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

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43 26	Key n	nessages:
44 45 46 28	•	Several barriers exist to the successful implementation of PrEP in local settings, and optimizing the efficiency of PrEP delivery is a public health priority
<sup>47</sup> 29 <sup>48</sup> 30 49	•	Targeting MSM infected with <i>Neisseria gonorrhoeae</i> and/or <i>Chlamydia trachomatis</i> increases the efficiency and effectiveness of PrEP delivery
50 31 51 32 52 33 53 54 55 56	•	Expanding levels of STI screening among MSM can significantly improve the impact of PrEP (with PrEP offered to those testing positive)
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### 34 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.

<sup>13</sup>41 **Results**: Assuming 60% uptake and 60% adherence, targeting PrEP to MSM diagnosed with NG/CT could reduce 14<sup>41</sup> 15<sup>42</sup> HIV incidence among MSM in Baltimore City by 12.4% [95% uncertainty range (UR): 10.3 – 14.4%] in 20 years, 16 <sup>43</sup> relative to no PrEP. Expanding the coverage of NG/CT screening (such that individuals experience a 50% annual 17 44 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 18 45 compared to alternative implementation scenarios, PrEP evaluation at NG/CT diagnosis increased impact of PrEP 20 47 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 21 48 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.

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<sup>3</sup> 54	Strengths and limitations of this study
4 5 55 6 56 7 57 8 58 9 59 10 60 11	<ul> <li>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.</li> </ul>
12 61 13 62 <sup>14</sup> 63 15 c4	<ul> <li>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.</li> </ul>
16 <sup>64</sup> 17 <sup>65</sup> 18 <sup>66</sup> 19 <sup>67</sup> 20 <sup>68</sup> 21 <sup>69</sup>	<ul> <li>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.</li> </ul>
22 70 23 71 24 72 25 73 26 73	<ul> <li>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.</li> </ul>
2777 2875 2976 3077 3178 32 3379	<ul> <li>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.</li> </ul>
<sup>34</sup> 80 <sup>35</sup> 81 36	<b>Keywords:</b> HIV Infections; Gonorrhoea; Chlamydia; Pre-Exposure Prophylaxis; Homosexuality, Computer Simulation
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### <sup>3</sup><sub>4</sub> 86 **BACKGROUND**

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5 87 Infection with Neisseria gonorrhoeae (NG) and/or Chlamydia trachomatis (CT) may impact HIV transmission in 6 88 multiple ways, particularly among men who have sex with men (MSM). From a biological standpoint, NG/CT 7 89 infection may increase one's susceptibility to HIV acquisition: rectal infection in particular has been linked to an 8 9 90 increased risk of HIV acquisition [1,2]. HIV and NG/CT also share many risk factors at the individual level (e.g., 1091 condomless sex) and network level (e.g., having sex within a high-prevalence network), such that the three 11 92 conditions are often epidemiologically linked [3]. Additionally, HIV-negative men have an increased risk of HIV 12<sub>93</sub> acquisition when in partnership with a HIV-positive partner who is also co-infected with NG/CT [4,5]. As a result, 13 14<sup>94</sup> better diagnosis and treatment of NG/CT can potentially reduce HIV incidence [6], and help to identify individuals . 15<sup>95</sup> at high risk of future HIV infection.

1696 Pre-Exposure Prophylaxis (PrEP) is part of comprehensive HIV prevention services in which HIV-negative people <sup>17</sup>97 take daily antiretroviral medication to lower risk of HIV transmission upon exposure. The U.S. Centers for Disease 18 19 19 20 99 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 2100 (STI) in the last 6 months, are in a HIV discordant partnership, or report a condomless sex act in the last 6 months. 22101 Despite this broad recommendation, the potential population-level impact of PrEP remains uncertain. Several 23102 barriers exist to the successful implementation of PrEP, including providers' perceived inability to deliver PrEP in 24103 primary care settings [8], individuals' limited knowledge of PrEP effectiveness [9], low self-perceived risk for HIV 25104 infection [10], patients' difficulty in maintaining adherence [11], and high costs (at over \$10,000 per person-year <sup>26</sup>105 27 for those without insurance or access to a medication assistance plan) [12,13].

281.06 Given these challenges, optimizing the efficiency of PrEP delivery is a public health priority. Specifically, it is 29107 important to tailor PrEP delivery to those who stand to gain the most from its preventive efficacy. Given the 3908 epidemiologic link between NG/CT infection and HIV among MSM, new NG/CT diagnoses may serve as a useful 3109 means to identify high-risk MSM for PrEP evaluation and delivery [7]. At present, the impact of such a strategy—in 32 110 33 terms of reducing HIV and NG/CT incidence at a population level—is not clear. To address this question, we used 34 34 surveillance data from Baltimore City, Maryland, to construct an agent-based simulation model of the co-3<u>4</u>12 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. 3413 37

#### 3814 **METHODS** 39

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).

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

Neisseria gonorrhoeae (NG) and Chlamydia trachomatis	Value	Reference
C() Parameters		
Proportion of cases symptomatic	74%	[16]
Urethral	20%	[10]
Rectal	10%	[18,19]
Pharyngeal	2070	[10,10]
Duration of infection (at each site) in the absence of treatment	[3-12] months <sup>2</sup>	[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 sit
Rectal	0.49	specific incidence of NG/CT
Pharyngeal	0.16	
Increase in HIV transmissibility (for those with urethral or	[1.5 – 2] fold <sup>1</sup>	[34–38]
rectal infection)		[40.00.00.00]
Increase in HIV susceptibility (for those with urethral or	[1 – 2.5] fold	[19,20,38,39]
	3	
NG/CI Calibration largets	Mean [Range]	
Annual diagnosis of NG/CT among MSM in Baltimore City		Values estimated from loca
Urethral	337 [269 – 405]	data on gonorrhea surveilla
Rectal	25 [18 – 33]	and STI clinic visitis in Baltin
Pharyngeal	42 [23 - 60]	City (See section 2 in the
		Supplementary Material)
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 <sup>1</sup>	[40,41]
Chronic	[8 –10] years	[42,43]
• Late stage <sup>4</sup>	[1 –3] years <sup>1</sup>	[42–44]
Mortality rate <sup>3</sup>		
Acute & Chronic, no ART	5 per 1000 person years	[45–47]
• Late stage, no ART	1/duration of late stage	
	0.50	
Reduction in mortality due to ART	0.58	
Reduction in mortality due to ART Time from ART discontinuation to pre-ART CD4 nadir <sup>5</sup>	0.58 ART treatment duration up to one year	[48–51]

<sup>1</sup> Values represent a pooled estimate of the reported measures for NG and CT infections

<sup>2</sup> Values are selected over uniform distributions across the ranges presented.

<sup>3</sup> 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).

<sup>4</sup> Mortality rate in late stage is defined as 1/(duration of late stage disease).

<sup>5</sup> Infectiousness assumed equal to that of the chronic disease.

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3	Average viral load (log10 copies/mL)		[42]
4	Acute, no ART	6.5	
5	Chronic, no ART	4.5	
6	Late stage, no ART	5	
7	On ART, partially suppressed	3.5	
8	On ART, fully suppressed	1.5	
9	Infectiousness per sexual contact	2.45 <sup>(log(VL)-4.5)</sup>	[42]
10	Weekly probability of engagement in HIV care	0.006	[53–55]
11	Weekly probability of ART discontinuation	0.015	[56]
12	Gap in care after ART discontinuation	26 weeks	[57]
13	Relative probability of accessing HIV care among black	0.5	[58]
14	MSM compared to white MSM		
15	HIV calibration targets		
16	HIV prevalence	0.22 per 100,000 person/year	[59]
17	HIV continuum of care: Proportion of cases		[59]
18	Diagnosed	0.86	
19	Linked to care	0.62	
20	Engaged in care	0.5	
21	On ART	0.39	
22	Virally suppressed	0.27	

25129 STI Screening: In addition to testing of symptomatic NG/CT diagnosis, we also assume screening of 26 130 27 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 39<sup>1</sup>40 continuously engaged in HIV care should undergo repeated NG/CT screening at least annually [15]. More 4041 frequent screening, such as screening every 3-6 months, is recommended for high-risk MSM, including 41142 those with an NG/CT diagnosis in the last year. Based on data from Baltimore City and a conservative 42143 estimate, we assume 40% adherence to these guidelines [62,63].

43 44<sup>144</sup> HIV Testing: In addition to combined HIV/STI testing that takes place as part of STI screening, we assume that all 4445 MSM experience an additional probability of HIV testing (in excess of testing though the STI program) can calibrate 4446 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 49 49 49 well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT 50449 epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City 51150 Health Department as part of the STD Surveillance Network Project (see section 2 of the Supplementary Material).
- 52 51 PrEP: Our primary outcome for this analysis is the projected incidence of HIV after 20 years of delivering PrEP to <sub>54</sub>152 MSM. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the 5**£**53 added benefit of targeting PrEP at individuals diagnosed with NG/CT. In all three scenarios, indication for PrEP use 5**£**54 (eligibility) is considered in accordance with CDC recommendations and Baltimore City PrEP guidelines [64] (See
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<sup>3</sup> 155 section 1 of the Supplementary Material) and includes HIV-negative individuals who are diagnosed with NG/CT in <sup>4</sup>156 the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual 6<sup>157</sup> partnership in the last 6 months. The three scenarios are thus:

- 7 158 PrEP delivery at NG/CT diagnosis ("targeted" strategy & primary analysis): all MSM diagnosed with NG/CT <sup>8</sup>159 are offered PrEP at the time of diagnosis 9
- 10160 PrEP evaluation at NG/CT screening/testing ("at-testing"): PrEP eligibility is evaluated at the time of 1161 screening/testing for NG/CT, and all eligible individuals are offered PrEP 12
- 1**3**162 Untargeted PrEP: PrEP eligibility is evaluated at random, and all eligible MSM are offered PrEP

<sup>14</sup>163 All else being equal, increasing the number of MSM on PrEP will result in larger effects on HIV incidence (as more 15 164 16 people are protected from HIV transmission). However, for a given number of MSM screened – or a given number 1<del>7</del>65 of MSM on PrEP (e.g., if resource constraints are such that not all MSM meeting the criteria for PrEP can be 1266 placed/maintained on PrEP) – targeting PrEP to those screened for/diagnosed with NG/CT may be more efficient. 1467 Our primary aim was to quantify the extent of this gain in efficiency; thus, we compared scenarios in which the 20168 same number of MSM would be evaluated for PrEP, or alternatively the same number of MSM would be 21169 maintained on PrEP. Furthermore, to illustrate the potential impact of reaching highly ambitious targets for 2470 improved STI screening, we considered a hypothetical scenario for improving the underlying level of NG/CT <sup>23</sup>171 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.

- 27174 In all scenarios, we assume that PrEP eligibility is reassessed every 3 months among patients receiving PrEP, and <sup>28</sup>175 those who remain eligible for PrEP continue to receive it over time. Furthermore, we assume that in each scenario, <sup>29</sup>176 a given proportion of eligible MSM who are offered PrEP will initiate prophylaxis (PrEP uptake ranging [0%-100%]) 30 3177 31 and adhere to it (PrEP adherence ranging [0%-100%]), with adherence defined as taking a sufficient number of 32<sup>178</sup> doses to provide 60% protection against HIV transmission [65]. As a criterion for initiation of PrEP, all eligible MSM 33179 are also screened and treated for NG/CT infection before starting PrEP.
- <sup>34</sup>180 <sup>35</sup>181 36 3782 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 38183 condom usage among MSM on PrEP to model behavioral disinhibition (section 3 of the Supplementary Material).
- <sup>39</sup>184 40 Patient and Public Involvement: Patients and/or public were not involved in this study.

#### 4**2**185 RESULTS

#### 43 4486 **Population overview**

45 187 46 The simulation models a population of 15,000 MSM in Baltimore City, projecting an average of 215 [95% UR: 181 – 47188 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% 4\$189 4**9**90 [47.4 – 50.6%] with non-urethral/rectal infection and 16.0% [14.8 – 17.2%] with pharyngeal-only infection. Point 50191 prevalence of NG/CT infection is estimated as 9.9% [8.4 – 11.5%], with 68.0% [63.5 – 72.5%] of infections 51192 occurring among black MSM (accounting for 58% of the MSM population) and 56.0% [54 – 58.2%] among MSM 52193 vounger than 30 years old (accounting for 28% of the MSM population). Overall, 81.5% [81.0 – 82.1%] of MSM <sup>53</sup>194 diagnosed with NG/CT in the model were tested on the basis of symptomatic presentation (rather than 54 195 55 asymptomatic screening), and 29.1% [23.1 – 35.0%] of MSM diagnosed with NG/CT were coinfected with HIV.

- 5996 Epidemiological impact of PrEP at NG/CT diagnosis
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<sup>3</sup> 197 At baseline, and in the absence of PrEP (steady-state equilibrium), 361 [95% UR: 298 – 427] MSM were annually <sup>4</sup>198 diagnosed and treated for NG/CT infection (calibrated). If 60% of MSM diagnosed with NG/CT could be started on 5 198 6 199 PrEP (i.e., uptake = 60%) and maintained at a degree to which 60% of subsequent HIV infections were averted (i.e., 7<sup>200</sup> 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 <sub>8</sub>201 9202 PrEP delivered, or 5479 [4330 – 6632] infections averted per 100,000 person-years of PrEP (Figure 2B). Under the 10203 current level of NG/CT diagnosis, the number of MSM receiving PrEP is projected to increase through the first 8 1204 years of the program (reaching a total of 332 [327 – 338] MSM on PrEP) and to fall afterward with declining  $12_{05}$ incidence of NG/CT (Figure 2C). Due to the increased level of NG/CT screening/treatment among those on PrEP <sup>13</sup>206 <sup>14</sup>207 15 (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).

1208 The impact of PrEP on HIV incidence can be further increased by expanding the coverage of NG/CT screening at 1209 the community level. In our baseline model, 25.0% [95% UR: 24.0 – 26.0%] of MSM undergo NG/CT
 18210 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 Relative impact of targeted versus untargeted PrEP

<sup>27</sup>216 NG/CT-integrated PrEP increased efficiency of PrEP delivery in at least two ways (Figure 3A). First, a higher 28 217 percentage of MSM were eligible for PrEP among those evaluated for PrEP (Figure 3B and 3C). In our model, 71.1% 29 -ź18 [95% UR: 65.0 – 77.2%] of all MSM diagnosed with NG/CT were eligible to receive PrEP (as 29% of this population 3219 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 3220 randomly selected MSM. Second, providing PrEP to MSM diagnosed with NG/CT targets individuals at higher risk 3221 of potential HIV infection (due to both biological factors and high-risk behavior), such that – under the baseline 3222 assumption of equal numbers of people receiving PrEP—impact of NG/CT-targeted PrEP on HIV incidence was 35223 greater than the other two scenarios (Figure 3D). Specifically, over 20 years of implementation, targeting PrEP to <sup>3</sup><sup>5</sup>224 <sup>37</sup>225 <sup>38</sup>226 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 3**3**26 number of individuals were evaluated for PrEP, the efficacy of NG/CT-integrated PrEP was increased even further 40<sup>2</sup>27 relative to other scenarios (Figure 3E through 3H).

4228 In one-way sensitivity analyses, the projected HIV incidence at 10 years in the absence of PrEP was sensitive to <sup>42</sup>229 parameters relating to HIV and NG/CT transmission (including level of HIV viral load, condom use, and condom 4<sup>2</sup>30 effectiveness) and parameters describing overall sexual activity (including the probabilities of starting new 4<u>3</u>231 partnerships and the level of sexual activity in the most sexually active class). A similar variation in HIV incidence 4&32 was observed in scenarios modeling PrEP evaluation at the time of NG/CT diagnosis, NG/CT screening or at 42233 random. Impact of PrEP in terms of reduction in HIV incidence in all scenarios relative to baseline was robust to 48234 reasonable variation of most model parameters (section 3 of the Supplementary Material). In additional 49235 sensitivity analyses, we studied the impact of decreased condom use among MSM on PrEP (behavioral <sup>50</sup>236 disinhibition) on the outcome of NG/CT-targeted PrEP, and the relative efficacy of STI-targeted scenario compared <sup>5</sup>237 <sup>52</sup>38 53 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 54<sup>239</sup> additional behavioural surveillance data characterizing changes in level of condom use and risky behaviours 5**£**40 among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis (increased

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<sup>3</sup> 241 effectiveness of PrEP implementation through an NG/CT targeted approach) remains robust to variation in rate of
 <sup>4</sup> 242 condom use reduction.

# <sup>8</sup><sub>9</sub>244 **DISCUSSION**

10 1245 11 This agent-based simulation of HIV transmission among MSM suggests that screening for NG/CT may be an 12<sup>246</sup> important and efficient entry point for PrEP evaluation and delivery. Specifically, if all MSM who currently test 13247 positive for NG/CT could be offered PrEP – assuming 60% uptake and sufficient adherence to maintain 60% 14248 protection – HIV incidence could be reduced by approximately 12%, averting one HIV infection annually per 1,000 15249 MSM population, with fewer than 20 per 1,000 taking PrEP every year. On the basis of infections averted per PrEP 16250 dose delivered, providing PrEP to MSM with NG/CT diagnosis is nearly twice as efficient as providing PrEP 17251 randomly among eligible MSM. Thus, use of NG/CT diagnosis as an entry point is a highly efficient and feasible <sup>18</sup>252 mechanism for PrEP delivery. If NG/CT screening could be expanded to 50% of MSM every year (with PrEP offered 19 253 20 only to those testing positive), this impact could be more than doubled. Given this substantial potential impact, it 2<sup>7</sup>254 will be important to assess willingness and uptake and identify best practices to support PrEP uptake and adherence among MSM diagnosed with NG/CT. 2255

<sup>23</sup>256 These findings are consistent with other studies of PrEP delivery among MSM [66,67]. Previous studies have <sup>24</sup> 257 shown that the population-level impact of PrEP depends strongly on PrEP uptake and adherence [14,66], as  $25^{257}$  $26^{258}$ suggested in our study as well. Importantly, NG/CT diagnosis may be useful in this regard, as MSM who have 27259 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 28260 2**2**61 at the time of an STI diagnosis [68]. Initiation of PrEP simultaneously with NG/CT diagnosis may also be a clinically 30262 feasible approach – as an STI diagnosis is already likely to prompt an HIV test (if not already performed), and MSM 3263 who are diagnosed with NG/CT have at least some level of health care access. Unlike performing detailed sexual <sup>32</sup>64 <sup>32</sup>65 <sup>34</sup>65 <sup>34</sup>66 <sup>35</sup>66 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 longerterm maintenance on PrEP) can be maintained in this population. Furthermore, the potential tradeoff between 367 the positive impact of PrEP on STI prevalence through enhanced screening and its negative impact through 3268 3269 behavioral disinhibition (if MSM on PrEP adopt riskier sexual behaviors) merits further investigation. Additional 39270 implementation research is also needed to identify effective mechanisms for improving adherence to CDC PrEP 40271 guidelines and overcoming barriers to acceptance and uptake of PrEP such as lack of awareness, lack of access, 4<u>2</u>72 financial strain, and stigma [11,71]. 42

43273 As with any modeling analysis, our findings are limited by necessary simplifying assumptions. These assumptions 44274 include exclusion of other STIs such as syphilis infection, combined estimates of NG/CT natural history parameters 45275 (e.g., pooled estimate of NG/CT symptomatic disease for each anatomic site), treating multi-site NG/CT infections <sup>46</sup>276 as occurring at a single primary site, the simplified approach for modeling the transmission of site-specific 4277 infections, applying the same sexual network for NG/CT and HIV transmission, simplification of sexual networks as 4978 49 comprising only stable and casual partnerships, exclusion of serosorting on HIV or PrEP, exclusion of HIV . 50<sup>2</sup>79 transmission through injection drugs or heterosexual sex, and exclusion of transgender and bisexual individuals <sub>5</sub>280 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

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- <sup>3</sup>285 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.,
- $_{6}^{5}$  287 probability of symptomatic infection). We also assume a future trajectory of HIV infection in the future that
- $\frac{7}{7}$  288 represents continuation of current trends; this trajectory is unlikely to remain constant for the next 20 years but
- 8289 may help to provide a useful conceptual construct for present-day decision-making, which is the ultimate goal of 9290 this analysis. Furthermore, our results are limited by exclusion of syphilis infection, another STI that is often
- **2**91 transmitted in the same populations and may affect transmission and acquisition of HIV. Finally, we did not 1**2**92 incorporate cost or other resource constraints into the present model; future analyses could evaluate the
- <sup>1</sup>293 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. 299 20 Future analyses could evaluate whether such approaches could even be cost-saving in the long term. Ultimately, -300 21<sup>2</sup>00 ending the HIV epidemic in MSM populations will require a combination of multiple activities, including 2<sup>3</sup>01 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.

### $23^{19}$ **Conflict of interest:**

 $^{2}$  All authors report no potential conflicts of interest.

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#### <sup>35</sup>328 **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.

#### 4332 Data sharing statement:

- 4233 Additional data are presented in the online Supplementary Material.

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   2500 2015;105:1960–4.
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# <sup>3</sup><sub>4</sub>505 **Figure legends:**

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<sup>7</sup>507 Figure 1: An agent-based model of gonorrhoea/chlamydia (NG/CT) and HIV co-transmission. The top panel <sup>8</sup>508 represents the HIV care continuum and natural history: Upon infection with HIV, individuals serially progress <sup>2</sup><sub>10</sub>509 through three disease stages over time; this progression can be halted by initiation of antiretroviral therapy (ART), 1<sup>510</sup> 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 1511 1\$12 initiation do not affect HIV transmission in the model). HIV-positive individuals in care are assumed to undergo 1**4**513 regular screening for NG/CT (marked in red) subject to patients presenting for scheduled visits and clinician 15514 decision to screen. The bottom panel represents the natural history of NG/CT: infection may be symptomatic or <sup>16</sup>515 asymptomatic, individuals remain infectious until diagnosis and treatment (which can occur either through <sup>1</sup>Ž16 symptomatic presentation to care or routine screening of asymptomatic individuals) or spontaneous resolution. 17 Upon diagnosis with incident NG/CT, we assume that individuals are also screened for HIV infection (marked in 20<sup>518</sup> 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.

31 32527 Figure 3: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CTintegrated PrEP (in green, also corresponding to the green line in Figure 2), compared against PrEP evaluation at 3≨28 34529 NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in 3530 the manuscript text. In the first set of experiments, the three strategies are compared under the assumption that 36531 the same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be <sup>37</sup>532 screened for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM 3& 33 approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and 34 panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-4<sup>535</sup> targeted scenario (similar pattern in panels E through H).





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.

124x106mm (300 x 300 DPI)



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.

317x317mm (300 x 300 DPI)





Figure 3: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CTintegrated 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).

338x208mm (300 x 300 DPI)

### 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 nonblack 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 onelevel 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.

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

#### Table S1: List of CSA group and member CSAs

#### **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.

	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%

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

#### 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*<sub>SA</sub>) 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 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:

$$\begin{split} P_{new\_stb} &= p_{Stb} \times c_{Part|Age} \\ P_{new\_csl} &= p_{Csl} \times p^*_{Csl|Stb} \times c_{Part|Age} \times c_{SA} \\ p^*_{Csl|Stb} &= \begin{bmatrix} p_{Csl|Stb} & number \ of \ stable \ partnerships > 0 \\ 1 & o.w. \end{split}$$

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*<sub>0</sub>), a random neighboring CSA in the same CSA group (*p*<sub>1</sub>) or non-neighbor CSA (*p*<sub>2</sub>). The geographical mixing probability (*pGM*=(*p*<sub>0</sub>, *p*<sub>1</sub>, *p*<sub>2</sub>)) 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.

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

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 <sub>stb</sub> (Number of reported partnerships)	ADSR <sub>csi</sub> (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	<u>0.6</u>	<u>0.74</u>





0.12



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/  $\mu$ L), stage 2 (CD4 count between 200-500 cells/  $\mu$ L) and stage 3 (CD4 count <200 cells/  $\mu$ L). 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 <u>achieve viral suppression 8 to 24 weeks</u> 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/  $\mu$ L) 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<sup>1</sup>. 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 free	uency of condom us	e in stable and casua	al partnerships from BESURE.
Tuble officeported field	1461169 01 601140111 45		

	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:

<sup>&</sup>lt;sup>1</sup> 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.

<sup>-</sup> 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.

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

#### 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<sub>Inf</sub>: Person Y's infectiousness

X<sub>sus</sub>: 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<sub>sexualPositionCoef</sub>: 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:

$$PPSC(S, A, R) = \frac{(13 - A)}{12} \times \frac{(S)}{3} \times pAccessCare(R) \times C$$

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 infections (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.

Parameter	Value	References
Partnerships		
Age Mixing (Absolute different in square root of ages)		
<ul> <li>Stable partnerships</li> </ul>	0.6	[33]
<ul> <li>Casual partnerships</li> </ul>	0.73	

## Table S7: Complete list of model parameters and values.

Race mixing (Likelihood of mixing with a partner of the same		
race)		[33]
- Black & Black	0.9	
- White & White	0.75	
- Stable nartnershins	[0 45 0 55 0 00]	[33]
- Casual partnerships	[0.47, 0.12, 0.41]	[33]
Sexual position preference	[0:, 0:, 0:]	
- Insertive only	0.42	[22]
- Receptive only	0.26	[33]
- Versatile	0.32	
Transmission coefficient for insertive relative to receptive sexual position	0.384	[34]
NG/CT		
Proportion of cases symptomatic		
- Urethral	74%	[26]
- Rectal	20%	[25,35]
- Pharyngeal	10%	[27,35]
Duration of infection in the absence of treatment	[3 – 12] months <sup>2</sup>	[15,36–49]
Duration of treatment	2 weeks	[15–17]
Regular GC screening intervals for HIV+ MSM on ART		
- All MSM	12 months	[50]
<ul> <li>MSM with a history of NG/CT in the last 6 months</li> </ul>	6 months	
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 <sup>3</sup>	[59–63]
Increase in HIV susceptibility (from urethral or rectal infection)	[1- 2.5] fold <sup>3</sup>	[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	U,	
- Urethral	35%	Calibrated to provide the site-
- Rectal	49%	specific incidence of NG/CT
- Pharyngeal	16%	
Weekly probability of symptomatic NG/CT testing		
- Urethral	0.009	Calibrated to provide the site-
- Rectal	0.001	specific diagnosis of NG/CT
- Pharyngeal	0.04	
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
		<u> </u>

<sup>2</sup> 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) <sup>3</sup> : Late stage	[6 – 9] weeks <sup>3</sup> [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 <sup>3</sup>	[68]
Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup>	ART treatment duration up to one year	[69–72]
Mortality rate <sup>3</sup> <ul> <li>Stage 1 &amp; 2, no ART</li> <li>Stage 3, no ART</li> <li>Reduction in mortality due to ART</li> </ul>	5 per 1000 person years 1/duration of stage 3 58%	[11–13]
Average viral load (log10 copies/mL) <ul> <li>Stage 1, no ART</li> <li>Stage 2, no ART</li> <li>Stage 3, no ART</li> <li>On ART, partially suppressed</li> <li>On ART, fully suppressed</li> </ul>	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]

<sup>4</sup> Infectiousness assumed equal to that of stage 2

<sup>&</sup>lt;sup>3</sup> Mortality rate in stage 3 is defined as 1/(duration of stage 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.





## 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.

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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/CTtargeted scenario.

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# **BMJ Open**

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

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39 40 '	24	official position of the Centers for Disease Control and Prevention, or the authors' affiliated institutions.	
41	25		
42 43	26	Key messages:	
44 45 46	27 28	<ul> <li>Several barriers exist to the successful implementation of PrEP in local settings, and optimizing the efficiency of PrEP delivery is a public health priority</li> </ul>	
47 48 40	29 30	<ul> <li>Targeting MSM infected with Neisseria gonorrhoeae and/or Chlamydia trachomatis increases the efficiency and effectiveness of PrEP delivery</li> </ul>	
50 ( 51 ( 52 53	31 32	<ul> <li>Expanding levels of STI screening among MSM can significantly improve the impact of PrEP (with PrEP offered to those testing positive)</li> </ul>	
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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 11<sup>38</sup> prevention of HIV through delivery of pre-exposure prophylaxis (PrEP).

12 39 Methods: To quantify the added value of targeting PrEP to those diagnosed with NG/CT, we simulated the co-<sup>13</sup> 40 epidemic of NG/CT and HIV among MSM in Baltimore City, and compared various strategies for implementation of 15 PrEP in this population.

16 42 Results: Assuming 60% uptake and 60% adherence, targeting PrEP to MSM diagnosed with NG/CT could reduce 17 43 HIV incidence among MSM in Baltimore City by 12.4% [95% uncertainty range (UR): 10.3 – 14.4%] in 20 years, 18 44 relative to no PrEP. Expanding the coverage of NG/CT screening (such that individuals experience a 50% annual 20 21 46 21 22 47 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 23 48 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 24 49 NG/CT screening/testing, and by 1.9 [95% UR 1.1 - 3.4] relative to evaluating random MSM from the community.

<sup>25</sup> 50 Conclusions: Targeting MSM infected with NG/CT increases the efficiency and effectiveness of PrEP delivery. If \_\_\_\_\_51 27<sup>51</sup> high levels of STI screening can be achieved at the community level, NG/CT diagnosis may be a highly effective <sub>28</sub> 52 entry point for PrEP initialization. 

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<sup>3</sup> 53	
4 5 54	Strengths and limitations of this study
6 7 55 8 56 9 57 10 58 11 59 12 60	<ul> <li>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.</li> </ul>
13 14 61 15 62 16 63	<ul> <li>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.</li> </ul>
17 64 18 65 19 66 20 67 21 68	<ul> <li>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.</li> </ul>
23 69 24 70 25 71 26 72 27 73 28 74	<ul> <li>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.</li> </ul>
29 75 30 76 31 76 32 77 33 78	<ul> <li>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.</li> </ul>
37 79 35	
36 80	Keywords: HIV Infections; Gonorrhoea; Chlamydia; Pre-Exposure Prophylaxis; Homosexuality, Computer
37 81 38 39 40 41	Simulation
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## 83 BACKGROUND

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7 84 Infection with Neisseria gonorrhoeae (NG) and/or Chlamydia trachomatis (CT) may impact HIV transmission in 8 9 85 multiple ways, particularly among men who have sex with men (MSM). From a biological standpoint, NG/CT 1086 infection may increase one's susceptibility to HIV acquisition: rectal infection in particular has been linked to an 11 87 increased risk of HIV acquisition [1,2]. HIV and NG/CT also share many risk factors at the individual level (e.g., 12 88 condomless sex) and network level (e.g., having sex within a high-prevalence network), such that the three <sup>13</sup>89 conditions are often epidemiologically linked [3]. Additionally, HIV-negative men have an increased risk of HIV 14 90 acquisition when in partnership with a HIV-positive partner who is also co-infected with NG/CT [4,5]. As a result, 16<sup>91</sup> better diagnosis and treatment of NG/CT can potentially reduce HIV incidence [6], and help to identify individuals 17 92 at high risk of future HIV infection.

<sup>18</sup> 93 Pre-Exposure Prophylaxis (PrEP) is part of comprehensive HIV prevention services in which HIV-negative people 19 94 take daily antiretroviral medication to lower risk of HIV transmission upon exposure. The U.S. Centers for Disease 20 20 21<sup>95</sup> Control and Prevention (CDC) has recommended PrEP for HIV-negative individuals at substantial risk of infection <sub>22</sub>96 [7]. Among MSM, this includes HIV-negative men who are either diagnosed with a sexually transmitted infection 23 97 (STI) in the last 6 months, are in a HIV discordant partnership, or report a condomless sex act in the last 6 months. 2498 Despite this broad recommendation, the potential population-level impact of PrEP remains uncertain. Several 25 99 barriers exist to the successful implementation of PrEP, including providers' perceived inability to deliver PrEP in 2600 primary care settings [8], individuals' limited knowledge of PrEP effectiveness [9], low self-perceived risk for HIV <sup>27</sup>101 infection [10], patients' difficulty in maintaining adherence [11], and high costs (at over \$10,000 per person-year <sup>28</sup>102 29 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 cotransmission 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.

## 49111 **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).

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

Neisseria gonorrhoeae (NG) and Chlamydia trachomatis	Value	Reference
(CT) Parameters		
Proportion of cases symptomatic <sup>1</sup>		[10]
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 <sup>2</sup>	[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
Rectal	0.49	specific incidence of NG/
Pharyngeal	0.16	
Increase in HIV transmissibility (for those with urethral or rectal infection)	[1.5 – 2] fold <sup>1</sup>	[34–38]
Increase in HIV susceptibility (for those with urethral or	[1 – 2.5] fold <sup>1</sup>	[19,20,38,39]
rectal infection)		
NG/CT Calibration Targets	Mean <sup>3</sup> [Range]	
Annual diagnosis of NG/CT among MSM in Baltimore City		Values estimated from lo
Urethral	337 [269 – 405]	data on gonorrhea surve
Rectal	25 [18 – 33]	and STI clinic visitis in Bal
Pharyngeal	42 [23 - 60]	City (See section 2 in the
		Supplementary Material)
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 <sup>1</sup>	[40,41]
Chronic	[8 –10] years <sup>1</sup>	[42,43]
• Late stage <sup>4</sup>	[1-3] years <sup>1</sup>	[42–44]
Mortality rate <sup>3</sup>		
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 <sup>5</sup>	ART treatment duration up to one year	[48–51]
	[	

<sup>1</sup> Values represent a pooled estimate of the reported measures for NG and CT infections

<sup>2</sup> Values are selected over uniform distributions across the ranges presented.

<sup>3</sup> 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).

<sup>4</sup> Mortality rate in late stage is defined as 1/(duration of late stage disease).

<sup>5</sup> Infectiousness assumed equal to that of the chronic disease.

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3	Average viral load (log10 copies/mL)		[42]
4	Acute, no ART	6.5	
5	Chronic, no ART	4.5	
6	Late stage, no ART	5	
7	On ART, partially suppressed	3.5	
8	On ART, fully suppressed	1.5	
9	Infectiousness per sexual contact	2.45 <sup>(log(VL)-4.5)</sup>	[42]
10	Weekly probability of engagement in HIV care	0.006	[53–55]
11	Weekly probability of ART discontinuation	0.015	[56]
12	Gap in care after ART discontinuation	26 weeks	[57]
13	Relative probability of accessing HIV care among black	0.5	[58]
14	MSM compared to white MSM		
15	HIV calibration targets		
16	HIV prevalence	0.22 per 100,000 person/year	[59]
17	HIV continuum of care: Proportion of cases		[59]
18	Diagnosed	0.86	
19	Linked to care	0.62	
20	Engaged in care	0.5	
21	• On ART	0.39	
22	Virally suppressed	0.27	

25125 STI Screening: In addition to testing of symptomatic NG/CT diagnosis, we also assume screening of <sup>26</sup>126 27 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).
- .35 • NG/CT screening for HIV-positive MSM in care: Based on CDC recommendations, most MSM who are 39**1**36 continuously engaged in HIV care should undergo repeated NG/CT screening at least annually [15]. More 40137 frequent screening, such as screening every 3-6 months, is recommended for high-risk MSM, including 41138 those with an NG/CT diagnosis in the last year. Based on data from Baltimore City and a conservative 42139 estimate, we assume 40% adherence to these guidelines [62,63].

43 44140 HIV Testing: In addition to combined HIV/STI testing that takes place as part of STI screening, we assume that all 4441 MSM experience an additional probability of HIV testing (in excess of testing though the STI program) can calibrate 46.42 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 49<sup>44</sup> well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT 50445 epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City 51146 Health Department as part of the STD Surveillance Network Project (see section 2 of the Supplementary Material).

52 47 PrEP: Our primary outcome for this analysis is the projected incidence of HIV after 20 years of delivering PrEP to 5448 MSM. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the 5**£**49 added benefit of targeting PrEP at individuals diagnosed with NG/CT. In all three scenarios, indication for PrEP use 5450 (eligibility) is considered in accordance with CDC recommendations and Baltimore City PrEP guidelines [64] (See

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<sup>3</sup> 151 section 1 of the Supplementary Material) and includes HIV-negative individuals who are diagnosed with NG/CT in 152 the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual ر 6<sup>153</sup> partnership in the last 6 months. The three scenarios are thus:

- 7 154 PrEP delivery at NG/CT diagnosis ("targeted" strategy & primary analysis): all MSM diagnosed with NG/CT <sup>8</sup> 155 are offered PrEP at the time of diagnosis 9
- 10156 PrEP evaluation at NG/CT screening/testing ("at-testing"): PrEP eligibility is evaluated at the time of 11157 screening/testing for NG/CT, and all eligible individuals are offered PrEP 12
- 1<u>3</u>158 Untargeted PrEP: PrEP eligibility is evaluated at random, and all eligible MSM are offered PrEP •

<sup>14</sup>159 All else being equal, increasing the number of MSM on PrEP will result in larger effects on HIV incidence (as more 15 160 16 people are protected from HIV transmission). However, for a given number of MSM screened – or a given number 1761 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. 18462 10463 Our primary aim was to quantify the extent of this gain in efficiency; thus, we compared scenarios in which the 20164 same number of MSM would be evaluated for PrEP, or alternatively the same number of MSM would be 21165 maintained on PrEP. Furthermore, to illustrate the potential impact of reaching highly ambitious targets for 2466 improved STI screening, we considered a hypothetical scenario for improving the underlying level of NG/CT <sup>23</sup>167 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.

- 27170 In all scenarios, we assume that PrEP eligibility is reassessed every 3 months among patients receiving PrEP, and <sup>28</sup>171 those who remain eligible for PrEP continue to receive it over time. Furthermore, we assume that in each scenario, <sup>29</sup> 172 a given proportion of eligible MSM who are offered PrEP will initiate prophylaxis (PrEP uptake ranging [0%-100%]) 30 31 31 31 and adhere to it (PrEP adherence ranging [0%-100%]), with adherence defined as taking a sufficient number of 32<sup>1</sup>74 doses to provide 60% protection against HIV transmission [65]. As a criterion for initiation of PrEP, all eligible MSM 33175 are also screened and treated for NG/CT infection before starting PrEP.
- <sup>34</sup>176 Sensitivity Analysis: A variety of sensitivity analyses were performed with the model. Using the HIV incidence at 35 36 36 10 years in absence and presence of PrEP (via all 3 scenarios) as the main output of interest, one-way sensitivity 3<del>7</del>78 analyses were performed to variation of all model parameters to +/- 25% of their original value. We also varied 3**§**179 condom usage among MSM on PrEP to model behavioral disinhibition (section 3 of the Supplementary Material).
- <sup>39</sup>180 40 Patient and Public Involvement: Patients and/or public were not involved in this study.

#### 41 42181 RESULTS

#### 43 44482 **Population overview**

45 183 46 The simulation models a population of 15,000 MSM in Baltimore City, projecting an average of 215 [95% UR: 181 – 4784 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% 4\$485 4**9**86 [47.4 – 50.6%] with non-urethral/rectal infection and 16.0% [14.8 – 17.2%] with pharyngeal-only infection. Point 50187 prevalence of NG/CT infection is estimated as 9.9% [8.4 – 11.5%], with 68.0% [63.5 – 72.5%] of infections 51188 occurring among black MSM (accounting for 58% of the MSM population) and 56.0% [54 – 58.2%] among MSM 52189 younger than 30 years old (accounting for 28% of the MSM population). Overall, 81.5% [81.0 – 82.1%] of MSM <sup>53</sup>190 <sup>54</sup>191 55 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.

- 5992 **Epidemiological impact of PrEP at NG/CT diagnosis** 57
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<sup>3</sup> 193 At baseline, and in the absence of PrEP (steady-state equilibrium), 361 [95% UR: 298 – 427] MSM were annually 4 \_\_\_\_\_\_194 diagnosed and treated for NG/CT infection (calibrated). If 60% of MSM diagnosed with NG/CT could be started on 5 , 6<sup>195</sup> PrEP (i.e., uptake = 60%) and maintained at a degree to which 60% of subsequent HIV infections were averted (i.e., <sub>7</sub>196 adherence = 60%), HIV incidence was estimated to decline by 12.4% [10.3 – 14.4%] over 20 years (Figure 2A). This <sub>8</sub>197 corresponds to averting 318 [253 – 385] potential HIV transmissions through 5808 [5730 – 5886] person-years of 9198 PrEP delivered, or 5479 [4330 – 6632] infections averted per 100,000 person-years of PrEP (Figure 2B). Under the 10199 current level of NG/CT diagnosis, the number of MSM receiving PrEP is projected to increase through the first 8 1200 years of the program (reaching a total of 332 [327 – 338] MSM on PrEP) and to fall afterward with declining 1201 incidence of NG/CT (Figure 2C). Due to the increased level of NG/CT screening/treatment among those on PrEP <sup>13</sup>202 <sup>14</sup>203 15 (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).

10204 The impact of PrEP on HIV incidence can be further increased by expanding the coverage of NG/CT screening at 17205 the community level. In our baseline model, 25.0% [95% UR: 24.0 – 26.0%] of MSM undergo NG/CT 18206 screening/testing at least once annually (CDC recommendation). In an expanded-screening scenario in which all 19 207 20 MSM experienced a 50% probability of screening for NG/CT annually, we projected a 180% increase in the 2708 27 baseline estimate of 4033 [3883 – 4182] annual NG/CT testing/screening events. Offering PrEP to those testing 2<del>2</del>09 positive for NG/CT subsequently provided a 22.0% [20.1 – 23.9%] decline in HIV incidence over 20 years, 23210 corresponding to 648 [589 – 710] potential HIV transmissions averted. For further information on levels of 24211 uncertainty in these results, see section 4 of the Supplementary Material. 25

## 2612 Relative impact of targeted versus untargeted PrEP

28 29<sup>13</sup> NG/CT-integrated PrEP increased efficiency of PrEP delivery in at least two ways (Figure 3A). First, a higher 30214 percentage of MSM were eligible for PrEP among those evaluated for PrEP (Figure 3B and 3C). In our model, 71.1% 3215 [95% UR: 65.0 – 77.2%] of all MSM diagnosed with NG/CT were eligible to receive PrEP (as 29% of this population 3216 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 3217 randomly selected MSM. Second, providing PrEP to MSM diagnosed with NG/CT targets individuals at higher risk 3218 of potential HIV infection (due to both biological factors and high-risk behavior), such that – under the baseline 35219 assumption of equal numbers of people receiving PrEP—impact of NG/CT-targeted PrEP on HIV incidence was <sup>3</sup><sup>6</sup>220 <sup>37</sup>221 <sup>38</sup>222 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 39222 NG/CT screening/testing, and by 1.6 [1.2 - 2.2] relative to untargeted PrEP. In another comparison, if the same 46223 number of individuals were evaluated for PrEP, the efficacy of NG/CT-integrated PrEP was increased even further 4224 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%

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Page 9 of 63

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<sup>3</sup> 236 protection – HIV incidence could be reduced by approximately 12%, averting one HIV infection annually per 1,000 <sup>4</sup>237 MSM population, with fewer than 20 per 1,000 taking PrEP every year. On the basis of infections averted per PrEP 5 6<sup>238</sup> 5 dose delivered, providing PrEP to MSM with NG/CT diagnosis is nearly twice as efficient as providing PrEP 7239 randomly among eligible MSM. Thus, use of NG/CT diagnosis as an entry point is a highly efficient and feasible <sub>8</sub>240 mechanism for PrEP delivery. If NG/CT screening could be expanded to 50% of MSM every year (with PrEP offered 9241 only to those testing positive), this impact could be more than doubled. Given this substantial potential impact, it 10242 will be important to assess willingness and uptake and identify best practices to support PrEP uptake and 1243 adherence among MSM diagnosed with NG/CT.

12 13244 These findings are consistent with other studies of PrEP delivery among MSM [66,67]. Previous studies have 1245 shown that the population-level impact of PrEP depends strongly on PrEP uptake and adherence [14,66], as 12246 suggested in our study as well. Importantly, NG/CT diagnosis may be useful in this regard, as MSM who have 16247 recently been diagnosed with an STI may be more aware of their HIV risk and more likely to accept and initiate 17248 PrEP. Past research has shown that HIV interventions may be more effective when they are conducted or initiated 18<u>2</u>49 at the time of an STI diagnosis [68]. Initiation of PrEP simultaneously with NG/CT diagnosis may also be a clinically 19 250 20 feasible approach – as an STI diagnosis is already likely to prompt an HIV test (if not already performed), and MSM -7251 21<sup>251</sup> who are diagnosed with NG/CT have at least some level of health care access. Unlike performing detailed sexual 22<sup>252</sup> histories, offering PrEP to all HIV-negative MSM diagnosed with NG/CT is a simple guideline that is easy for most 2253 clinicians to follow [69,70]. Further research is needed to assess the feasibility of this approach in the field, 24254 especially in ascertaining the degree to which the continuum of PrEP care (including linkage to care and longer-22255 term maintenance on PrEP) can be maintained in this population. Furthermore, the potential tradeoff between 26256 the positive impact of PrEP on STI prevalence through enhanced screening and its negative impact through <sup>27</sup>257 behavioral disinhibition (if MSM on PrEP adopt riskier sexual behaviors) merits further investigation. Additional <sup>28</sup>258 29 30 30 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, 3́7́60 financial strain, and stigma [11,71].

<sup>32</sup>61 As with any modeling analysis, our findings are limited by necessary simplifying assumptions. Given the overlap in <sup>33</sup>262 clinical practice for treating NG and CT and the substantial uncertainty regarding the natural history of the two 34 3263 35 infections (e.g., duration of infectiousness, propensity toward asymptomatic infection), we have combined these 36<sup>2</sup>64 infections as a single entity (NG/CT) and have used composite parameter values to describe the natural history of 3765 both diseases. However, there are still important differences between NG and CT, and to the extent that the 38266 natural history of each disease may differ, our findings may over- or under-estimate the impact of PrEP targeted at 39267 these STIs. For example, an infection with a shorter infectious period and a higher transmission probability per sex 40268 act will concentrate more strongly in high risk networks and may provide a more effective entry point for HIV PrEP. 4269 Further research can extend our analysis by considering the impact of each disease separately on HIV transmission 4270 dynamics. Furthermore, due to limited data on site-specific transmission dynamics (e.g., relative frequency of oral-4<u>3</u> 271 only versus oral-plus-anal versus anal-only sex among MSM in Baltimore), we adopted a simplified approach that 45<sup>47</sup>272 does not fully capture the complete transmission dynamics but should result in the appropriate distributions of 4**6**73 NG/CT infections at each anatomical site. Additional simplifying assumptions used in the underlying HIV simulation 47274 model include applying the same sexual network for NG/CT and HIV transmission; simplification of sexual 42275 networks as comprising only stable and casual partnerships; simplified definition of sexual activity classes as a 4**2**76 lifetime attribute among MSM; exclusion of serosorting on HIV, sexual activity class or PrEP; exclusion of HIV 50277 transmission through injection drugs or heterosexual sex; and exclusion of transgender individuals from the <sup>5</sup>278 simulated population. To the extent that these dynamics result in higher concentration of NG/CT among MSM at 52 279 53 high-risk for HIV infection, our model may underestimate the impact of STI-targeted PrEP.

5480 We excluded the potential existence of behavioral disinhibition for MSM on PrEP in the main analysis and applied 5281 a simplified approach for modeling the combined role of PrEP uptake/adherence for HIV protection. In additional

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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

<sup>1</sup><sup>2</sup>89 rate of condom use reduction.

12 1,290 There are strong racial disparities in HIV incidence and healthcare access in the US, such that the highest risk 14291 populations may be the ones least likely to have access to PrEP [72]; these disparities were not included in our 15292 simplified cascade of PrEP. Our model calibration was limited to the scope of local surveillance data, and available 1⁄293 literature for values lacking direct empiric estimates from Baltimore City (e.g., probability of symptomatic 1794 infection). We also assumed a future trajectory of HIV infection in the future that represents continuation of 18295 current trends; this trajectory is unlikely to remain constant for the next 20 years but may help to provide a useful 19 296 conceptual construct for present-day decision-making, which is the ultimate goal of this analysis. Our results are 2<sup>297</sup> further limited by exclusion of syphilis infection, another STI that is often transmitted in the same populations and 2<del>2</del>98 may affect transmission and acquisition of HIV. Finally, we did not incorporate cost or other resource constraints 23299 into the present model; future analyses could evaluate the efficiency of NG/CT-targeted PrEP delivery from a cost-24300 effectiveness or budget impact perspective.

25 26 26 In summary, this stochastic agent-based model representing the co-dynamics of NG/CT and HIV transmission 27<sup>3</sup>02 among MSM suggests that NG/CT diagnosis may serve as an efficient and effective entry point for PrEP. If linkage 2803 between STI and HIV control programs can be effectively developed, further investment in NG/CT screening 29304 (followed by PrEP initiation) can have major impact, not only on the incidence and prevalence of NG/CT, but also 30305 on transmission of HIV – potentially averting up to 20% of all HIV infections through NG/CT-targeted PrEP alone. 3306 Future analyses could evaluate whether such approaches could even be cost-saving in the long term. Ultimately, 32307 ending the HIV epidemic in MSM populations will require a combination of multiple activities, including <sup>33</sup>308 strengthening the continuum of HIV care, ensuring continued access to clinical services, and prevention through 34 3309 both behavioral approaches (e.g., condom use) and PrEP. Using NG/CT diagnosis as an entry point for PrEP 36<sup>3</sup>10 initiation may serve as an important component of such a combined prevention approach.

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## <sup>14</sup><sub>320</sub> 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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### <sup>38</sup>336 **Disclaimer:** 39

4@37The findings and conclusions in this report are those of the authors and do not necessarily reflect the official4B38position of the Centers for Disease Control and Prevention, or the authors' affiliated institutions.

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## 4440 Data sharing statement:

- 4341 Additional data are presented in the online Supplementary Material.
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## <sup>5</sup><sub>6</sub>515 **Figure legends:**

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<sup>9</sup>517 Figure 1: An agent-based model of gonorrhoea/chlamydia (NG/CT) and HIV co-transmission. The top panel  $10^{11}$  $15^{18}$ represents the HIV care continuum and natural history: Upon infection with HIV, individuals serially progress 12<sup>519</sup> through three disease stages over time; this progression can be halted by initiation of antiretroviral therapy (ART), 1,520 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 14521 15522 initiation do not affect HIV transmission in the model). HIV-positive individuals in care are assumed to undergo 16523 regular screening for NG/CT (marked in red) subject to patients presenting for scheduled visits and clinician <sup>17</sup>524 decision to screen. The bottom panel represents the natural history of NG/CT: infection may be symptomatic or <sup>18</sup>525 asymptomatic, individuals remain infectious until diagnosis and treatment (which can occur either through 19<sup>23</sup> 20<sup>25</sup> symptomatic presentation to care or routine screening of asymptomatic individuals) or spontaneous resolution. 2<sup>527</sup> 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. 22528

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.

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Figure 3: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CT-34537 35538 integrated PrEP (in green, also corresponding to the green line in Figure 2), compared against PrEP evaluation at 36539 NG/CT screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in 37540 the manuscript text. In the first set of experiments, the three strategies are compared under the assumption that <sup>38</sup>541 the same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be <sup>39</sup>542 screened for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM 40<sup>-</sup> 41<sup>-</sup>43 approached for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and 4<del>5</del>44 panel D the cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CTtargeted scenario (similar pattern in panels E through H). 4,545

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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.

145x124mm (300 x 300 DPI)



NG/CT every year, with those testing positive for NG/CT also offered PrEP.

317x317mm (300 x 300 DPI)





Figure 3: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CTintegrated 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).

338x208mm (300 x 300 DPI)
# 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 nonblack 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 onelevel 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.

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	

# Table S1: List of CSA group and member CSAs

#### 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 venuebased 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.

	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%

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

#### **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*<sub>SA</sub>) 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:

$$\begin{split} P_{new\_stb} &= p_{Stb} \times c_{Part|Age} \\ P_{new\_csl} &= p_{Csl} \times p^*_{Csl|Stb} \times c_{Part|Age} \times c_{SA} \\ p^*_{Csl|Stb} &= \begin{bmatrix} p_{Csl|Stb} & number \ of \ stable \ partnerships > 0 \\ 1 & o.w. \end{split}$$

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.

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

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.

<b>BESURE Waves:</b>	<b>ADSR</b> <sub>stb</sub>	ADSR <sub>csi</sub>
	(Number of reported partnerships)	(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	<u>0.6</u>	<u>0.74</u>



# 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/  $\mu$ L), stage 2 (CD4 count between 200-500 cells/  $\mu$ L) and stage 3 (CD4 count <200 cells/  $\mu$ L). 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 <u>achieve viral suppression 8 to 24 weeks</u> 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/  $\mu$ L) 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<sup>1</sup>. 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

<sup>&</sup>lt;sup>1</sup> 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.

<sup>-</sup> 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(X, Y, 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<sub>Inf</sub>: Person Y's infectiousness

X<sub>Sus</sub>: 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<sub>sexualPositionCoef</sub>: 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:

$$PPSC(S,A,R) = \frac{(13-A)}{12} \times \frac{(S)}{3} \times pAccessCare(R) \times C$$

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).

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

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

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

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**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.

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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 individuallevel 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 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/CTtargeted 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) <ul> <li>Stable partnerships</li> <li>Casual partnerships</li> </ul>	0.6	[35]
Race mixing (Likelihood of mixing with a partner of the same	0.75	
race) - Black & Black - White & White	0.9 0.75	[35]
Likelihood of condom use <ul> <li>Stable partnerships</li> <li>Casual partnerships</li> </ul>	[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 <sup>2</sup>	[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 <sup>3</sup>	[61–65]
Increase in HIV susceptibility (from urethral or rectal infection)	[1- 2.5] fold <sup>3</sup>	[16,28,65,66]

<sup>2</sup> Values are selected over uniform distributions across the ranges presented

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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	35%	Calibrated to provide the site-
- Rectal	49%	specific incidence of NG/CT
- Pharyngeal	16%	
Weekly probability of symptomatic NG/CT testing		
- Urethral	0.009	Calibrated to provide the site-
- Rectal	0.001	specific diagnosis of NG/CT
- Pharyngeal	0.04	
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]
ні		
Disease stage duration		
<ul> <li>Stage 1 (CD4 &gt;500 cells/μL): Acute</li> </ul>	[6 – 9] weeks <sup>3</sup>	
<ul> <li>Stage 2 (CD4 200-499 cells/μL): Chronic</li> </ul>	[8 – 10] years	[5,67,68] [5,69] [5,67,69]
- Stage 3 (CD4 <200 cells/μL) <sup>3</sup> : Late stage	[1 – 3] years	
Time from ART initiation to full viral suppression	[4-24] weeks <sup>3</sup>	[70]
Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup>	ART treatment duration up to one year	[71–74]
Mortality rate <sup>3</sup>		
- Stage 1 & 2, no ART	5 per 1000 person years	
- Stage 3, no ART	1/duration of stage 3	[12–14]
- Reduction in mortality due to ART	58%	
Average viral load (log10 copies/mL)		
- Stage 1, no ART	6.5	
- Stage 2, no ART	4.5	
- Stage 3, no ART	5	[5]
- On ART, partially suppressed	3.5	
- On ART, fully suppressed	1.5	
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]

<sup>3</sup> Mortality rate in stage 3 is defined as 1/(duration of stage 3).

<sup>4</sup> Infectiousness assumed equal to that of stage 2

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Gap in	care after ART discontinuation	26 weeks	[15]
Weekly	probability of		
-	Screening for HIV only (not NG/CT)	0.0065	Calibrated to provide the HIV
-	Linkage to care (if HIV-positive and not linked)	0.0065	cascade of care
-	Starting ART (if engaged)	0.095	
Relativ	e 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 Je eing tv nent). 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.





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**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.

# 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

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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%

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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

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7	Viral load level in HIV stage3 (late) +	
8	Viral load level in HIV stage2 (chronic) +	
9	Viral load level in HIV stage2 (chronic) -	
10	Viral load level in HIV stage1 (early) +	
11	Prob. of starting new stable partnerships +	
12		
13	Prob. of starting new stable partnerships -	
14	Prob. of starting new casual partnerships +	
15	Prob. of starting new casual partnerships -	
10 17	Prob. of never using condoms in casual partnerships +	
1/ 10	Prob. of never using condoms in casual partnerships -	
19	Condom effectiveness for HIV transmission +	
20	Condom effectiveness for HIV transmission -	
21	Coef. of NG/CT transmission +	
22	Coof of new partnerships for high sexual activity class +	
23		
24	Coet. of new partnerships for age 20 to 25 +	
25	Coef. of new casual partnerships for those with a stable partner +	
26	Coef. of new casual partnerships for those with a stable partner -	
27	Coef. of HIV transmission +	
28	Coef. of HIV transmission -	
29	Coef. of age mixing for stable partnerships +	
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32	-1	100 -50 0 50 100 %Difference from baseline
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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

Viral load level in HIV stage3 (late)	+						
Viral load level in HIV stage2 (chronic)	+						
Viral load level in HIV stage2 (chronic)	) -						
Viral load level in HIV stage1 (early)	+				12		
Prob. of starting new stable partnerships	+						
Prob. of starting new stable partnerships							
Prob. of starting new casual partnerships	+		_				
Prob. of starting new casual partnerships							
Prob. of never using condoms in casual partnerships	+						
Prob. of never using condoms in casual partnerships							
Condom effectiveness for HIV transmission	+						
Condom effectiveness for HIV transmission	-						
Coef. of NG/CT transmission	+						
Coef. of new partnerships for high sexual activity class	+						
Coef. of new partnerships for age 20 to 25	+						
Coef. of new casual partnerships for those with a stable partner	+						
Coef. of new casual partnerships for those with a stable partner	r -						
Coef. of HIV transmission	+						
Coef. of HIV transmission	-						
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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.

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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

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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/CTtargeted scenario.

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### **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.

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# **BMJ Open**

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

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42 43	26	Key messages:	
44.		Several barriers exist to the successful implementation of PrEP in local settings, and optimizing the	
45 <u>(</u> 46 •	28	efficiency of PrEP delivery is a public health priority	
47 48 49	29 30	<ul> <li>Targeting MSM infected with Neisseria gonorrhoeae and/or Chlamydia trachomatis increases the efficiency and effectiveness of PrEP delivery</li> </ul>	
50 g 51 g	31 32	<ul> <li>Expanding levels of STI screening among MSM can significantly improve the impact of PrEP (with PrEP offered to those testing positive)</li> </ul>	
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# 34 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.

<sup>13</sup>41 **Results**: Assuming 60% uptake and 60% adherence, targeting PrEP to MSM diagnosed with NG/CT could reduce 14<sup>41</sup> 15<sup>42</sup> HIV incidence among MSM in Baltimore City by 12.4% [95% uncertainty range (UR): 10.3 – 14.4%] in 20 years, 16<sup>43</sup> relative to no PrEP. Expanding the coverage of NG/CT screening (such that individuals experience a 50% annual 17 44 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 20 47 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 21 48 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.

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5 52 4	Strengths and limitations of this study
5 53 6 54 7 55 8 56 9 57 10 58 11	<ul> <li>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.</li> </ul>
12 59 13 60 <sup>14</sup> 61 <sup>15</sup> 62	<ul> <li>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.</li> </ul>
16 02 17 63 18 64 19 65 20 66 21 67	<ul> <li>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.</li> </ul>
22 68 23 69 24 70 25 71 26 71 27 72	<ul> <li>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.</li> </ul>
28 73 29 74 30 75 31 76 32	<ul> <li>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.</li> </ul>
<sup>33</sup> 77 <sup>34</sup> 78 <sup>35</sup> 79	<b>Keywords:</b> HIV Infections; Gonorrhoea; Chlamydia; Pre-Exposure Prophylaxis; Homosexuality, Computer Simulation
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# <sup>3</sup><sub>4</sub> 80 **BACKGROUND**

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5 81 Infection with Neisseria gonorrhoeae (NG) and/or Chlamydia trachomatis (CT) may impact HIV transmission in 6 82 multiple ways, particularly among men who have sex with men (MSM). From a biological standpoint, NG/CT 7 83 infection may increase one's susceptibility to HIV acquisition: rectal infection in particular has been linked to an 8 9 84 increased risk of HIV acquisition [1,2]. HIV and NG/CT also share many risk factors at the individual level (e.g., 10 85 condomless sex) and network level (e.g., having sex within a high-prevalence network), such that the three 11 86 conditions are often epidemiologically linked [3]. Additionally, HIV-negative men have an increased risk of HIV <sup>12</sup> 87 acquisition when in partnership with a HIV-positive partner who is also co-infected with NG/CT [4,5]. As a result, 14<sup>88</sup> 13 better diagnosis and treatment of NG/CT can potentially reduce HIV incidence [6], and help to identify individuals 15 <sup>89</sup> at high risk of future HIV infection.

16<sub>90</sub> Pre-Exposure Prophylaxis (PrEP) is part of comprehensive HIV prevention services in which HIV-negative people 17<sup>-</sup>91 take daily antiretroviral medication to lower risk of HIV transmission upon exposure. The U.S. Centers for Disease 18 91 19 92 Control and Prevention (CDC) has recommended PrEP for HIV-negative individuals at substantial risk of infection 20<sup>93</sup> [7]. Among MSM, this includes HIV-negative men who are either diagnosed with a sexually transmitted infection 21 94 (STI) in the last 6 months, are in a HIV discordant partnership, or report a condomless sex act in the last 6 months. 22 95 Despite this broad recommendation, the potential population-level impact of PrEP remains uncertain. Several 23 96 barriers exist to the successful implementation of PrEP, including providers' perceived inability to deliver PrEP in 2497 primary care settings [8], individuals' limited knowledge of PrEP effectiveness [9], low self-perceived risk for HIV 25 98 infection [10], patients' difficulty in maintaining adherence [11], and high costs (at over \$10,000 per person-year 26<sub>99</sub> for those without insurance or access to a medication assistance plan) [12,13]. 27

28100 Given these challenges, optimizing the efficiency of PrEP delivery is a public health priority. Specifically, it is 29101 important to tailor PrEP delivery to those who stand to gain the most from its preventive efficacy. Given the 3902 epidemiologic link between NG/CT infection and HIV among MSM, new NG/CT diagnoses may serve as a useful <sup>3</sup>103 <sup>32</sup>104 <sup>33</sup>104 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 34<sup>105</sup> surveillance data from Baltimore City, Maryland, to construct an agent-based simulation model of the co-3**4**06 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. 36107 37

### 38108 **METHODS** 39

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).

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

Neisseria gonorrhoeae (NG) and Chlamydia trachomatis	Value	Reference
(CT) Parameters		
Proportion of cases symptomatic <sup>1</sup>	7/0/	[16]
Urethral	20%	[10] [17 19]
Rectal	10%	[17,10]
Pharyngeal	10/0	
Duration of infection (at each site) in the absence of treatment	[3 – 12] months <sup>2</sup>	[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 s
• Rectal	0.49	specific incidence of NG/C
Pharyngeal	0.16	
Increase in HIV transmissibility (for those with urethral or rectal infection)	[1.5 – 2] fold <sup>1</sup>	[34–38]
Increase in HIV susceptibility (for those with urethral or	[1-2.5] fold <sup>1</sup>	[19,20,38,39]
rectal infection)		
NG/CT Calibration Targets	Mean <sup>3</sup> [Range]	
Annual diagnosis of NG/CT among MSM in Baltimore City		Values estimated from loca
Urethral	337 [269 – 405]	data on gonorrhea surveilla
• Rectal	25 [18 – 33]	and STI clinic visitis in Balti
Pharyngeal	42 [23 – 60]	City (See section 2 in the
	6	Supplementary Material)
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 <sup>1</sup>	[40,41]
Chronic	[8 –10] years <sup>1</sup>	[42,43]
• Late stage <sup>4</sup>	[1-3] years <sup>1</sup>	[42-44]
Mortality rate <sup>3</sup>		
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	
-	ART treatment duration up to one year	[48–51]
Time from ART discontinuation to pre-ART CD4 nadir <sup>5</sup>		

<sup>1</sup> Values represent a pooled estimate of the reported measures for NG and CT infections

<sup>2</sup> Values are selected over uniform distributions across the ranges presented.

<sup>3</sup> 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).

<sup>4</sup> Mortality rate in late stage is defined as 1/(duration of late stage disease).

<sup>5</sup> 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	
<ul> <li>On ART, partially suppressed</li> </ul>	3.5	
On ART, fully suppressed	1.5	
Infectiousness per sexual contact	2.45 <sup>(log(VL)-4.5)</sup>	[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	0.5	[58]
MSM compared to white MSM		
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	

25122 STI Screening: In addition to testing of symptomatic NG/CT diagnosis, we also assume screening of <sup>26</sup>123 27 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 39<sup>1</sup>33 continuously engaged in HIV care should undergo repeated NG/CT screening at least annually [15]. More 40134 frequent screening, such as screening every 3-6 months, is recommended for high-risk MSM, including 4135 those with an NG/CT diagnosis in the last year. Based on data from Baltimore City and a conservative 42136 estimate, we assume 40% adherence to these guidelines [62,63].

43 44137 HIV Testing: In addition to combined HIV/STI testing that takes place as part of STI screening, we assume that all 4,438 MSM experience an additional probability of HIV testing (in excess of testing though the STI program) can calibrate 46139 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 49<sup>41</sup> well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT 5042 epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City 51143 Health Department as part of the STD Surveillance Network Project (see section 2 of the Supplementary Material).

52 44 PrEP: Our primary outcome for this analysis is the projected incidence of HIV after 20 years of delivering PrEP to 54<sup>145</sup> MSM. We measure this outcome in three different PrEP delivery scenarios, selected for purposes of evaluating the 5**£**46 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 5447

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<sup>3</sup>148 section 1 of the Supplementary Material) and includes HIV-negative individuals who are diagnosed with NG/CT in 149 the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual ر 6<sup>150</sup> partnership in the last 6 months. The three scenarios are thus:

- 7 151 PrEP delivery at NG/CT diagnosis ("targeted" strategy & primary analysis): all MSM diagnosed with NG/CT <sup>8</sup> 152 are offered PrEP at the time of diagnosis 9
- 10153 PrEP evaluation at NG/CT screening/testing ("at-testing"): PrEP eligibility is evaluated at the time of 11154 screening/testing for NG/CT, and all eligible individuals are offered PrEP 12
- 1<u>3</u>155 Untargeted PrEP: PrEP eligibility is evaluated at random, and all eligible MSM are offered PrEP

<sup>14</sup>156 All else being equal, increasing the number of MSM on PrEP will result in larger effects on HIV incidence (as more <sup>15</sup> 157 people are protected from HIV transmission). However, for a given number of MSM screened – or a given number 1<sup>758</sup> 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. 18159 10460 Our primary aim was to quantify the extent of this gain in efficiency; thus, we compared scenarios in which the 20161 same number of MSM would be evaluated for PrEP, or alternatively the same number of MSM would be 21162 maintained on PrEP. Furthermore, to illustrate the potential impact of reaching highly ambitious targets for 2463 improved STI screening, we considered a hypothetical scenario for improving the underlying level of NG/CT <sup>23</sup>164 <sup>24</sup>165 25 26 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.

27167 In all scenarios, we assume that PrEP eligibility is reassessed every 3 months among patients receiving PrEP, and <sup>28</sup>168 those who remain eligible for PrEP continue to receive it over time. Furthermore, we assume that in each scenario, <sup>29</sup>169 30 3170 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 32171 doses to provide 60% protection against HIV transmission [65]. As a criterion for initiation of PrEP, all eligible MSM 33172 are also screened and treated for NG/CT infection before starting PrEP.

<sup>34</sup>173 Sensitivity Analysis: A variety of sensitivity analyses were performed with the model. Using the HIV incidence at 36<sup>174</sup> 10 years in absence and presence of PrEP (via all 3 scenarios) as the main output of interest, one-way sensitivity 37175 analyses were performed to variation of all model parameters to +/- 25% of their original value. We also varied 3**§**176 condom usage among MSM on PrEP to model behavioral disinhibition (section 3 of the Supplementary Material).

<sup>39</sup>177 40 Patient and Public Involvement: Patients and/or public were not involved in this study.

#### RESULTS 42<sup>178</sup>

#### 43 44179 **Population overview**

45 180 46 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% 4\$182 4**9**83 [47.4 – 50.6%] with non-urethral/rectal infection and 16.0% [14.8 – 17.2%] with pharyngeal-only infection. Point 50184 prevalence of NG/CT infection was estimated as 9.9% [8.4 – 11.5%], with 68.0% [63.5 – 72.5%] of infections 51185 occurring among black MSM (accounting for 58% of the MSM population). New infections occurred primarily in 52186 younger individuals, with 74% [72 – 78%] of new NG/CT infections occurring in MSM younger than 35 years old, <sup>53</sup>187 <sup>54</sup>188 55 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 56189 accounted for 33% of the simulated population (Figure 2C and 2D). Overall, 81.5% [81.0 – 82.1%] of MSM

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<sup>3</sup> 190 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.

### 6 192 Epidemiological impact of PrEP at NG/CT diagnosis

7 8 193 At baseline, and in the absence of PrEP (steady-state equilibrium), 361 [95% UR: 298 – 427] MSM were annually 9194 diagnosed and treated for NG/CT infection (calibrated). If 60% of MSM diagnosed with NG/CT could be started on 10195 PrEP (i.e., uptake = 60%) and maintained at a degree to which 60% of subsequent HIV infections were averted (i.e., 11196 adherence = 60%), HIV incidence was estimated to decline by 12.4% [10.3 – 14.4%] over 20 years (Figure 3A). This 12,97 corresponds to averting 318 [253 – 385] potential HIV transmissions through 5808 [5730 – 5886] person-years of 13198 PrEP delivered, or 5479 [4330 – 6632] infections averted per 100,000 person-years of PrEP (Figure 3B). Under the  $^{14}_{199}$ 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 1<del>7</del>01 incidence of NG/CT (Figure 3C). Due to the increased level of NG/CT screening/treatment among those on PrEP 1&02 (through reassessment every 3 months), the prevalence of NG/CT was estimated to decline by 43.3% [41.6 -1203 44.9%] over 20 years of PrEP implementation (Figure 3D).

04 The impact of PrEP on HIV incidence can be further increased by expanding the coverage of NG/CT screening at 21 22<sup>205</sup> the community level. In our baseline model, 25.0% [95% UR: 24.0 – 26.0%] of MSM undergo NG/CT 2206 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 2207 2208 baseline estimate of 4033 [3883 – 4182] annual NG/CT testing/screening events. Offering PrEP to those testing 2009 positive for NG/CT subsequently provided a 22.0% [20.1 – 23.9%] decline in HIV incidence over 20 years, 27/10 corresponding to 648 [589 – 710] potential HIV transmissions averted. For further information on levels of <sup>28</sup>211 uncertainty in these results, see section 4 of the Supplementary Material. 29

# Relative impact of targeted versus untargeted PrEP

32 NG/CT-integrated PrEP increased efficiency of PrEP delivery in at least two ways (Figure 4A). First, a higher 33213 34214 percentage of MSM were eligible for PrEP among those evaluated for PrEP (Figure 4B and 4C). In our model, 71.1% 35215 [95% UR: 65.0 – 77.2%] of all MSM diagnosed with NG/CT were eligible to receive PrEP (as 29% of this population <sup>36</sup>216 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 3217 randomly selected MSM. Second, providing PrEP to MSM diagnosed with NG/CT targets individuals at higher risk 38, 18 of potential HIV infection (due to both biological factors and high-risk behavior), such that – under the baseline 36 40<sup>219</sup> assumption of equal numbers of people receiving PrEP—impact of NG/CT-targeted PrEP on HIV incidence was 4220 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 4221 43222 NG/CT screening/testing, and by 1.6 [1.2 - 2.2] relative to untargeted PrEP. In another comparison, if the same 44223 number of individuals were evaluated for PrEP, the efficacy of NG/CT-integrated PrEP was increased even further 45/24 relative to other scenarios (Figure 4E through 4H). 46

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).

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# <sup>3</sup><sub>4</sub>232 **DISCUSSION**

5 <sub>6</sub>233 This agent-based simulation of HIV transmission among MSM suggests that screening for NG/CT may be an 7 2 3 4 important and efficient entry point for PrEP evaluation and delivery. Specifically, if all MSM who currently test 8235 positive for NG/CT could be offered PrEP – assuming 60% uptake and sufficient adherence to maintain 60% 9236 protection – HIV incidence could be reduced by approximately 12%, averting one HIV infection annually per 1,000 10237 MSM population, with fewer than 20 per 1,000 taking PrEP every year. On the basis of infections averted per PrEP 1338 dose delivered, providing PrEP to MSM with NG/CT diagnosis is nearly twice as efficient as providing PrEP 1239 13 14 14 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 1<u>5</u>41 only to those testing positive), this impact could be more than doubled. Given this substantial potential impact, it 1242 will be important to assess willingness and uptake and identify best practices to support PrEP uptake and adherence among MSM diagnosed with NG/CT. 17243

18 19<sup>44</sup> These findings are consistent with other studies of PrEP delivery among MSM [66,67]. Previous studies have 20245 shown that the population-level impact of PrEP depends strongly on PrEP uptake and adherence [14,66], as 2246 suggested in our study as well. Importantly, NG/CT diagnosis may be useful in this regard, as MSM who have 22247 recently been diagnosed with an STI may be more aware of their HIV risk and more likely to accept and initiate 23248 PrEP. Past research has shown that HIV interventions may be more effective when they are conducted or initiated 22/249 at the time of an STI diagnosis [68]. Initiation of PrEP simultaneously with NG/CT diagnosis may also be a clinically 25250 feasible approach – as an STI diagnosis is already likely to prompt an HIV test (if not already performed), and MSM <sup>26</sup>251 who are diagnosed with NG/CT have at least some level of health care access. Unlike performing detailed sexual 27 27 252 28 histories, offering PrEP to all HIV-negative MSM diagnosed with NG/CT is a simple guideline that is easy for most 29253 clinicians to follow [69,70]. Further research is needed to assess the feasibility of this approach in the field, -254 36254 especially in ascertaining the degree to which the continuum of PrEP care (including linkage to care and longer-3255 term maintenance on PrEP) can be maintained in this population. Furthermore, the potential tradeoff between 32256 the positive impact of PrEP on STI prevalence through enhanced screening and its negative impact through 33257 behavioral disinhibition (if MSM on PrEP adopt riskier sexual behaviors) merits further investigation. Additional 34,58 implementation research is also needed to identify effective mechanisms for improving adherence to CDC PrEP <sup>35</sup>259 guidelines and overcoming barriers to acceptance and uptake of PrEP such as lack of awareness, lack of access, 36 260 37 financial strain, and stigma [11,71].

38261 As with any modeling analysis, our findings are limited by necessary simplifying assumptions. Given the overlap in 3262 clinical practice for treating NG and CT and the substantial uncertainty regarding the natural history of the two <sup>40</sup>263 infections (e.g., duration of infectiousness, propensity toward asymptomatic infection), we have combined these <sup>4</sup><sup>1</sup><sub>264</sub> <sup>42</sup> <sup>42</sup> <sup>42</sup> <sup>42</sup> <sup>45</sup> 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 4**4**266 history of each disease may differ, our findings may over- or under-estimate the impact of PrEP targeted at these 4**⊋**67 STIs. For example, an infection with a shorter infectious period and a higher transmission probability per sex act will 4268 concentrate more strongly in high risk networks and may provide a more effective entry point for HIV PrEP. Further 42269 research can extend our analysis by considering the impact of each disease separately on HIV transmission dynamics. 4&70 Furthermore, due to limited data on site-specific transmission dynamics (e.g., relative frequency of oral-only versus 4271 oral-plus-anal versus anal-only sex among MSM in Baltimore), we adopted a simplified approach that does not fully <sup>50</sup>272 capture the complete transmission dynamics but should result in the appropriate distributions of NG/CT infections 51/252/7352/7352/74at 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 <sub>54</sub>275 only stable and casual partnerships; simplified definition of sexual activity classes as a lifetime attribute among 5**≩**76 MSM; exclusion of serosorting on HIV, sexual activity class or PrEP; exclusion of HIV transmission through injection 56277 drugs or heterosexual sex; and exclusion of transgender individuals from the simulated population. To the extent

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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.

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6280 We excluded the potential existence of behavioral disinhibition for MSM on PrEP in the main analysis and applied 7281 a simplified approach for modeling the combined role of PrEP uptake/adherence for HIV protection. In additional <sup>8</sup>282 sensitivity analyses, we studied the impact of decreased condom use among MSM on PrEP on the outcome of <sup>9</sup>283 NG/CT-targeted PrEP, and the relative efficacy of STI-targeted scenario compared to the other comparators (See 17<sup>84</sup> section 3 of the Supplementary Material). As expected, the projected impact of NG/CT-targeted PrEP on incidence 12<sup>285</sup> of HIV and NG/CT declined with reduced levels of condom use among PrEP users. This further highlights the need 1,286 for additional behavioural surveillance data characterizing changes in level of condom use and risky behaviours 12287 among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis (increased 15288 effectiveness of PrEP implementation through an NG/CT targeted approach) remained robust to variation in the 16289 rate of condom use reduction.

17 18290 There are strong racial disparities in HIV incidence and healthcare access in the US, such that the highest risk 19291 populations may be the ones least likely to have access to PrEP [72]; these disparities were not included in our 20292 simplified cascade of PrEP. Our model calibration was limited to the scope of local surveillance data, and available 2293 literature for values lacking direct empiric estimates from Baltimore City (e.g., probability of symptomatic 2294 infection). We also assumed a future trajectory of HIV infection in the future that represents continuation of <sup>23</sup>295 current trends; this trajectory is unlikely to remain constant for the next 20 years but may help to provide a useful <sup>24</sup>296 conceptual construct for present-day decision-making, which is the ultimate goal of this analysis. Our results are 26<sup>-2</sup>97 further limited by exclusion of syphilis infection, another STI that is often transmitted in the same populations and 2<sup>798</sup> may affect transmission and acquisition of HIV. Finally, we did not incorporate cost or other resource constraints 2**&**99 into the present model; future analyses could evaluate the efficiency of NG/CT-targeted PrEP delivery from a cost-2\$300 effectiveness or budget impact perspective.

30 31<sup>301</sup> In summary, this stochastic agent-based model representing the co-dynamics of NG/CT and HIV transmission 32<sup>3</sup>02 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 3303 34304 (followed by PrEP initiation) can have major impact, not only on the incidence and prevalence of NG/CT, but also 35305 on transmission of HIV – potentially averting up to 20% of all HIV infections through NG/CT-targeted PrEP alone. 36306 Future analyses could evaluate whether such approaches could even be cost-saving in the long term. Ultimately, 37307 ending the HIV epidemic in MSM populations will require a combination of multiple activities, including 38308 strengthening the continuum of HIV care, ensuring continued access to clinical services, and prevention through 39ี 309 both behavioral approaches (e.g., condom use) and PrEP. Using NG/CT diagnosis as an entry point for PrEP 40 4<sup>3</sup>10 initiation may serve as an important component of such a combined prevention approach.

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#### 12<sup>319</sup> 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.

# $20^{2}$ **Conflict of interest:**

 $^{2}$  All authors report no potential conflicts of interest.

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### 35 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.

### 4B39 Data sharing statement:

- **2**40 Additional data are presented in the online Supplementary Material.

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# <sup>3</sup><sub>4</sub>509 **Figure legends:**

#### 5 6 510

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<sup>7</sup>511 Figure 1: An agent-based model of gonorrhoea/chlamydia (NG/CT) and HIV co-transmission. The top panel 8 512 represents the HIV care continuum and natural history: Upon infection with HIV, individuals serially progress <sup>9</sup><sub>10</sub>513 through three disease stages over time; this progression can be halted by initiation of antiretroviral therapy (ART), 1<sub>1</sub>514 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 12515 1\$16 initiation do not affect HIV transmission in the model). HIV-positive individuals in care are assumed to undergo 14517 regular screening for NG/CT (marked in red) subject to patients presenting for scheduled visits and clinician 15518 decision to screen. The bottom panel represents the natural history of NG/CT: infection may be symptomatic or <sup>16</sup>519 asymptomatic, individuals remain infectious until diagnosis and treatment (which can occur either through <sup>1</sup>7 520 symptomatic presentation to care or routine screening of asymptomatic individuals) or spontaneous resolution. 18 19<sup>20</sup> 19<sup>21</sup> Upon diagnosis with incident NG/CT, we assume that individuals are also screened for HIV infection (marked in 20<sup>5</sup>22 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.

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36 3<del>⊅</del>35 Figure 4: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CTintegrated PrEP (in red, also corresponding to the red line in Figure 3), compared against PrEP evaluation at NG/CT ვდ536 3\$537 screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the 4538 manuscript text. In the first set of experiments, the three strategies are compared under the assumption that the 4539 same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be screened <sup>4</sup><del>3</del>40 for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM approached <sup>43</sup>541 for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the 44 542 cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted 48<sup>543</sup> scenario (similar pattern in panels E through H).

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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.

145x124mm (300 x 300 DPI)



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.

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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.

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Page 21 of 63

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Figure 4: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CTintegrated 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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# 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 nonblack 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 onelevel 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.

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

### Table S1: List of CSA group and member CSAs

### 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.

	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*<sub>SA</sub>) 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:

$$\begin{split} P_{new\_stb} &= p_{Stb} \times c_{Part|Age} \\ P_{new\_csl} &= p_{Csl} \times p^*_{Csl|Stb} \times c_{Part|Age} \times c_{SA} \\ p^*_{Csl|Stb} &= \begin{bmatrix} p_{Csl|Stb} & number \ of \ stable \ partnerships > 0 \\ 1 & o.w. \end{split}$$

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
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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.

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

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 <sub>Stb</sub>		<b>ADSR</b> <sub>Csl</sub>	
	(Number of partnerships)	reported	(Number partners	of reported ships)
Wave 2	0.62 (66)		0.72 (75)	
Wave 3	0.68 (71)		0.73 (87)	
Wave 4	0.51 (62)		0.76 (77)	
<u>Average estimate</u>	<u>0.6</u>		<u>0.74</u>	





# 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/  $\mu$ L), stage 2 (CD4 count between 200-500 cells/  $\mu$ L) and stage 3 (CD4 count <200 cells/  $\mu$ L). 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 <u>achieve viral suppression 8 to 24 weeks</u> 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/  $\mu$ L) 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<sup>1</sup>. 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

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<sup>&</sup>lt;sup>1</sup> 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.

<sup>-</sup> 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(X, Y, 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<sub>Inf</sub>: Person Y's infectiousness

X<sub>Sus</sub>: 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<sub>sexualPositionCoef</sub>: 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:

$$PPSC(S,A,R) = \frac{(13-A)}{12} \times \frac{(S)}{3} \times pAccessCare(R) \times C$$

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).

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

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

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 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 infections (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.



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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 individuallevel 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 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/CTtargeted 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) <ul> <li>Stable partnerships</li> <li>Casual partnerships</li> </ul>	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 <ul> <li>Stable partnerships</li> <li>Casual partnerships</li> </ul>	[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 <sup>2</sup>	[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]

<sup>2</sup> Values are selected over uniform distributions across the ranges presented

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Increase in HIV transmissibility (from urethral or rectal infection)	[1.5 – 2] fold <sup>3</sup>	[61–65]
Increase in HIV susceptibility (from urethral or rectal infection)	[1- 2.5] fold <sup>3</sup>	[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	25%	Calibrated to provide the site
- Ofernal	3378	calibrated to provide the site-
- Pharyngeal	49% 16%	specific incidence of NG/CI
Weekly probability of symptomatic NG/CT testing		
- Urethral	0.009	Calibrated to provide the site-
- Rectal	0.001	specific diagnosis of NG/CT
- Pharyngeal	0.04	
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
		Calibrated to provide the relative
Probability that NG/CT screening only at urethral site	0.94	diagnosis of extragenital to
		genital NG/CT
Relative likelihood of NG/CT screening among Black MSM relative to White MSM	0.5	[22]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM	0.5	[22]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM HIV Disease stage duration	0.5	[22]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM HIV Disease stage duration - Stage 1 (CD4 >500 cells/µL): Acute	0.5	
Relative likelihood of NG/CT screening among Black MSM relative to White MSM HIV Disease stage duration - Stage 1 (CD4 >500 cells/µL): Acute - Stage 2 (CD4 200-499 cells/µL): Chronic Stage 2 (CD4 200 cells/µL): Lato stage	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years	[22] [5,67,68] [5,69] [5,67,69]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years	[22] [5,67,68] [5,69] [5,67,69]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup>	[22] [5,67,68] [5,69] [5,67,69] [70]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup>	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup>	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration gentre 2	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 3, no ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58%	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 1 & 2, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL)	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58%	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 1 & 2, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14]
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Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART - Stage 3, no ART - Stage 3, no ART - Stage 3, no ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5 5	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14] [5]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART - Stage 3, no ART - On ART, partially suppressed	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5 5 3.5	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14] [5]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART - Stage 2, no ART - Stage 3, no ART - Stage 3, no ART - On ART, partially suppressed - On ART, fully suppressed	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5 5 3.5 1.5	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14] [5]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 1, no ART - Stage 2, no ART - Stage 3, no ART - Stage 3, no ART - On ART, partially suppressed - On ART, fully suppressed Efficacy of condoms to prevent HIV transmission	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5 5 3.5 1.5 80%	[22] [5,67,68] [5,69] [5,67,69] [70] [71-74] [12-14] [5] [75,76]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 1 & 2, no ART - Stage 1, no ART - Reduction in mortality due to ART 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 Efficacy of condoms to prevent HIV transmission Infectiousness per sexual contact	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5 5 3.5 1.5 80% 2.45 <sup>(log(VL)-4.5)</sup>	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14] [5] [75,76] [5]

<sup>3</sup> Mortality rate in stage 3 is defined as 1/(duration of stage 3).

<sup>4</sup> Infectiousness assumed equal to that of stage 2

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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		
<ul> <li>Screening for HIV only (not NG/CT)</li> </ul>	0.0065	Calibrated to provide the HIV
<ul> <li>Linkage to care (if HIV-positive and not linked)</li> </ul>	0.0065	cascade of care
<ul> <li>Starting ART (if engaged)</li> </ul>	0.095	
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.



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**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.

# 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

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7	Viral load level in HIV stage3 (late) +	
8	Viral load level in HIV stage2 (chronic) +	
9	Viral load level in HIV stage2 (chronic) -	
10	Viral load level in HIV stage1 (early) +	
11	Prob. of starting new stable partnerships +	
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13	Prob. of starting new stable partnerships -	
14	Prob. of starting new casual partnerships +	
15	Prob. of starting new casual partnerships -	
10 17	Prob. of never using condoms in casual partnerships +	
1/ 10	Prob. of never using condoms in casual partnerships -	
19	Condom effectiveness for HIV transmission +	
20	Condom effectiveness for HIV transmission -	
21	Coef. of NG/CT transmission +	
22	Coof of new partnerships for high sexual activity class +	
23		
24	Coet. of new partnerships for age 20 to 25 +	
25	Coef. of new casual partnerships for those with a stable partner +	
26	Coef. of new casual partnerships for those with a stable partner -	
27	Coef. of HIV transmission +	
28	Coef. of HIV transmission -	
29	Coef. of age mixing for stable partnerships +	
30		
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32	-1	100 -50 0 50 100 %Difference from baseline
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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

Viral load level in HIV stage3 (late	) +						
Viral load level in HIV stage2 (chronic	)+						
Viral load level in HIV stage2 (chronic	:) -						
Viral load level in HIV stage1 (early	)+				15		
Prob. of starting new stable partnership	; ; +						
Prob. of starting new stable partnership	s -						
Prob. of starting new casual partnerships	s +						
Prob. of starting new casual partnership	s -						
Prob. of never using condoms in casual partnership	s +						
Prob. of never using condoms in casual partnership	s -						
Condom effectiveness for HIV transmission	+						
Condom effectiveness for HIV transmissior	ı -		-				
Coef. of NG/CT transmission	+						
Coef. of new partnerships for high sexual activity class	s +						
Coef. of new partnerships for age 20 to 2	5 +				1		
Coef. of new casual partnerships for those with a stable partne	r +						
Coef. of new casual partnerships for those with a stable partne	r -		1				
Coef. of HIV transmission	+						
Coef. of HIV transmissior	ı -						
	-1	00	-50	0	50	100	
		%	Differe	nce fror	n baseli	ine	

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.

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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/CTtargeted scenario.

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## **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.



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# **BMJ Open**

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

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## 27 ABSTRACT

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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).

1938 **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.

21 22 40 **Results**: Assuming 60% uptake and 60% adherence, targeting PrEP to MSM diagnosed with NG/CT could reduce 23 41 HIV incidence among MSM in Baltimore City by 12.4% [95% uncertainty range (UR): 10.3 – 14.4%] in 20 years, 24 42 relative to no PrEP. Expanding the coverage of NG/CT screening (such that individuals experience a 50% annual 25 43 probability of NG/CT screening and evaluation for PrEP upon NG/CT diagnosis), can further increase the impact of 26 4 4 targeted PrEP to generate a 22.0% [95% UR 20.1 – 23.9%] reduction in HIV incidence within 20 years. When 27 45 compared to alternative implementation scenarios, PrEP evaluation at NG/CT diagnosis increased impact of PrEP <sup>28</sup>46 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 <sup>29</sup> 30<sup>40</sup> 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.
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<sup>3</sup> 52	Strengths and limitations of this study
5 53 6 54	<ul> <li>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.</li> </ul>
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o 9 56 10 57	<ul> <li>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.</li> </ul>
11 58	
12 59 13 60	<ul> <li>This model offers policymakers a support tool to estimate and compare the population-level impact of various prevention/control programs.</li> </ul>
<sup>14</sup> 61	
16 16 17 63 18 64	<ul> <li>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,</li> </ul>
19 65	and exclusion of transgender and bisexual individuals from the simulated population.
20 66	
21 67 22 68 23	<ul> <li>Due to limited data as to whether MSM change their behavior while taking PrEP, behavioral disinhibition was excluded from this analysis.</li> </ul>
24 69	
<sup>25</sup> 70 26 71	<b>Keywords:</b> HIV Infections; Gonorrhoea; Chlamydia; Pre-Exposure Prophylaxis; Homosexuality, Computer Simulation
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## <sup>3</sup><sub>4</sub> 72 **BACKGROUND**

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5 73 Infection with Neisseria gonorrhoeae (NG) and/or Chlamydia trachomatis (CT) may impact HIV transmission in 6 74 multiple ways, particularly among men who have sex with men (MSM). From a biological standpoint, NG/CT 7 8 75 infection may increase one's susceptibility to HIV acquisition: rectal infection in particular has been linked to an 9 76 increased risk of HIV acquisition [1,2]. HIV and NG/CT also share many risk factors at the individual level (e.g., 1077 condomless sex) and network level (e.g., having sex within a high-prevalence network), such that the three 11 78 conditions are often epidemiologically linked [3]. Additionally, HIV-negative men have an increased risk of HIV <sup>12</sup> 79 acquisition when in partnership with a HIV-positive partner who is also co-infected with NG/CT [4,5]. As a result, 13 14<sup>80</sup> better diagnosis and treatment of NG/CT can potentially reduce HIV incidence [6], and help to identify individuals 15 <sup>81</sup> at high risk of future HIV infection.

<sup>16</sup> 82 Pre-Exposure Prophylaxis (PrEP) is part of comprehensive HIV prevention services in which HIV-negative people <sup>17</sup>83 take daily antiretroviral medication to lower risk of HIV transmission upon exposure. The U.S. Centers for Disease 10 84 19 <sup>84</sup> 18 Control and Prevention (CDC) has recommended PrEP for HIV-negative individuals at substantial risk of infection 20 85 [7]. Among MSM, this includes HIV-negative men who are either diagnosed with a sexually transmitted infection <sub>21</sub> 86 (STI) in the last 6 months, are in a HIV discordant partnership, or report a condomless sex act in the last 6 months. 22 87 Despite this broad recommendation, the potential population-level impact of PrEP remains uncertain. Several 23 88 barriers exist to the successful implementation of PrEP, including providers' perceived inability to deliver PrEP in 24 89 primary care settings [8], individuals' limited knowledge of PrEP effectiveness [9], low self-perceived risk for HIV 25 90 infection [10], patients' difficulty in maintaining adherence [11], and high costs (at over \$10,000 per person-year <sup>26</sup>91 for those without insurance or access to a medication assistance plan) [12,13]. 27

28 92 Given these challenges, optimizing the efficiency of PrEP delivery is a public health priority. Specifically, it is 29 93 important to tailor PrEP delivery to those who stand to gain the most from its preventive efficacy. Given the 30 94 epidemiologic link between NG/CT infection and HIV among MSM, new NG/CT diagnoses may serve as a useful <sup>31</sup>95 means to identify high-risk MSM for PrEP evaluation and delivery [7]. At present, the impact of such a strategy—in <sup>32</sup>96 terms of reducing HIV and NG/CT incidence at a population level—is not clear. To address this question, we used 33 96 34 97 surveillance data from Baltimore City (Maryland, USA) to construct an agent-based simulation model of the co-35 98 transmission of HIV and NG/CT among MSM, [14] and applied this model to study the added value of targeting 36 99 PrEP to MSM diagnosed with NG/CT, in terms of population-level impact on HIV incidence over time. 37

#### 38100 **METHODS** 39

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).

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

Neisseria gonorrhoeae (NG) and Chlamydia trachomatis (CT) Parameters	Value	Reference
Proportion of cases symptomatic <sup>1</sup>		
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 <sup>2</sup>	[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
Rectal	0.49	specific incidence of NG/C
Pharyngeal	0.16	
Increase in HIV transmissibility (for those with urethral or rectal infection)	[1.5 – 2] fold <sup>1</sup>	[34–38]
Increase in HIV susceptibility (for those with urethral or	[1 – 2.5] fold <sup>1</sup>	[19,20,38,39]
rectal infection)		
NG/CT Calibration Targets	Mean <sup>3</sup> [Range]	
Annual diagnosis of NG/CT among MSM in Baltimore City		Values estimated from loc
Urethral	337 [269 – 405]	data on gonorrhea surveil
Rectal	25 [18 – 33]	and STI clinic visitis in Balt
Pharyngeal	42 [23 - 60]	City (See section 2 in the
, .	<u> </u>	Supplementary Material)
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 <sup>1</sup>	[40,41]
Chronic	[8 –10] years <sup>1</sup>	[42,43]
• Late stage <sup>4</sup>	[1-3] years <sup>1</sup>	[42-44]
Mortality rate <sup>3</sup>		
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 <sup>5</sup>	ART treatment duration up to one year	[48–51]
•		

<sup>1</sup> Values represent a pooled estimate of the reported measures for NG and CT infections

<sup>2</sup> Values are selected over uniform distributions across the ranges presented.

<sup>3</sup> 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).

<sup>4</sup> Mortality rate in late stage is defined as 1/(duration of late stage disease).

<sup>5</sup> 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 <sup>(log(VL)-4.5)</sup>	[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	0.5	[58]
MSM compared to white MSM		
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	

25114 STI Screening: In addition to testing of symptomatic NG/CT diagnosis, we also assume screening of <sup>26</sup>115 27 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 3g125 continuously engaged in HIV care should undergo repeated NG/CT screening at least annually [15]. More 40126 frequent screening, such as screening every 3-6 months, is recommended for high-risk MSM, including 4127 those with an NG/CT diagnosis in the last year. Based on data from Baltimore City and a conservative 42128 estimate, we assume 40% adherence to these guidelines [62,63].

43 44129 HIV Testing: In addition to combined HIV/STI testing that takes place as part of STI screening, we assume that all 4,430 MSM experience an additional probability of HIV testing (in excess of testing though the STI program) can calibrate 46131 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 49<sup>1</sup>33 well as the estimated continuum of HIV care, in Baltimore City. Calibration targets pertaining to NG/CT 50134 epidemiology are derived from data on gonorrhoea surveillance and STI clinic visits collected by the Baltimore City 51135 Health Department as part of the STD Surveillance Network Project (see section 2 of the Supplementary Material).

52 36 PrEP: Our primary outcome for this analysis is the projected incidence of HIV after 20 years of delivering PrEP to 54<sup>137</sup> 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 5£138 5439 (eligibility) is considered in accordance with CDC recommendations and Baltimore City PrEP guidelines [64] (See

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<sup>3</sup> 140 section 1 of the Supplementary Material) and includes HIV-negative individuals who are diagnosed with NG/CT in 141 the last 6 months, live in a serodiscordant partnership, or report an unprotected sex act or a new casual 6<sup>142</sup> partnership in the last 6 months. The three scenarios are thus:

- 7 143 PrEP delivery at NG/CT diagnosis ("targeted" strategy & primary analysis): all MSM diagnosed with NG/CT <sup>8</sup> 144 are offered PrEP at the time of diagnosis 9
- 10145 PrEP evaluation at NG/CT screening/testing ("at-testing"): PrEP eligibility is evaluated at the time of 1146 screening/testing for NG/CT, and all eligible individuals are offered PrEP 12
  - Untargeted PrEP: PrEP eligibility is evaluated at random, and all eligible MSM are offered PrEP

<sup>14</sup>148 All else being equal, increasing the number of MSM on PrEP will result in larger effects on HIV incidence (as more 15 149 16 people are protected from HIV transmission). However, for a given number of MSM screened – or a given number . 1750 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. 1¢151 10152 Our primary aim was to quantify the extent of this gain in efficiency; thus, we compared scenarios in which the 20153 same number of MSM would be evaluated for PrEP, or alternatively the same number of MSM would be 21154 maintained on PrEP. Furthermore, to illustrate the potential impact of reaching highly ambitious targets for 2455 improved STI screening, we considered a hypothetical scenario for improving the underlying level of NG/CT <sup>23</sup>156 screening (such that individual MSM not on PrEP experience a 50% annual probability of NG/CT screening and 2425252626evaluation for PrEP upon NG/CT diagnosis), and studied the additional gain in effectiveness of NG/CT-targeted PrEP under this assumption.

- 27159 In all scenarios, we assume that PrEP eligibility is reassessed every 3 months among patients receiving PrEP, and 28160 29161 30162 31 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 3,163 doses to provide 60% protection against HIV transmission [65]. As a criterion for initiation of PrEP, all eligible MSM 33164 are also screened and treated for NG/CT infection before starting PrEP.
- <sup>34</sup>165 35 36 36 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 3<u>7</u>67 analyses were performed to variation of all model parameters to +/- 25% of their original value. We also varied 3**§**168 condom usage among MSM on PrEP to model behavioral disinhibition (section 3 of the Supplementary Material).
- <sup>39</sup>169 40 Patient and Public Involvement: Patients and/or public were not involved in this study.

#### 42<sup>170</sup> RESULTS

#### 43 **Population overview** 44171

45 172 The simulation models a population of 15,000 MSM in Baltimore City, projecting an average of 215 [95% UR: 181 – 4773 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% 48174 4**9**.75 [47.4 – 50.6%] with non-urethral/rectal infection and 16.0% [14.8 – 17.2%] with pharyngeal-only infection. Point 50176 prevalence of NG/CT infection was estimated as 9.9% [8.4 – 11.5%], with 68.0% [63.5 – 72.5%] of infections 51177 occurring among black MSM (accounting for 58% of the MSM population). New infections occurred primarily in 52178 younger individuals, with 74% [72 – 78%] of new NG/CT infections occurring in MSM younger than 35 years old, <sup>53</sup>179 and 69% [66 – 72%] of new HIV infections occurring among MSM between the ages of 25 and 45 (Figure 2A and B). 54 54 55 Over half of new HIV and NG/CT infections occurred among MSM in the high sexual activity class, which accounted 56181 for 33% of the simulated population (Figure 2C and 2D). Overall, 81.5% [81.0 – 82.1%] of MSM diagnosed with

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<sup>3</sup> 182 NG/CT in the model were tested on the basis of symptomatic presentation (rather than asymptomatic screening),
 <sup>4</sup> 183 and 20% [18.0 - 22.0%] of incident NG/CT cases were coinfected with HIV.

### 6 184 Epidemiological impact of PrEP at NG/CT diagnosis

7 <sub>8</sub> 185 At baseline, and in the absence of PrEP (steady-state equilibrium), 361 [95% UR: 298 – 427] MSM were annually o 186 diagnosed and treated for NG/CT infection (calibrated). If 60% of MSM diagnosed with NG/CT could be started on 10187 PrEP (i.e., uptake = 60%) and maintained at a degree to which 60% of subsequent HIV infections were averted (i.e., 11188 adherence = 60%), HIV incidence was estimated to decline by 12.4% [10.3 – 14.4%] over 20 years (Figure 3A). This 12,89 corresponds to averting 318 [253 – 385] potential HIV transmissions through 5808 [5730 – 5886] person-years of 13190 PrEP delivered, or 5479 [4330 – 6632] infections averted per 100,000 person-years of PrEP (Figure 3B). Under the  $^{14}_{191}$ 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 . 1793 incidence of NG/CT (Figure 3C). Due to the increased level of NG/CT screening/treatment among those on PrEP 18<sup>1</sup>94 (through reassessment every 3 months), the prevalence of NG/CT was estimated to decline by 43.3% [41.6 -1¢195 44.9%] over 20 years of PrEP implementation (Figure 3D).

<sup>20</sup>196 The impact of PrEP on HIV incidence can be further increased by expanding the coverage of NG/CT screening at 21 -197 22 the community level. In our baseline model, 25.0% [95% UR: 24.0 – 26.0%] of MSM undergo NG/CT 23<sup>198</sup> 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 2499 2200 baseline estimate of 4033 [3883 – 4182] annual NG/CT testing/screening events. Offering PrEP to those testing 2001 positive for NG/CT subsequently provided a 22.0% [20.1 – 23.9%] decline in HIV incidence over 20 years, 2702 corresponding to 648 [589 – 710] potential HIV transmissions averted. For further information on levels of 28<u>203</u> uncertainty in these results, see section 4 of the Supplementary Material. 29

30<br/>3 204Relative impact of targeted versus untargeted PrEP

32 33205 NG/CT-integrated PrEP increased efficiency of PrEP delivery in at least two ways (Figure 4A). First, a higher 34206 percentage of MSM were eligible for PrEP among those evaluated for PrEP (Figure 4B and 4C). In our model, 71.1% 35207 [95% UR: 65.0 – 77.2%] of all MSM diagnosed with NG/CT were eligible to receive PrEP (as 29% of this population 36208 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 <sup>3</sup>209 randomly selected MSM. Second, providing PrEP to MSM diagnosed with NG/CT targets individuals at higher risk <sup>38</sup>210 of potential HIV infection (due to both biological factors and high-risk behavior), such that – under the baseline 36 40<sup>2</sup>11 assumption of equal numbers of people receiving PrEP—impact of NG/CT-targeted PrEP on HIV incidence was 4212 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 4213 43214 NG/CT screening/testing, and by 1.6 [1.2 - 2.2] relative to untargeted PrEP. In another comparison, if the same 42/15 number of individuals were evaluated for PrEP, the efficacy of NG/CT-integrated PrEP was increased even further 45216 relative to other scenarios (Figure 4E through 4H). 46

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).

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## <sup>3</sup><sub>4</sub>224 **DISCUSSION**

5 <sub>6</sub>225 This agent-based simulation of HIV transmission among MSM suggests that screening for NG/CT may be an 7226 important and efficient entry point for PrEP evaluation and delivery. Specifically, if all MSM who currently test 8227 positive for NG/CT could be offered PrEP – assuming 60% uptake and sufficient adherence to maintain 60% 9228 protection – HIV incidence could be reduced by approximately 12%, averting one HIV infection annually per 1,000 10229 MSM population, with fewer than 20 per 1,000 taking PrEP every year. On the basis of infections averted per PrEP 1330 dose delivered, providing PrEP to MSM with NG/CT diagnosis is nearly twice as efficient as providing PrEP  $12 \\ 231 \\ 13 \\ 231$ randomly among eligible MSM. Thus, use of NG/CT diagnosis as an entry point is a highly efficient and feasible 1232 14 mechanism for PrEP delivery. If NG/CT screening could be expanded to 50% of MSM every year (with PrEP offered 1<u>5</u>233 only to those testing positive), this impact could be more than doubled. Given this substantial potential impact, it 1¢34 will be important to assess willingness and uptake and identify best practices to support PrEP uptake and adherence among MSM diagnosed with NG/CT. 17235

18 19<sup>36</sup> These findings are consistent with other studies of PrEP delivery among MSM [66,67]. Previous studies have . 20<sup>2</sup>37 shown that the population-level impact of PrEP depends strongly on PrEP uptake and adherence [14,66], as 2238 suggested in our study as well. Importantly, NG/CT diagnosis may be useful in this regard, as MSM who have 22239 recently been diagnosed with an STI may be more aware of their HIV risk and more likely to accept and initiate 23240 PrEP. Past research has shown that HIV interventions may be more effective when they are conducted or initiated 22/241 at the time of an STI diagnosis [68]. Initiation of PrEP simultaneously with NG/CT diagnosis may also be a clinically 25242 feasible approach – as an STI diagnosis is already likely to prompt an HIV test (if not already performed), and MSM <sup>26</sup>243 who are diagnosed with NG/CT have at least some level of health care access. Unlike performing detailed sexual 27 27 244 28 histories, offering PrEP to all HIV-negative MSM diagnosed with NG/CT is a simple guideline that is easy for most 29245 clinicians to follow [69,70]. Further research is needed to assess the feasibility of this approach in the field, 36246 especially in ascertaining the degree to which the continuum of PrEP care (including linkage to care and longer-3247 term maintenance on PrEP) can be maintained in this population. Furthermore, the potential tradeoff between 32248 the positive impact of PrEP on STI prevalence through enhanced screening and its negative impact through 33249 behavioral disinhibition (if MSM on PrEP adopt riskier sexual behaviors) merits further investigation. Additional 34,50 implementation research is also needed to identify effective mechanisms for improving adherence to CDC PrEP <sup>35</sup>251 guidelines and overcoming barriers to acceptance and uptake of PrEP such as lack of awareness, lack of access, 36 252 37 financial strain, and stigma [11,71].

38253 As with any modeling analysis, our findings are limited by necessary simplifying assumptions. Given the overlap in 39254 clinical practice for treating NG and CT and the substantial uncertainty regarding the natural history of the two 49255 infections (e.g., duration of infectiousness, propensity toward asymptomatic infection), we have combined these 41 256 infections as a single entity (NG/CT) and have used composite parameter values to describe the natural history of 42 257 43 both diseases. However, there are still important differences between NG and CT, and to the extent that the natural 4**4**58 history of each disease may differ, our findings may over- or under-estimate the impact of PrEP targeted at these 4**₽**59 STIs. For example, an infection with a shorter infectious period and a higher transmission probability per sex act will 4**@**60 concentrate more strongly in high risk networks and may provide a more effective entry point for HIV PrEP. Further 4261 research can extend our analysis by considering the impact of each disease separately on HIV transmission dynamics. 4262 Furthermore, due to limited data on site-specific transmission dynamics (e.g., relative frequency of oral-only versus 4263 oral-plus-anal versus anal-only sex among MSM in Baltimore), we adopted a simplified approach that does not fully <sup>50</sup>264 capture the complete transmission dynamics but should result in the appropriate distributions of NG/CT infections 51 5265 52 at each anatomical site. Additional simplifying assumptions used in the underlying HIV simulation model include 5<u>3</u>266 applying the same sexual network for NG/CT and HIV transmission; simplification of sexual networks as comprising <sub>54</sub>267 only stable and casual partnerships; simplified definition of sexual activity classes as a lifetime attribute among 5**£**68 MSM; exclusion of serosorting on HIV, sexual activity class or PrEP; exclusion of HIV transmission through injection 5269 drugs or heterosexual sex; and exclusion of transgender individuals from the simulated population. To the extent

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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.

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6272 We excluded the potential existence of behavioral disinhibition for MSM on PrEP in the main analysis and applied 7273 a simplified approach for modeling the combined role of PrEP uptake/adherence for HIV protection. In additional <sup>8</sup>274 sensitivity analyses, we studied the impact of decreased condom use among MSM on PrEP on the outcome of <sup>9</sup>275 NG/CT-targeted PrEP, and the relative efficacy of STI-targeted scenario compared to the other comparators (See 1<sup>776</sup> section 3 of the Supplementary Material). As expected, the projected impact of NG/CT-targeted PrEP on incidence 12<sup>77</sup> 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 1,278 1279 among PrEP users in local settings. Despite this behaviour, the main outcome of our analysis (increased 15280 effectiveness of PrEP implementation through an NG/CT targeted approach) remained robust to variation in the 16281 rate of condom use reduction.

17 18282 There are strong racial disparities in HIV incidence and healthcare access in the US, such that the highest risk 19283 populations may be the ones least likely to have access to PrEP [72]; these disparities were not included in our 20284 simplified cascade of PrEP. Our model calibration was limited to the scope of local surveillance data, and available 2285 literature for values lacking direct empiric estimates from Baltimore City (e.g., probability of symptomatic 22286 infection). We also assumed a future trajectory of HIV infection in the future that represents continuation of <sup>23</sup>287 current trends; this trajectory is unlikely to remain constant for the next 20 years but may help to provide a useful <sup>24</sup> 288 25 conceptual construct for present-day decision-making, which is the ultimate goal of this analysis. Our results are -<u>7</u>289 26 further limited by exclusion of syphilis infection, another STI that is often transmitted in the same populations and 2<sup>7</sup>290 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-28291 29292 effectiveness or budget impact perspective.

3Q 93 In summary, this stochastic agent-based model representing the co-dynamics of NG/CT and HIV transmission 31 32<sup>294</sup> 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 33295 34296 (followed by PrEP initiation) can have major impact, not only on the incidence and prevalence of NG/CT, but also 3297 on transmission of HIV – potentially averting up to 20% of all HIV infections through NG/CT-targeted PrEP alone. 36298 Future analyses could evaluate whether such approaches could even be cost-saving in the long term. Ultimately, 3799 ending the HIV epidemic in MSM populations will require a combination of multiple activities, including 38300 strengthening the continuum of HIV care, ensuring continued access to clinical services, and prevention through 39 301 40 both behavioral approaches (e.g., condom use) and PrEP. Using NG/CT diagnosis as an entry point for PrEP 4<sup>3</sup>02 initiation may serve as an important component of such a combined prevention approach.

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#### 11 12<sup>311</sup> 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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 $^{2}$  All authors report no potential conflicts of interest.

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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.

### 4B31 Data sharing statement:

- 4232 Additional data are presented in the online Supplementary Material.
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## <sup>3</sup><sub>4</sub>501 **Figure legends:**

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<sup>7</sup>503 Figure 1: An agent-based model of gonorrhoea/chlamydia (NG/CT) and HIV co-transmission. The top panel <sup>8</sup>504 9504 represents the HIV care continuum and natural history: Upon infection with HIV, individuals serially progress <sup>2</sup><sub>10</sub>505 through three disease stages over time; this progression can be halted by initiation of antiretroviral therapy (ART), 1<sup>506</sup> 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 1507 13508 initiation do not affect HIV transmission in the model). HIV-positive individuals in care are assumed to undergo 1**5**09 regular screening for NG/CT (marked in red) subject to patients presenting for scheduled visits and clinician 15510 decision to screen. The bottom panel represents the natural history of NG/CT: infection may be symptomatic or <sup>16</sup>511 <sup>17</sup>512 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. 18 19<sup>12</sup> 19 Upon diagnosis with incident NG/CT, we assume that individuals are also screened for HIV infection (marked in 26<sup>514</sup> 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.

## 35526

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36 30 37527 Figure 4: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CTintegrated PrEP (in red, also corresponding to the red line in Figure 3), compared against PrEP evaluation at NG/CT 3¢528 3\$529 screening/testing (in red) and untargeted PrEP (in yellow), with full description of these scenarios given in the 4530 manuscript text. In the first set of experiments, the three strategies are compared under the assumption that the 4531 same number of MSM would receive PrEP (panels A through D), or the same number of MSM would be screened <sup>42</sup>532 for PrEP (panels E through H). Panel A gives the annual incidence of HIV, panel B the number of MSM approached 33 for PrEP, panel C the number of MSM on PrEP at any point in time (all three lines overlapping), and panel D the 34 cumulative reduction in HIV incidence per PrEP person/year in untargeted scenarios relative to NG/CT-targeted 48<sup>535</sup> scenario (similar pattern in panels E through H).

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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.

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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.

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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.

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Page 21 of 63

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Figure 4: Relative impact of NG/CT-integrated PrEP. Shown in this figure is the relative impact of NG/CTintegrated 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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# 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 nonblack 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].

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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 onelevel 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.

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

#### Table S1: List of CSA group and member CSAs

### 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.

	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.

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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*<sub>SA</sub>) 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:

$$\begin{split} P_{new\_stb} &= p_{Stb} \times c_{Part|Age} \\ P_{new\_csl} &= p_{Csl} \times p^*_{Csl|Stb} \times c_{Part|Age} \times c_{SA} \\ p^*_{Csl|Stb} &= \begin{bmatrix} p_{Csl|Stb} & number \ of \ stable \ partnerships > 0 \\ 1 & o.w. \end{split}$$

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 ( $pGM=(p_0, p_1, p_2)$ )

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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

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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.

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

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 <sub>Stb</sub>		<b>ADSR</b> <sub>Csl</sub>	
	(Number of partnerships)	reported	(Number partners	of reported ships)
Wave 2	0.62 (66)		0.72 (75)	
Wave 3	0.68 (71)		0.73 (87)	
Wave 4	0.51 (62)		0.76 (77)	
<u>Average estimate</u>	<u>0.6</u>		<u>0.74</u>	





# 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/  $\mu$ L), stage 2 (CD4 count between 200-500 cells/  $\mu$ L) and stage 3 (CD4 count <200 cells/  $\mu$ L). 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 <u>achieve viral suppression 8 to 24 weeks</u> 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/  $\mu$ L) 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<sup>1</sup>. 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

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<sup>&</sup>lt;sup>1</sup> 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.

<sup>-</sup> 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(X, Y, 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<sub>Inf</sub>: Person Y's infectiousness

X<sub>Sus</sub>: 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<sub>sexualPositionCoef</sub>: 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:

$$PPSC(S,A,R) = \frac{(13-A)}{12} \times \frac{(S)}{3} \times pAccessCare(R) \times C$$

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).

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

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

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 infections (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.



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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 individuallevel 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 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/CTtargeted 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) <ul> <li>Stable partnerships</li> <li>Casual partnerships</li> </ul>	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 <ul> <li>Stable partnerships</li> <li>Casual partnerships</li> </ul>	[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 <sup>2</sup>	[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]				

<sup>2</sup> Values are selected over uniform distributions across the ranges presented

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Increase in HIV transmissibility (from urethral or rectal infection)	[1.5 – 2] fold <sup>3</sup>	[61–65]
Increase in HIV susceptibility (from urethral or rectal infection)	[1- 2.5] fold <sup>3</sup>	[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	35%	Calibrated to provide the site.
- Ofernal	3378	calibrated to provide the site-
- Pharyngeal	49% 16%	specific incidence of NG/CI
Weekly probability of symptomatic NG/CT testing		
- Urethral	0.009	Calibrated to provide the site-
- Rectal	0.001	specific diagnosis of NG/CT
- Pharyngeal	0.04	
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
		Calibrated to provide the relative
Probability that NG/CT screening only at urethral site	0.94	diagnosis of extragenital to
		genital NG/CT
Relative likelihood of NG/CT screening among Black MSM relative to White MSM	0.5	[22]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM	0.5	[22]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM HIV Disease stage duration	0.5	[22]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM HIV Disease stage duration - Stage 1 (CD4 >500 cells/µL): Acute	0.5	
Relative likelihood of NG/CT screening among Black MSM relative to White MSM HIV Disease stage duration - Stage 1 (CD4 >500 cells/µL): Acute - Stage 2 (CD4 200-499 cells/µL): Chronic Stage 2 (CD4 200 cells/µL): Lato stage	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years	[22] [5,67,68] [5,69] [5,67,69]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years	[22] [5,67,68] [5,69] [5,67,69]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup>	[22] [5,67,68] [5,69] [5,67,69] [70]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup>	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup>	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration gentre 2	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 3, no ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58%	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 1 & 2, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL)	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58%	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 1 & 2, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 1 & 2, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 1 & 2, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART - Stage 3, no ART - Stage 3, no ART - Stage 3, no ART	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5 5	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14] [5]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART - Stage 3, no ART - On ART, partially suppressed	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5 5 3.5	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14] [5]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 2, no ART - Stage 2, no ART - Stage 3, no ART - On ART, partially suppressed - On ART, fully suppressed	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5 5 3.5 1.5	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14] [5]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART Average viral load (log10 copies/mL) - Stage 1, no ART - Stage 1, no ART - Stage 2, no ART - Stage 3, no ART - Stage 3, no ART - On ART, partially suppressed - On ART, fully suppressed Efficacy of condoms to prevent HIV transmission	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5 5 3.5 1.5 80%	[22] [5,67,68] [5,69] [5,67,69] [70] [71-74] [12-14] [5] [75,76]
Relative likelihood of NG/CT screening among Black MSM relative to White MSM 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) <sup>3</sup> : Late stage Time from ART initiation to full viral suppression Time from ART discontinuation to pre-ART CD4 nadir <sup>4</sup> Mortality rate <sup>3</sup> - Stage 1 & 2, no ART - Stage 1 & 2, no ART - Stage 3, no ART - Reduction in mortality due to ART 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 Efficacy of condoms to prevent HIV transmission Infectiousness per sexual contact	0.5 [6 - 9] weeks <sup>3</sup> [8 - 10] years [1 - 3] years [4-24] weeks <sup>3</sup> ART treatment duration up to one year 5 per 1000 person years 1/duration of stage 3 58% 6.5 4.5 5 3.5 1.5 80% 2.45 <sup>(log(VL)-4.5)</sup>	[22] [5,67,68] [5,69] [5,67,69] [70] [71–74] [12–14] [5] [75,76] [5]

<sup>3</sup> Mortality rate in stage 3 is defined as 1/(duration of stage 3).

<sup>4</sup> Infectiousness assumed equal to that of stage 2

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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		
<ul> <li>Screening for HIV only (not NG/CT)</li> </ul>	0.0065	Calibrated to provide the HIV
<ul> <li>Linkage to care (if HIV-positive and not linked)</li> </ul>	0.0065	cascade of care
<ul> <li>Starting ART (if engaged)</li> </ul>	0.095	
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.



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**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.

# 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

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7	Viral load level in HIV stage3 (late) +	
8	Viral load level in HIV stage2 (chronic) +	
9	Viral load level in HIV stage2 (chronic) -	
10	Viral load level in HIV stage1 (early) +	
11	Prob. of starting new stable partnerships +	
12		
13	Prob. of starting new stable partnerships -	
14	Prob. of starting new casual partnerships +	
15	Prob. of starting new casual partnerships -	
10 17	Prob. of never using condoms in casual partnerships +	
17 18	Prob. of never using condoms in casual partnerships -	
10	Condom effectiveness for HIV transmission +	
20	Condom effectiveness for HIV transmission -	
21	Coef. of NG/CT transmission +	
22	Coef, of new partnerships for high sexual activity class +	
23	Coof of now partnerships for ago 20 to 25 ±	
24	Coel. of new partnerships for age 20 to 25 +	
25	Coef. of new casual partnerships for those with a stable partner +	
26	Coef. of new casual partnerships for those with a stable partner -	
27	Coef. of HIV transmission +	
28	Coef. of HIV transmission -	
29	Coef. of age mixing for stable partnerships +	
30		_
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32		%Difference from baseline
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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

Viral load level in HIV stage3 (late	) +						
Viral load level in HIV stage2 (chronic	) +						
Viral load level in HIV stage2 (chronic	;) -						
Viral load level in HIV stage1 (early	)+				12		
Prob. of starting new stable partnership	; +						
Prob. of starting new stable partnership	s -						
Prob. of starting new casual partnerships	s +						
Prob. of starting new casual partnership	s -						
Prob. of never using condoms in casual partnership	s +						
Prob. of never using condoms in casual partnership	s -						
Condom effectiveness for HIV transmission	+						
Condom effectiveness for HIV transmissior	1 -						
Coef. of NG/CT transmission	+						
Coef. of new partnerships for high sexual activity class	s +						
Coef. of new partnerships for age 20 to 2	5 +				1		
Coef. of new casual partnerships for those with a stable partne	r +						
Coef. of new casual partnerships for those with a stable partne	r -		1				
Coef. of HIV transmission	+						
Coef. of HIV transmissior	1 -						
	-1	00	-50	0	50	100	
		%	Differe	nce fron	n baseli	ine	

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.

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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/CTtargeted scenario.

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#### **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.



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