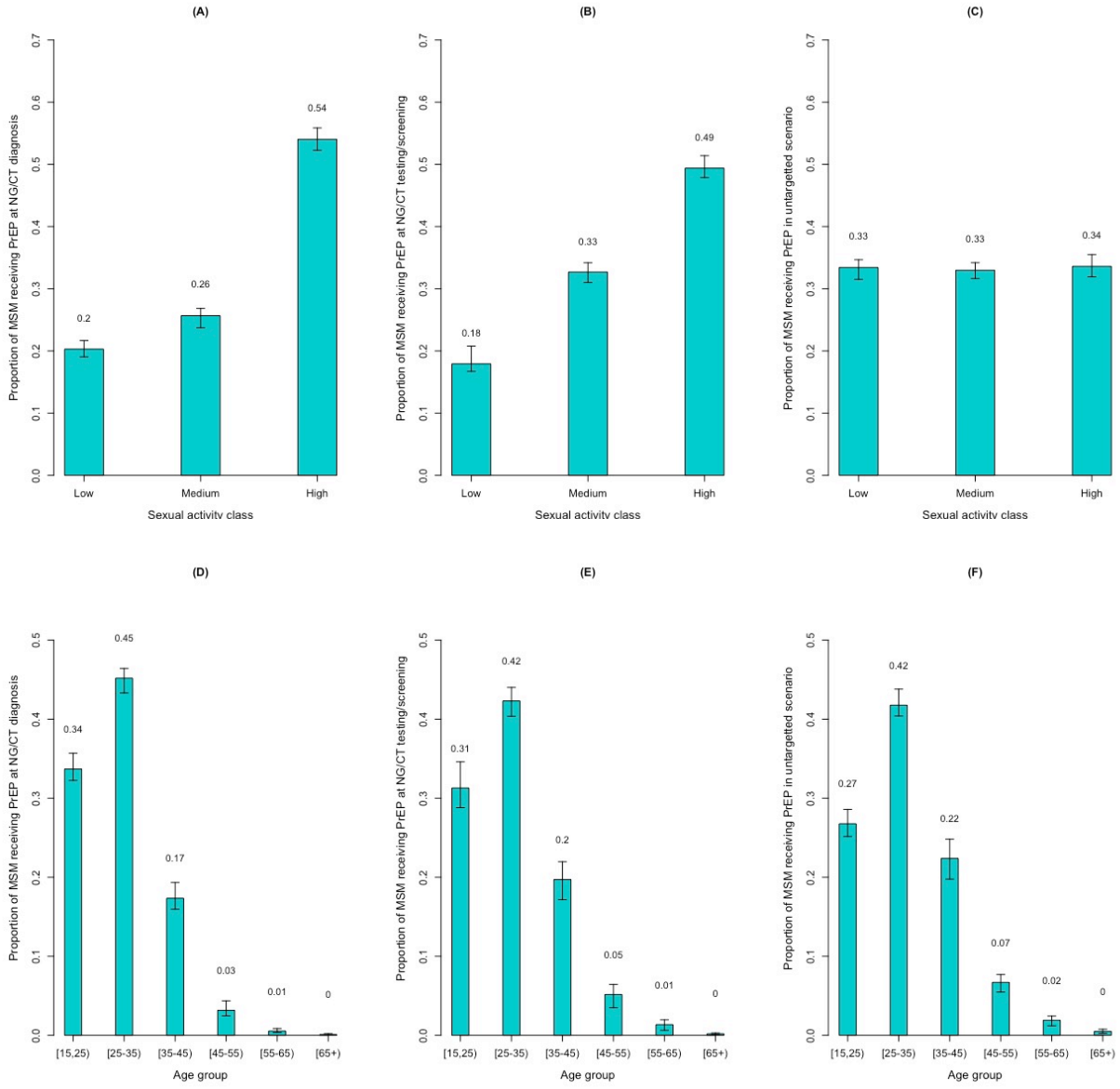

Figure S12: Model projections of the distribution of MSM receiving PrEP in each sexual activity class (top row) and each age group (bottom row) in each PrEP scenario. Panels A and D depict this distribution under NG/CT-targeted PREP; panels B and E illustrate PrEP evaluation at NG/CT screening and testing; and panels C and F represent untargeted PrEP. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

3 SENSITIVITY ANALYSIS

One-way sensitivity analysis of simulation results was performed with regard to all model parameters (listed in Table S7). For this purpose, we changed each parameter to +/- 25% of its original value, one at a

time (keeping all others fixed at the original value) and evaluated the main simulation outputs after such variation. The primary output of interest for the sensitivity analysis was HIV incidence at 10 years without PrEP (baseline) and with PrEP (under each PrEP campaign). For this analysis, we assumed an uptake and adherence of 60% to PrEP. The tornado graphs (Figure S13 to S16) represent the results of the one-way sensitivity analysis. Figure S13 presents the results for HIV incidence at year 10 in Baseline (absence of PrEP), and Figure S14 through Figure S16 present HIV incidence in year 10 of a PrEP campaign targeting MSM at the time of NG/CT-diagnosis (Figure S14), at the time of NG/CT screening (Figure S15) or through a community-wide campaign (Figure S16).

Assuming a threshold of 25% to detect significant changes, the projected HIV incidence at baseline and in absence of PrEP (Figure S13) was sensitive to variation of parameters relating to 1) transmission of HIV including the coefficient of HIV transmission, viral load as a measure of infectiousness, and condom use and effectiveness; 2) the coefficient of NG/CT transmission; and 3) parameters describing overall sexual activity including the probabilities of starting new partnerships, and the level of sexual activity in the most sexually active class. Similar behavior was observed in scenarios modeling the implementation of PrEP at NG/CT diagnosis (Figure S14), at the time of NG/CT screening (Figure S15) or through a community-wide campaign (Figure S16). None of the sensitivity analysis scenarios resulted in significant variation (>25%) of HIV incidence in PrEP scenarios compared to the baseline.

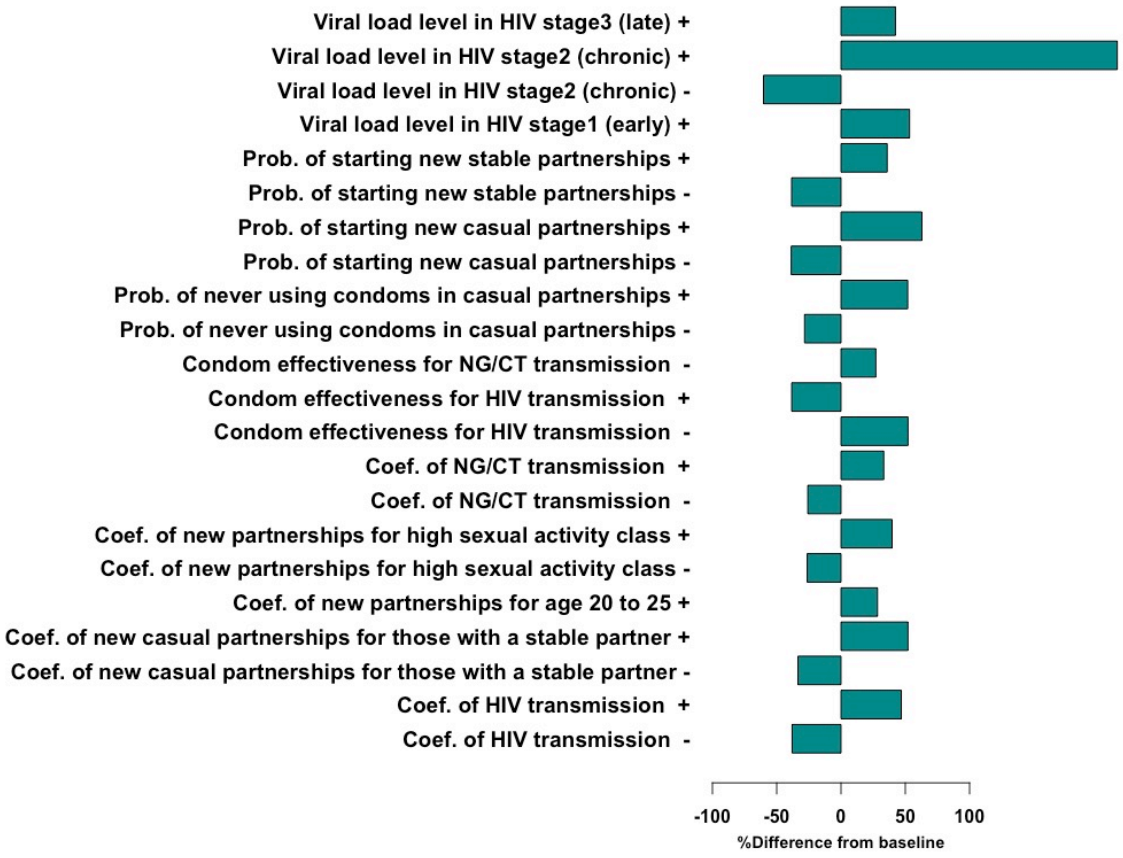

Figure S13: Sensitivity analysis of HIV incidence at year 10 to variation of model parameters in the Baseline (absence of PrEP) scenario. Input parameters are listed on the left, +/- corresponding to 25%

increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant.

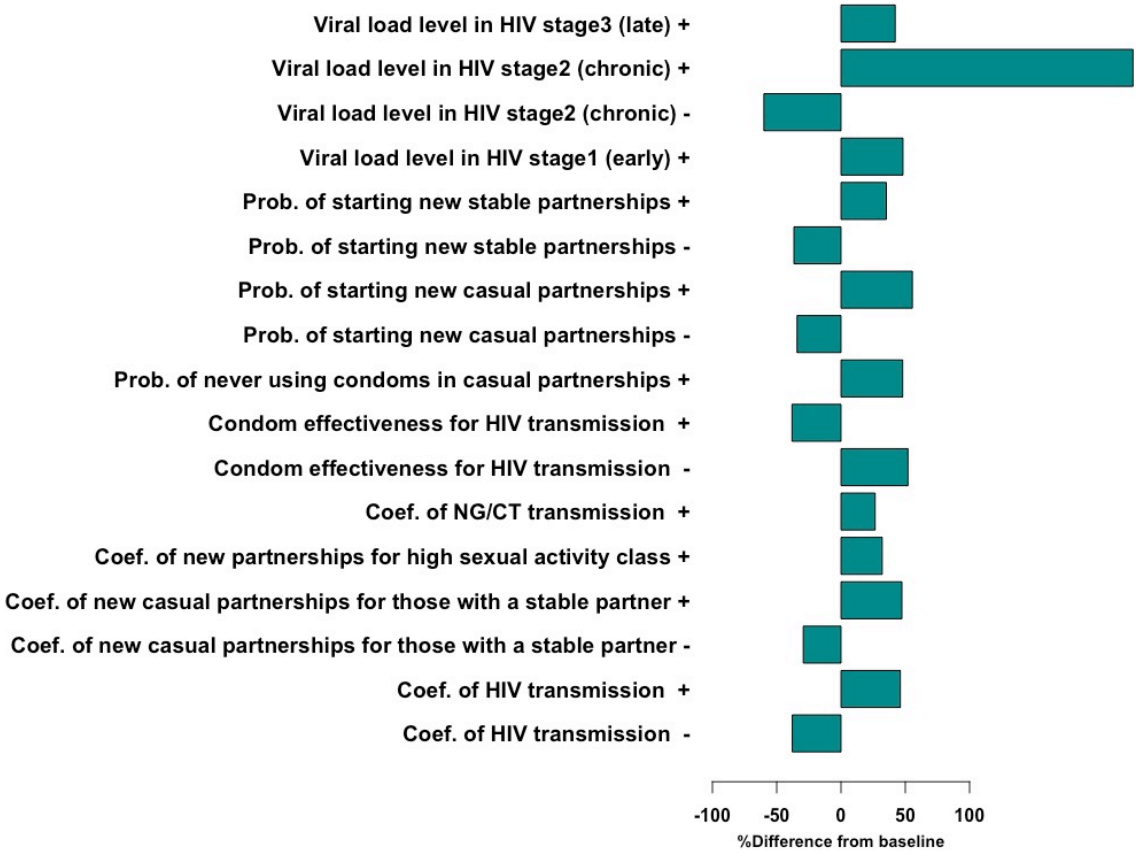

Figure S14: Sensitivity analysis of HIV incidence in year 10 to variation of model parameters in the scenario of a PrEP campaign targeting MSM at the time of NG/CT-diagnosis. Input parameters are listed on the left, +/- corresponding to 25% increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant

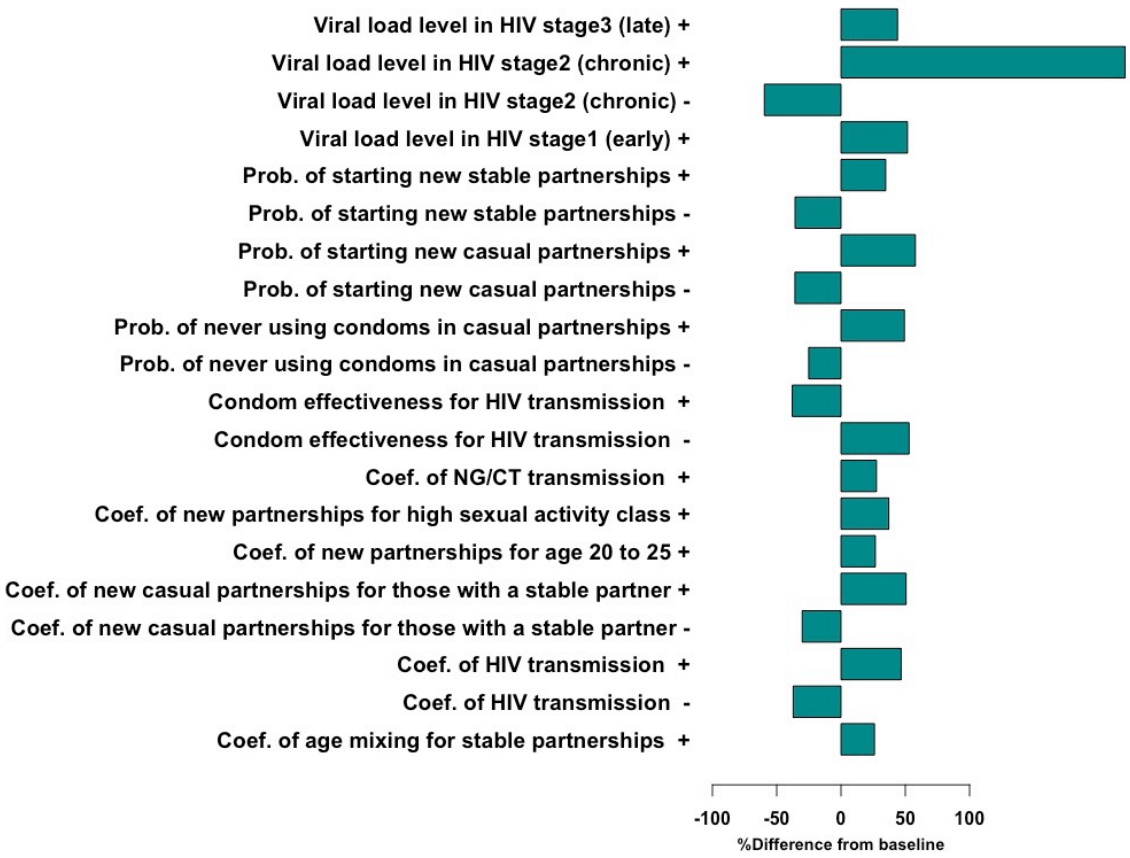

Figure S15: Sensitivity analysis of HIV incidence in year 10 to variation in model parameters in the scenario of a PrEP campaign targeting MSM at the time of NG/CT screening. Input parameters are listed on the left, +/- corresponding to 25% increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant

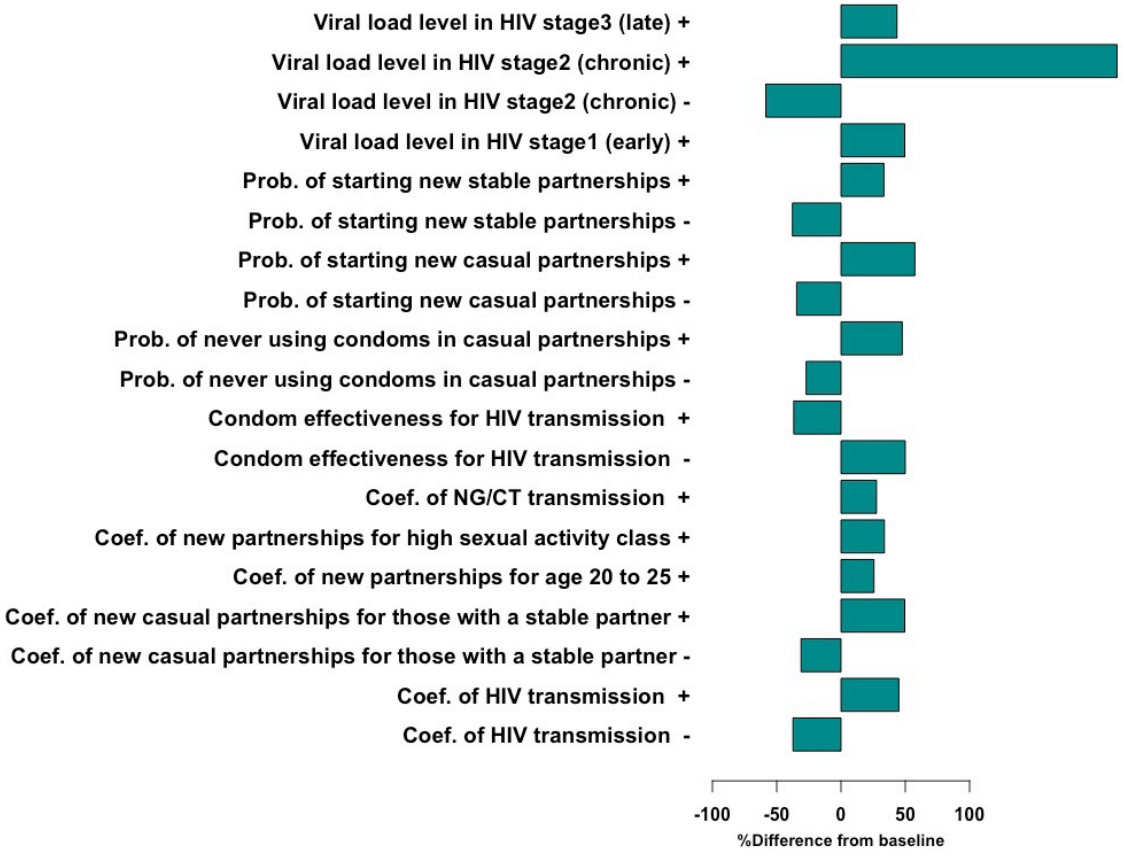

Figure S16: Sensitivity analysis of HIV incidence in year 10 to variation in model parameters in the scenario of a PrEP campaign targeting MSM through a community-wide campaign. Input parameters are listed on the left, +/- corresponding to 25% increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant.

3.1 Sensitivity analysis to impact of behavioral disinhibition

In the absence of strong data on existence of behaviour change for people on PrEP, we have elected to keep the model in the simplest format as possible. However, we acknowledge that this may limit the applicability of our findings to settings in which such behaviour may occur. To further study the impact of such assumption on our findings, we performed an additional sensitivity analysis of results to impact of behavioural disinhibition. For this purpose, we model behavioural disinhibition as %reduction in rate of condom use among MSM taking PrEP (reflected equally on rate of condom use in casual and stable partnerships), varied from 0% (no behavioural disinhibition) to 100% (no condom use).

Figure S17 compares the projected impact of NG/CT targeted PrEP at different rates of condom use reduction among PrEP users. The red line represents the baseline scenario in the model in absence of behavioral disinhibition. As expected, the projected impact of NG/CT-targeted PrEP on HIV incidence declines with reduced levels of condom use among PrEP users. For example, at baseline and in absence

of behavioural disinhibition, the NG/CT targeted PrEP results in 12% [10.4% - 14.1%] reduction in HIV incidence over 20 years. Decreasing the condom use among PrEP users by 25% and 50% will consequently results in lower impact of PrEP at the population level, corresponding to 9.8% [7.7% - 11.9%] and 7.2% [5.1% - 9.4%] reductions in HIV incidence over 20-years. Reduction in rate of condom use among PrEP users can further reduce the potential impact of PrEP (through increased STI screening) on incidence and prevalence of NG/CT. At very high levels of behavioural disinhibition (light green line representing a 75% reduction in condom use among PrEP users), implementation of PrEP can in turn increase the rate of STI transmission and incidence over time.

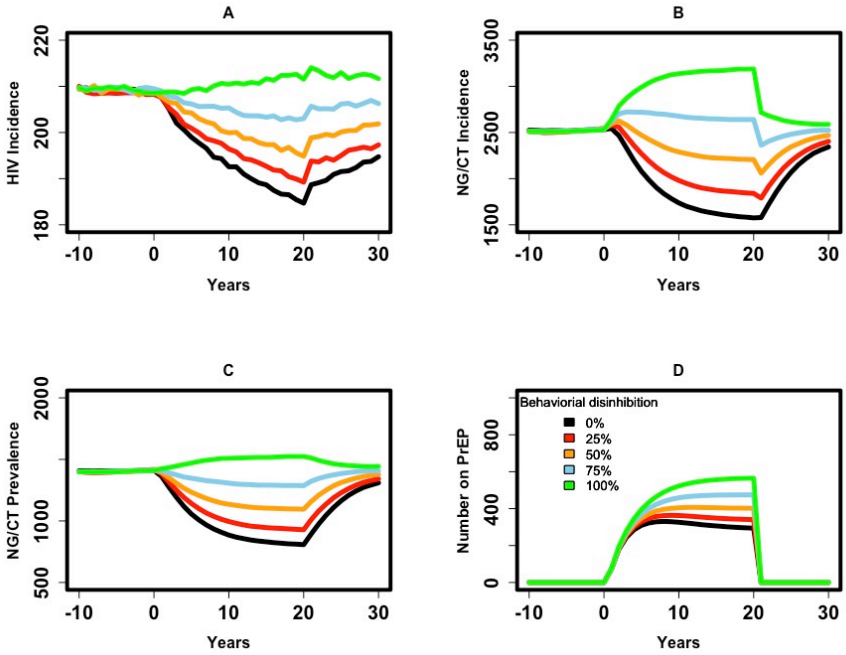

Figure S17: Sensitivity of the impact of NG/CT targeted PrEP to variation in rate of condom use among PrEP users. Shown on the y-axes are the annual incidence of HIV (A), incidence of NG/CT (B), prevalence of NG/CT (C) and number of MSM on PrEP and (D). Different colors represent PrEP scenarios at various levels of reduction in condom use among PrEP users, ranging from 0% (the baseline analysis in the main manuscript, shown in black) to 100% (no condom use among PrEP users, shown in light green).

Figure S18 further compares the impact of 3 PrEP scenarios that were discussed in the main text at various levels of behavioural disinhibition. Despite sensitivity of PrEP outcomes to variation in rate of condom use reduction in each scenario, the relative impact of NG/CT targeted PrEP scenario on HIV incidence compared to the other two scenarios (PrEP evaluation at NG/CT screening/testing and Untargeted PrEP) shows little sensitivity to underlying assumptions regarding behavioural disinhibition (Panel D in each set of graphs), and only begins to decline at very high levels of condom use reduction (last set of graphs for 75% reduction in condom use).

These results further characterize the impact of behavioural disinhibition on population-level impact of PrEP on incidence of HIV and other STIs as proposed by previous studies. This further highlight the need for additional behavioural surveillance data characterizing the changes in level of condom use and risky behaviours among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis

for increased efficacy of PrEP implementation through a NG/CT targeted approach remains robust to variation in rate of condom use reduction.

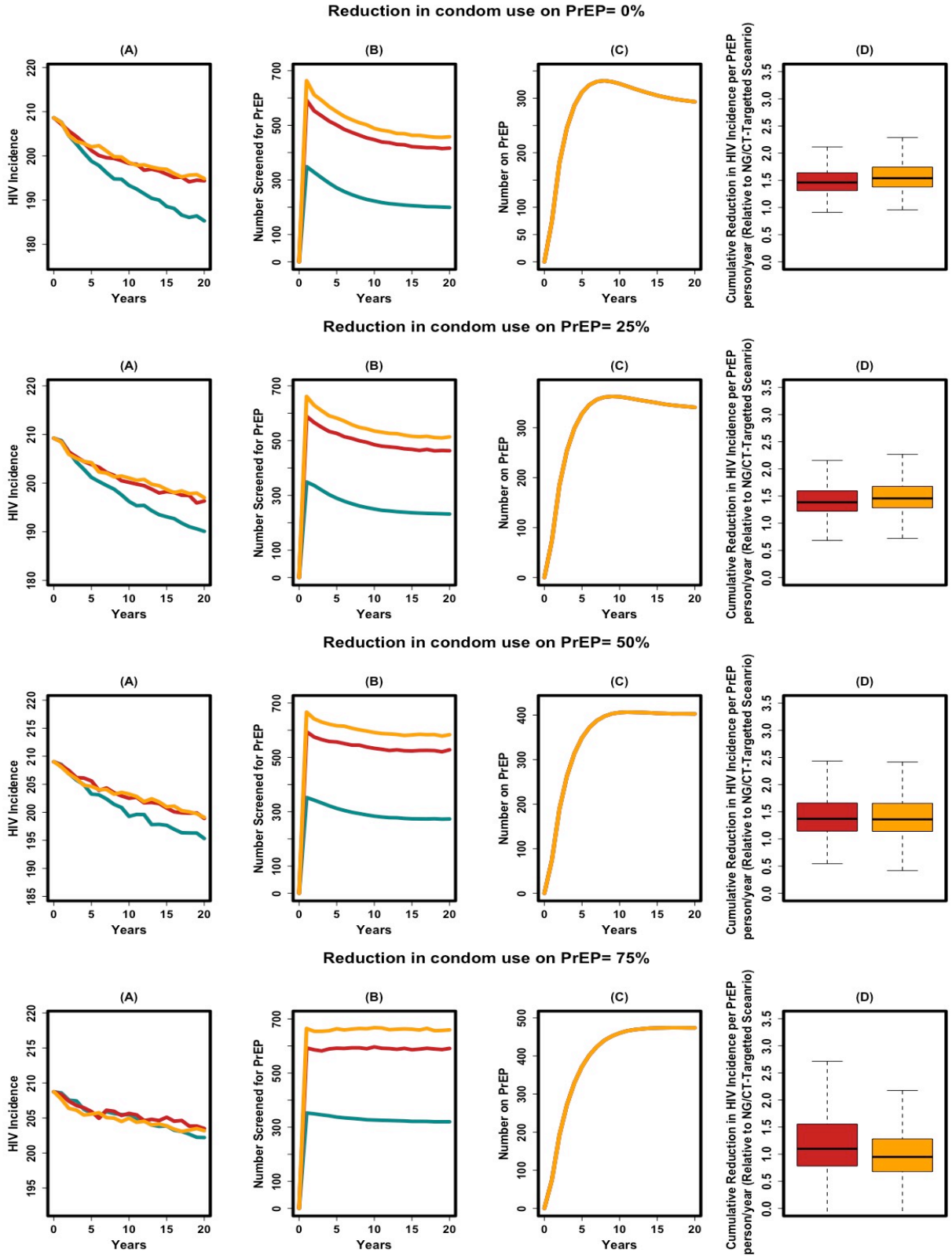

Figure S18: Sensitivity of the impact of all PrEP scenarios to variation in rate of condom use among PrEP users. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in green) compared against

PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. The three strategies are compared under the assumption that the same number of MSM would receive PrEP, at various levels of reduction in condom use among PrEP users. Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenario.

4 ADDITIONAL FIGURES

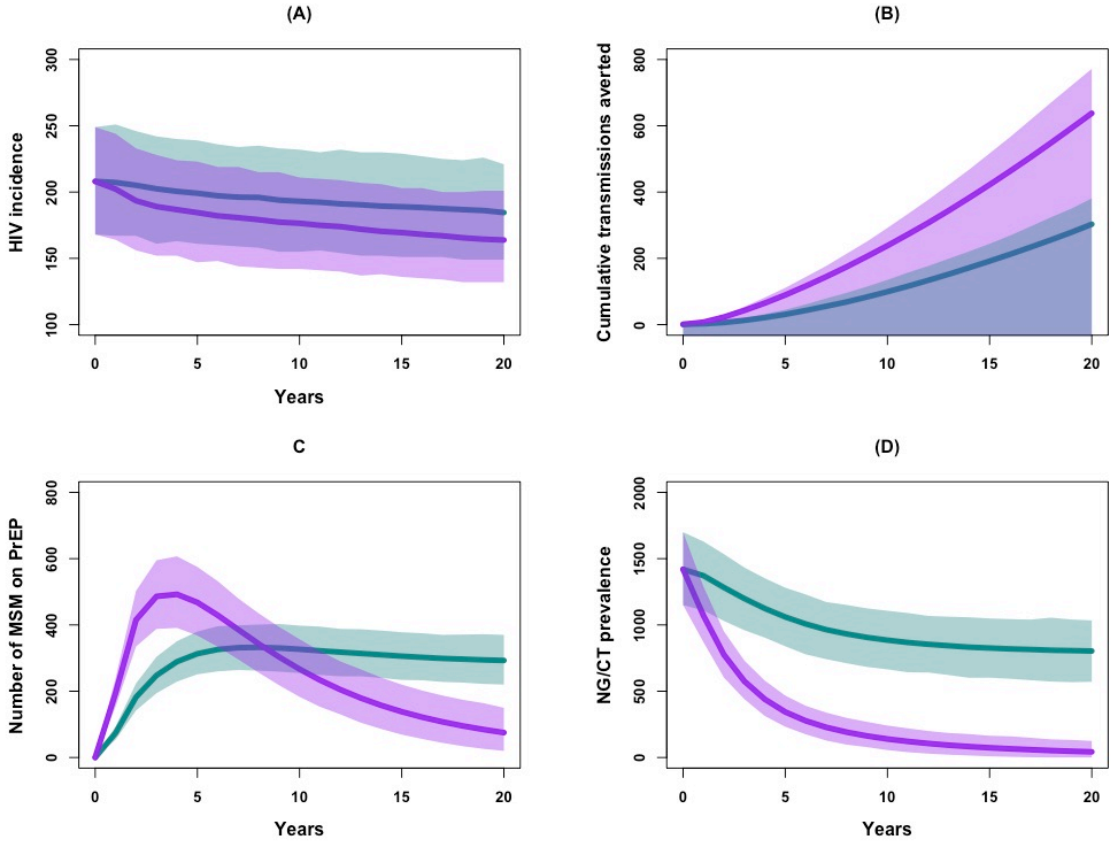

Figure S19: Impact of NG/CT-integrated PrEP, according to frequency of NG/CT screening/testing, with uncertainty ranges shown. Shown on the y-axes are the annual incidence of HIV (A), cumulative number of transmissions averted (B), (C) number of MSM on PrEP and (D) NG/CT prevalence. The green line depicts a scenario in which all MSM currently diagnosed with NG/CT are placed on PrEP with 60% uptake and adherence (NG/CT-integrated PrEP scenario in the main text), and the purple line shows a hypothetical scenario in which 50% of MSM are screened for NG/CT every year, with those testing positive for NG/CT also offered PrEP. Shaded areas represent the 95% uncertainty ranges of simulated data. This figure corresponds to Figure 3 in the main manuscript, but with uncertainty ranges given.

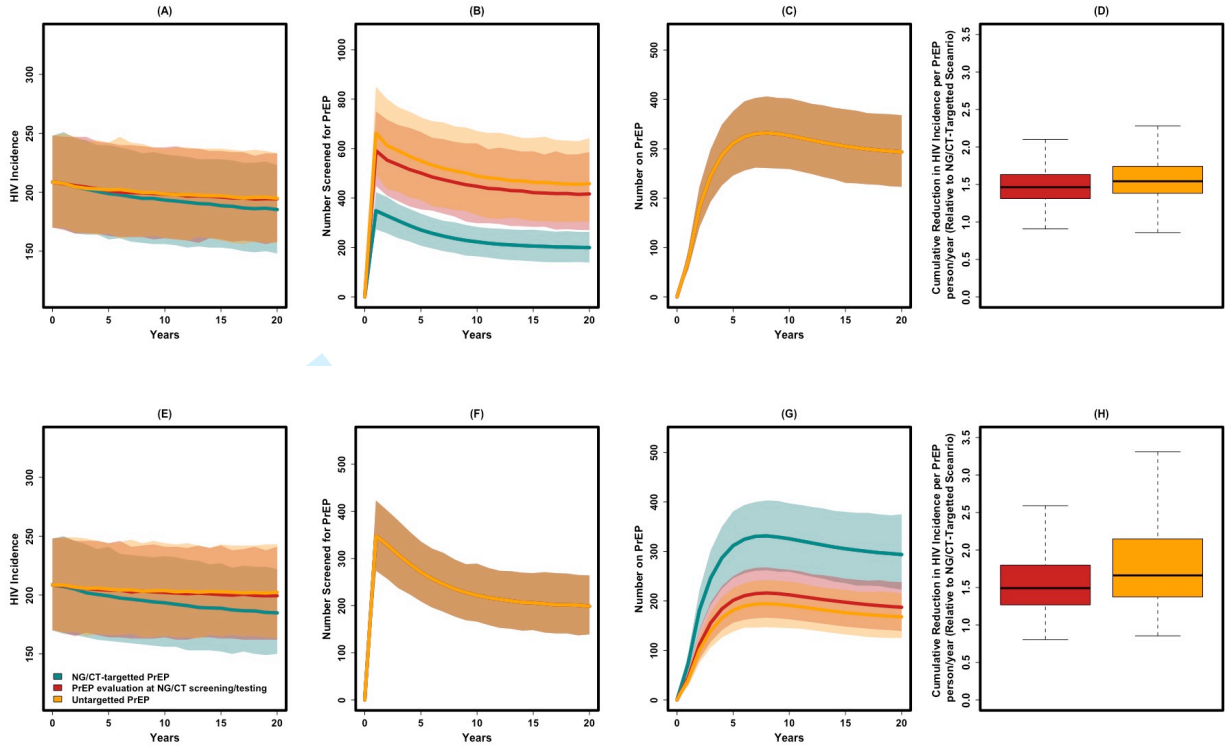

Figure S20: Relative impact of NG/CT-integrated PrEP with uncertainty ranges. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in green, also corresponding to the green line in Figure S19), compared against PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. In the first set of experiments, the three strategies are compared under the assumption that the same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be screened for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenarios (similar pattern in panels E through H). This figure corresponds to Figure 4 in the main manuscript, but with uncertainty ranges given.

REFERENCES

1. Alliance BNI. Vital Signs 12 [Internet]. 2012. Available: http://bniajfi.org/vital_signs/
2. Maryland Department of Health and Mental Hygiene, MDHMH. 2012 Baltimore City Annual HIV Epidemiological Profile. Baltimore; 2012.
3. World Health Organization. Life tables by country United States of America. In: Global Health Observatory Data Repository [Internet]. 2013. Available: http://apps.who.int/gho/data/view.main.61780?lang=en
4. Lieb S, Fallon SJ, Friedman SR, Thompson DR, Gates GJ, Liberti TM, et al. Statewide Estimation of Racial/Ethnic Populations of Men Who Have Sex with Men in the U.S. Public Health Rep. 2011;126: 60–72.
5. Beyrer C, Baral SD, van Griensven F, Goodreau SM, Chariyalertsak S, Wirtz AL, et al. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012;380: 367–77.
6. Marshall BD, Paczkowski MM, Seemann L, Tempalski B, Pouget ER, Galea S, et al. A complex systems approach to evaluate HIV prevention in metropolitan areas: preliminary implications for combination intervention strategies. PLoS One. 2012;7: e44833.
7. Escobar E, Durgham R, Dammann O, Stopka T. Agent-based computational model of the prevalence of gonococcal infections after the implementation of HIV pre-exposure prophylaxis guidelines. Online Journal of Public Health Informatics. 2015. doi:10.5210/ojphi.v7i3.6104
8. German D. BESURE Study: National HIV Behavioral Surveillance Study in Baltimore [Internet]. Available: http://www.jhsph.edu/faculty/research/map/US/1413/8192
9. Vieira IT, Senna V de, Pereira. HB de B. A small world model for the spread of HIV infection. Pesqui Operacional. 2011;31: 373–389.
10. Kasaie P, Pennington J, Berry SA, Shah MS, German D, Flynn CP, et al. The impact of pre-exposure prophylaxis among men who have sex Withmen in Baltimore City: an agent-based simulation. JAIDS J Acquir Immune Defic Syndr. 2017;75: 175–183.
11. Egan JE, Frye V, Kurtz SP, Latkin C, Chen M, Tobin K, et al. Migration, neighborhoods, and networks: approaches to understanding how urban environmental conditions affect syndemic adverse health outcomes among gay, bisexual and other men who have sex with men. AIDS Behav. 2011;15: 35–50.
12. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373: 795–807.
13. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009;360: 1815–1826.
14. Palella Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med. 1998;338: 853–860.
15. Rana AI, Liu T, Gillani FS, Reece R, Kojic EM, Zlotnick C, et al. Multiple gaps in care common among newly diagnosed HIV patients. AIDS Care. 2015;27: 697–687.
16. Beck EEC, Birkett M, Armbruster B, Mustanski B. A data-driven simulation of HIV spread among young men who Hhave sex with men: role of age and race mixing and STIs. JAIDS J Acquir Immune Defic Syndr. 2015;70: 186–194.

17. Vriend HJ, Lugnér AK, Xiridou M, Schim van der Loeff MF, Prins M, de Vries HJC, et al. Sexually transmitted infections screening at HIV treatment centers for MSM can be cost-effective. AIDS. 2013;27: 2281–90. doi:10.1097/QAD.0b013e32836281ee

18. Chen MI, Ghani AC, Edmunds WJ. A metapopulation modelling framework for gonorrhoea and other sexually transmitted infections in heterosexual populations. J R Soc Interface. 2009;6: 775–91. doi:10.1098/rsif.2008.0394

19. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. MMWR recomm. 2015.

20. Virginia Department of Health. STD Surveillance Network Report. 2013; Available: http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf

21. Castro JG, Alcaide ML. High rates of STIs in HIV-infected patients attending an STI clinic. South Med J. 2016;109: 1–4.

22. Sullivan PS, Peterson J, Rosenberg ES, Kelley CF, Cooper H, Vaughan A, et al. Understanding racial HIV/STI disparities in black and white men who have sex with men: a multilevel approach. PLoS One. 2014;9: e90514.

23. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States-2014: a clinical practice guideline. 2014.

24. Centers for Disease Control and Prevention. PrEP for men who have sex with men [Internet]. 2018. Available: https://prepmaryland.org/sites/default/files/download-resources/PrEP - MSM both sides March 2017.pdf

25. Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TP, Prevention D of S. Sexually transmitted disease surveillance 2013. 2014.

26. Lister N, Smith A, Tabrizi S, Hayes P. Screening for neisseria gonorrhoeae and chlamydia trachomatis in men who have sex with men at male-only saunas. Sex Transm Dis. 2003;30: 886–889.

27. Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis. 2005;41: 67–74.

28. Morris SR, Klausner JD, Buchbinder SP, Wheeler SL, Koblin B, Coates T, et al. Prevalence and incidence of pharyngeal gonorrhea in a longitudinal sample of men who have sex with men: the EXPLORE study. Clin Infect Dis. 2006;43: 1284–1289.

29. Soni S, White J. Self-screening for Neisseria gonorrhoeae and Chlamydia trachomatis in the human immunodeficiency virus clinic—high yields and high acceptability. Sex Transm Dis. 2011; Available: http://journals.lww.com/stdjournal/Abstract/2011/12000/Self_Screening_for_Neisseria_gonorrhoeae_and.6.aspx

30. Heiligenberg M, Rijnders B. High prevalence of sexually transmitted infections in HIV-infected men during routine outpatient visits in the Netherlands. Sex Transm. 2012; Available: http://journals.lww.com/stdjournal/Abstract/2012/01000/High_Prevalence_of_Sexually_Transmitted_Infections.2.aspx

31. Rieg G, Lewis R, Miller L, Witt M. Asymptomatic sexually transmitted infections in HIV-infected men who have sex with men: prevalence, incidence, predictors, and screening strategies. AIDS Patient Care. 2008; Available: http://online.liebertpub.com/doi/abs/10.1089/apc.2007.0240

32. Patton ME, Kidd S, Llata E, Stenger M, Braxton J, Asbel L, et al. Extragenital gonorrhea and chlamydia testing and infection among men who have sex with men--STD Surveillance Network, United States, 2010-2012. Clin Infect Dis. 2014;58: 1564–70. doi:10.1093/cid/ciu184

33. Chamberlain N, Crosby RA, Mena L, Chan PA, Mayer KH. Is Patient-Reported Exposure a Reliable Indicator for Anogenital Gonorrhea and Chlamydia Screening in Young Black Men Who Have Sex With Men? Sex Transm Dis. 2017;44: 390–392. doi:10.1097/OLQ.0000000000000619

34. Health VD of. STD Surveillance Network Report. 2013; Available: http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf

35. Maryland Department of Health and Mental Hygiene. BESURE Study 2004-2014: Baltimore site of National HIV Behavioral Surveillance (NHBS) [Internet]. 2015.

36. Jenness S, Goodreau S. Impact of the centers for disease control's HIV preexposure prophylaxis guidelines for men who have sex with men in the United States. J Infect Dis. 2016;14: 1800–1807.

37. Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. Genitourin Med. 1996;72: 422–6.

38. Kretzschmar M, Duynhoven Y van. Modeling prevention strategies for gonorrhea and chlamydia using stochastic network simulations. Am J Epidemiol. 1996;144: 306–317.

39. Korenromp EL, Sudaryo MK, de Vlas SJ, Gray RH, Sewankambo NK, Serwadda D, et al. What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? Int J STD AIDS. 2002;13: 91–101.

40. Althaus CL, Heijne JCM, Roellin A, Low N. Transmission dynamics of chlamydia trachomatis affect the impact of screening programmes. Epidemics. 2010;2: 123–131.

41. Price MJ, Ades AE, Angelis D De, Welton NJ, Macleod J, Soldan K, et al. Mixture-of-exponentials models to explain heterogeneity in studies of the duration of Chlamydia trachomatis infection. Stat Med. 2013;32: 1547–1560.

42. Turner KM, Adams EJ, Gay N, Ghani AC, Mercer C, Edmunds WJ. Developing a realistic sexual network model of chlamydia transmission in Britain. Theor Biol Med Model. 2006;3: 3.

43. Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. J Acquir Immune Defic Syndr. 2000;24: 48–56.

44. Chesson HW, Bernstein KT, Gift TL, Marcus JL, Pipkin S, Kent CK. The cost-effectiveness of screening men who have sex with men for rectal chlamydial and gonococcal infection to prevent HIV Infection. Sex Transm Dis. 2013;40: 366–71.

45. Tuite A, Jayaraman G, Allen V. Estimation of the burden of disease and costs of genital Chlamydia trachomatis infection in Canada. Sex Transm Dis. 2012;39: 260–267.

46. Vries R De, Bergen J Van. Systematic screening for Chlamydia trachomatis: estimating cost-effectiveness using dynamic modeling and Dutch data. Value in. 2006;9: 1–1.

47. Adams EJ, Turner KME, Edmunds WJ. The cost effectiveness of opportunistic chlamydia screening in England. Sex Transm Infect. 2007;83: 267-74; discussion 274–5.

48. Andersen B, Gundgaard J, Kretzschmar M. Prediction of costs, effectiveness, and disease control of a population-based program using home sampling for diagnosis of urogenital Chlamydia trachomatis. Sex Transm Dis. 2006;33: 407–415.

49. Gillespie P, O'Neill C, Adams E, Turner K. The cost and cost-effectiveness of opportunistic screening for Chlamydia trachomatis in Ireland. Sex Transm Dis. 2012;88: 222–228.

50. Roberts T, Robinson S, Barton P, Bryan S. Cost effectiveness of home based population screening for Chlamydia trachomatis in the UK: economic evaluation of chlamydia screening studies (ClaSS) project. Bmj. 2007;335: 291.

51. Welte R, Kretzschmar M, Leidl R, Hoek A Van Den, Jager JC, Postma MJ. Cost-effectiveness of screening programs for Chlamydia trachomatis: a population-based dynamic approach. Sex Transm Dis. 2000;27: 518–529.

52. Sexually transmitted diseases treatment guidelines, 2006. MMWR recomm. 2006; Available: http://origin.glb.cdc.gov/mmWR/preview/mmwrhtml/rr5511a1.htm

53. Berry SA. Gonorrhoea and chlamydia screening in HIV clinics: time for new tools and targets. Sex Transm Infect. 2014;90: 574–575.

54. Berry SA, Ghanem KG, Page KR, Gange SJ, Thio CL, Moore RD, et al. Increased gonorrhoea and chlamydia testing did not increase case detection in an HIV clinical cohort 1999-2007. Sex Transm Infect. NIH Public Access; 2011;87: 469–475.

55. Hutchinson J, Goold P, Wilson H, Jones K, Estcourt C. Sexual health care of HIV-positive patients: an audit of a local service. Int J STD AIDS. 2003;14: 493–496.

56. Hamlyn E, Barrett S, Kelsey J, Lockyer S, Welz T, Poulton M. Improvement in screening for sexually transmitted infections in HIV-positive patients following implementation of a nurse-led clinic. Int J STD AIDS. 2007;18: 424–426. Available: http://www.ncbi.nlm.nih.gov/pubmed/17609038

57. Hoover KW, Butler M, Workowski K, Carpio F, Follansbee S, Gratzer B, et al. STD screening of HIV-infected MSM in HIV clinics. Sex Transm Dis. 2010;37: 771–776.

58. Teague R, Mijch A, Fairley CK, Sidat M, Watson K, Boyd K, et al. Testing rates for sexually transmitted infections among HIV-infected men who have sex with men attending two different HIV services. Int J STD AIDS. 2008;19: 200–2.

59. Joesoef MR, Linnan M, Barakbah Y, Idajadi a, Kambodji a, Schulz K. Patterns of sexually transmitted diseases in female sex workers in Surabaya, Indonesia. Int J STD AIDS. 1997;8: 576–80. doi:10.1258/0956462971920811

60. Darrow WW. Condom Use and Use-Effectiveness in High-Risk Populations. SexTransmDis. 1989;16: 157–160.

61. Cohen M. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. Lancet. 1998;351: S5–S7.

62. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect. 1999;75: 3–17.

63. Winter AJ, Taylor S, Workman J, White D, Ross JD, Swan A V, et al. Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. Sex Transm Infect. 1999;75: 261–263.

64. Cohen MS, Hoffman IF, Royce RA, Kazembe P, Dyer JR, Daly CC, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. Lancet. 1997;349: 1868–1873.

65. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions

between classic sexually transmitted diseases and HIV. Sex Transm Dis. 2001;28: 579–597.

66. Jin F, Prestage GP, Imrie J, Kippax SC, Donovan B, Templeton DJ, et al. Anal sexually transmitted infections and risk of HIV infection in homosexual men. J Acquir Immune Defic Syndr. 2010;53: 144–149.

67. Baggaley RF, Ferguson NM, Garnett GP. The epidemiological impact of antiretroviral use predicted by mathematical models: a review. Emerg Themes Epidemiol. 2005;2: 9.

68. Salomon JA, Hogan DR, Stover J, Stanecki KA, Walker N, Ghys PD, et al. Integrating HIV prevention and treatment: from slogans to impact. PLoS Med. 2005;2: e16.

69. Alam SJ, Meyer R, Norling E. A model for HIV spread in a South African village. Multi-Agent-Based Simul IX. 2009; 33–45.

70. Clotet B, Feinberg J, Lunzen J van, Khuong-Josses M. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised. Lancet. 2014;383: 2222–2231.

71. Wit FW, Blanckenberg DH, Brinkman K, Prins JM, Ende ME van der, Schneider MM, et al. Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. AIDS. 2005;19: 345–348.

72. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callegaro A, Suter F. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. AIDS. 2004;18: 439–446.

73. Ortiz GM, Wellons M, Brancato J, Vo HT, Zinn RL, Clarkson DE, et al. Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects. Proc Natl Acad Sci. 2001;98: 3288–13293.

74. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. New Engl J Med. 2006;355: 2283–2296.

75. Sc W, Davis-Beaty. Condom effectiveness in reducing heterosexual HIV transmission (Review). Available: http://www.thecochranelibrary.com

76. Holmes KK, Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. Bull World Health Organ. 2004;82: 454–461.

77. Hill T, Bansi L, Sabin C, Phillips A, Dunn D. Data linkage reduces loss to follow-up in an observational HIV cohort study. J Clin. 2010;63: 1101–1109.

78. Mocroft A, Kirk O, Aldins P, Chies A, Blaxhult A. Loss to follow-up in an international, multicentre observational study. HIV Med. 2008;9: 261–269.

79. Ndiaye B, Ould-Kaci K, Salleron J, Bataille P. Characteristics of and outcomes in HIV-infected patients who return to care after loss to follow-up. AIDS. 2009;23: 1786–1789.

80. Mills E, Nachega J, Buchan I, Orbinski J. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. Jama. 2006;296: 679–690.

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Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study

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Title: Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study

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ABSTRACT

Objectives: *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) increase the risk of HIV transmission among men who have sex with men (MSM). Diagnosis of NG/CT may provide an efficient entry point for prevention of HIV through delivery of pre-exposure prophylaxis (PrEP); however, the additional population-level impact of targeting PrEP to MSM diagnosed with NG/CT is unknown.

Design: An agent-based simulation model of NG/CT and HIV co-circulation among MSM, calibrated against census data, disease surveillance reports and the United States National HIV Behavioral Surveillance study.

Setting: Baltimore City, Maryland, USA

Interventions: PrEP implementation was modeled under three alternative scenarios: a) PrEP delivery at NG/CT diagnosis (targeted delivery), b) PrEP evaluation at NG/CT screening/testing, and c) PrEP evaluation in the general community (untargeted).

Main outcome: The projected incidence of HIV after 20 years of PrEP delivery under two alternatives: when equal numbers of MSM are a) screened for PrEP, or b) receive PrEP in each year.

Results: Assuming 60% uptake and 60% adherence, targeting PrEP to MSM diagnosed with NG/CT could reduce HIV incidence among MSM in Baltimore City by 12.4% [95% uncertainty range (UR): 10.3 – 14.4%] in 20 years, relative to no PrEP. Expanding the coverage of NG/CT screening (such that individuals experience a 50% annual probability of NG/CT screening and evaluation for PrEP upon NG/CT diagnosis), can further increase the impact of targeted PrEP to generate a 22.0% [95% UR 20.1 – 23.9%] reduction in HIV incidence within 20 years. When compared to alternative implementation scenarios, PrEP evaluation at NG/CT diagnosis increased impact of PrEP on HIV incidence by 1.7 [95% UR 1.0 – 2.6] relative to a scenario in which PrEP evaluation happened at the time of NG/CT screening/testing, and by 1.9 [95% UR 1.1 – 3.4] relative to evaluating random MSM from the community.

Conclusions: Targeting MSM infected with NG/CT increases the efficiency and effectiveness of PrEP delivery. If high levels of STI screening can be achieved at the community level, NG/CT diagnosis may be a highly effective entry point for PrEP initialization.

Strengths and limitations of this study

- This study helps to quantify the added value of targeting PrEP to MSM diagnosed with NG/CT, in terms of population-level impact on disease incidence over time.
- The model is calibrated to a wide array of data including census data, disease surveillance reports and a nationally representative survey of HIV-related behaviors.
- This model offers policymakers a support tool to estimate and compare the population-level impact of various prevention/control programs.
- Study findings are limited by simplifying assumptions including (but not limited to) exclusion of other STIs such as syphilis, simplified representation of NG/CT natural history, simplification of sexual networks for NG/CT and HIV transmission, exclusion of HIV transmission through injection drugs or heterosexual sex, and exclusion of transgender and bisexual individuals from the simulated population.
- Due to limited data as to whether MSM change their behavior while taking PrEP, behavioral disinhibition was excluded from this analysis.

Keywords: HIV Infections; Gonorrhoea; Chlamydia; Pre-Exposure Prophylaxis; Homosexuality, Computer Simulation

BACKGROUND

Infection with *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT) may impact HIV transmission in multiple ways, particularly among men who have sex with men (MSM). From a biological standpoint, NG/CT infection may increase one's susceptibility to HIV acquisition: rectal infection in particular has been linked to an increased risk of HIV acquisition [1,2]. HIV and NG/CT also share many risk factors at the individual level (e.g., condomless sex) and network level (e.g., having sex within a high-prevalence network), such that the three conditions are often epidemiologically linked [3]. Additionally, HIV-negative men have an increased risk of HIV acquisition when in partnership with a HIV-positive partner who is also co-infected with NG/CT [4,5]. As a result, better diagnosis and treatment of NG/CT can potentially reduce HIV incidence [6], and help to identify individuals at high risk of future HIV infection.

Pre-Exposure Prophylaxis (PrEP) is part of comprehensive HIV prevention services in which HIV-negative people take daily antiretroviral medication to lower risk of HIV transmission upon exposure. The U.S. Centers for Disease Control and Prevention (CDC) has recommended PrEP for HIV-negative individuals at substantial risk of infection [7]. Among MSM, this includes HIV-negative men who are either diagnosed with a sexually transmitted infection (STI) in the last 6 months, are in a HIV discordant partnership, or report a condomless sex act in the last 6 months. Despite this broad recommendation, the potential population-level impact of PrEP remains uncertain. Several barriers exist to the successful implementation of PrEP, including providers' perceived inability to deliver PrEP in primary care settings [8], individuals' limited knowledge of PrEP effectiveness [9], low self-perceived risk for HIV infection [10], patients' difficulty in maintaining adherence [11], and high costs (at over $10,000 per person-year for those without insurance or access to a medication assistance plan) [12,13].

Given these challenges, optimizing the efficiency of PrEP delivery is a public health priority. Specifically, it is important to tailor PrEP delivery to those who stand to gain the most from its preventive efficacy. Given the epidemiologic link between NG/CT infection and HIV among MSM, new NG/CT diagnoses may serve as a useful means to identify high-risk MSM for PrEP evaluation and delivery [7]. At present, the impact of such a strategy—in terms of reducing HIV and NG/CT incidence at a population level—is not clear. To address this question, we used surveillance data from Baltimore City (Maryland, USA) to construct an agent-based simulation model of the co-transmission of HIV and NG/CT among MSM, [14] and applied this model to study the added value of targeting PrEP to MSM diagnosed with NG/CT, in terms of population-level impact on HIV incidence over time.

METHODS

We base our depiction of HIV on a published agent-based model of HIV transmission among MSM in Baltimore City [14] (Figure 1-top panel), and we extend this model to include coinfection of HIV with NG and CT infections (see section 1 of the Supplementary Material).

NG/CT infection: NG and CT share similarities in natural history, including their acute nature, symptomatology, frequent co-diagnosis, and co-treatment [15]. Given these similarities, and for simplicity of modeling, we model NG/CT as a single biological entity. We assume that NG/CT infection may occur at the urethral, rectal or pharyngeal site – each with different probabilities of symptomatic presentation, diagnosis and treatment, and effects on HIV transmission, as shown in Table 1. We include both asymptomatic and symptomatic infection and fit the model to the annual number of diagnoses at each clinical site (urethral, rectal, or pharyngeal) among MSM in Baltimore City (see section 2 of the Supplementary Material).

Table 1: List of selected simulation parameters and calibration targets.

Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT) Parameters	Value	Reference
Proportion of cases symptomatic[1]		
• **Urethral**	74%	[16]
• **Rectal**	20%	[17,18]
• **Pharyngeal**	10%	[18,19]
Duration of infection (at each site) in the absence of treatment	[3 – 12] months[2]	[4,20–33]
Coefficient of NG/CT transmission per week	0.294	Calibrated to provide the incidence of NG/CT
Proportion of NG/CT infections assigned to each site		
• **Urethral**	0.35	Calibrated to provide the site-specific incidence of NG/CT
• **Rectal**	0.49	
• **Pharyngeal**	0.16	
Increase in HIV transmissibility (for those with urethral or rectal infection)	[1.5 – 2] fold [1]	[34–38]
Increase in HIV susceptibility (for those with urethral or rectal infection)	[1 – 2.5] fold [1]	[19,20,38,39]
NG/CT Calibration Targets	**Mean[3] [Range]**	
Annual diagnosis of NG/CT among MSM in Baltimore City		Values estimated from local data on gonorrhea surveillance and STI clinic visitis in Baltimore City (See section 2 in the Supplementary Material)
• **Urethral**	337 [269 – 405]	
• **Rectal**	25 [18 – 33]	
• **Pharyngeal**	42 [23 – 60]	
Site specific annual incidence of NG/CT among MSM in Baltimore City		
• **Urethral**	944 [753 – 1135]	
• **Rectal**	1251 [998 – 1505]	
• **Pharyngeal**	409 [326 – 492]	
HIV Parameters		
Disease duration		
• **Acute**	[6 – 9] weeks[1]	[40,41]
• **Chronic**	[8 –10] years[1]	[42,43]
• **Late stage** [4]	[1 –3] years[1]	[42–44]
Mortality rate[3]		
• **Acute & Chronic, no ART**	5 per 1000 person years	[45–47]
• **Late stage, no ART**	1/duration of late stage	
Reduction in mortality due to ART	0.58	
Time from ART discontinuation to pre-ART CD4 nadir[5]	ART treatment duration up to one year	[48–51]
Time from ART initiation to full viral suppression	[4 – 24] weeks[1]	[52]

[1] Values represent a pooled estimate of the reported measures for NG and CT infections

[2] Values are selected over uniform distributions across the ranges presented.

[3] Values represent the reported levels of NG/CT diagnosis among Baltimore City's MSM, and they are likely to underestimate the proportion of ongoing rectal and pharyngeal infections. We therefore consider such potential underestimation in estimating the annual incidence of NG/CT (see section 2 of the Supplementary Material) and have calibrated the model to represent realistic levels of prevalence (see the section on population overview in the main text).

[4] Mortality rate in late stage is defined as 1/(duration of late stage disease).

[5] Infectiousness assumed equal to that of the chronic disease.

Average viral load (log10 copies/mL)		[42]
• **Acute, no ART**	6.5	
• **Chronic, no ART**	4.5	
• **Late stage, no ART**	5	
• **On ART, partially suppressed**	3.5	
• **On ART, fully suppressed**	1.5	
Infectiousness per sexual contact	$2.45^{(\log(VL)-4.5)}$	[42]
Weekly probability of engagement in HIV care	0.006	[53–55]
Weekly probability of ART discontinuation	0.015	[56]
Gap in care after ART discontinuation	26 weeks	[57]
Relative probability of accessing HIV care among black MSM compared to white MSM	0.5	[58]
HIV calibration targets		
HIV prevalence	0.22 per 100,000 person/year	[59]
HIV continuum of care: Proportion of cases		[59]
• **Diagnosed**	0.86	
• **Linked to care**	0.62	
• **Engaged in care**	0.5	
• **On ART**	0.39	
• **Virally suppressed**	0.27	

STI Screening: In addition to testing of symptomatic NG/CT diagnosis, we also assume screening of asymptomatic individuals as follows (Figure 1- bottom panel):

- **Guidelines-based screening for HIV and NG/CT:** MSM may present to HIV/STI care providers (e.g., STI clinics, community health centers, HIV counseling programs) for a variety of reasons, and get tested for HIV and other STIs. We model visits for STI screening as a fixed weekly probability that reflects an individual's age-group and sexual activity such that younger MSM with higher propensity of partnerships experience a higher likelihood of visits [60,61]. We further assume that NG/CT is always screened at the urethral site, and a proportion of patients are also screened at the rectal and pharyngeal sites (calibrated to match the reported level of NG/CT infections diagnosis at each site among MSM in Baltimore City, as shown in Table 1).
- **NG/CT screening for HIV-positive MSM in care:** Based on CDC recommendations, most MSM who are continuously engaged in HIV care should undergo repeated NG/CT screening at least annually [15]. More frequent screening, such as screening every 3-6 months, is recommended for high-risk MSM, including those with an NG/CT diagnosis in the last year. Based on data from Baltimore City and a conservative estimate, we assume 40% adherence to these guidelines [62,63].

HIV Testing: In addition to combined HIV/STI testing that takes place as part of STI screening, we assume that all MSM experience an additional probability of HIV testing (in excess of testing though the STI program) can calibrate this probability to match the reported level of HIV diagnosis among MSM in Baltimore City.

Calibration: The model was calibrated against aggregate estimates of HIV and NG/CT incidence and prevalence, as well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City Health Department as part of the STD Surveillance Network Project (see section 2 of the Supplementary Material).

PrEP: Our primary outcome for this analysis is the projected incidence of HIV after 20 years of delivering PrEP to MSM. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the added benefit of targeting PrEP at individuals diagnosed with NG/CT. In all three scenarios, indication for PrEP use (eligibility) is considered in accordance with CDC recommendations and Baltimore City PrEP guidelines [64] (See

section 1 of the Supplementary Material) and includes HIV-negative individuals who are diagnosed with NG/CT in the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual partnership in the last 6 months. The three scenarios are thus:

- **PrEP delivery at NG/CT diagnosis** ("targeted" strategy & primary analysis)**:** all MSM diagnosed with NG/CT are offered PrEP at the time of diagnosis
- **PrEP evaluation at NG/CT screening/testing** ("at-testing")**:** PrEP eligibility is evaluated at the time of screening/testing for NG/CT, and all eligible individuals are offered PrEP
- **Untargeted PrEP:** PrEP eligibility is evaluated at random, and all eligible MSM are offered PrEP

All else being equal, increasing the number of MSM on PrEP will result in larger effects on HIV incidence (as more people are protected from HIV transmission). However, for a given number of MSM screened – or a given number of MSM on PrEP (e.g., if resource constraints are such that not all MSM meeting the criteria for PrEP can be placed/maintained on PrEP) – targeting PrEP to those screened for/diagnosed with NG/CT may be more efficient. Our primary aim was to quantify the extent of this gain in efficiency; thus, we compared scenarios in which the same number of MSM would be evaluated for PrEP, or alternatively the same number of MSM would be maintained on PrEP. Furthermore, to illustrate the potential impact of reaching highly ambitious targets for improved STI screening, we considered a hypothetical scenario for improving the underlying level of NG/CT screening (such that individual MSM not on PrEP experience a 50% annual probability of NG/CT screening and evaluation for PrEP upon NG/CT diagnosis), and studied the additional gain in effectiveness of NG/CT-targeted PrEP under this assumption.

In all scenarios, we assume that PrEP eligibility is reassessed every 3 months among patients receiving PrEP, and those who remain eligible for PrEP continue to receive it over time. Furthermore, we assume that in each scenario, a given proportion of eligible MSM who are offered PrEP will initiate prophylaxis (PrEP uptake ranging [0%-100%]) and adhere to it (PrEP adherence ranging [0%-100%]), with adherence defined as taking a sufficient number of doses to provide 60% protection against HIV transmission [65]. As a criterion for initiation of PrEP, all eligible MSM are also screened and treated for NG/CT infection before starting PrEP.

Sensitivity Analysis: A variety of sensitivity analyses were performed with the model. Using the HIV incidence at 10 years in absence and presence of PrEP (via all 3 scenarios) as the main output of interest, one-way sensitivity analyses were performed to variation of all model parameters to +/- 25% of their original value. We also varied condom usage among MSM on PrEP to model behavioral disinhibition (section 3 of the Supplementary Material).

Patient and Public Involvement: Patients and/or public were not involved in this study.

RESULTS

Population overview

The simulation models a population of 15,000 MSM in Baltimore City, projecting an average of 215 [95% UR: 181 – 251] incident HIV cases per year. Within this population, the co-epidemic of NG/CT was calibrated to 2598 [2204 – 2996] incident cases annually among which 35.0% [33.4 – 36.5%] of cases appear with urethral infection, 49.0% [47.4 – 50.6%] with non-urethral/rectal infection and 16.0% [14.8 – 17.2%] with pharyngeal-only infection. Point prevalence of NG/CT infection was estimated as 9.9% [8.4 – 11.5%], with 68.0% [63.5 – 72.5%] of infections occurring among black MSM (accounting for 58% of the MSM population). New infections occurred primarily in younger individuals, with 74% [72 – 78%] of new NG/CT infections occurring in MSM younger than 35 years old, and 69% [66 – 72%] of new HIV infections occurring among MSM between the ages of 25 and 45 (Figure 2A and B). Over half of new HIV and NG/CT infections occurred among MSM in the high sexual activity class, which accounted for 33% of the simulated population (Figure 2C and 2D). Overall, 81.5% [81.0 – 82.1%] of MSM diagnosed with

NG/CT in the model were tested on the basis of symptomatic presentation (rather than asymptomatic screening), and 20% [18.0 – 22.0%] of incident NG/CT cases were coinfected with HIV.

Epidemiological impact of PrEP at NG/CT diagnosis

At baseline, and in the absence of PrEP (steady-state equilibrium), 361 [95% UR: 298 – 427] MSM were annually diagnosed and treated for NG/CT infection (calibrated). If 60% of MSM diagnosed with NG/CT could be started on PrEP (i.e., uptake = 60%) and maintained at a degree to which 60% of subsequent HIV infections were averted (i.e., adherence = 60%), HIV incidence was estimated to decline by 12.4% [10.3 – 14.4%] over 20 years (Figure 3A). This corresponds to averting 318 [253 – 385] potential HIV transmissions through 5808 [5730 – 5886] person-years of PrEP delivered, or 5479 [4330 – 6632] infections averted per 100,000 person-years of PrEP (Figure 3B). Under the current level of NG/CT diagnosis, the number of MSM receiving PrEP is projected to increase through the first 8 years of the program (reaching a total of 332 [327 – 338] MSM on PrEP) and to fall afterward with declining incidence of NG/CT (Figure 3C). Due to the increased level of NG/CT screening/treatment among those on PrEP (through reassessment every 3 months), the prevalence of NG/CT was estimated to decline by 43.3% [41.6 – 44.9%] over 20 years of PrEP implementation (Figure 3D).

The impact of PrEP on HIV incidence can be further increased by expanding the coverage of NG/CT screening at the community level. In our baseline model, 25.0% [95% UR: 24.0 – 26.0%] of MSM undergo NG/CT screening/testing at least once annually (CDC recommendation). In an expanded-screening scenario in which all MSM experienced a 50% probability of screening for NG/CT annually, we projected a 180% increase in the baseline estimate of 4033 [3883 – 4182] annual NG/CT testing/screening events. Offering PrEP to those testing positive for NG/CT subsequently provided a 22.0% [20.1 – 23.9%] decline in HIV incidence over 20 years, corresponding to 648 [589 – 710] potential HIV transmissions averted. For further information on levels of uncertainty in these results, see section 4 of the Supplementary Material.

Relative impact of targeted versus untargeted PrEP

NG/CT-integrated PrEP increased efficiency of PrEP delivery in at least two ways (Figure 4A). First, a higher percentage of MSM were eligible for PrEP among those evaluated for PrEP (Figure 4B and 4C). In our model, 71.1% [95% UR: 65.0 – 77.2%] of all MSM diagnosed with NG/CT were eligible to receive PrEP (as 29% of this population is HIV-positive), compared to 45.2% [43.2 – 48.2%] of MSM screened for NG/CT, and 41.3% [39.1 – 43.5%] of randomly selected MSM. Second, providing PrEP to MSM diagnosed with NG/CT targets individuals at higher risk of potential HIV infection (due to both biological factors and high-risk behavior), such that – under the baseline assumption of equal numbers of people receiving PrEP—impact of NG/CT-targeted PrEP on HIV incidence was greater than the other two scenarios (Figure 4D). Specifically, over 20 years of implementation, targeting PrEP to MSM diagnosed with NG/CT infection increased impact of PrEP by 1.5 [1.1 – 1.9] relative to PrEP evaluation at NG/CT screening/testing, and by 1.6 [1.2 – 2.2] relative to untargeted PrEP. In another comparison, if the same number of individuals were evaluated for PrEP, the efficacy of NG/CT-integrated PrEP was increased even further relative to other scenarios (Figure 4E through 4H).

In one-way sensitivity analyses, the projected HIV incidence at 10 years in the absence of PrEP was sensitive to parameters relating to HIV and NG/CT transmission (including level of HIV viral load, condom use, and condom effectiveness) and parameters describing overall sexual activity (including the probabilities of starting new partnerships and the level of sexual activity in the most sexually active class). A similar variation in HIV incidence was observed in scenarios modeling PrEP evaluation at the time of NG/CT diagnosis, NG/CT screening or at random. Impact of PrEP in terms of reduction in HIV incidence in all scenarios relative to baseline was robust to reasonable variation of most model parameters (section 3 of the Supplementary Material).

DISCUSSION

This agent-based simulation of HIV transmission among MSM suggests that screening for NG/CT may be an important and efficient entry point for PrEP evaluation and delivery. Specifically, if all MSM who currently test positive for NG/CT could be offered PrEP – assuming 60% uptake and sufficient adherence to maintain 60% protection – HIV incidence could be reduced by approximately 12%, averting one HIV infection annually per 1,000 MSM population, with fewer than 20 per 1,000 taking PrEP every year. On the basis of infections averted per PrEP dose delivered, providing PrEP to MSM with NG/CT diagnosis is nearly twice as efficient as providing PrEP randomly among eligible MSM. Thus, use of NG/CT diagnosis as an entry point is a highly efficient and feasible mechanism for PrEP delivery. If NG/CT screening could be expanded to 50% of MSM every year (with PrEP offered only to those testing positive), this impact could be more than doubled. Given this substantial potential impact, it will be important to assess willingness and uptake and identify best practices to support PrEP uptake and adherence among MSM diagnosed with NG/CT.

These findings are consistent with other studies of PrEP delivery among MSM [66,67]. Previous studies have shown that the population-level impact of PrEP depends strongly on PrEP uptake and adherence [14,66], as suggested in our study as well. Importantly, NG/CT diagnosis may be useful in this regard, as MSM who have recently been diagnosed with an STI may be more aware of their HIV risk and more likely to accept and initiate PrEP. Past research has shown that HIV interventions may be more effective when they are conducted or initiated at the time of an STI diagnosis [68]. Initiation of PrEP simultaneously with NG/CT diagnosis may also be a clinically feasible approach – as an STI diagnosis is already likely to prompt an HIV test (if not already performed), and MSM who are diagnosed with NG/CT have at least some level of health care access. Unlike performing detailed sexual histories, offering PrEP to all HIV-negative MSM diagnosed with NG/CT is a simple guideline that is easy for most clinicians to follow [69,70]. Further research is needed to assess the feasibility of this approach in the field, especially in ascertaining the degree to which the continuum of PrEP care (including linkage to care and longer-term maintenance on PrEP) can be maintained in this population. Furthermore, the potential tradeoff between the positive impact of PrEP on STI prevalence through enhanced screening and its negative impact through behavioral disinhibition (if MSM on PrEP adopt riskier sexual behaviors) merits further investigation. Additional implementation research is also needed to identify effective mechanisms for improving adherence to CDC PrEP guidelines and overcoming barriers to acceptance and uptake of PrEP such as lack of awareness, lack of access, financial strain, and stigma [11,71].

As with any modeling analysis, our findings are limited by necessary simplifying assumptions. Given the overlap in clinical practice for treating NG and CT and the substantial uncertainty regarding the natural history of the two infections (e.g., duration of infectiousness, propensity toward asymptomatic infection), we have combined these infections as a single entity (NG/CT) and have used composite parameter values to describe the natural history of both diseases. However, there are still important differences between NG and CT, and to the extent that the natural history of each disease may differ, our findings may over- or under-estimate the impact of PrEP targeted at these STIs. For example, an infection with a shorter infectious period and a higher transmission probability per sex act will concentrate more strongly in high risk networks and may provide a more effective entry point for HIV PrEP. Further research can extend our analysis by considering the impact of each disease separately on HIV transmission dynamics. Furthermore, due to limited data on site-specific transmission dynamics (e.g., relative frequency of oral-only versus oral-plus-anal versus anal-only sex among MSM in Baltimore), we adopted a simplified approach that does not fully capture the complete transmission dynamics but should result in the appropriate distributions of NG/CT infections at each anatomical site. Additional simplifying assumptions used in the underlying HIV simulation model include applying the same sexual network for NG/CT and HIV transmission; simplification of sexual networks as comprising only stable and casual partnerships; simplified definition of sexual activity classes as a lifetime attribute among MSM; exclusion of serosorting on HIV, sexual activity class or PrEP; exclusion of HIV transmission through injection drugs or heterosexual sex; and exclusion of transgender individuals from the simulated population. To the extent

that these dynamics result in higher concentration of NG/CT among MSM at high-risk for HIV infection, our model may underestimate the impact of STI-targeted PrEP.

We excluded the potential existence of behavioral disinhibition for MSM on PrEP in the main analysis and applied a simplified approach for modeling the combined role of PrEP uptake/adherence for HIV protection. In additional sensitivity analyses, we studied the impact of decreased condom use among MSM on PrEP on the outcome of NG/CT-targeted PrEP, and the relative efficacy of STI-targeted scenario compared to the other comparators (See section 3 of the Supplementary Material) . As expected, the projected impact of NG/CT-targeted PrEP on incidence of HIV and NG/CT declined with reduced levels of condom use among PrEP users. This further highlights the need for additional behavioural surveillance data characterizing changes in level of condom use and risky behaviours among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis (increased effectiveness of PrEP implementation through an NG/CT targeted approach) remained robust to variation in the rate of condom use reduction.

There are strong racial disparities in HIV incidence and healthcare access in the US, such that the highest risk populations may be the ones least likely to have access to PrEP [72]; these disparities were not included in our simplified cascade of PrEP. Our model calibration was limited to the scope of local surveillance data, and available literature for values lacking direct empiric estimates from Baltimore City (e.g., probability of symptomatic infection). We also assumed a future trajectory of HIV infection in the future that represents continuation of current trends; this trajectory is unlikely to remain constant for the next 20 years but may help to provide a useful conceptual construct for present-day decision-making, which is the ultimate goal of this analysis. Our results are further limited by exclusion of syphilis infection, another STI that is often transmitted in the same populations and may affect transmission and acquisition of HIV. Finally, we did not incorporate cost or other resource constraints into the present model; future analyses could evaluate the efficiency of NG/CT-targeted PrEP delivery from a cost-effectiveness or budget impact perspective.

In summary, this stochastic agent-based model representing the co-dynamics of NG/CT and HIV transmission among MSM suggests that NG/CT diagnosis may serve as an efficient and effective entry point for PrEP. If linkage between STI and HIV control programs can be effectively developed, further investment in NG/CT screening (followed by PrEP initiation) can have major impact, not only on the incidence and prevalence of NG/CT, but also on transmission of HIV – potentially averting up to 20% of all HIV infections through NG/CT-targeted PrEP alone. Future analyses could evaluate whether such approaches could even be cost-saving in the long term. Ultimately, ending the HIV epidemic in MSM populations will require a combination of multiple activities, including strengthening the continuum of HIV care, ensuring continued access to clinical services, and prevention through both behavioral approaches (e.g., condom use) and PrEP. Using NG/CT diagnosis as an entry point for PrEP initiation may serve as an important component of such a combined prevention approach.

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Contributions

Designed the study [PK and DWD]; Wrote the model code [PK]; Provided data [CS,JJ,ST,DG], Analyzed the data [PK]; supervised the analyses [DWD]; reviewed results [MS,SB, KH, TG, HC]; wrote the first draft of the manuscript [PK]; revised the manuscript and contributed intellectual content [PK, SB, MS, ER, KH, TG, HC]; All authors saw and approved the final manuscript.

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Data sharing statement:

Additional data are presented in the online Supplementary Material.

REFERENCES

1 Katz D, Dombrowski J, Bell T. HIV incidence among men who have sex with men after diagnosis with sexually transmitted infections. *Sex Transm Dis* 2016;**43**:249–54.

2 Pathela P, Braunstein S, Blank S. HIV incidence among men with and without sexually transmitted rectal infections: estimates from matching against an HIV case registry. *Clin Infect Dis* 2013;**57**:1203–9.

3 Ward H, Rönn M. Contribution of sexually transmitted infections to the sexual transmission of HIV. *Curr Opin HIV AIDS* 2010;**5**:305–10.

4 Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. *J Acquir Immune Defic Syndr* 2000;**24**:48–56.

5 Fleming DTDT, Wasserheit JNJN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;**75**:3–17.

6 Grosskurth H, Mosha F, Todd J, *et al.* Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530–6.

7 Centers for Disease Control Prevention. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline. 2014.

8 Krakower D, Ware N, Mitty JA, *et al.* HIV providers' perceived barriers and facilitators to implementing pre-exposure prophylaxis in care Settings: a qualitative study. *AIDS Behav* 2014;**18**:1712–21.

9 Eaton L, Driffin D, Bauermeister J. Minimal awareness and stalled uptake of pre-exposure prophylaxis (PrEP) among at risk, HIV-negative, black men who have sex with men. *AIDS Patient Care STDS* 2015;**29**:423–9.

10 Galindo G, Ja'Nina J. Community member perspectives from transgender women and men who have sex with men on pre-exposure prophylaxis as an HIV prevention strategy: implications for implementation. *Implement Sci* 2012;**7**:116.

11 Golub SA, Gamarel KE, Rendina HJ, *et al.* From efficacy to effectiveness: facilitators and barriers to PrEP acceptability and motivations for adherence among MSM and transgender women in New York City. *AIDS Patient Care STDS* 2013;**27**:248–54.

12 Juusola JL, Brandeau ML, Owens DK, *et al.* The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. *Ann Intern Med* 2012;**156**:541–50.

13 Koppenhaver RRT, Sorensen SSW, Farnham PG, *et al.* The cost-effectiveness of pre-exposure prophylaxis in men who have sex with men in the United States: an epidemic model. *AIDS J Acquir Immune Defic Syndr* 2011;**58**:e51–2.

14 Kasaie P, Pennington J, Berry SA, *et al.* The impact of pre-exposure prophylaxis among men who have sex Withmen in Baltimore City: an agent-based simulation. *JAIDS J Acquir Immune Defic Syndr* 2017;**75**:175–83.

15 Workowski KA, Bolan GA. Sexually Transmitted Diseases Treatment Guidelines, 2015. *Morb Mortal*

Wkly Rep 2015;**64(RR3)**:1–137.

16 Kent CK, Chaw JK, Wong W, *et al.* Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. *Clin Infect Dis* 2005;**41**:67–74.

17 Lister N, Smith A, Tabrizi S, *et al.* Screening for neisseria gonorrhoeae and chlamydia trachomatis in men who have sex with men at male-only saunas. *Sex Transm Dis* 2003;**30**:886–9.

18 Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. *Genitourin Med* 1996;**72**:422–6.

19 Morris SR, Klausner JD, Buchbinder SP, *et al.* Prevalence and incidence of pharyngeal gonorrhea in a longitudinal sample of men who have sex with men: the EXPLORE study. *Clin Infect Dis* 2006;**43**:1284–9.

20 Beck EEC, Birkett M, Armbruster B, *et al.* A data-driven simulation of HIV spread among young men who Hhave sex with men: role of age and race mixing and STIs. *JAIDS J Acquir Immune Defic Syndr* 2015;**70**:186–94.

21 Kretzschmar M, Duynhoven Y van. Modeling prevention strategies for gonorrhea and chlamydia using stochastic network simulations. *Am J Epidemiol* 1996;**144**:306–17.

22 Korenromp EL, Sudaryo MK, de Vlas SJ, *et al.* What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *Int J STD AIDS* 2002;**13**:91–101.

23 Althaus CL, Heijne JCM, Roellin A, *et al.* Transmission dynamics of chlamydia trachomatis affect the impact of screening programmes. *Epidemics* 2010;**2**:123–31.

24 Price MJ, Ades AE, Angelis D De, *et al.* Mixture-of-exponentials models to explain heterogeneity in studies of the duration of Chlamydia trachomatis infection. *Stat Med* 2013;**32**:1547–60.

25 Turner KM, Adams EJ, Gay N, *et al.* Developing a realistic sexual network model of chlamydia transmission in Britain. *Theor Biol Med Model* 2006;**3**:3.

26 Chesson HW, Bernstein KT, Gift TL, *et al.* The cost-effectiveness of screening men who have sex with men for rectal chlamydial and gonococcal infection to prevent HIV Infection. *Sex Transm Dis* 2013;**40**:366–71.

27 Tuite A, Jayaraman G, Allen V. Estimation of the burden of disease and costs of genital Chlamydia trachomatis infection in Canada. *Sex Transm Dis* 2012;**39**:260–7.

28 Vries R De, Bergen J Van. Systematic screening for Chlamydia trachomatis: estimating cost-effectiveness using dynamic modeling and Dutch data. *Value in* 2006;**9**:1–1.

29 Adams EJ, Turner KME, Edmunds WJ. The cost effectiveness of opportunistic chlamydia screening in England. *Sex Transm Infect* 2007;**83**:267-74-5.

30 Andersen B, Gundgaard J, Kretzschmar M. Prediction of costs, effectiveness, and disease control of a population-based program using home sampling for diagnosis of urogenital Chlamydia trachomatis. *Sex Transm Dis* 2006;**33**:407–15.

31 Gillespie P, O'Neill C, Adams E, *et al.* The cost and cost-effectiveness of opportunistic screening for

Chlamydia trachomatis in Ireland. *Sex Transm Dis* 2012;**88**:222–8.

32 Roberts T, Robinson S, Barton P, *et al.* Cost effectiveness of home based population screening for Chlamydia trachomatis in the UK: economic evaluation of chlamydia screening studies (ClaSS) project. *Bmj* 2007;**335**:291.

33 Welte R, Kretzschmar M, Leidl R, *et al.* Cost-effectiveness of screening programs for Chlamydia trachomatis: a population-based dynamic approach. *Sex Transm Dis* 2000;**27**:518–29.

34 Cohen M. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. *Lancet* 1998;**351**:S5–7.

35 Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;**75**:3–17.

36 Winter AJ, Taylor S, Workman J, *et al.* Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. *Sex Transm Infect* 1999;**75**:261–3.

37 Cohen MS, Hoffman IF, Royce RA, *et al.* Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet* 1997;**349**:1868–73.

38 Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV. *Sex Transm Dis* 2001;**28**:579–97.

39 Jin F, Prestage GP, Imrie J, *et al.* Anal sexually transmitted infections and risk of HIV infection in homosexual men. *J Acquir Immune Defic Syndr* 2010;**53**:144–9.

40 Little SJ, McLean AR, Spina CA, *et al.* Viral dynamics of acute HIV-1 infection. *J Exp Med 1* 1999;**90**:841–50.

41 Leynaert B n d., Downs AM, de Vincenzi I. Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. *Am J Epidemiol* 1998;**148**:88–96.

42 Beyrer C, Baral SD, van Griensven F, *et al.* Global epidemiology of HIV infection in men who have sex with men. *Lancet* 2012;**380**:367–77.

43 Alam SJ, Meyer R, Norling E. A model for HIV spread in a South African village. *Multi-Agent-Based Simul IX* 2009;:33–45.

44 Baggaley RF, Ferguson NM, Garnett GP. The epidemiological impact of antiretroviral use predicted by mathematical models: a review. *Emerg Themes Epidemiol* 2005;**2**:9.

45 The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;**373**:795–807.

46 Kitahata MM, Gange SJ, Abraham AG, *et al.* Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009;**360**:1815–26.

47 Palella Jr FJ, Delaney KM, Moorman AC, *et al.* Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;**338**:853–60.

48 Wit FW, Blanckenberg DH, Brinkman K, *et al.* Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. *AIDS* 2005;**19**:345–8.

49 Maggiolo F, Ripamonti D, Gregis G, *et al.* Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. *AIDS* 2004;**18**:439–46.

50 Ortiz GM, Wellons M, Brancato J, *et al.* Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects. *Proc Natl Acad Sci* 2001;**98**:3288–13293.

51 El-Sadr WM, Lundgren JD, Neaton JD, *et al.* CD4+ count-guided interruption of antiretroviral treatment. *New Engl J Med* 2006;**355**:2283–96.

52 Clotet B, Feinberg J, Lunzen J van, *et al.* Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised. *Lancet* 2014;**383**:2222–31.

53 Hill T, Bansi L, Sabin C, *et al.* Data linkage reduces loss to follow-up in an observational HIV cohort study. *J Clin* 2010;**63**:1101–9.

54 Mocroft A, Kirk O, Aldins P, *et al.* Loss to follow-up in an international, multicentre observational study. *HIV Med* 2008;**9**:261–9.

55 Ndiaye B, Ould-Kaci K, Salleron J, *et al.* Characteristics of and outcomes in HIV-infected patients who return to care after loss to follow-up. *AIDS* 2009;**23**:1786–9.

56 Mills E, Nachega J, Buchan I, *et al.* Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *Jama* 2006;**296**:679–90.

57 Rana AI, Liu T, Gillani FS, *et al.* Multiple gaps in care common among newly diagnosed HIV patients. *AIDS Care* 2015;**27**:697–687.

58 Rosenberg ES, Millett GA, Sullivan PS, *et al.* Understanding the HIV disparities between black and white men who have sex with men in the USA using the HIV care continuum: a modelling study. *Lancet HIV* 2014;**1**:e112–8.

59 Maryland Department of Health and Mental Hygiene, MDHMH. 2012 Baltimore City Annual HIV Epidemiological Profile. Baltimore: 2012.

60 Virginia Department of Health. STD Surveillance Network Report. Published Online First: 2013.http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf (accessed 30 Jun2017).

61 Castro JG, Alcaide ML. High rates of STIs in HIV-infected patients attending an STI clinic. *South Med J* 2016;**109**:1–4.

62 Berry SA. Gonorrhoea and chlamydia screening in HIV clinics: time for new tools and targets. *Sex Transm Infect* 2014;**90**:574–5.

63 Hoover KW, Butler M, Workowski K, *et al.* STD screening of HIV-infected MSM in HIV clinics. *Sex Transm Dis* 2010;**37**:771–6.

64 CDC. PrEP for men who have sex with men. 2018. https://prepmaryland.org/sites/default/files/download-resources/PrEP - MSM both sides March 2017.pdf

65 Koenig L, Lyles C, Smith D. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis.

Am J Prev 2013;**44**:S91–8.

66 Jenness S, Goodreau S. Impact of the centers for disease control's HIV preexposure prophylaxis guidelines for men who have sex with men in the United States. *J Infect Dis* 2016;**14**:1800–7.

67 Vissers DCJ, Voeten HACM, Nagelkerke NJD, *et al.* The impact of pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: a simulation study. *PLoS One* 2008;**3**:e2077.

68 Bolu OO, Lindsey C, Kamb ML, *et al.* Is HIV/sexually transmitted disease prevention counseling effective among vulnerable populations? a subset analysis of data collected for a randomized, controlled trial evaluating counseling efficacy (Project RESPECT). *Sex Transm Dis* 2003;**31**:469–74.

69 Carter JW, Hart-Cooper GD, Butler MO, *et al.* Provider barriers prevent recommended sexually transmitted disease screening of HIV-infected men who have sex with men. *Sex Transm Dis* 2014;**41**:137–42.

70 Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States-2014: a clinical practice guideline. 2014.

71 Calabrese SK, Underhill K. How stigma surrounding the use of HIV preexposure prophylaxis undermines prevention and pleasure: a call to destigmatize 'Truvada Whores'. *Am J Public Health* 2015;**105**:1960–4.

72 Highleyman L. PrEP use is rising fast in US, but large racial disparities remain. Aidsmap. 2016.http://www.aidsmap.com/PrEP-use-is-rising-fast-in-US-but-large-racial-disparities-remain/page/3065545/ (accessed 14 May2018).

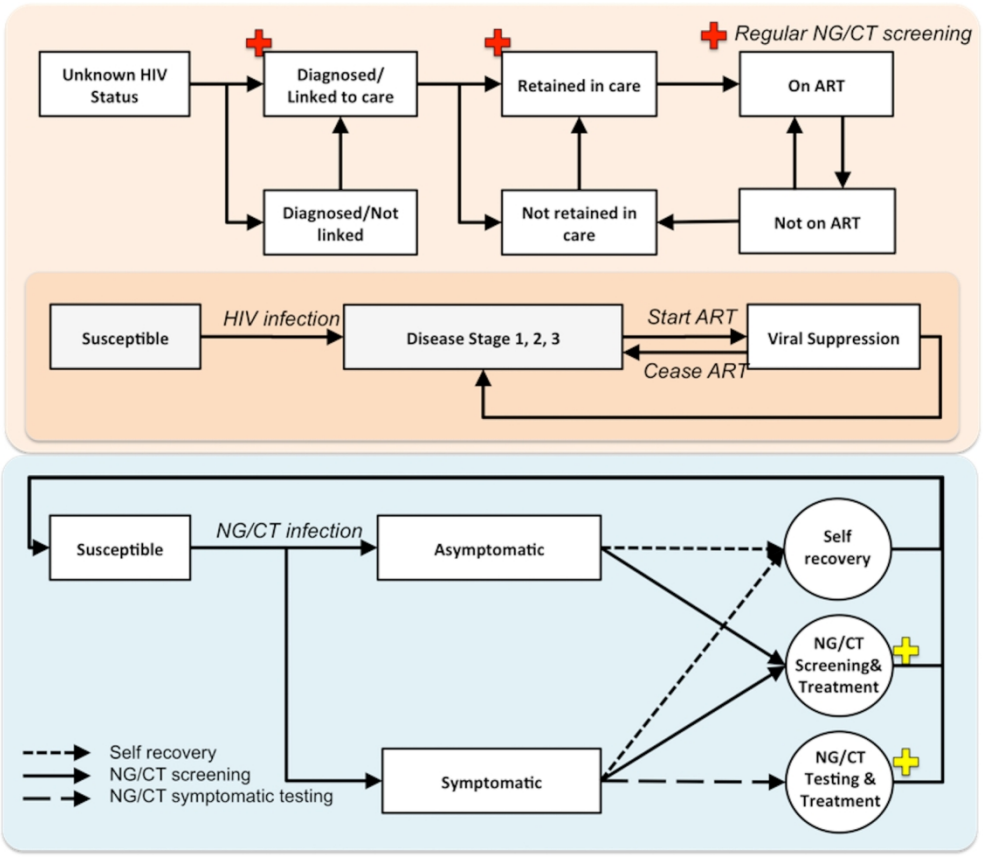
Figure legends:

Figure 1: An agent-based model of gonorrhoea/chlamydia (NG/CT) and HIV co-transmission. The top panel represents the HIV care continuum and natural history: Upon infection with HIV, individuals serially progress through three disease stages over time; this progression can be halted by initiation of antiretroviral therapy (ART), which is assumed to result – if taken – in viral suppression within 4 to 24 weeks (see Table 1) [52]. We assume, for simplicity, that engagement in care involves initiation of ART (as episodes of care engagement not resulting in ART initiation do not affect HIV transmission in the model). HIV-positive individuals in care are assumed to undergo regular screening for NG/CT (marked in red) subject to patients presenting for scheduled visits and clinician decision to screen. The bottom panel represents the natural history of NG/CT: infection may be symptomatic or asymptomatic, individuals remain infectious until diagnosis and treatment (which can occur either through symptomatic presentation to care or routine screening of asymptomatic individuals) or spontaneous resolution. Upon diagnosis with incident NG/CT, we assume that individuals are also screened for HIV infection (marked in yellow); if HIV-negative, we consider the possibility of PrEP delivery in this analysis.

Figure 2: Model projections of the distribution of new infections by age and sexual activity level. Shown on the y-axes are the distribution of HIV (A) and NG/CT (B) incidence by age-group and the distribution of HIV (C) and NG/CT (D) incidence by the sexual activity level. Bars represent the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

Figure 3: Impact of NG/CT-integrated PrEP, according to frequency of NG/CT screening/testing. Shown on the y-axes are the annual incidence of HIV (A), cumulative number of transmissions averted (B), number of MSM on PrEP (C) and NG/CT prevalence (D). The red line depicts a scenario in which all MSM currently diagnosed with NG/CT are placed on PrEP with 60% uptake and adherence (NG/CT-integrated PrEP scenario in the main text), and the blue line shows a hypothetical scenario in which 50% of MSM are screened for NG/CT every year, with those testing positive for NG/CT also offered PrEP.

Figure 4: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in red, also corresponding to the red line in Figure 3), compared against PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. In the first set of experiments, the three strategies are compared under the assumption that the same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be screened for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenario (similar pattern in panels E through H).



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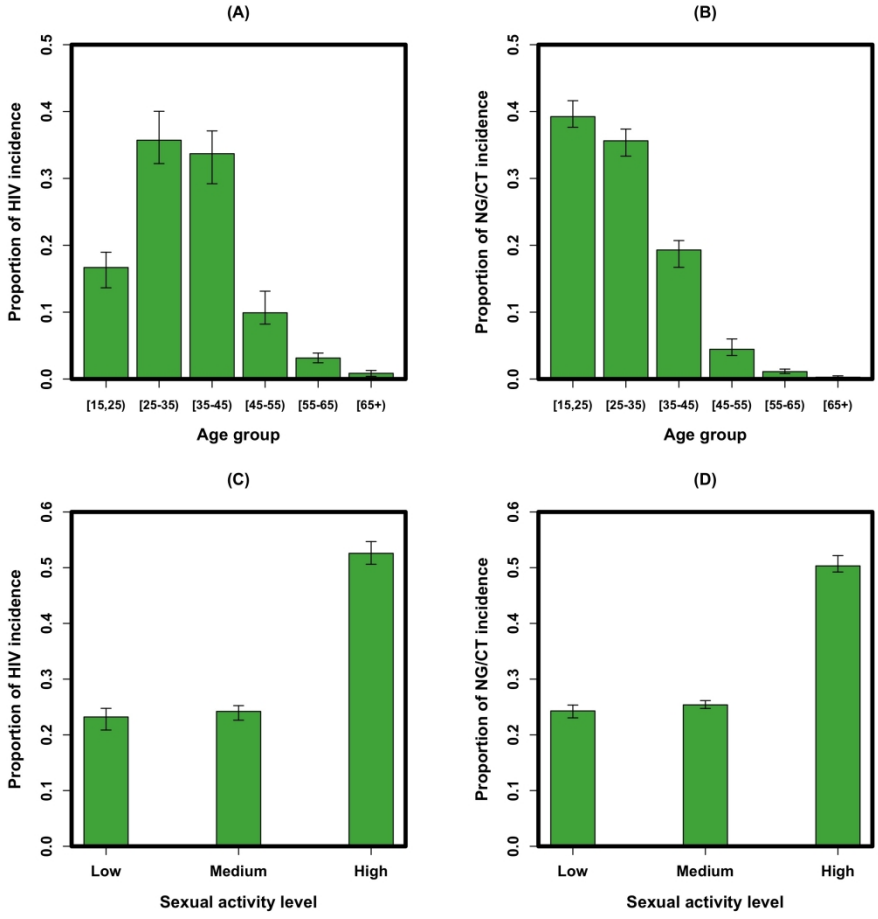

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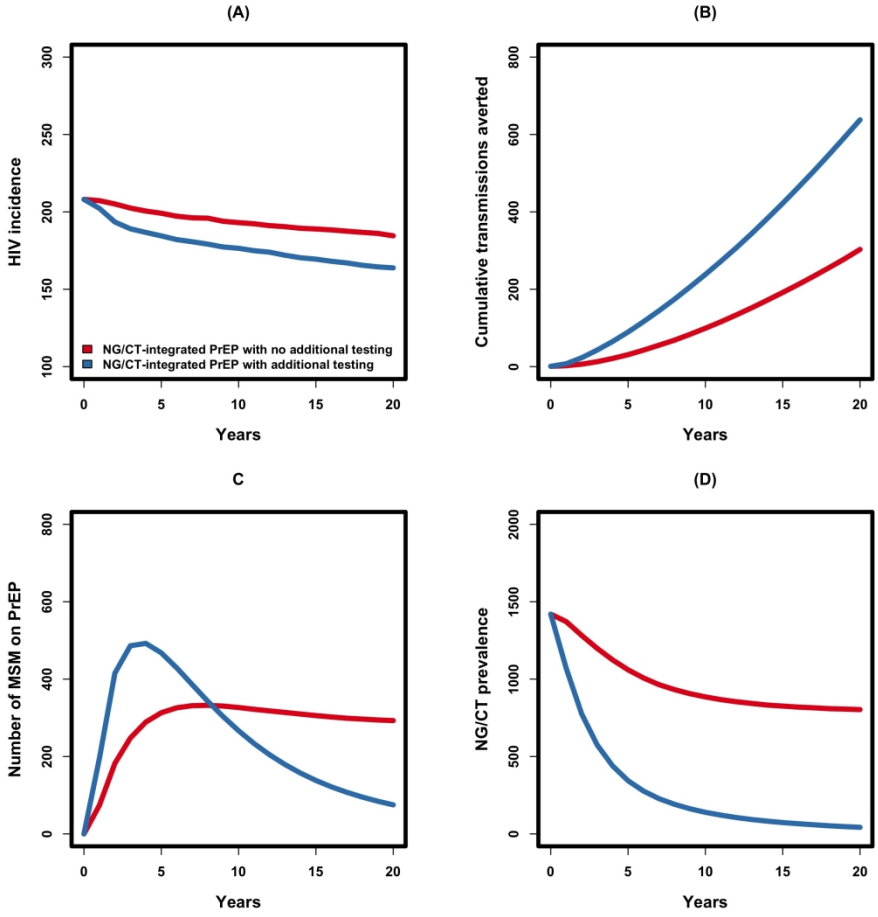

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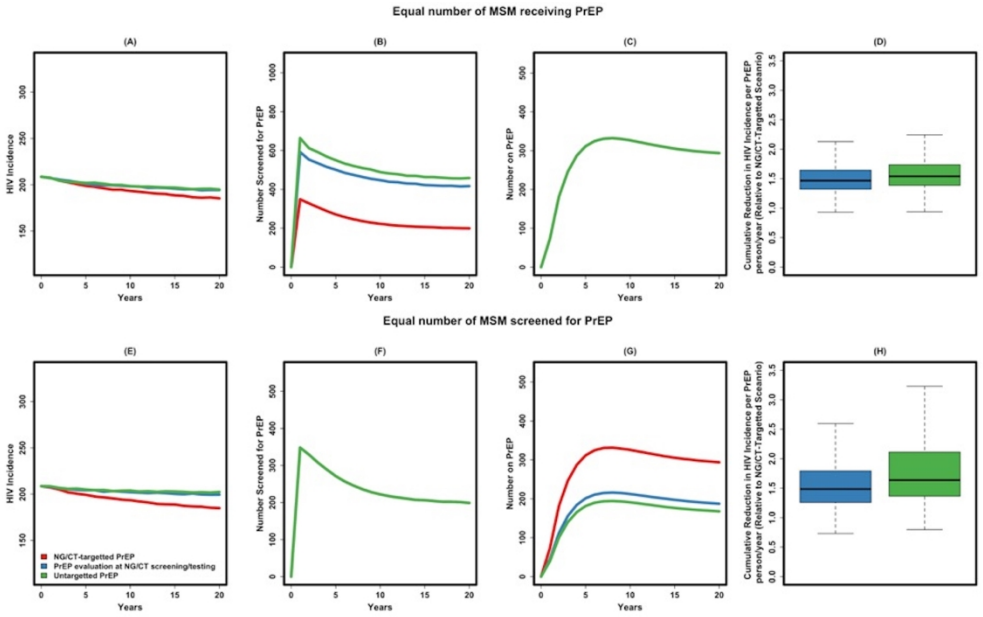

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SUPPLEMENTARY MATERIAL

Title: Gonorrhoea and chlamydia diagnosis as an entry point for HIV pre-exposure prophylaxis: A modeling study

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1 HIV SIMULATION MODEL DESIGN

Overview

Our agent-based simulation model of the HIV epidemic among MSM in Baltimore City is structured as a collection of modules that govern population demographics, sexual partnerships, the epidemiological aspects of disease with regard to HIV natural history, cascade of care and transmission. Each "agent" represents a single MSM in Baltimore City, characterized by age, race, and place of residence, and the model is evaluated in a series of one-week time steps. The HIV natural history module characterizes the progression of HIV among infected individuals according to disease stage. Each stage is associated with a different per-act risk of HIV transmission, and disease progression from stage 2 to stage 3 can be prevented (and/or reversed) by provision of ART. The HIV cascade of care estimates probabilities of HIV testing, linkage to care, disengagement/re-engagement, and ART provision/viral suppression at each time step. The sexual network and transmission module create and modify the population's sexual networks (as a series of stable and casual partnerships) at each step, modeling HIV transmission as a per-act probability among serodiscordant partnerships according to frequency and safety of sex act, HIV stage of the infected partner, and ART/PrEP use. Sexual partnerships are modeled as assortative according to age, race, and location of residence. Finally, the population demographic module accounts for aging, death, and birth processes.

1.1 Population Demographic Module

This module characterizes the initial population structure and governs various procedures for aging, death, and birth at end of each simulated year. We model the population of MSM in Baltimore City between the ages of 15 to 75. The population is structured as a collection of population groups corresponding to Baltimore's Community Statistical Areas (CSA) [1]. CSAs are clusters of neighborhoods and are organized according to census tract boundaries, which are consistent statistical boundaries. In some cases, CSA boundaries may cross neighborhood boundaries. There are 55 CSAs in Baltimore City. Neighborhood lines often do not fall along CSA boundaries, but CSAs are representations of the conditions occurring within those particular neighborhoods. Simulated population groups are characterized with regard to their geographical location (CSA of residence) and racial structure (black and non-black). We do not model the spatial distribution of individuals within each CSA; rather geographical assignments are made at the CSA level by assigning the corresponding CSA-center coordinates to each MSM living in that CSA. The initial HIV distribution across CSAs is estimated according to publicly available data from Maryland's Department of Health and Mental Hygiene (MDHMH) [2].

Individuals age with the simulation clock (years) and exit the model according to an age-specific natural mortality rate [3], or by reaching the age of 75, or via an additional mortality rate associated with HIV infection. To maintain the initial population decomposition without disturbing the CSA structures, we model a natural birth process at the CSA level for replenishing the population size over time. The birth process is modeled via a non-stationary Poisson process tuned to maintain each CSA's population at a constant mean over time. Newborns enter the MSM population at age of 15 to 20 years old and follow the corresponding racial structure of the CSA of residence.

Using the current estimate of Baltimore City male population (approximately 287,000) who are 15 year or older in age (about 232,000), and estimated percentage of adult MSMs in each racial group (7.5% of non-black males and 5.8% of black males [4]), we estimate the size of Baltimore City's MSM population at approximately 15,000.

Forming CSA-groups: To determine groupings of similar CSAs, we first ranked the CSAs according to the median income level and racial makeup based on available information from Baltimore City census [1].

For simplicity, levels of income (Figure S1-left panel) and proportion of population that is Black/African-American (Figure S1-right panel) were coded into values from 1 to 5 (representative of various shades in Figure S1), and two values were assigned to each CSA. For example, CSA "Midtown" (T-shaped in the center of the map) was assigned a rank of 3 for median household income, and 2 for the proportion of population that is Black/African-American.

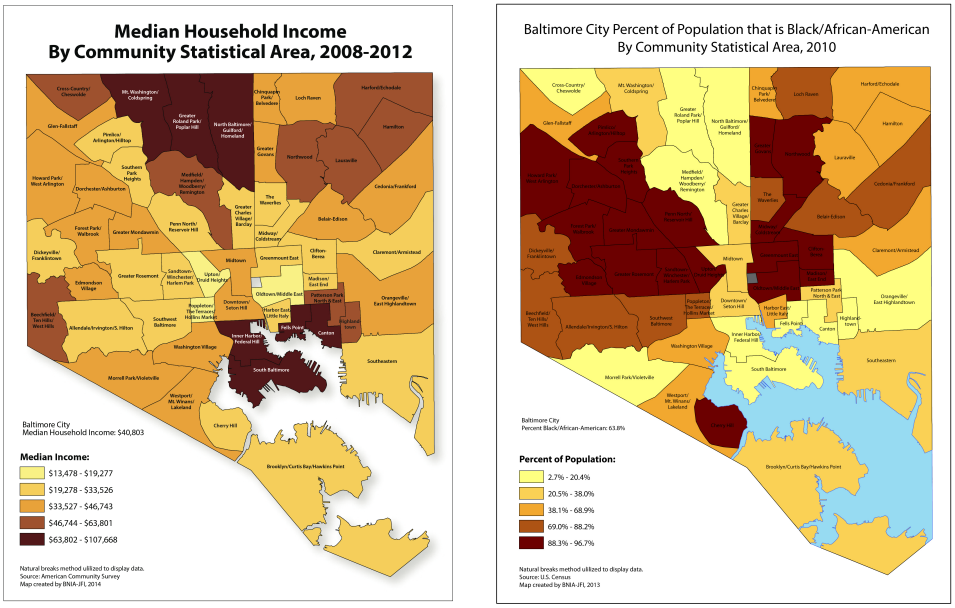

Figure S1: Baltimore City CSA ranking according to median income and racial structure [1].

We defined a CSA-group to include a number of neighboring CSAs (sharing a border) with at most a one-level difference in their ranked levels of income and racial makeup. To determine the CSA-groups throughout the city, we implemented a random search mechanism using a branch and bound logic. The search was started from a random CSA and branched through all neighboring CSAs to determine how many could belong to the same CSA-group. The search was bounded by those CSAs representing a difference of more than one level in ranked income and racial makeup but continued for those CSAs that belonged to the same group and branched further to test their other neighbors, until it was bounded in all directions. At the end of each iteration, a list of CSAs grouped by relative similarity across the whole city was generated. This search was repeated many times and the CSA groups that were most likely (i.e., high frequency) to form were identified. Overlapping CSA-groups were further checked for the possibility of combination into a single group. Finally, we had 16 CSA-groups across Baltimore City, representing geographically approximate neighborhoods with similar levels of income and racial makeup (Figure S2). Using CSA numbers as identifiers, a complete list of CSA groups is provided in Table S1.

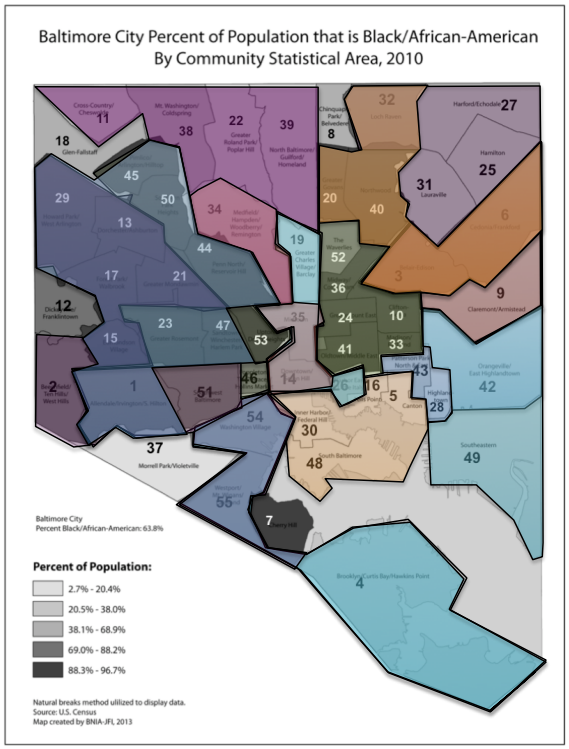

Figure S2: Baltimore City CSA ID's and CSA groups structure. Each CSA group is marked with a closed border in a different color. Some groups overlap such that some CSAs belong to more than one group. Some CSAs may not belong to any groups and are considered by themselves.

Table S1: List of CSA group and member CSAs

Group ID	CSA members
1	11 22 34 38 39
2	3 6 9
3	28 42 43
4	3 6 8 25 27 31 32
5	42 49
6	10 24 33 36 41 52
7	5 16 28 30 43 48
8	3 6 20 32 40
9	4 14 19 26 35 54 55
10	14 34 35
11	1 23 44 45 46 47 50 51 53
12	1 51 54 55
13	4 14 19 26 35 54 55
14	2 13 15 17 21 29
15	1 12 13 15 17 21 23 29 44 45 47 50 51
16	3 6 10 20 24 33 36 52

1.2 Sexual Partnership Module

This module governs the network of sexual partnerships and runs in discrete time steps, each representing a week. Following previous models of sexual contact networks [5–7], we conceptualize the network of sexual partnerships at an individual level (with regard to age, race, geography, sexual positioning, etc.) and calibrate the simulation parameters using local behavioral surveillance data available through the BESURE study, the Baltimore City branch of the National HIV Behavioral Surveillance System (NHBS) [8]. BESURE is a CDC funded project operated by the Maryland Department of Health and Mental Hygiene and the Johns Hopkins Bloomberg School of Public Health. Starting in 2004, BESURE has conducted four venue-based sampling surveys among Baltimore's MSM (Table S2). We use this data to extract information on several behavioral parameters at the individual level (e.g., preference toward using condoms in each type of partnerships) that will be directly implemented at the agent level, as well as population-level estimates for calibrating the unknown variables (e.g., frequency of the annual sexual partnerships). For those measures available across multiple BESURE waves, we use a pooled estimate of the reported values.

Table S2: Survey methods and sample characteristics, BESURE MSM 2004-2010

	Wave 1	Wave 2	Wave 3	Wave 4
Date	June 04-April 05	Jul-Oct 2008	Aug-Dec 2011	Jun-Dec 2014
Total MSM	645	448	404	455
HIV prevalence	37.7%	37.5%	42.6%	30.6%
Proportion of HIV that was unrecognized	58.4%	78.4%	67.3%	33.1%

1.3 Partnership types and formation

We model two types of partnerships representing long-term "stable" and short-term "casual" partnerships. Stable partnerships can last for several years [5], while casual partnerships will only last a single time step (one week) in the model. We assume that individuals can have multiple casual partnerships from one week to the next [9], but they can only engage in a maximum of one stable and one casual partnership at any time step. All partnerships are updated at the end of each simulation week, and those partnerships reaching their pre-specified duration will be dissolved. At the beginning of each following week, individuals' tendency to engage in a new partnership is evaluated and "eligible" individuals will select the geographical search domain for meeting their future partners based on their location of residence. Once the partnership domains are established for all eligible MSM, individuals will follow a search mechanism based on a combination of race- and age-dependent mixing patterns, as well as sexual role preference, to select their future partner from the pool of eligible people at the selected domain. This process is modeled in 3 steps:

1.3.1 Step 1. Evaluating an individual's probability of engaging in a new partnership

Each individual's likelihood of engaging in a new partnership is modeled as a function of his age, the level of sexual activity, and current partnership status.

In accordance with the heterogeneous frequency of reported partnerships by age, we define a partnership coefficient for modeling the likelihood of engaging in new partnerships as a function of individual's age ($c_{Part|Age}$) (assumed to be a fixed level for each age group).

Sexual activity class: In order to represent the heterogeneous level of sexual activity among MSM, we defined three sexual activity classes ("low", "medium" and "high"), each corresponding to a lifetime level of engagement in casual partnerships. An individual's sexual activity class (c_{SA}) is determined at the time of birth (entry to population) and remains fixed throughout his life (though within each sexual activity class, the actual level of partnership formation changes with age – for example, partnership formation declines with older age in all three classes). This attribute represents a combination of factors determining an individual's tendency for engaging in casual partnerships, reflecting the diversity of sexual activity seen in real populations. As described in a previously published modeling construct [10], we implement the simplified definition of the 3 sexual activity classes in order to more accurately represent "tails" in the observed distribution of (self-reported) sexual activity in data from Baltimore City. Individuals with particularly high sexual frequency are potentially important drivers of STI transmission dynamics but are not easily represented assuming a simple Poisson process of sexual partnership formation. We therefore arbitrarily assign equal numbers of individuals to these three sexual activity classes, and then calibrate the relative frequency of casual partnership formation in each of these classes to most closely fit the observed distribution among MSM in Baltimore City.

Finally, we model each agent's tendency for engaging in casual and stable partnerships at any point of time via two additional parameters (p_{Csl} and p_{Stb}) at the agent-level, and also define the conditional likelihood of engaging in new casual partnerships concurrent to an existing stable partnership via a separate parameter ($p_{Csl|Stb}$).

With these definitions, an individual's likelihood of engaging in a new stable (P_{new_stb}) or casual (P_{new_csl}) partnership at each timestep can be estimated as follow:

$$P_{new\_stb} = p_{Stb} \times c_{Part|Age}$$

$$P_{new\_csl} = p_{Csl} \times p^{*}_{Csl|Stb} \times c_{Part|Age} \times c_{SA}$$

$$p^{*}_{Csl|Stb} = \begin{cases} p_{Csl|Stb} & number\ of\ stable\ partnerships > 0 \\ 1 & o.w. \end{cases}$$

At each time step, an individual's likelihood for engaging in a new partnership is evaluated and eligible individuals are added to the pool of available people at their CSA of residence to find their potential partners in the next steps.

1.3.2 Step 2. Choosing the partnership domain

The partnership domain is determined according to a discrete mixing structure at the CSA level (Figure S3). In order to model the spatial mixing patterns across the population and among various subgroups, we first define sets of "neighboring" CSA groups with regard to geographical proximity and similar socioeconomic status (income levels) and racial structure [1]. Upon seeking a new partnership, an individual's search scope (for choosing the new partner) is determined according to a discrete geographical mixing probability (*pGM*) for selecting one's own CSA (p_0), a random neighboring CSA in the same CSA group (p_1) or non-neighbor CSA (p_2). The geographical mixing probability ($pGM=(p_0, p_1, p_2)$)

represents a measure of geographical/socioeconomic clustering in the network of partnerships, where *pGM*=(1,0,0) translates into an isolated mixing pattern for partnership only with individuals in one's CSA of residence, and *pGM*=(0.33,0.33,0.33) translates into a homogeneous mixing structure across the entire population. In our initial analysis, we calibrate the geographical mixing likelihoods at *pGM* = (0.5, 0.3, 0.2) according to available estimates from [11].

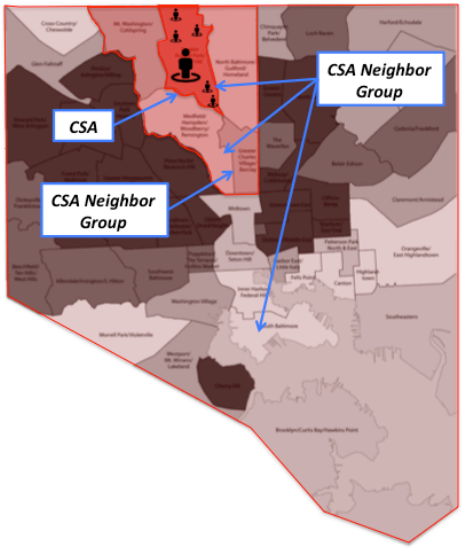

Figure S3: Partnership search domains. Individuals can choose their future partner from their own CSA or a random CSA within or outside their neighbor group.

1.3.3 Step 3. Modeling the search mechanism within the partnership domain

Once the partnership domain is established, individuals follow a search mechanism for finding their new partners from the pool of eligible members in the selected domain. The probability of partnership between two people is evaluated according to an age- and race-mixing structure, as well as sexual role preference. Assuming independent patterns of age- and race-specific mixing, the age-race mixing probability is computed as the product of age-mixing and race-mixing probabilities for each pair of potential partners. A random search mechanism is implemented to evaluate the probability of partnership with each potential partner in the selected domain until a successful match is found or the entire domain is searched. Potential partners are also checked for their compatibility with regard to sexual role and incompatible pairs (e.g., receptive-receptive or insertive-insertive) are dismissed. Upon a successful match, a new partnership is formed for both parties, who are then excluded from the pool of eligible partners for other individuals.

1.3.4 Age-Specific Mixing

Age-specific mixing is modeled based on absolute difference in the square root (ADSR) of men's ages [5]. The ADSR provides a closer fit to the observed age-mixing matrix than does age directly. This statistic also has the desirable property that the same absolute difference in age becomes less important over time. Using data on participant's age and their last male partner's age from BESURE, we estimate the reported ADSR level for main/casual partnerships ($ADSR_{partnership}$) as shown in Table S3. The probability of age-mixing between person *p* and *q* for each partnership type (*pAgeMixing*) is then computed as a function of

partners' age and the target ADSR level for each type of partnerships. Figure S4-A and S4-B compare the simulated distribution of ADSR values among casual and stable partnerships in the baseline simulation model.

$$pAgeMixing = \text{Min}(ADSR_{p,q,2} \times ADSR_{partnership} - ADSR_{p,q}) / ADSR_{partnership}$$

where

$$ADSR_{p,q} = \left| \sqrt{p_{age}} - \sqrt{q_{age}} \right|$$

$$ADSR_{partnership} = (ADSR_{Stb}, ADSR_{Csl})$$

Table S3: Estimates of reported ADSR for Stable/Casual partnerships in BESURE. Estimates are made based on the participant's age and their last male partner's age.

BESURE Waves:	$ADSR_{Stb}$ (Number of reported partnerships)	$ADSR_{Csl}$ (Number of reported partnerships)
Wave 2	0.62 (66)	0.72 (75)
Wave 3	0.68 (71)	0.73 (87)
Wave 4	0.51 (62)	0.76 (77)
Average estimate	**0.6**	**0.74**

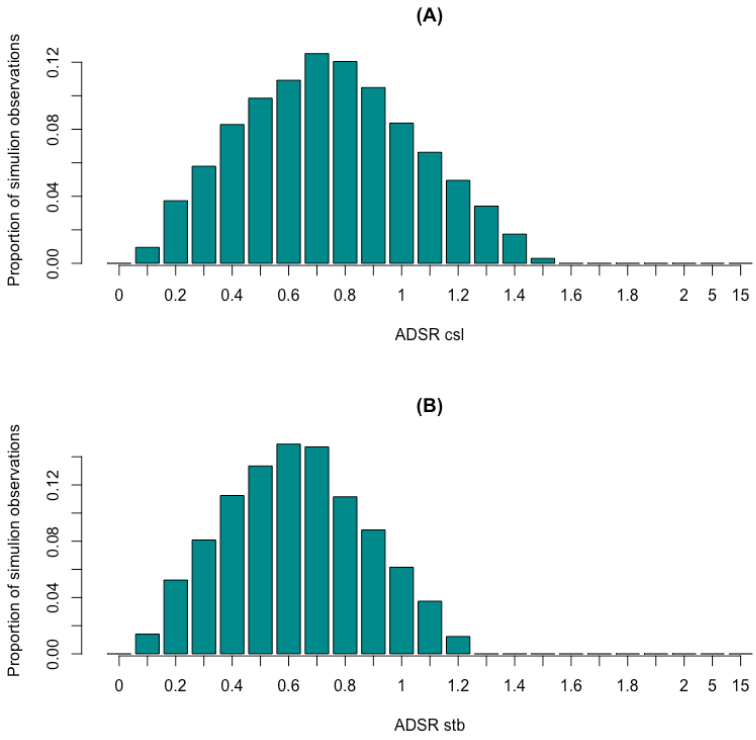

Figure S4: Distribution of ADSR in simulated casual (Panel A) and stable (Panel B) partnerships at the baseline model.

1.3.5 Race-Mixing

We model the probability of partnership between MSM of the same sex by estimating the reported ratio of same-sex partnerships for Black MSM at 90% and for White MSM at 75% through BESURE data.

1.3.6 Sexual Role Preference

Each MSM is assigned an individual sexual role preference (insertive only, receptive only, versatile) at the time of birth (entry to population). The sexual role preferences prohibit the partnerships between two men who are insertive only or those who are receptive only (allowing for 5 partnership configuration). The type of sexual act in partnerships between two versatile men is determined via uniform probability distribution between 0 and 1 (e.g., 50% chance of insertive/receptive act for each man) and will be updated at each time step for their active partnerships. Using data from BESURE, we estimate the proportions of population that fall within each category at 42% insertive-only, 26% receptive-only, and 32% versatile.

1.4 HIV Epidemiological Module

This module governs various aspects of HIV natural history and cascade of care, and it is updated at the end of each time step (week).

1.4.1 HIV Natural History

Upon a successful HIV transmission event, individuals experience a gradual increase in viral load (VL) and move through various stages of disease (Figure 1, main manuscript). We consider three disease stages in absence of ART, including stage 1 (CD4 count > 500 cells/ μL), stage 2 (CD4 count between 200-500 cells/ μL) and stage 3 (CD4 count <200 cells/ μL). Each disease stage is characterized with regard to duration of disease (as a crude measure of CD4 decline over time), mean VL level (determining the level of infectiousness) as well as the HIV mortality rate. In this model, we do not model the dynamics in the number of CD4 counts directly, but rather use the defined disease stages as surrogate marker of VL and mortality level for all HIV+ individuals.

1.4.2 HIV Cascade of Care

The continuum of care for infected individuals is modeled in five levels corresponding to those 1) unaware of their HIV infection, 2) diagnosed with HIV but not linked to care, 3) linked to care but not engaged in care, 4) engaged in care and on ART, and 5) engaged in care but not taking ART (Figure 1, main manuscript).

HIV-positive individuals are subject to a probability of screening for HIV at the beginning of each week. Upon diagnosis with HIV, individuals experience a fixed likelihood of linking to care over the following weeks. Once linked to care, individuals are assumed to engage in HIV care and start ART immediately. Individuals who are adherent to their ARV regimens and do not harbor resistance mutations to the component drugs can generally achieve viral suppression 8 to 24 weeks after ART initiation; rarely, in some patients it may take longer. Taking ART will further lower the disease mortality rate at each disease stage to a certain degree [12–14]. We assume that individuals starting ART through stage 3 (with CD4 count < 200 cells/ μL) will continue to experience the stage 3 mortality level (adjusted with ART reduction factor) for one year before reverting back to stage 2 (and experiencing stage 2 mortality level adjusted with ART reduction factor).

Those on ART can become non-adherent to treatment over time and/or become disengaged in care[1]. These individuals are subject to a weekly probability of reengagement in care and reinitiating ART in the future, but cannot reinitiate ART for 6 months after discontinuation [15]. Once off ART, individuals are assumed to lose viral suppression immediately and to experience a rapid decline in their CD4 counts. For simplicity, we assume that the effect of ART on CD4 count levels is maintained for one year following discontinuation (unless the agent was not previously on ART for a year, in which case the duration of ART is used) – and we also add this amount of time to the individual's "clock" of progression for HIV disease. Thus, for example, an individual starting ART in stage 2 and taking ART for 6 months before discontinuation will go back to stage 2, but the time until progression to stage 3 is prolonged by 6 additional months. We further assume that those starting ART in stage 1 will return to stage 2 if they discontinue treatment, and

[1] At ART discontinuation, if the person has started ART during Chronic disease, they are assumed to return to stage 2 with the same level of infectiousness and will be subjected to the corresponding mortality level. The duration of stage 2 is assumed to be the lesser of the preceding duration of ART (before loss to follow-up) or one year. If the person had started ART during stage 3, they will can return to stage 2 or stage 3 depending on the duration of treatment:

- If duration of treatment is smaller than the time spent in stage 3, agents return to stage 3 with the same level of infectiousness and mortality. The duration of stage 3 is extended for the duration of treatment up to one year.
- If duration of treatment is greater than the time spent in stage 3, agents return to stage 2. The duration of stage 2 will be expanded for the duration of treatment minus time spent in stage 3.

those beginning ART through stage 3 can revert to stage 2 or stage 3 depending on the duration of treatment.

1.5 HIV Transmission module

HIV transmission is evaluated for all active partnerships between HIV-positive individuals and susceptible partners at the end of each week. The probability of transmission is modeled as a function of an infected partner's infectiousness for transmitting HIV, the immunity of the negative partner toward transmission with HIV (through PrEP), potential protection through condom use, and an additional coefficient tuning the overall probability of transmission. HIV infectiousness is modeled as a function of an individual's VL corresponding to his disease stage and care status, as noted in Table 1 of the main manuscript. An individual's immunity to infection is modeled as a function of PrEP use and adherence, ranging from 0 (in absence of PrEP) to 1 (full adherence to PrEP). The probabilities of condom use in casual and stable partnerships are estimated based on reported levels through BESURE (Table S4). Finally, the transmission coefficient captures the baseline probability of HIV transmission per contact and is calibrated to reflect disease prevalence at equilibrium.

Table S4: Reported frequency of condom use in stable and casual partnerships from BESURE.

	Never	Part-time	The whole time
Stable partnership	0.45	0.55	0
Casual partnership	0.47	0.12	0.4

With these definitions, the weekly likelihood of HIV transmission through an active sexual contact is estimated as follow:

$$Ptrans(\mathrm{X},\mathrm{Y},\mathrm{Q}) = C \times X_{Inf} \times Y_{sus} \times (1 - pCondumUse(Q) \times cCondomEffectiveness) \times Y_{sexualPositionCoef}$$

where

Ptrans(*X,Y,Q*): Per week probability of transmission from person *X* (infected) to *Y* (susceptible) in a partnership type Q (stable, casual)

C: Simulation coefficient

Y_{Inf}: Person Y's infectiousness

X_{Sus}: Person *X's susceptibility* toward infection

pCondomUse(*Q*): Probability of using condom in partnership type Q

cCondomEffectiveness: condom effectiveness in reducing the risk of transmission

$Y_{sexualPositionCoef}$: Person Y's increased probability of transmission based on sexual positioning

1.6 GC Epidemiological Module

We consider NG/CT as a 'SIS'-type disease; specifically, individuals become infectious after an initial infection and remain infectious until treatment or spontaneous resolution, at which time they become immediately susceptible to recurrent infection. We assume that NG/CT is spread through sexual (genital-genital, genital-rectal, genital-oral, or oral-rectal) contact, and that infection may be either symptomatic or asymptomatic. Symptomatic individuals experience a fixed probability of seeking care in each week. We include only those care-seeking episodes that would trigger a clinical decision to test for NG/CT at the appropriate site and would result in treatment if the test were positive; other care-seeking episodes (whether for unrelated conditions [e.g., upper respiratory infections] or for symptoms of NG/CT that are either not recognized or would not result in treatment even if the test were positive) are ignored. We assume that individuals remain infectious during the week of treatment and one week thereafter [16–18]. In addition to this symptomatic testing behavior, all MSM (whether infected with NG/CT or not) can further undergo regular screening for NG/CT (i.e., in the absence of symptoms) according to CDC recommended criteria for MSM based on their HIV status, PrEP status, and STI history [19]. The duration of untreated disease (d) is based on literature estimates, and the weekly probability of spontaneous resolution is set to inverse of this duration ($1/d$).

1.6.1 Site of infection

We differentiate three types of NG/CT infections based on the site of infection as Urethral, Rectal or Pharyngeal infections. Given the low degree of overlap for simultaneous infections in multiple sites, and the higher likelihood of symptomatic disease in urethral infections for those co-infected with rectal and pharyngeal infections, we only allow for a single-site NG/CT infection in each individual and will exclude the possibility of simultaneous infections in various sites (allowing for no reinfection while the original infection lasts). Each type of infection is further associated with a specific likelihood of developing symptomatic disease (Table 1 of the main manuscript). Among HIV- individuals, a rectal/urethral NG/CT can increase the transmissibility of HIV to sexual contacts among HIV infected MSM and also increase the susceptibility for HIV acquisition among HIV uninfected MSM.

1.6.2 NG/CT Transmission dynamics

NG/CT-infected individuals can transmit the disease to other individuals through exiting network of sexual contacts (previously built and calibrated for the HIV model). Due to complications in conceptualizing all various pathways for transmission of disease from one site to another with regard to different types of sex acts, unknown level of individuals' preferences for each sexual role and the degree of versatility to change this role in each partnership, in addition to the lack of data informing the risk of NG/CT infection through each mode of transmission, we adopt a simplifying assumption to combine various modes of transmission for all types of infections through a single transmission event modeled over each active sexual contact between an infected and uninfected MSM at each time step. Upon transmission with NG/CT, the clinical site of the recipient infection is randomly assigned in such a way as to replicate the relative incidence of infection at each site as estimated from local surveillance report in Baltimore City (see Table 1 of the main manuscript).

1.6.3 Computing the probability of presenting to STI care

MSM may present to HIV/STI care providers (e.g., STD clinics, community health centers, HIV counseling programs) for a variety of reasons, and get tested for HIV and other STIs. We model visits for STI screening as a fixed weekly probability that reflects an individual's age-group (modeled in 12 classes for MSM age 15 to 75) and sexual activity level (modeled in 3 classes of sexual activity), such that younger MSM with higher propensity of partnerships experience a higher likelihood of visits [20,21].

We let *S* represent the individuals' sexual activity class (values ranging from 1 to 3 representing low-, medium- and high-activity classes) and we let A represent the individual's age-group (values ranging from 1 to 12 representing age groups of 5 years each: [15,19], [20-24], …, [70,75]). Finally, according to previous assumptions for lower level of access to HIV care among Black MSM compared to White MSM in the baseline simulation model, we modify the probability of accessing to STI care (*pAccessCare*) by race (R) set at 50% for Black MSM relative to White MSM [22]. Given these assumptions, an individual's probability of presenting to STI care (*PPSC*) at each week is computed as follow:

$$PPSC\ (\mathrm{S},\mathrm{A},\mathrm{R}) = {}^{(13-\mathrm{A})}/_{12} \times {}^{(\mathrm{S})}/_{3} \times pAccessCare(\mathrm{R}) \times C$$

where C is the fixed coefficient for fine-tuning the probability of presenting to STI care.

1.7 PrEP module

PrEP Eligibility criteria: Our primary outcome for the current analysis is the projected incidence of HIV after 20 years of delivering PrEP to MSM in Baltimore City. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the added benefit of targeting PrEP at individuals diagnosed with NG/CT. In all three scenarios, indication for PrEP use (eligibility) is considered in accordance with CDC recommendations [23] and Baltimore City's PrEP guidelines [24].

The CDC guidelines for PrEP use among MSM use the following criteria as indications for PrEP: sexually active HIV negative adult MSM who are not in a monogamous partnership with an HIV-negative male partner and who in the last 6 months: report any condomless anal sex, have any STI reported or diagnosed, or report having an ongoing sex partner with HIV [23]. The PrEP guidelines in Baltimore City further suggest that all HIV negative MSM who 1) may not have access to condom or always ask a partner to use a condom, 2) are diagnosed with a STI in the last 6 months, 3) are in a serodiscordant relationship with a HIV-infected partner (who may or may not be on HIV treatment), 4) are unsure of HIV-status of their sexual partner, or 5) inject drugs or are in a sexual partnership with a person who inject drugs should consider PrEP. As such, we modelled the criteria for PrEP eligibility among MSM to include HIV-negative MSM who are diagnosed with NG/CT in the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual partnership in the last 6 months.

2 SIMULATION CALIBRATION

Individual-level parameters in our models fall into two categories: "fixed" parameters estimated based on available literature or data, and "variable" parameters that are unknown and will be calibrated based on epidemiological setting. Fixed (known) parameters include those associated with the natural history of HIV (such as viral load levels in each disease stage) and those defining behavioral characteristics (e.g., likelihood of condom use). Variable parameters include descriptors of HIV and NG/CT transmission and

care that are defined at the individual-level and will be calibrated to provide the corresponding calibration targets (at the population-level) from Baltimore City (e.g., tuning the individual's probability of presenting to care for HIV screening to provide the target proportion of infected population diagnosed in Baltimore City). Table 1 in the main manuscript includes a list of main calibration targets for HIV and NG/CT modules.

2.1 Calibration Targets

2.1.1 HIV prevalence and continuum of care

Using the latest report of public HIV surveillance data from Baltimore City (year 2012) [2], we estimate the prevalence of HIV among MSM at a total of 3329 people, which corresponds to a prevalence of 22% in our simulated population. Furthermore, we estimate the reported proportion of HIV-infected MSM in each step of the cascade at 86% for those diagnosed but not linked to care, 62% for those linked to care but not engaged, 50% for those engaged but not on ART, 39% for those on ART but not virally suppressed and finally 27% for those virally suppressed.

2.1.2 NG/CT incidence

In this section, we provide details of our estimation procedure for NG/CT incidence using data made available to us through several sources including 1) the gonorrhoea Surveillance dataset, 2) STD Surveillance Network, and 3) BCHD facility dataset in Baltimore City.

Estimating the annual diagnosis of gonorrhoea infection in Baltimore City: The gonorrhoea Surveillance dataset includes all males residing in Baltimore City who were reported to the Baltimore City Health Department for infection with gonorrhoea at one or more anatomic site, regardless of sex partner gender, beginning with cases diagnosed on 1/1/09 and ending with cases reported through 5/31/16. Due to changes in testing technology, we only consider data from 2011 and later for estimating gonorrhoea diagnosis as that is when the STD clinics started using NAATs for extragenital swabs (due to the lab becoming validated for this) which is more in line with practices moving forward. We further restrict the data to the end of 2015, to cover the annual number of diagnosis in each full year (Table S5). We further analyze this data by reported site of infection and estimate the range of reported gonorrhoea diagnosis in each body site (Table S6).

Table S5: Annual number of reported gonorrhoea diagnosis among men in Baltimore City.

	2011	2012	2013	2014	2015
Gonorrhoea diagnosis	1139	901	1052	1083	1297

Table S6: Annual gonorrhoea diagnosis among men by site of infection in Baltimore City.

Site of infection	Lower bound	Upper bound
Urethral	681	1026
Rectal	46	83
Pharyngeal	58	151

Adjusting for MSM risk group: The surveillance dataset does not include information on gender of sex partners for all persons diagnosed with gonorrhoea infection. This information is however available for a

subset of population through STD Surveillance Network (SSuN). SSuN attendees are randomly selected from MSM diagnosed with gonorrhoea who will then agree to complete a SSuN interview. Within this group, 26% to 30% of all male patients identified themselves as MSM in Baltimore City.

Adjusting for non-overlapping Chlamydia infections: The BCHD facility dataset provides information on diagnosis of gonorrhoea or chlamydia infection among all male patients visiting the two STD clinics in Baltimore City. This data is further stratified for MSM by including men who reported male sex partners in the past 3 months OR self-identified as gay or bisexual. For patients who visited the clinic multiple times, if he was classified as MSM at any visit, we included all his clinic visits. The dataset provides information on all episodes of visit and diagnosis with gonorrhoea or chlamydia infection among these men. Based on the reported number of diagnosis, we estimate the proportion of diagnosed chlamydia infection that did not overlap with gonorrhoea infection relative to overall number of gonorrhoea diagnosis at 40%, and use this value to adjust the annual number of gonorrhoea diagnosis among MSM to include non-overlapping chlamydia infections as well. This estimate also agrees with the reported level of chlamydia infection relative gonorrhoea infection in Baltimore City through the STD Surveillance Network (SSuN) 2013 [25].

Adjusting for proportion of symptomatic cases not seeking care: In order to derive the true incidence of disease from the current estimates of the number diagnosis, we further adjust our estimate to account for the proportion of symptomatic cases not seeking care. Based on literature, we estimate that approximately 60% symptomatic population may not seek direct care for their disease (56% for Urethral infection, 60% for Rectal and 70% for Pharyngeal infection) [26], and inflate the number of symptomatic cases in our sample (approximately 78% of sample) by 250% to account for these cases.

Adjusting for the number of asymptomatic infection: Given the restrictions in capturing the underlying level of asymptomatic disease from the estimated of NG/CT diagnosis, we rely on our estimate of the symptomatic NG/CT incidence, and assume that each episode of NG/CT infection is associated with a 74% likelihood of symptomatic infection for urethral, 20% for Rectal, and 10% for Pharyngeal disease [26–28]. Based on this assumption, we derive the estimate for annual incidence of NG/CT among MSM by site of infection as follow:

- Incidence of urethral infection [725 – 1135] Person/year
- Incidence of rectal infection [144 – 259] Person/year
- Incidence of pharyngeal infection [327 – 852] Person/year

Challenges in interpreting local estimates: Despite general expectations, our estimated ratio of rectal/pharyngeal to urethral infections is very small. This pattern does not agree with the previously reported prevalence of extragenital relative to genital NG/CT in different populations that estimate the average prevalence ratio of rectal to urethral infections at 4.1 (ranging from 2.43 to 6.23) and pharyngeal to urethral infections at 1.5 (ranging from 1.35 to 1.71) [29–31]. In a previous analysis of SSuN data, researcher reported a similarly low proportion of extragenital to genital NG/CT infections among MSM attending STD clinics [32], and attributed it to low rate of extragenital NG/CT screening at STD clinics that results in missing those infections [33].

Given that our estimates of the genital and extragenital NG/CT infections based on local datasets from Baltimore City are more in line with the observed trends in the SSuN data, we believe that the same pattern of underestimation is evident for the true incidence of extragenital NG/CT infection in this population. In order to fix this problem, we chose to rely on the estimated incidence of genital (urethral)

NG/CT infection from the surveillance dataset in Baltimore City (assuming appropriate level of genital-site testing/screening and reporting), and to estimate the incidence of rectal and pharyngeal infections by applying the reported prevalence ratio of each infection site relative to urethral infection.

Estimating the incidence of rectal and pharyngeal infection: We assume that diagnosed NG/CT will be treated very rapidly, such that the relative duration of disease is driven by the proportion of infections for which people are not treated - whether because they are asymptomatic, symptoms are not sufficient to drive care-seeking, or the clinical presentation (e.g., sore throat) does not prompt testing or treatment for NG/CT. Screening is assumed to have relatively little impact on the *relative* duration of infection (i.e., screening can occur, but it does not pick up so many more prevalent urethral infections than pharyngeal infections, for example, that it drives the ratio of disease duration in the population to a significant degree). We further assume that the asymptomatic disease is likely to go undetected and therefore 26% of urethral infections, as well as 80% of rectal and 90% of pharyngeal infections will go untreated [26–28].

Based on these assumptions, we derive the incidence ratios based on prevalence ratios as follow:

- Incidence ratio of rectal to urethral disease: 4.08 (prevalence ratio) * 0.26 /0.8 (proportion of untreated cases) = 1.33
- Incidence ratio of pharyngeal to urethral disease: 1.5 (prevalence ratio) * 0.26 /0.9 (proportion of untreated cases) = 0.43

Using the estimated incidence ratios, we estimate the incidence of rectal and pharyngeal NG/CT among MSM as follow:

- Incidence of urethral NG/CT among Baltimore's MSM: [735-1135] Person/year
- Incidence of rectal NG/CT among Baltimore's MSM: [998-1505] Person/year
- Incidence of pharyngeal NG/CT among Baltimore's MSM: [326-492] Person/year

2.2 Calibration procedure

Upon collection of all individual-level data and incorporation into the model (fixed parameters), we calibrated the model as a whole against population-level targets (above) to ensure that the model provides realistic outputs. This was done via a random search mechanism to find the best combination of parameter values that minimizes the observed difference between simulated outputs and the calibration targets.

Burn-in Period: The model starts from a randomly generated population of MSM with no active partnership at time zero with a randomly assigned pattern of HIV infection (randomly according to age, race and location of residence). In order to create a realistic pattern of sexual partnerships with age, we allowed the original population to age and evolve for at least one generation before reaching a stable level of HIV incidence in the absence of PrEP – thus generating a full burn-in period of 100 years (a decision made on an a-priori basis).

2.3 Calibrating partnerships

BESURE surveys (2004 – 2014) provided the main source of local information available on the network of MSM partnerships in Baltimore. The data included aggregate information on the reported number of sexual partners (by age group) and type of those partnerships in the last 12 months. Assuming a fixed mixing structure over time, we used this information to calibrate the individual-level likelihood of engaging in a stable or casual partnership at each simulated time step (week). We further used the coefficients of sexual activity to calibrate the right and left tail of the partnership frequency distribution

(for those MSM reporting 0 or more than 5 partners in a given year). The partnership calibration results are summarized in Figure S5.

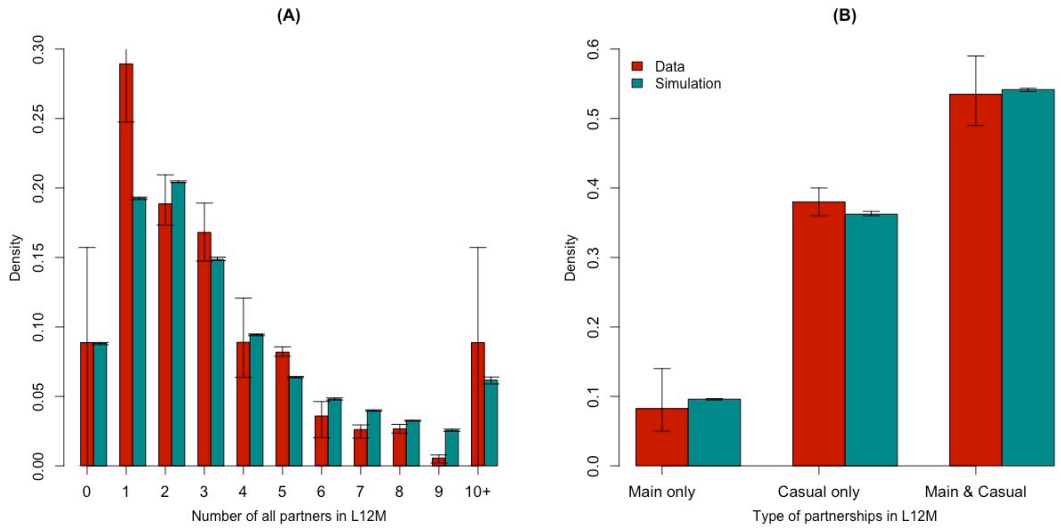

Figure S5: Model calibration to partnership data. Shown are the mean values of simulations (in green) compared against empirical data (in red). The error bars around simulated values represent the 95% uncertainty range of observations around each simulated measure, and the error bars around the data represent the range of annual observations through the 4 BESURE surveys from 2004 to 2014.

2.3.1 Frequency of partnerships by age and sexual activity

The age-dependent coefficients of partnerships in each sexual activity class were calibrated to accurately portray the right and left tails of the partnership frequency distribution for all MSM and in each age group. The calibration results are summarized in Figure S6.

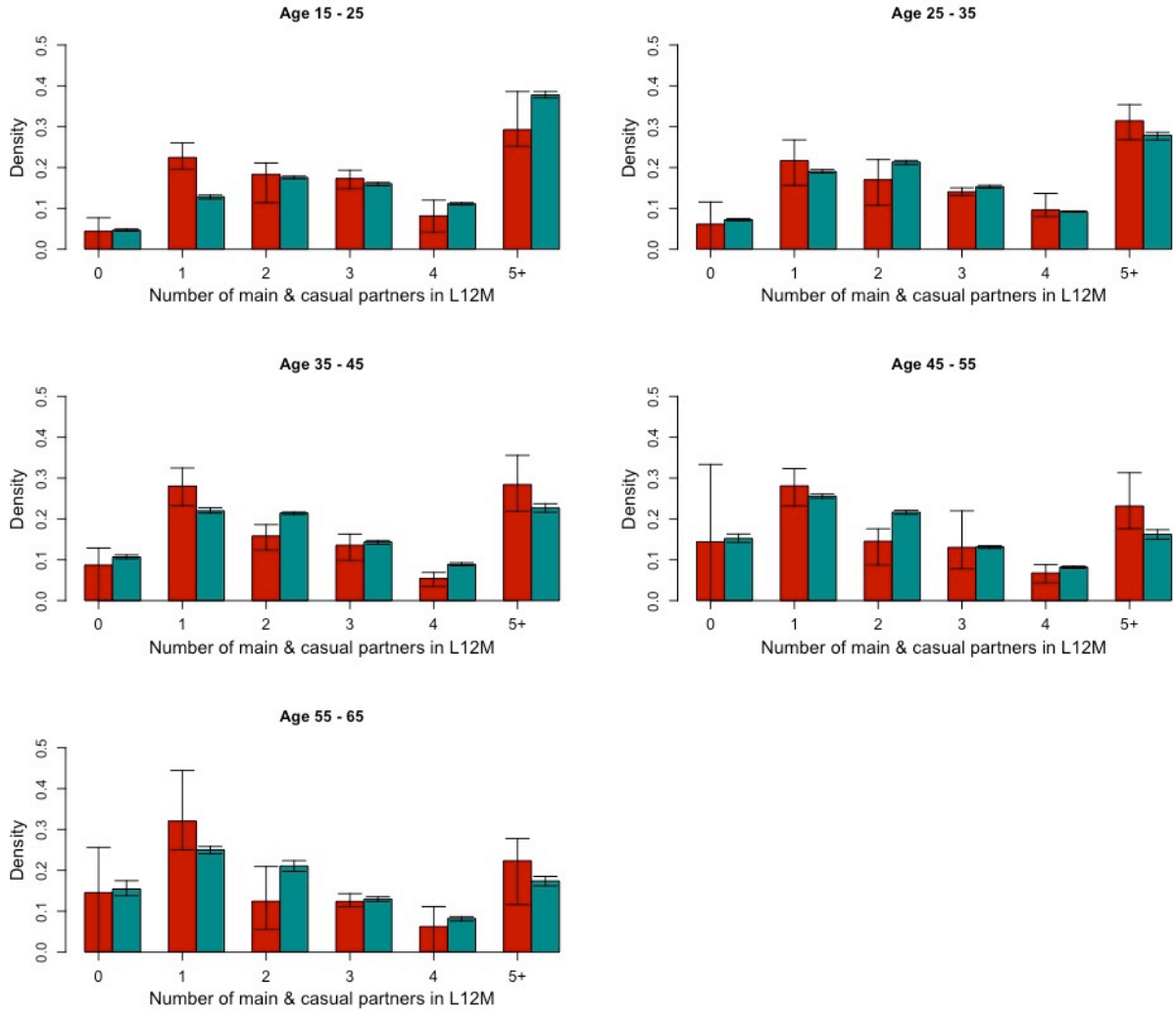

Figure S6: Frequency of reported partnerships in each age group in the last 12 months (L12M), comparing model results to the data against which the model was calibrated. Shown are the mean values across all simulations (in green) compared against empirical data (in red). The error bars around simulated bars represent the 95% uncertainty range of simulated values and the error bars around the data represent the range of annual observations through the 4 BESURE surveys from 2004 to 2014.

There were conceptual challenges with the use of BESURE data as the main data source for calibrating the network of sexual partnerships. Specifically, BESURE applies a venue-based sampling method, which is more likely to capture a representative sample of young (as opposed to older) MSM. Based on discussions with the BESURE investigators, we felt that the general population of older MSM was likely to have lower numbers of sex partners than reported in BESURE and therefore allowed for a lower frequency of partnerships among older MSM.

Furthermore, given the strong bimodal distribution of partnerships among young adults, we were not able to replicate these empirical distributions precisely and thus chose to minimize the estimation error at the tails of this distribution. To further assist the calibration of tails, we defined sexual activity classes

according to the mean number of casual partnerships to represent natural heterogeneity in in individual-level partnerships. Addition of high versus low/medium sexual activity classes allowed us to calibrate the overall frequency of partnerships in each age group with more precision. Figure S7 represents model projections of the frequency of partnerships in each sexual activity class. This figure illustrates that, after calibration to BESURE data, the low and medium sexual activity classes behave very similarly (and may likely be represented equally well as a single class). Given the lack of representative data against which to explicitly calibrate these distributions, this presumed distribution of sexual partnerships is an assumption/limitation of the current model.

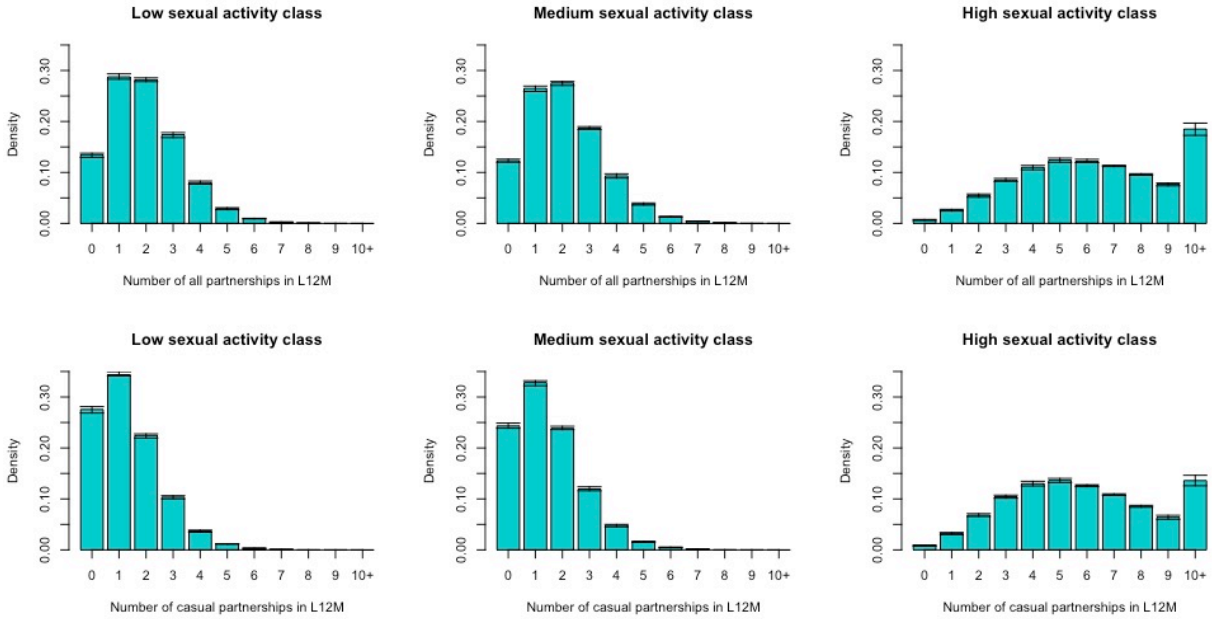

Figure S7: Model projections of the frequency of partnerships in the last 12 months (L12M) in each sexual activity class. Panels represent the distribution of all (top row) and casual (bottom row) partnerships in low, medium and high sexual activity classes. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

2.4 Calibrating HIV and NG/CT epidemiology

Using the population-level targets for annual diagnosis and incidence of NG/CT as well as HIV prevalence and cascade of care (section 3.1), we calibrate the simulation model to provide these outcomes within an acceptable range (Figure S8 A through D).

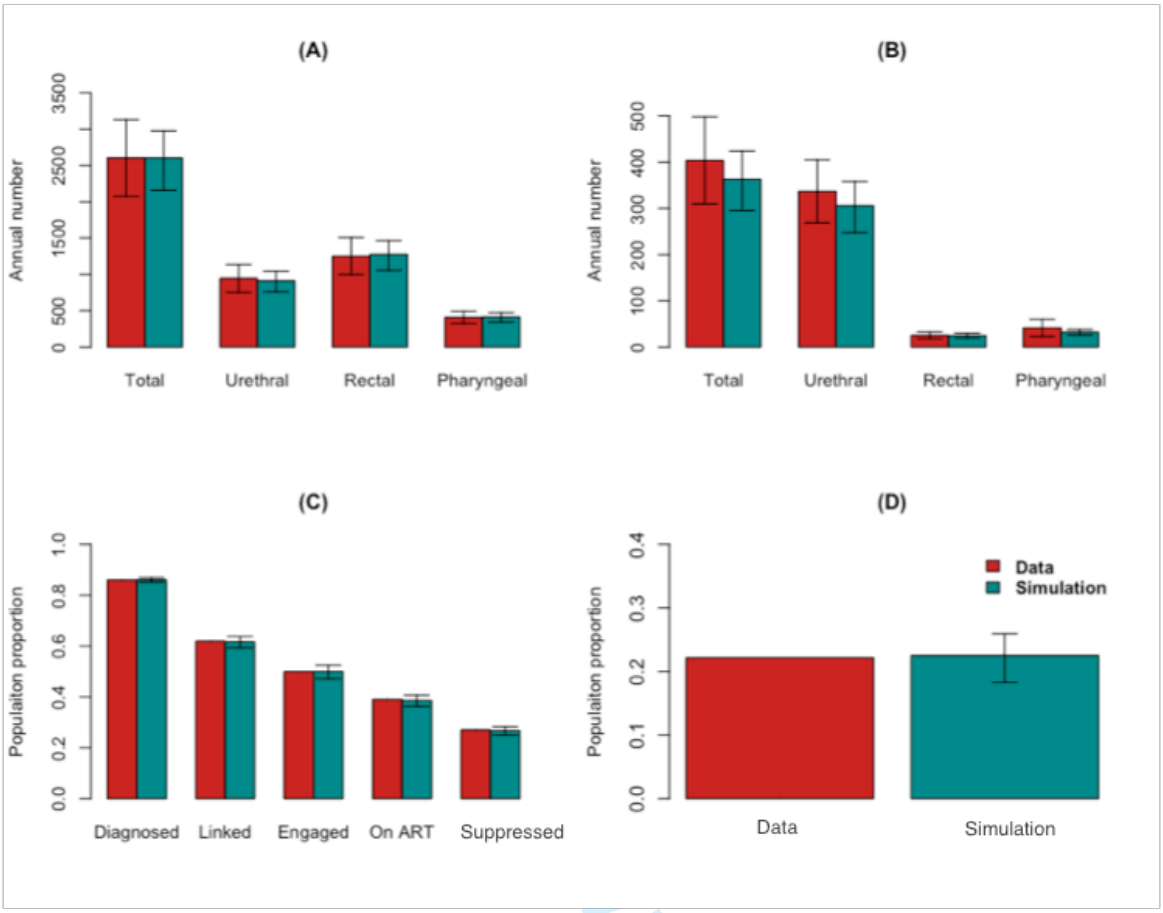

Figure S8: Closeness of model fit to epidemiological data for (A) annual incidence of NG/CT, (B) annual diagnosis of NG/CT, (C) Cascade of HIV Care, and (D) HIV prevalence. These graphs illustrate the effectiveness of the calibration procedure and are not a validation of the underlying data or the model itself. Shown are the mean values of 200 simulations (in green) compared against empirical data (in red). The error bars around simulated values represent the 95% uncertainty range of observations around each simulated measure, and the error bars around the data in panel A&B represent the range of annual observations through the Baltimore City surveillance dataset (2011 – 2015). Data used for calibration in panel C&D is only available as point estimate in year 2012.

Given the lack of data regarding the anatomical site of infection and the relative frequency of oral-only versus oral-plus-anal versus anal-only sex to model site-specific transmission dynamics for NG/CT, we adopted a simplified approach that does not fully capture the complete transmission dynamics but should result in the appropriate distributions of NG/CT infection at each anatomical site. For this purpose, we combined various modes of transmission for all types of infections through a single transmission event modeled over each active sexual contact between an infected and uninfected MSM at each time step. Upon transmission with NG/CT, the clinical site of the recipient infection was randomly assigned in such a way as to replicate the relative incidence of infection at each site as estimated from local surveillance report in Baltimore City (see Table 1). The final calibration results in a probability of 35% for urethral, 49% for rectal and 16% for pharyngeal infections modeled upon each successful transmission event. Since the goal of this model is not to comprehensively represent the dynamics of NG/CT transmission but rather to estimate the impact of PrEP strategies for HIV that incorporate NG/CT screening and treatment, we

adopted this simplified approach (which may have some inaccuracies regarding the specific transmission dynamics but should result in the appropriate marginal distributions of infection by each anatomical site), rather than incorporating data-free assumptions about the relative frequency of oral-only versus oral-plus-genital sex and the relative transmissibility of NG/CT from each anatomical site to the other.

2.4.1 HIV and NG/CT co-infection:

As described above, our calibration targets were limited to the marginal distributions of HIV and NG/CT infections among MSM, and excluded the co-infection rates due to data unavailability. Unpublished results from analysis of STD Surveillance Network (SSuN) data [34] from 2008 to 2013 in 12 jurisdictions suggest that 8% of patients diagnosed with NG had a previous HIV diagnosis, and among the remaining individuals diagnosed with NG, 69% received an HIV test within 30 days of their STI diagnosis. However, the proportion of patients diagnosed with HIV coinfection on that test is not recorded. We therefore took a conservative approach, assuming that the only correlations between HIV and NG/CT would be induced by age- and race-specific assortative mixing, plus differentiation of individuals into three different sexual activity classes. Figure S9A represents the projected levels of HIV and NG/CT prevalence at the end of each year in the model, corresponding to 22% of MSM infected with HIV (calibration target), 10% infected with NG/CT (calibration target) and 2.5% infected with HIV and NG/CT (a cross survey estimate). Figure S9B represents the proportion of incident cases who were co-infected with NG/CT and HIV at the time of HIV or STI infection. For example, this figure suggests that 20% of incident HIV cases are co-infected with NG/CT at the time of disease transmission. These results suggest that our underlying sexual activity assumptions do not impose a high rate of correlation between the two diseases; as a result, our estimates of the impact of STI-based PrEP may be conservative. To the extent that HIV and NG/CT co-locate among similar populations beyond age, race, and tertiles of sexual activity, one would expect that NG/CT-targeted PrEP strategies would have even greater impact than projected in this model.

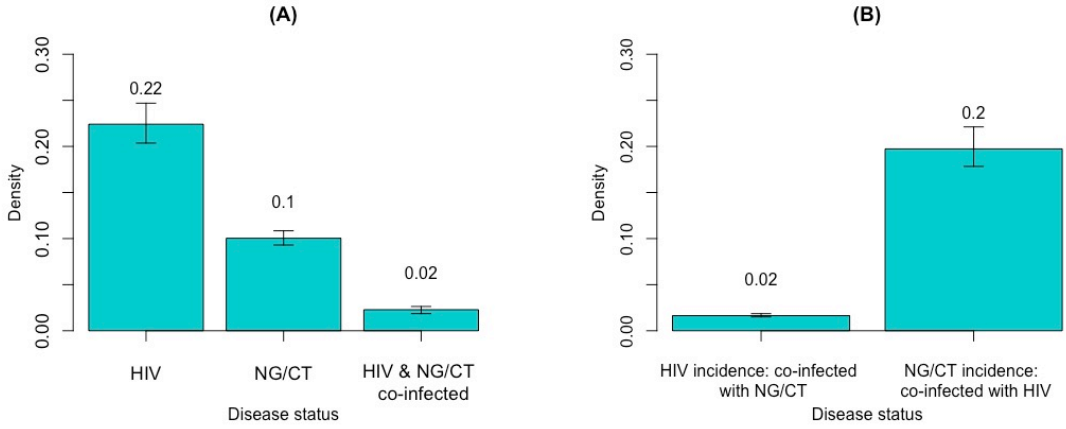

Figure S9: Model projections of the distribution of HIV, NG/CT, and coinfection among MSM (Panel A) and the proportion of HIV and NG/CT incident cases coinfected at the time of transmission (Panel B). Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

2.5 Complete list of model parameters

Table S7 provides a complete list of model parameters and values.

Table S7: Complete list of model parameters and values.

Parameter	Value	References
Partnerships		
Proportion of population in each sexual activity (SA) **class**	0.33	
Rate of casual partnership formation in each sexual activity class relative to the medium sexual activity class	Low sexual activity class 0.85 High sexual activity class 5.0	
Rate of casual partnership by age group	[15-25): 0.5 [25-45): 0.3 [45-55): 0.25 [55-75+): 0.3	
Age Mixing (Absolute different in square root of ages) • Stable partnerships • Casual partnerships	 0.6 0.73	 [35]
Race mixing (Likelihood of mixing with a partner of the same race) - Black & Black - White & White	 0.9 0.75	[35]
Likelihood of condom use - Stable partnerships - Casual partnerships	[Never, Partially, Always] [0.45, 0.55, 0.00] [0.47, 0.12, 0.41]	 [35]
Sexual position preference - Insertive only - Receptive only - Versatile	 0.42 0.26 0.32	[35]
Transmission coefficient for insertive relative to receptive sexual position	0.384	[36]
NG/CT		
Proportion of cases symptomatic - Urethral - Rectal - Pharyngeal	 74% 20% 10%	 [27] [26,37] [28,37]
Duration of infection in the absence of treatment	[3 – 12] months [2]	[16,38,47–51,39–46]
Duration of treatment	2 weeks	[16–18]
Regular GC screening intervals for HIV+ MSM on ART - All MSM - MSM with a history of NG/CT in the last 6 months	 12 months 6 months	 [52]
Likelihood of compliance with CDC guideline for NG/CT screening	40%	[53–58]
Efficacy of condoms to prevent NG/CT transmission	70%	[16,59,60]

[2] Values are selected over uniform distributions across the ranges presented

Increase in HIV transmissibility (from urethral or rectal infection)	[1.5 – 2] fold [3]	[61–65]
Increase in HIV susceptibility (from urethral or rectal infection)	[1 – 2.5] fold [3]	[16,28,65,66]
Probability of NG/CT transmission per act	0.294	Calibrated to provide the incidence of NG/CT
Proportion of NG/CT infections assigned to each site - Urethral - Rectal - Pharyngeal	 35% 49% 16%	Calibrated to provide the site-specific incidence of NG/CT
Weekly probability of symptomatic NG/CT testing - Urethral - Rectal - Pharyngeal	 0.009 0.001 0.04	Calibrated to provide the site-specific diagnosis of NG/CT
Weekly probability of screening high-risk (according to age and sexual activity class) MSM for HIV and NG/CT	0.014	Calibrated to provide the annual diagnosis of NG/CT and HIV
Probability that NG/CT screening only at urethral site	0.94	Calibrated to provide the relative diagnosis of extragenital to genital NG/CT
Relative likelihood of NG/CT screening among Black MSM relative to White MSM	0.5	[22]
HIV		
Disease stage duration - Stage 1 (CD4 >500 cells/µL): Acute - Stage 2 (CD4 200-499 cells/µL): Chronic - Stage 3 (CD4 <200 cells/µL)[3]: Late stage	 [6 – 9] weeks [3] [8 – 10] years [1 – 3] years	[5,67,68] [5,69] [5,67,69]
Time from ART initiation to full viral suppression	[4-24] weeks [3]	[70]
Time from ART discontinuation to pre-ART CD4 nadir[4]	ART treatment duration up to one year	[71–74]
Mortality rate [3] - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART	 5 per 1000 person years 1/duration of stage 3 58%	[12–14]
Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART - Stage 3, no ART - On ART, partially suppressed - On ART, fully suppressed	 6.5 4.5 5 3.5 1.5	[5]
Efficacy of condoms to prevent HIV transmission	80%	[75,76]
Infectiousness per sexual contact	$2.45^{(\log(VL)-4.5)}$	[5]

[3] Mortality rate in stage 3 is defined as 1/(duration of stage 3).

[4] Infectiousness assumed equal to that of stage 2

Individual's weekly likelihood of engagement in HIV care	0.00577	[77–79]
Weekly probability of ART discontinuation	0.0015	[80]
Gap in care after ART discontinuation	26 weeks	[15]
Weekly probability of - Screening for HIV only (not NG/CT) - Linkage to care (if HIV-positive and not linked) - Starting ART (if engaged)	 0.0065 0.0065 0.095	 Calibrated to provide the HIV cascade of care
Relative likelihood of accessing HIV care among Black MSM	0.5	[22]

2.6 Additional analysis

Since sexual activity class is a modeling construct rather than a measurable feature of an individual (see section 1.3.1), there are no data to describe assortative mixing by activity class per se. Similarly, lacking data on serosorting among primary and casual partnerships, we did not explicitly incorporate this into the model. In order to further elucidate model dynamics, we have generated additional figures to report the simulated frequency of sexual partnerships by sexual activity classes (e.g., High-High, High-Med, etc.) and also HIV serostatus (Figure S10 and S11). Note that, since sexual activity class was assumed to reflect casual partnerships only, the frequency of stable partnerships is similar and randomly distributed across all classes (with partnerships across classes being twice as likely as partnerships within classes, reflecting the laws of probability with random assortment).

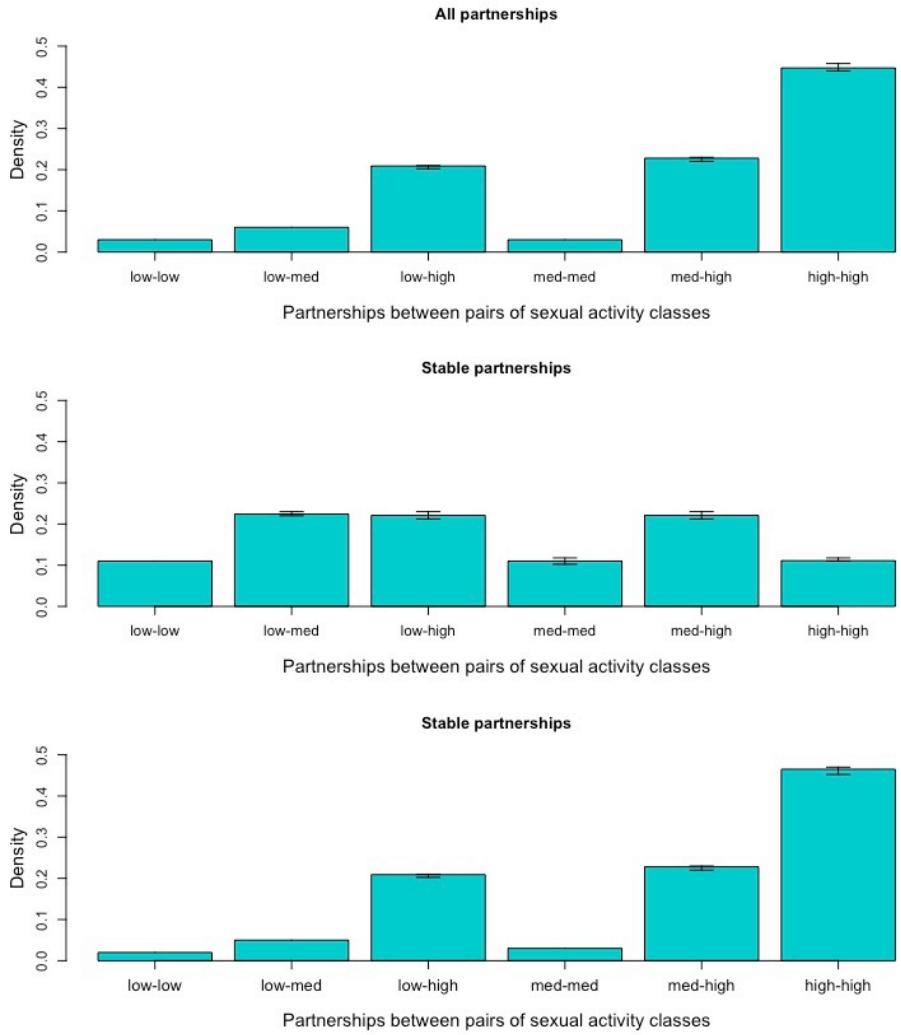

Figure S10: Model projections of the distribution of partnerships among MSM by sexual activity class. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

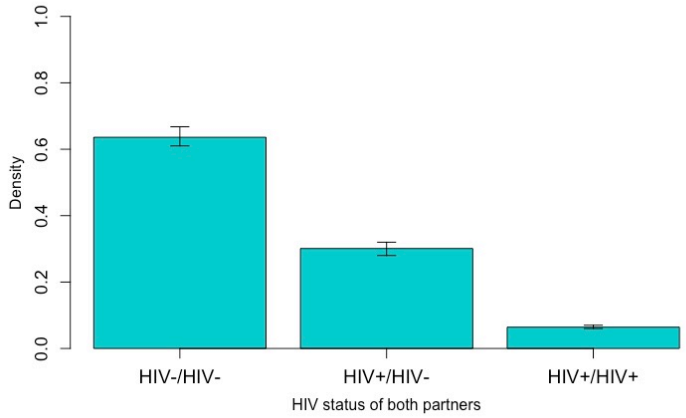

Figure S11: Model projections of the distribution of partnerships by HIV status. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

In order to better illustrate the implications of these modeling assumptions on impact of STI targeted PrEP, we also checked the distribution of MSM receiving PrEP in the model by sexual activity class an age (Figure S12). As expected, targeting PrEP at MSM diagnosed with STIs provides an efficient approach for providing PrEP to high-risk individuals in the high sexual activity class and younger age groups (Figure S12-Panels A & D)

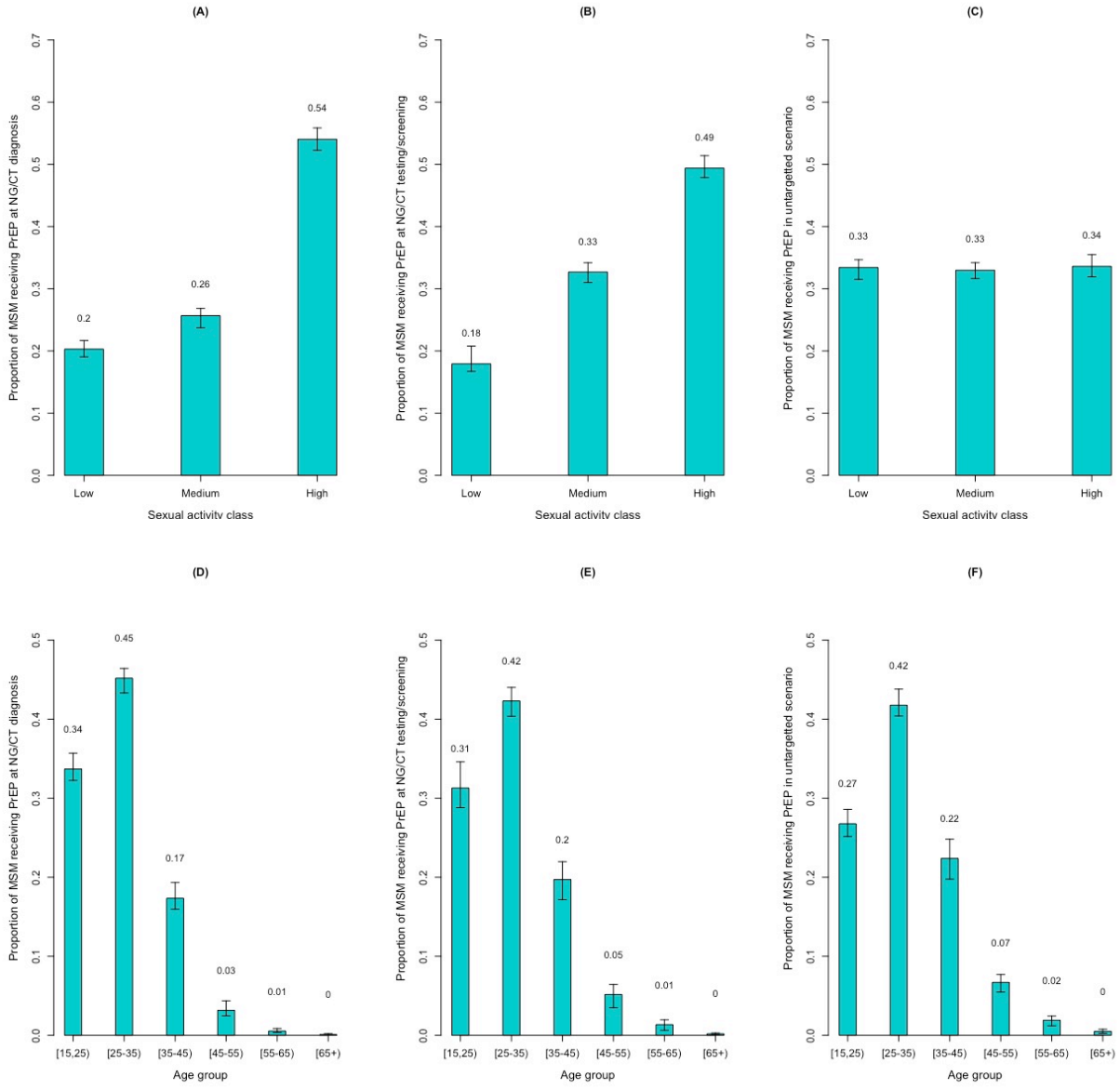

Figure S12: Model projections of the distribution of MSM receiving PrEP in each sexual activity class (top row) and each age group (bottom row) in each PrEP scenario. Panels A and D depict this distribution under NG/CT-targeted PREP; panels B and E illustrate PrEP evaluation at NG/CT screening and testing; and panels C and F represent untargeted PrEP. Shown are the mean values of simulations (in green) with error bars representing the 95% uncertainty range of observations around each simulated measure.

3 SENSITIVITY ANALYSIS

One-way sensitivity analysis of simulation results was performed with regard to all model parameters (listed in Table S7). For this purpose, we changed each parameter to +/- 25% of its original value, one at a

time (keeping all others fixed at the original value) and evaluated the main simulation outputs after such variation. The primary output of interest for the sensitivity analysis was HIV incidence at 10 years without PrEP (baseline) and with PrEP (under each PrEP campaign). For this analysis, we assumed an uptake and adherence of 60% to PrEP. The tornado graphs (Figure S13 to S16) represent the results of the one-way sensitivity analysis. Figure S13 presents the results for HIV incidence at year 10 in Baseline (absence of PrEP), and Figure S14 through Figure S16 present HIV incidence in year 10 of a PrEP campaign targeting MSM at the time of NG/CT-diagnosis (Figure S14), at the time of NG/CT screening (Figure S15) or through a community-wide campaign (Figure S16).

Assuming a threshold of 25% to detect significant changes, the projected HIV incidence at baseline and in absence of PrEP (Figure S13) was sensitive to variation of parameters relating to 1) transmission of HIV including the coefficient of HIV transmission, viral load as a measure of infectiousness, and condom use and effectiveness; 2) the coefficient of NG/CT transmission; and 3) parameters describing overall sexual activity including the probabilities of starting new partnerships, and the level of sexual activity in the most sexually active class. Similar behavior was observed in scenarios modeling the implementation of PrEP at NG/CT diagnosis (Figure S14), at the time of NG/CT screening (Figure S15) or through a community-wide campaign (Figure S16). None of the sensitivity analysis scenarios resulted in significant variation (>25%) of HIV incidence in PrEP scenarios compared to the baseline.

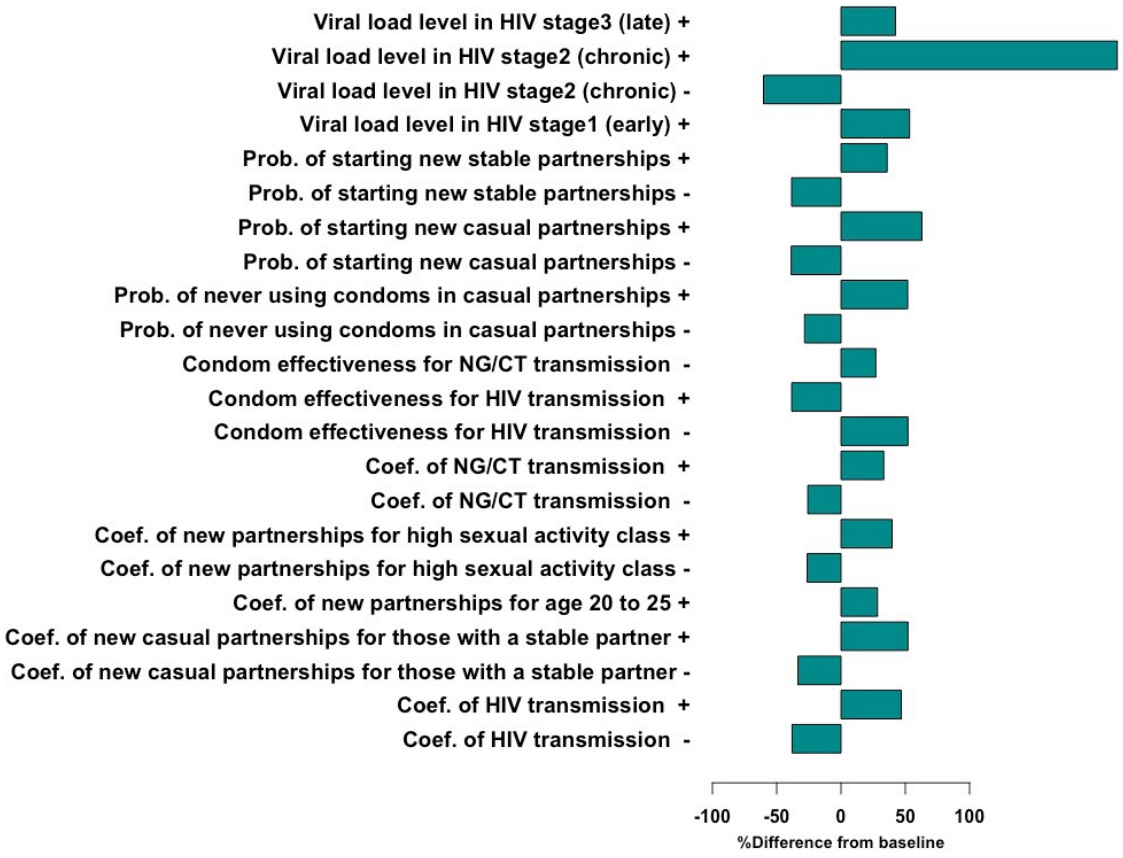

Figure S13: Sensitivity analysis of HIV incidence at year 10 to variation of model parameters in the Baseline (absence of PrEP) scenario. Input parameters are listed on the left, +/- corresponding to 25%

increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant.

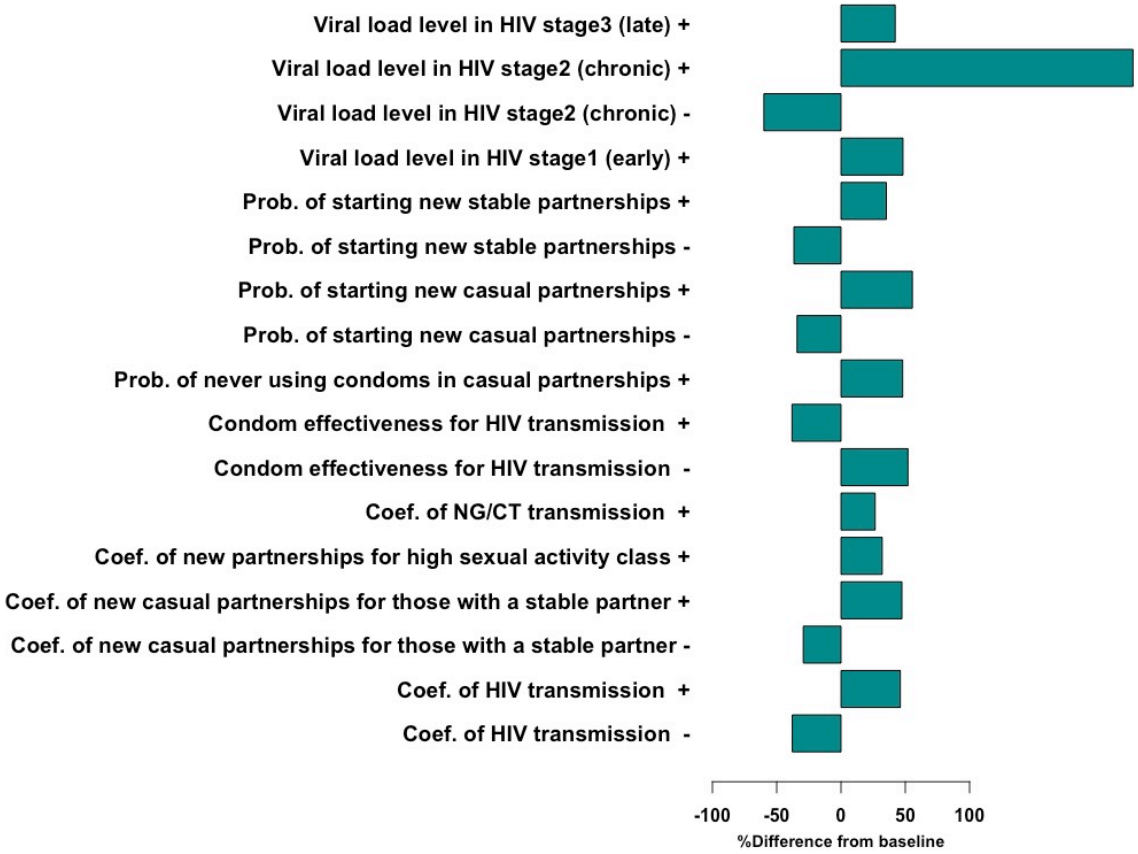

Figure S14: Sensitivity analysis of HIV incidence in year 10 to variation of model parameters in the scenario of a PrEP campaign targeting MSM at the time of NG/CT-diagnosis. Input parameters are listed on the left, +/- corresponding to 25% increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant

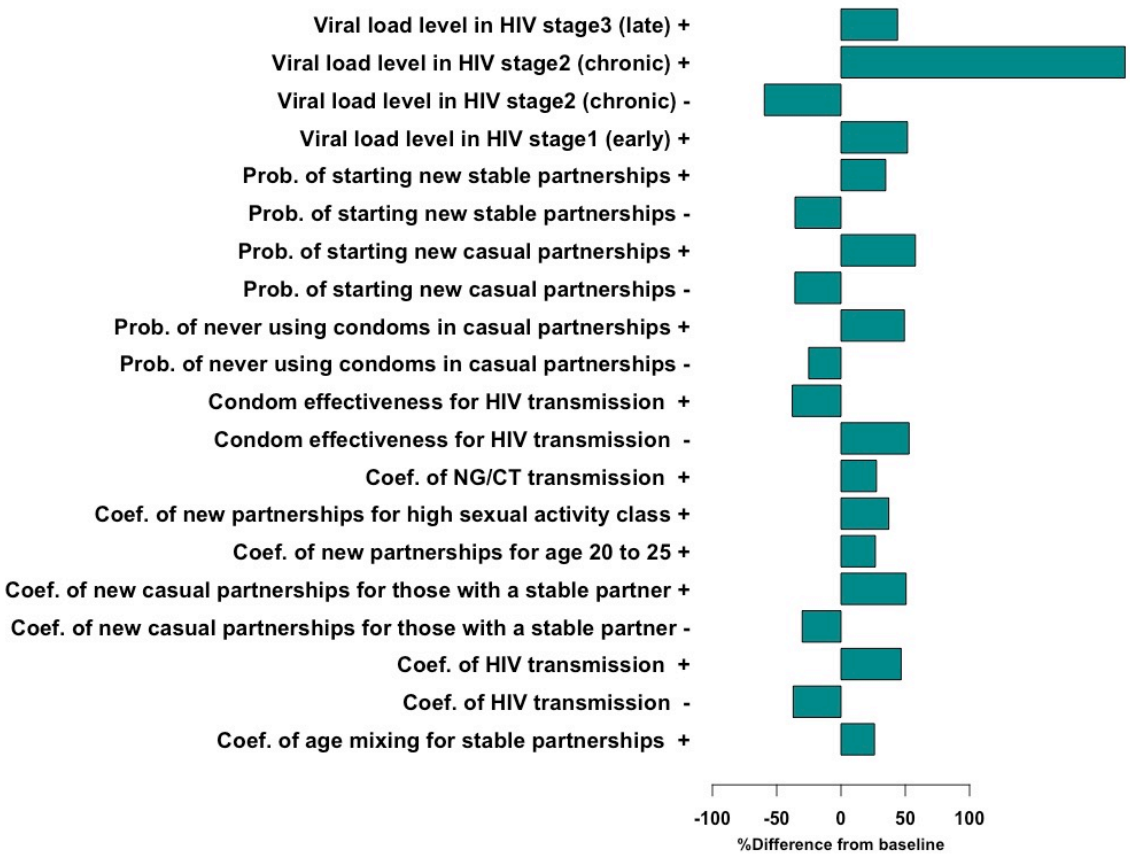

Figure S15: Sensitivity analysis of HIV incidence in year 10 to variation in model parameters in the scenario of a PrEP campaign targeting MSM at the time of NG/CT screening. Input parameters are listed on the left, +/- corresponding to 25% increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant

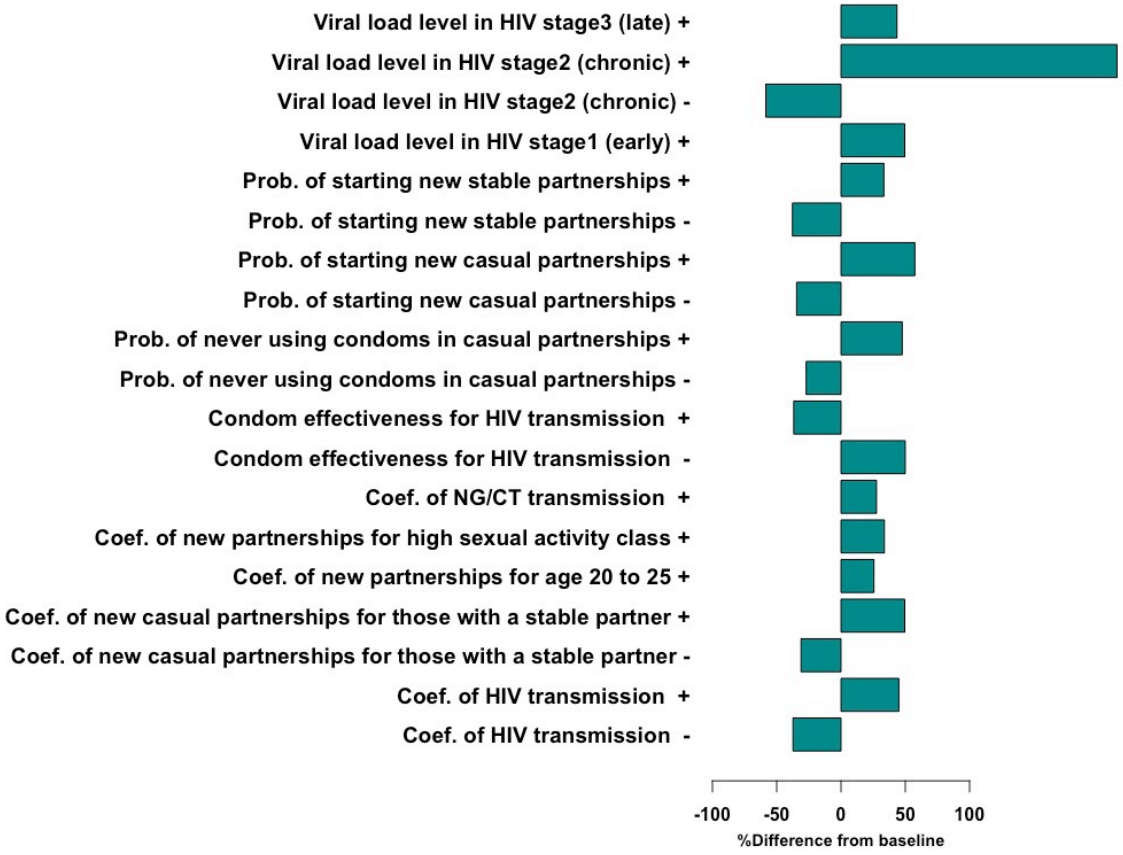

Figure S16: Sensitivity analysis of HIV incidence in year 10 to variation in model parameters in the scenario of a PrEP campaign targeting MSM through a community-wide campaign. Input parameters are listed on the left, +/- corresponding to 25% increases/decreases, and bars reflecting corresponding differences in output. The y-axis shows the percent difference in the value of selected output from the baseline model (before parameter change). Differences more than 25% are considered as significant.

3.1 Sensitivity analysis to impact of behavioral disinhibition

In the absence of strong data on existence of behaviour change for people on PrEP, we have elected to keep the model in the simplest format as possible. However, we acknowledge that this may limit the applicability of our findings to settings in which such behaviour may occur. To further study the impact of such assumption on our findings, we performed an additional sensitivity analysis of results to impact of behavioural disinhibition. For this purpose, we model behavioural disinhibition as %reduction in rate of condom use among MSM taking PrEP (reflected equally on rate of condom use in casual and stable partnerships), varied from 0% (no behavioural disinhibition) to 100% (no condom use).

Figure S17 compares the projected impact of NG/CT targeted PrEP at different rates of condom use reduction among PrEP users. The red line represents the baseline scenario in the model in absence of behavioral disinhibition. As expected, the projected impact of NG/CT-targeted PrEP on HIV incidence declines with reduced levels of condom use among PrEP users. For example, at baseline and in absence

of behavioural disinhibition, the NG/CT targeted PrEP results in 12% [10.4% - 14.1%] reduction in HIV incidence over 20 years. Decreasing the condom use among PrEP users by 25% and 50% will consequently results in lower impact of PrEP at the population level, corresponding to 9.8% [7.7% - 11.9%] and 7.2% [5.1% - 9.4%] reductions in HIV incidence over 20-years. Reduction in rate of condom use among PrEP users can further reduce the potential impact of PrEP (through increased STI screening) on incidence and prevalence of NG/CT. At very high levels of behavioural disinhibition (light green line representing a 75% reduction in condom use among PrEP users), implementation of PrEP can in turn increase the rate of STI transmission and incidence over time.

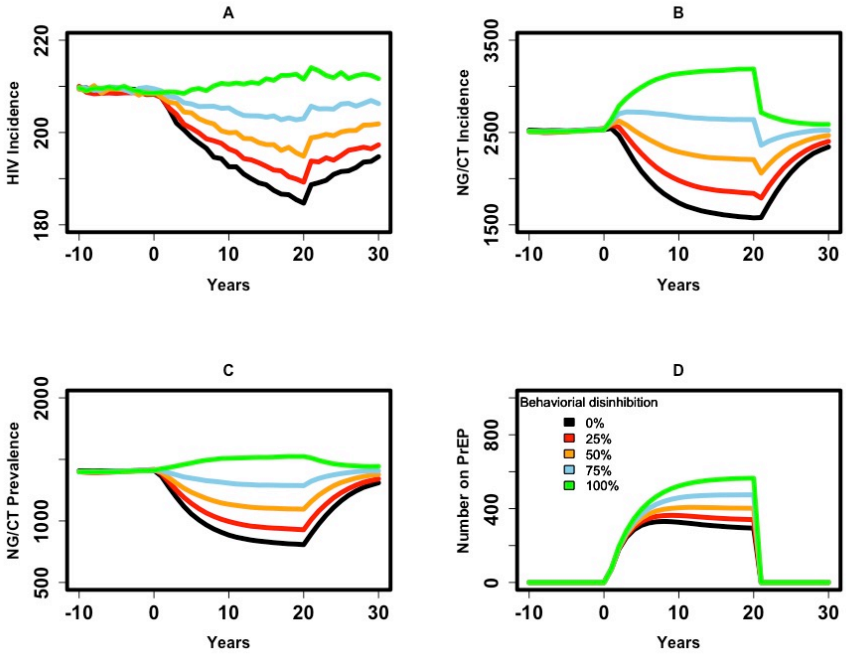

Figure S17: Sensitivity of the impact of NG/CT targeted PrEP to variation in rate of condom use among PrEP users. Shown on the y-axes are the annual incidence of HIV (A), incidence of NG/CT (B), prevalence of NG/CT (C) and number of MSM on PrEP and (D). Different colors represent PrEP scenarios at various levels of reduction in condom use among PrEP users, ranging from 0% (the baseline analysis in the main manuscript, shown in black) to 100% (no condom use among PrEP users, shown in light green).

Figure S18 further compares the impact of 3 PrEP scenarios that were discussed in the main text at various levels of behavioural disinhibition. Despite sensitivity of PrEP outcomes to variation in rate of condom use reduction in each scenario, the relative impact of NG/CT targeted PrEP scenario on HIV incidence compared to the other two scenarios (PrEP evaluation at NG/CT screening/testing and Untargeted PrEP) shows little sensitivity to underlying assumptions regarding behavioural disinhibition (Panel D in each set of graphs), and only begins to decline at very high levels of condom use reduction (last set of graphs for 75% reduction in condom use).

These results further characterize the impact of behavioural disinhibition on population-level impact of PrEP on incidence of HIV and other STIs as proposed by previous studies. This further highlight the need for additional behavioural surveillance data characterizing the changes in level of condom use and risky behaviours among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis

for increased efficacy of PrEP implementation through a NG/CT targeted approach remains robust to variation in rate of condom use reduction.

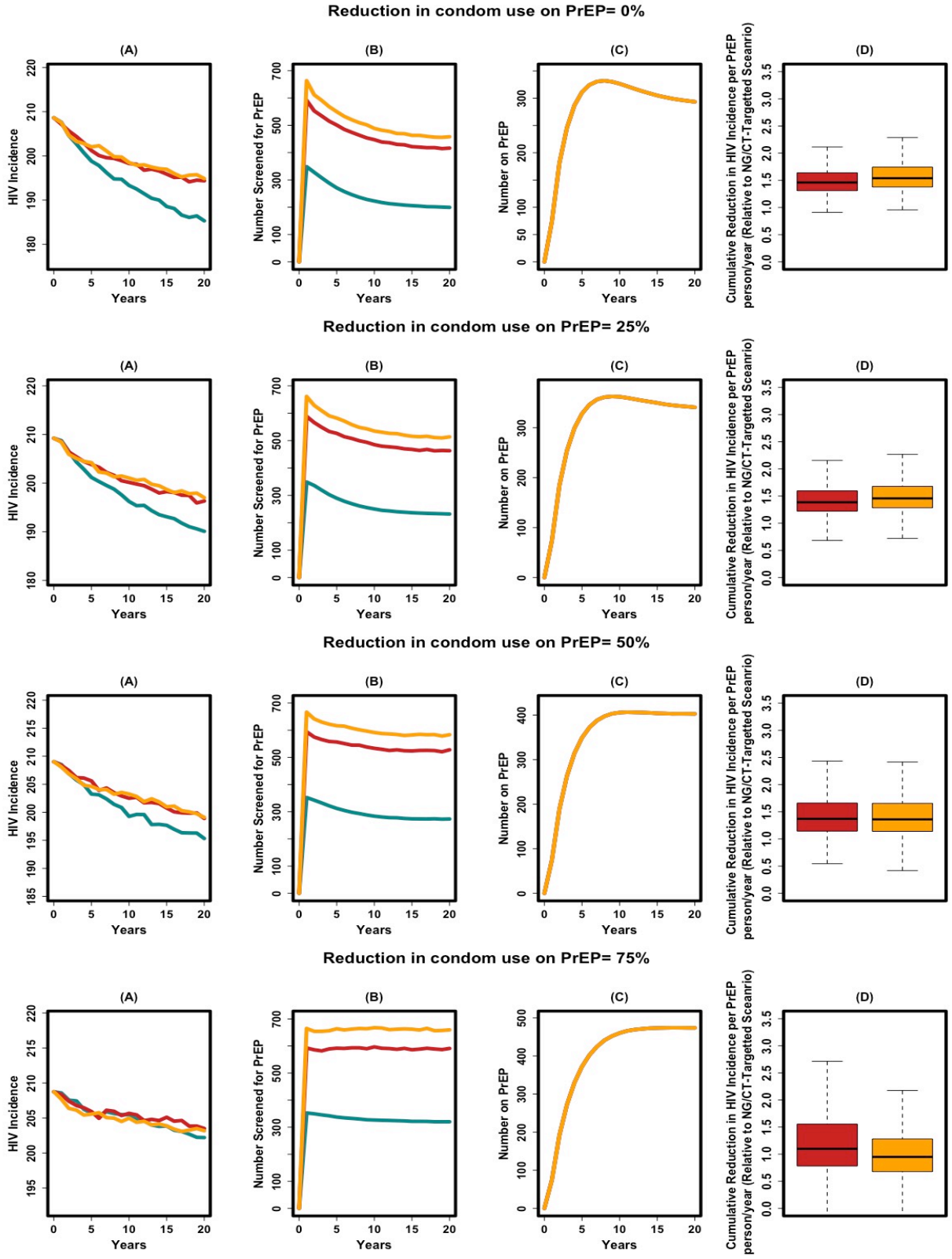

Figure S18: Sensitivity of the impact of all PrEP scenarios to variation in rate of condom use among PrEP users. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in green) compared against

PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. The three strategies are compared under the assumption that the same number of MSM would receive PrEP, at various levels of reduction in condom use among PrEP users. Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenario.

4 ADDITIONAL FIGURES

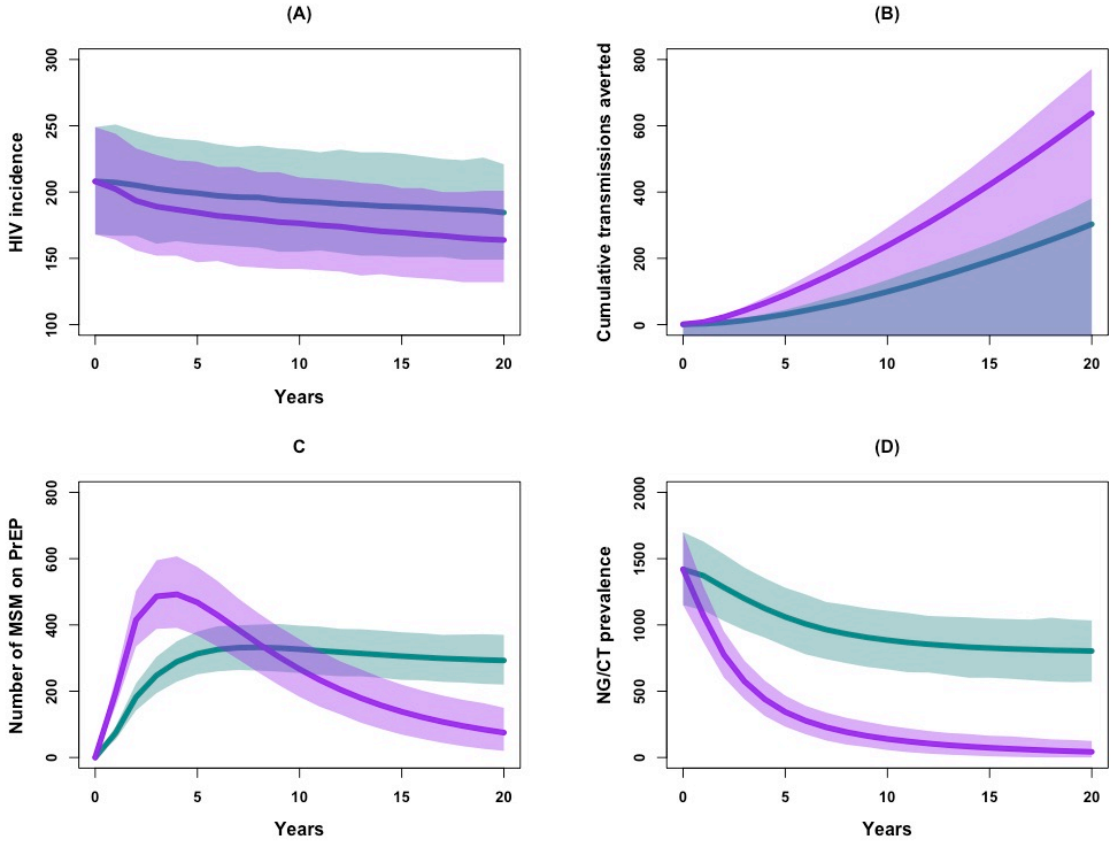

Figure S19: Impact of NG/CT-integrated PrEP, according to frequency of NG/CT screening/testing, with uncertainty ranges shown. Shown on the y-axes are the annual incidence of HIV (A), cumulative number of transmissions averted (B), (C) number of MSM on PrEP and (D) NG/CT prevalence. The green line depicts a scenario in which all MSM currently diagnosed with NG/CT are placed on PrEP with 60% uptake and adherence (NG/CT-integrated PrEP scenario in the main text), and the purple line shows a hypothetical scenario in which 50% of MSM are screened for NG/CT every year, with those testing positive for NG/CT also offered PrEP. Shaded areas represent the 95% uncertainty ranges of simulated data. This figure corresponds to Figure 3 in the main manuscript, but with uncertainty ranges given.

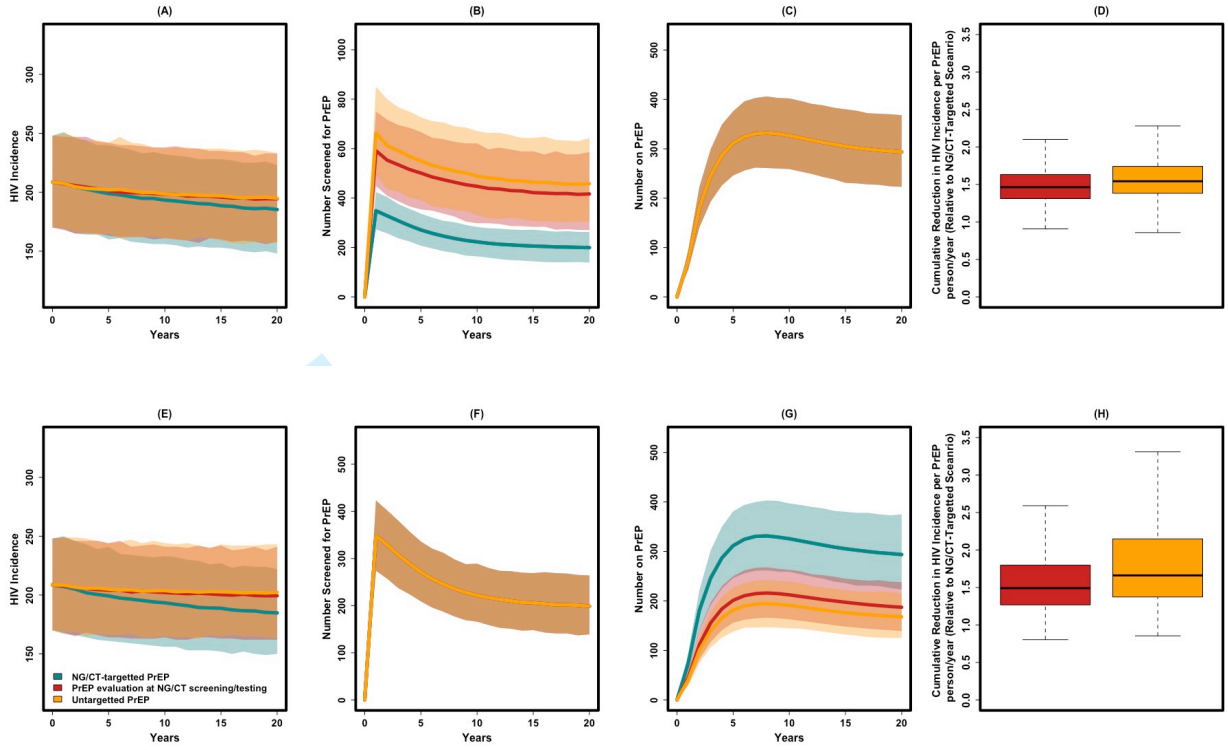

Figure S20: Relative impact of NG/CT-integrated PrEP with uncertainty ranges. Shown in this figure is the relative impact of NG/CT-integrated PrEP (in green, also corresponding to the green line in Figure S19), compared against PrEP evaluation at NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the manuscript text. In the first set of experiments, the three strategies are compared under the assumption that the same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be screened for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted scenarios (similar pattern in panels E through H). This figure corresponds to Figure 4 in the main manuscript, but with uncertainty ranges given.

REFERENCES

1. Alliance BNI. Vital Signs 12 [Internet]. 2012. Available: http://bniajfi.org/vital_signs/
2. Maryland Department of Health and Mental Hygiene, MDHMH. 2012 Baltimore City Annual HIV Epidemiological Profile. Baltimore; 2012.
3. World Health Organization. Life tables by country United States of America. In: Global Health Observatory Data Repository [Internet]. 2013. Available: http://apps.who.int/gho/data/view.main.61780?lang=en
4. Lieb S, Fallon SJ, Friedman SR, Thompson DR, Gates GJ, Liberti TM, et al. Statewide Estimation of Racial/Ethnic Populations of Men Who Have Sex with Men in the U.S. Public Health Rep. 2011;126: 60–72.
5. Beyrer C, Baral SD, van Griensven F, Goodreau SM, Chariyalertsak S, Wirtz AL, et al. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012;380: 367–77.
6. Marshall BD, Paczkowski MM, Seemann L, Tempalski B, Pouget ER, Galea S, et al. A complex systems approach to evaluate HIV prevention in metropolitan areas: preliminary implications for combination intervention strategies. PLoS One. 2012;7: e44833.
7. Escobar E, Durgham R, Dammann O, Stopka T. Agent-based computational model of the prevalence of gonococcal infections after the implementation of HIV pre-exposure prophylaxis guidelines. Online Journal of Public Health Informatics. 2015. doi:10.5210/ojphi.v7i3.6104
8. German D. BESURE Study: National HIV Behavioral Surveillance Study in Baltimore [Internet]. Available: http://www.jhsph.edu/faculty/research/map/US/1413/8192
9. Vieira IT, Senna V de, Pereira. HB de B. A small world model for the spread of HIV infection. Pesqui Operacional. 2011;31: 373–389.
10. Kasaie P, Pennington J, Berry SA, Shah MS, German D, Flynn CP, et al. The impact of pre-exposure prophylaxis among men who have sex Withmen in Baltimore City: an agent-based simulation. JAIDS J Acquir Immune Defic Syndr. 2017;75: 175–183.
11. Egan JE, Frye V, Kurtz SP, Latkin C, Chen M, Tobin K, et al. Migration, neighborhoods, and networks: approaches to understanding how urban environmental conditions affect syndemic adverse health outcomes among gay, bisexual and other men who have sex with men. AIDS Behav. 2011;15: 35–50.
12. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373: 795–807.
13. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009;360: 1815–1826.
14. Palella Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med. 1998;338: 853–860.
15. Rana AI, Liu T, Gillani FS, Reece R, Kojic EM, Zlotnick C, et al. Multiple gaps in care common among newly diagnosed HIV patients. AIDS Care. 2015;27: 697–687.
16. Beck EEC, Birkett M, Armbruster B, Mustanski B. A data-driven simulation of HIV spread among young men who Hhave sex with men: role of age and race mixing and STIs. JAIDS J Acquir Immune Defic Syndr. 2015;70: 186–194.

17. Vriend HJ, Lugnér AK, Xiridou M, Schim van der Loeff MF, Prins M, de Vries HJC, et al. Sexually transmitted infections screening at HIV treatment centers for MSM can be cost-effective. AIDS. 2013;27: 2281–90. doi:10.1097/QAD.0b013e32836281ee

18. Chen MI, Ghani AC, Edmunds WJ. A metapopulation modelling framework for gonorrhoea and other sexually transmitted infections in heterosexual populations. J R Soc Interface. 2009;6: 775–91. doi:10.1098/rsif.2008.0394

19. Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. MMWR recomm. 2015.

20. Virginia Department of Health. STD Surveillance Network Report. 2013; Available: http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf

21. Castro JG, Alcaide ML. High rates of STIs in HIV-infected patients attending an STI clinic. South Med J. 2016;109: 1–4.

22. Sullivan PS, Peterson J, Rosenberg ES, Kelley CF, Cooper H, Vaughan A, et al. Understanding racial HIV/STI disparities in black and white men who have sex with men: a multilevel approach. PLoS One. 2014;9: e90514.

23. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States-2014: a clinical practice guideline. 2014.

24. Centers for Disease Control and Prevention. PrEP for men who have sex with men [Internet]. 2018. Available: https://prepmaryland.org/sites/default/files/download-resources/PrEP - MSM both sides March 2017.pdf

25. Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TP, Prevention D of S. Sexually transmitted disease surveillance 2013. 2014.

26. Lister N, Smith A, Tabrizi S, Hayes P. Screening for neisseria gonorrhoeae and chlamydia trachomatis in men who have sex with men at male-only saunas. Sex Transm Dis. 2003;30: 886–889.

27. Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis. 2005;41: 67–74.

28. Morris SR, Klausner JD, Buchbinder SP, Wheeler SL, Koblin B, Coates T, et al. Prevalence and incidence of pharyngeal gonorrhea in a longitudinal sample of men who have sex with men: the EXPLORE study. Clin Infect Dis. 2006;43: 1284–1289.

29. Soni S, White J. Self-screening for Neisseria gonorrhoeae and Chlamydia trachomatis in the human immunodeficiency virus clinic—high yields and high acceptability. Sex Transm Dis. 2011; Available: http://journals.lww.com/stdjournal/Abstract/2011/12000/Self_Screening_for_Neisseria_gonorrhoeae_and.6.aspx

30. Heiligenberg M, Rijnders B. High prevalence of sexually transmitted infections in HIV-infected men during routine outpatient visits in the Netherlands. Sex Transm. 2012; Available: http://journals.lww.com/stdjournal/Abstract/2012/01000/High_Prevalence_of_Sexually_Transmitted_Infections.2.aspx

31. Rieg G, Lewis R, Miller L, Witt M. Asymptomatic sexually transmitted infections in HIV-infected men who have sex with men: prevalence, incidence, predictors, and screening strategies. AIDS Patient Care. 2008; Available: http://online.liebertpub.com/doi/abs/10.1089/apc.2007.0240

32. Patton ME, Kidd S, Llata E, Stenger M, Braxton J, Asbel L, et al. Extragenital gonorrhea and chlamydia testing and infection among men who have sex with men--STD Surveillance Network, United States, 2010-2012. Clin Infect Dis. 2014;58: 1564–70. doi:10.1093/cid/ciu184

33. Chamberlain N, Crosby RA, Mena L, Chan PA, Mayer KH. Is Patient-Reported Exposure a Reliable Indicator for Anogenital Gonorrhea and Chlamydia Screening in Young Black Men Who Have Sex With Men? Sex Transm Dis. 2017;44: 390–392. doi:10.1097/OLQ.0000000000000619

34. Health VD of. STD Surveillance Network Report. 2013; Available: http://www.vdh.virginia.gov/content/uploads/sites/10/2016/01/2013-SSuN-Annual-Report-09-18-13-1.pdf

35. Maryland Department of Health and Mental Hygiene. BESURE Study 2004-2014: Baltimore site of National HIV Behavioral Surveillance (NHBS) [Internet]. 2015.

36. Jenness S, Goodreau S. Impact of the centers for disease control's HIV preexposure prophylaxis guidelines for men who have sex with men in the United States. J Infect Dis. 2016;14: 1800–1807.

37. Sherrard J, Barlow D. Gonorrhoea in men: clinical and diagnostic aspects. Genitourin Med. 1996;72: 422–6.

38. Kretzschmar M, Duynhoven Y van. Modeling prevention strategies for gonorrhea and chlamydia using stochastic network simulations. Am J Epidemiol. 1996;144: 306–317.

39. Korenromp EL, Sudaryo MK, de Vlas SJ, Gray RH, Sewankambo NK, Serwadda D, et al. What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? Int J STD AIDS. 2002;13: 91–101.

40. Althaus CL, Heijne JCM, Roellin A, Low N. Transmission dynamics of chlamydia trachomatis affect the impact of screening programmes. Epidemics. 2010;2: 123–131.

41. Price MJ, Ades AE, Angelis D De, Welton NJ, Macleod J, Soldan K, et al. Mixture-of-exponentials models to explain heterogeneity in studies of the duration of Chlamydia trachomatis infection. Stat Med. 2013;32: 1547–1560.

42. Turner KM, Adams EJ, Gay N, Ghani AC, Mercer C, Edmunds WJ. Developing a realistic sexual network model of chlamydia transmission in Britain. Theor Biol Med Model. 2006;3: 3.

43. Chesson HW, Pinkerton SD. Sexually transmitted diseases and the increased risk for HIV transmission: implications for cost-effectiveness analyses of sexually transmitted disease prevention interventions. J Acquir Immune Defic Syndr. 2000;24: 48–56.

44. Chesson HW, Bernstein KT, Gift TL, Marcus JL, Pipkin S, Kent CK. The cost-effectiveness of screening men who have sex with men for rectal chlamydial and gonococcal infection to prevent HIV Infection. Sex Transm Dis. 2013;40: 366–71.

45. Tuite A, Jayaraman G, Allen V. Estimation of the burden of disease and costs of genital Chlamydia trachomatis infection in Canada. Sex Transm Dis. 2012;39: 260–267.

46. Vries R De, Bergen J Van. Systematic screening for Chlamydia trachomatis: estimating cost-effectiveness using dynamic modeling and Dutch data. Value in. 2006;9: 1–1.

47. Adams EJ, Turner KME, Edmunds WJ. The cost effectiveness of opportunistic chlamydia screening in England. Sex Transm Infect. 2007;83: 267-74; discussion 274–5.

48. Andersen B, Gundgaard J, Kretzschmar M. Prediction of costs, effectiveness, and disease control of a population-based program using home sampling for diagnosis of urogenital Chlamydia trachomatis. Sex Transm Dis. 2006;33: 407–415.

49. Gillespie P, O'Neill C, Adams E, Turner K. The cost and cost-effectiveness of opportunistic screening for Chlamydia trachomatis in Ireland. Sex Transm Dis. 2012;88: 222–228.

50. Roberts T, Robinson S, Barton P, Bryan S. Cost effectiveness of home based population screening for Chlamydia trachomatis in the UK: economic evaluation of chlamydia screening studies (ClaSS) project. Bmj. 2007;335: 291.

51. Welte R, Kretzschmar M, Leidl R, Hoek A Van Den, Jager JC, Postma MJ. Cost-effectiveness of screening programs for Chlamydia trachomatis: a population-based dynamic approach. Sex Transm Dis. 2000;27: 518–529.

52. Sexually transmitted diseases treatment guidelines, 2006. MMWR recomm. 2006; Available: http://origin.glb.cdc.gov/mmWR/preview/mmwrhtml/rr5511a1.htm

53. Berry SA. Gonorrhoea and chlamydia screening in HIV clinics: time for new tools and targets. Sex Transm Infect. 2014;90: 574–575.

54. Berry SA, Ghanem KG, Page KR, Gange SJ, Thio CL, Moore RD, et al. Increased gonorrhoea and chlamydia testing did not increase case detection in an HIV clinical cohort 1999-2007. Sex Transm Infect. NIH Public Access; 2011;87: 469–475.

55. Hutchinson J, Goold P, Wilson H, Jones K, Estcourt C. Sexual health care of HIV-positive patients: an audit of a local service. Int J STD AIDS. 2003;14: 493–496.

56. Hamlyn E, Barrett S, Kelsey J, Lockyer S, Welz T, Poulton M. Improvement in screening for sexually transmitted infections in HIV-positive patients following implementation of a nurse-led clinic. Int J STD AIDS. 2007;18: 424–426. Available: http://www.ncbi.nlm.nih.gov/pubmed/17609038

57. Hoover KW, Butler M, Workowski K, Carpio F, Follansbee S, Gratzer B, et al. STD screening of HIV-infected MSM in HIV clinics. Sex Transm Dis. 2010;37: 771–776.

58. Teague R, Mijch A, Fairley CK, Sidat M, Watson K, Boyd K, et al. Testing rates for sexually transmitted infections among HIV-infected men who have sex with men attending two different HIV services. Int J STD AIDS. 2008;19: 200–2.

59. Joesoef MR, Linnan M, Barakbah Y, Idajadi a, Kambodji a, Schulz K. Patterns of sexually transmitted diseases in female sex workers in Surabaya, Indonesia. Int J STD AIDS. 1997;8: 576–80. doi:10.1258/0956462971920811

60. Darrow WW. Condom Use and Use-Effectiveness in High-Risk Populations. SexTransmDis. 1989;16: 157–160.

61. Cohen M. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. Lancet. 1998;351: S5–S7.

62. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect. 1999;75: 3–17.

63. Winter AJ, Taylor S, Workman J, White D, Ross JD, Swan A V, et al. Asymptomatic urethritis and detection of HIV-1 RNA in seminal plasma. Sex Transm Infect. 1999;75: 261–263.

64. Cohen MS, Hoffman IF, Royce RA, Kazembe P, Dyer JR, Daly CC, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. Lancet. 1997;349: 1868–1873.

65. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions

between classic sexually transmitted diseases and HIV. Sex Transm Dis. 2001;28: 579–597.

66. Jin F, Prestage GP, Imrie J, Kippax SC, Donovan B, Templeton DJ, et al. Anal sexually transmitted infections and risk of HIV infection in homosexual men. J Acquir Immune Defic Syndr. 2010;53: 144–149.

67. Baggaley RF, Ferguson NM, Garnett GP. The epidemiological impact of antiretroviral use predicted by mathematical models: a review. Emerg Themes Epidemiol. 2005;2: 9.

68. Salomon JA, Hogan DR, Stover J, Stanecki KA, Walker N, Ghys PD, et al. Integrating HIV prevention and treatment: from slogans to impact. PLoS Med. 2005;2: e16.

69. Alam SJ, Meyer R, Norling E. A model for HIV spread in a South African village. Multi-Agent-Based Simul IX. 2009; 33–45.

70. Clotet B, Feinberg J, Lunzen J van, Khuong-Josses M. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised. Lancet. 2014;383: 2222–2231.

71. Wit FW, Blanckenberg DH, Brinkman K, Prins JM, Ende ME van der, Schneider MM, et al. Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. AIDS. 2005;19: 345–348.

72. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, Callegaro A, Suter F. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. AIDS. 2004;18: 439–446.

73. Ortiz GM, Wellons M, Brancato J, Vo HT, Zinn RL, Clarkson DE, et al. Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects. Proc Natl Acad Sci. 2001;98: 3288–13293.

74. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. New Engl J Med. 2006;355: 2283–2296.

75. Sc W, Davis-Beaty. Condom effectiveness in reducing heterosexual HIV transmission (Review). Available: http://www.thecochranelibrary.com

76. Holmes KK, Levine R, Weaver M. Effectiveness of condoms in preventing sexually transmitted infections. Bull World Health Organ. 2004;82: 454–461.

77. Hill T, Bansi L, Sabin C, Phillips A, Dunn D. Data linkage reduces loss to follow-up in an observational HIV cohort study. J Clin. 2010;63: 1101–1109.

78. Mocroft A, Kirk O, Aldins P, Chies A, Blaxhult A. Loss to follow-up in an international, multicentre observational study. HIV Med. 2008;9: 261–269.

79. Ndiaye B, Ould-Kaci K, Salleron J, Bataille P. Characteristics of and outcomes in HIV-infected patients who return to care after loss to follow-up. AIDS. 2009;23: 1786–1789.

80. Mills E, Nachega J, Buchan I, Orbinski J. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. Jama. 2006;296: 679–690.