

Proportion of Incident Human Immunodeficiency Virus Cases Among Men Who Have Sex With Men Attributable to Gonorrhea and Chlamydia: A Modeling Analysis

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Background: Sexually transmitted infections (STIs) are associated with an increased risk of human immunodeficiency virus (HIV) acquisition and transmission. We estimated the proportion of HIV incidence among men who have sex with men attributable to infection with the 2 most common bacterial STIs, *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT). **Methods:** We used a stochastic, agent-based model of a sexual network of MSM with cocirculating HIV, NG, and CT infections. Relative risk (RR) multipliers, specific to anatomic site of infection, modified the risk of HIV transmission and acquisition based on STI status. We estimated the effect of NG and CT on HIV incidence overall and on HIV acquisition and HIV transmission separately. Each scenario was simulated for 10 years. The population attributable fraction (PAF) was determined for each combination of RRs by comparing the incidence in the final year of a scenario to a scenario in which the RRs associated with NG and CT were set to 1.0. **Results:** Overall, 10.2% (interquartile range [IQR], 7.9–12.4) of HIV infections were attributable to NG/CT infection. Then in sensitivity analyses, the PAF for HIV transmission ranged from 3.1% (IQR, 0.5–5.2) to 20.4% (IQR, 17.8–22.5) and the PAF for HIV acquisition ranged from 2.0% (IQR, –0.7 to 4.3) to 13.8% (IQR, 11.7–16.0).

Conclusions: Despite challenges in estimating the causal impact of NG/CT on HIV risk, modeling is an alternative approach to quantifying plausible ranges of effects given uncertainty in the biological cofactors. Our estimates represent idealized public health interventions in which STI could be maximally prevented, setting targets for real-world STI interventions that seek to reduce HIV incidence.

Biological plausibility for a causal relationship between sexually transmitted infection (STI) and human immunodeficiency virus (HIV) incidence is strong^{1–8}; however, the population-level effect of common STIs, including *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG), on HIV incidence has been challenging to estimate. Further, most estimates have been obtained among heterosexual populations rather than men who have sex with men (MSM), with varying results from different studies.^{9,10} One challenge has been to separate the effects of NG/CT on HIV acquisition and transmission risks. NG/CT are thought to increase the risk of HIV acquisition by damaging the genital or rectal epithelium or by increasing the availability of HIV target cells in the genital or rectal tracts.¹¹ Increased HIV transmission is thought to occur from increased viral shedding of HIV associated with prevalent NG/CT infection.¹¹

Behavioral confounding may contribute to the observed association between prevalent STI and incident HIV. MSM with multiple sexual partners are more likely to be diagnosed with both HIV and STIs.^{12,13} Because transmission for both STIs and HIV occur across the same network of sexual partnerships, it is difficult to separate the confounding factor of increased behavioral risk factors from the direct causal effects that STIs have on HIV risk.¹⁴

In this study, we used agent-based modeling to estimate the population attributable fraction (PAF) of NG/CT infection on HIV incidence among MSM in the United States. This approach allows the simulation of synthetic populations to directly observe the causal effect of NG/CT without confounding biases that are inherent in empirical observational study designs. Despite uncertainty from empirical studies regarding the effect of NG/CT on HIV risk, previous modeling studies have used fixed effects to model the relationship. By modeling the cocirculation of HIV, CT, and NG in this population we tested a range of plausible values for the effect of NG and CT infections on HIV acquisition and transmission that could set targets for the maximal effects on HIV incidence that could be achieved by a STI prevention intervention. We estimated the proportion of incident HIV infections attributable to NG and CT infections by comparing incidence in scenarios in which NG/CT contributed to HIV risk to a scenario in which NG/CT had no effect on HIV risk.

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METHODS

In previous research, we developed a robust mathematical model for HIV/STI transmission dynamics for US MSM using the *EpiModel* software platform (www.epimodel.org).¹⁵ The *EpiModel* platform allows for simulating epidemics over dynamic sexual networks. The overall model structure, parameters, and outcomes are similar to Jenness et al.¹⁶ Networks are comprised of dyads representing anal sex partnerships that may be 1-time sexual encounters; casual, ongoing but shorter-duration partnerships; or main, longer-duration partnerships. Predictors of partnership formation included age of partners, sexual role preferences, number of ongoing partnerships, and partner type. Behavioral components of the model were parameterized in part based on data from empirical sexual network studies conducted in Atlanta, Georgia.^{17,18} Sexual activity within extant partnerships, including sexual position and condom use, was simulated on a weekly time step. Condom use varied based on partnership type (main, casual, and 1 time), HIV diagnosis, and HIV status disclosure within partnerships. Specific parameter values and model structure are described in detail in the Appendix, <http://links.lww.com/OLQ/A345> (Sections 2–3).

HIV/STI Transmission and Disease Progression

Among partnerships that were discordant on HIV or STI status, transmission of HIV, NG, and CT occurred within simulated acts of anal intercourse. Probability of HIV transmission was modified by NG/CT infection (described in more detail below), viral load of the infected partner,¹⁹ CCR5-delta 32 genetic allele status of the susceptible partner,²⁰ condom use,²¹ sexual role,²² and circumcision status of insertive partners.²³ After infection, HIV disease progressed through acute, chronic, and AIDS stages dependent on current ART treatment status. HIV viral load was simulated as a continuous function of time since infection, disease stage, and current ART status. NG and CT infection remained active until diagnosis and antibiotic treatment (average treatment duration, 7 days) or natural clearance (average duration, 246 and 310 days, respectively).

Effect of STI on HIV Transmission and Acquisition

Model parameters for relative risks (RRs) increased the per-act probability of transmission or acquisition of HIV conditional on prevalent NG/CT status. Relative risks were constant across the duration of NG/CT infection.

An overall PAF, combining the effects of STI on HIV acquisition and transmission, was calculated by comparing the scenario with RRs for which we have the strongest evidence to a scenario in which acquisition and transmission RRs were set to 1.0. The “strongest evidence” RRs were the acquisition RRs from the base case scenario (rectal acquisition RR, 1.97; urethral acquisition RR, 1.48) and the transmission RRs were based on empirical evidence²⁴ (rectal and urethral transmission RR, 1.3).

We also conducted sensitivity analyses to obtain a plausible range for the effect of NG/CT on HIV transmission and acquisition risk in isolation. The NG/CT RRs affected HIV transmission or acquisition based on anatomical site of infection and sexual role. Relative risks for HIV transmission applied if (1) the HIV-infected partner had urethral NG or CT *and* was insertive during the sexual act, *or* (2) the HIV-infected partner had rectal NG or CT *and* was receptive during the sexual act. Similarly, RRs for HIV acquisition applied if (1) the HIV-uninfected partner had urethral NG or CT *and* was insertive during the sexual act, *or* (2) the HIV-uninfected partner had rectal NG or CT *and* was receptive during the sexual act.

We examined the effect of NG/CT on HIV incidence under a range of plausible RRs for HIV transmission and acquisition. Separate analyses were conducted to isolate the effects of HIV transmission versus HIV acquisition. To assess the potential impact of increased risk of HIV acquisition due to NG/CT, acquisition RRs (Table 1) were varied while holding the transmission RR constant. In our previous applications, we only modeled the RR for each STI on HIV acquisition, with no increased risk for HIV transmission associated with prevalent STI.¹⁶ To account for the effect of HIV transmission in the acquisition RR scenarios, a “best evidence” value RR of 1.3 was used for the effect of NG and CT infection on HIV transmission based on data obtained in

TABLE 1. RRs for HIV Transmission and Acquisition Based on Site of STI Across Modeled Scenarios

Relative Risk of Transmission Analysis				
	Transmission RRs		Acquisition RRs	
	Gonorrhea	Chlamydia	Rectal	Urethral
Current base case scenario; referent for HIV transmission analysis	1.0	1.0	1.97	1.48
	1.0	2.0	1.97	1.48
	1.0	3.0	1.97	1.48
	2.0	1.0	1.97	1.48
	2.0	2.0	1.97	1.48
	2.0	3.0	1.97	1.48
	3.0	1.0	1.97	1.48
	3.0	2.0	1.97	1.48
	3.0	3.0	1.97	1.48
RR of acquisition analysis	Transmission RRs		Acquisition RRs	
	Gonorrhea	Chlamydia	Rectal	Urethral
Base case acquisition RRs	1.3	1.3	1.97	1.48
Referent for HIV acquisition analysis	1.3	1.3	1.0	1.0
	1.3	1.3	1.0	2.0
	1.3	1.3	1.0	3.0
	1.3	1.3	2.0	1.0
	1.3	1.3	2.0	2.0
	1.3	1.3	2.0	3.0
	1.3	1.3	3.0	1.0
	1.3	1.3	3.0	2.0
	1.3	1.3	3.0	3.0

an African cohort study.²⁴ No estimates of a transmission RR, as defined above, exist for MSM populations.

To assess the potential impact of increased risk of HIV transmission, transmission RRs were varied in separate models (Table 1), holding acquisition RR constant. Acquisition RRs were held constant at the levels that the base case of the model is calibrated to (rectal infection RR, 1.97; urethral infection RR, 1.48).

Estimates are not available for the effect of NG/CT coinfection. Thus, we conducted a sensitivity analysis evaluating 2 plausible biological mechanisms: (1) the highest RR from NG or CT prevailed; or (2) the coinfection RR was the product of the individual NG and CT RRs. We observed no clinically meaningful differences between these 2 scenarios. Results under the scenario that the highest RR prevailed are presented below; results under the multiplicative assumption are presented in the Appendix, <http://links.lww.com/OLQ/A345>.

Model Scenarios

Burn-in simulations were conducted to calibrate the model to observed HIV prevalence (15%²⁵) and NG/CT incidence (3.5^{26,27} and 5.6²⁶ incident infections/100 person-years, respectively). NG/CT incidence included both symptomatic and asymptomatic infections. Burn-in simulations were generated using the base case HIV acquisition RRs, which were estimated for the acquisition RRs and fixed for the transmission RRs. Experimental scenarios for each combination of relative risks were simulated 256 times for 10 years each using the same starting burn-in simulation.

Measures

Outcomes were estimated using the final year of the 10-year follow-up. The incidence rate per 100 PYAR was determined for each scenario in that interval. The PAF of NG/CT on HIV incidence was defined as:

$$\text{PAF} = \frac{(\text{IR}_i - \text{IR}_{\text{ref}})}{\text{IR}_i}$$

where IR_i is a scenario with specified RRs and IR_{ref} is the scenario with null RRs (ie, $\text{RR} = 1.0$). To calculate the PAF for HIV acquisition attributable to NG/CT, the scenario in which all acquisition relative risks were set equal to 1.0 was the referent (IR_{ref}).

The relative frequency of sexual acts resulting in HIV transmission was quantified based on the anatomical site of exposure and the prevalent NG/CT status of the newly infected partner. As with the determination of the PAFs, the proportions reflect incident NG/CT that were role- and site-specific. First, transmission events were categorized based on whether a rectal or urethral NG/CT

infection was present. STIs were only counted if present in a role-specific site that could contribute to infection (eg, prevalent urethral NG/CT in an insertive partner). Second, transmission events were categorized based on the NG/CT status of the newly HIV-infected partner.

The median and IQR of the PAF were determined for the final year of each comparison scenario using the null as the reference. All analyses were conducted in R 3.4.3. Analysis scripts and simulation data can be accessed at https://github.com/EpiModel/sti_paf.

RESULTS

The estimated prevalence of HIV, NG, and CT over the last year of the burn-in model, which provided the starting point for each of the scenarios modeled, was 14.7% (interquartile range [IQR], 14.3–15.1), 1.3% (IQR, 0.9–1.5), and 3.7% (IQR, 3.3–4.1), respectively. Overall, considering the effects of NG/CT on HIV acquisition and transmission together, the PAF of NG/CT on HIV was 10.2% (IQR, 7.9–12.4) when comparing the “best estimate” scenario to the null effects scenario.

The results of the sensitivity analysis examining the effect of increased HIV transmission due to NG/CT are presented in Table 2. Holding the effect of NG/CT on HIV acquisition constant, the incidence of HIV increased as the RRs of NG/CT on HIV transmission increased. In the scenario assuming NG/CT did not affect HIV transmission, estimated incidence across simulations was 1.90 infections/100 PYAR (IQR, 1.86–1.94). The highest incidence was observed in the scenario with the highest RRs for NG/CT on HIV transmission (2.39/100 PYAR; IQR, 2.31–2.45). The PAF increased as the RRs of NG/CT on HIV transmission increased. Observed PAFs ranged from median values of 3.1% (IQR, 0.5–5.2) to 20.4% (IQR, 17.8–22.5).

The results of the sensitivity analysis examining the effect of increased HIV acquisition due to NG/CT are presented in Table 3. When NG/CT did not have an effect on HIV acquisition, the incidence rate was 1.83/100 PYAR (IQR, 1.78–1.87). The highest incidence rate was observed in the scenario with the highest RRs for NG/CT on HIV acquisition (2.12/100 PYAR; IQR, 2.07–2.17). In the base case scenario, with relative risks reflecting previous empirical and modeling work, the incidence rate was 1.96/100 PYAR (IQR, 1.91–2.01). The PAF of STI on HIV acquisition ranged from a low of 2.0% (IQR, –0.7 to 4.3) to a high of 13.8% (IQR, 11.7–16.0). In the base case scenario, the median PAF was 7.1% (IQR, 4.6–9.3).

Table 4 presents the proportions of HIV transmission events in which NG or CT infection were present at the site of sexual activity for 1 or both partners. Although these proportions do not indicate that NG/CT were causally related to the HIV

TABLE 2. The Effect of RR for HIV Transmission on HIV Incidence

RR of HIV Transmission by STI		HIV Incidence Rate	PAF
Gonorrhea	Chlamydia	Rate per 100 PYAR* (IQR)	% (IQR)
1.0	1.0	1.90 (1.86–1.94)	Reference [†]
1.0	2.0	2.02 (1.97–2.06)	5.9 (3.4–7.9)
1.0	3.0	2.13 (2.08–2.18)	10.7 (8.6–12.9)
2.0	1.0	1.96 (1.91–2.00)	3.1 (0.5–5.2)
2.0	2.0	2.11 (2.06–2.16)	10.1 (8.0–12.2)
2.0	3.0	2.27 (2.21–2.33)	16.2 (14.1–18.5)
3.0	1.0	2.01 (1.96–2.05)	5.6 (3.0–7.5)
3.0	2.0	2.18 (2.11–2.24)	12.8 (10.2–15.1)
3.0	3.0	2.39 (2.31–2.45)	20.4 (17.8–22.5)

HIV acquisition relative risks were held constant at base case values, rectal RR, 1.97; urethral RR, 1.48.

*Person years at risk.

[†]Base case scenario.

TABLE 3. The Effect of RR for HIV Acquisition on HIV Incidence

RR of HIV Acquisition by STI Anatomic Site		HIV Incidence Rate	PAF
Rectal	Urethral	Rate per 100 PYAR* (IQR)	% (IQR)
1.97	1.48	1.96 (1.91–2.01)	7.1 (4.6–9.3)
1.0	1.0	1.83 (1.78–1.87)	Reference
1.0	2.0	1.86 (1.81–1.91)	2.0 (–0.7–4.3)
1.0	3.0	1.89 (1.84–1.93)	3.2 (0.8–5.3)
2.0	1.0	1.93 (1.89–1.98)	5.6 (3.6–7.8)
2.0	2.0	1.98 (1.94–2.02)	7.7 (5.9–9.8)
2.0	3.0	2.00 (1.95–2.04)	8.6 (6.4–10.7)
3.0	1.0	2.02 (1.97–2.07)	9.6 (7.4–11.9)
3.0	2.0	2.07 (2.03–2.12)	12.0 (10.0–13.9)
3.0	3.0	2.12 (2.07–2.17)	13.8 (11.7–16.0)

HIV transmission relative risks were held constant at rectal RR, 1.3 and urethral RR, 1.3.

*Person years at risk.

transmission event, this table provides the distribution of NG/CT infection across these events. The proportion of transmission events in which NG or CT were present increased as the RRs for transmission and acquisition increased. Across the range of scenarios in which the relative risks for HIV transmission were varied, STI was present in 1 or both partners between 13.8% and 28.6% of the time. When the relative risk for HIV acquisition was varied, STIs were present in 1 or both partners between 11.2% and 21.0% of the time.

The proportion of HIV transmission events in which the newly HIV-infected partner had prevalent STI at the site of sexual activity is presented in Table 5. Overall, the proportion of HIV transmission events in which NG and CT were both present (ie, dual-infection) never exceeded 1.0%. Across the range of transmission RRs, single- or dual-infection was present in 11.3% to 18.3% of newly HIV-infected partners. Across the range of acquisition relative risks, single- or dual-infection was present in 7.5%–16.3% of newly HIV-infected partners.

Prevalence of NG/CT was unaffected by changes in the HIV transmission and acquisition RRs. Across all scenarios, prevalence of any NG infection was 1% and prevalence of any CT infection was 3%.

DISCUSSION

We used agent-based modeling to estimate the potential population-level effects of highly prevalent bacterial STIs, NG and CT, on HIV incidence among MSM in the United States. We distinguished the effects of NG/CT on (1) HIV transmission from STI and HIV-infected men and (2) HIV acquisition by HIV-uninfected and STI-infected men. HIV incidence increased as the relative risks associated with HIV transmission and acquisition from an STI increased. Comparing a scenario in which our best estimates of the effect of NG/CT on HIV acquisition and transmission were in effect compared with a null condition in which there was no effect of NG/CT on HIV risk, we estimated that approximately 10% of HIV infections among MSM were

TABLE 4. Proportion of Transmission Events in Which Site- and Role-Specific Rectal or Urethral STI Were Present

RR of HIV Transmission by STI		Anatomic Sites of Sexual Activity With Prevalent STI			
Gonorrhea	Chlamydia	Median (IQR) Proportion of Transmission Events			
		Rectal and Urethral	Rectal Only	Urethral Only	Neither
1.0	1.0	6.6 (6.3–7.0)	5.4 (5.1–5.9)	2.7 (2.4–3.0)	85.3 (84.1–86.2)
1.0	2.0	8.7 (8.4–9.2)	5.5 (5.1–5.8)	4.0 (3.6–4.2)	81.9 (80.8–83.0)
1.0	3.0	10.2 (9.8–10.5)	5.5 (5.2–5.9)	4.9 (4.6–5.2)	79.3 (78.4–80.4)
2.0	1.0	7.6 (7.1–7.9)	5.6 (5.2–6.0)	3.1 (2.8–3.3)	83.7 (82.8–84.8)
2.0	2.0	10.1 (9.8–10.6)	6.2 (5.8–6.5)	4.5 (4.1–4.8)	79.2 (78.1–80.3)
2.0	3.0	12.0 (11.7–12.3)	6.8 (6.5–7.2)	5.7 (5.4–6.0)	75.4 (74.5–76.4)
3.0	1.0	8.5 (8.1–8.9)	6.1 (5.7–6.2)	3.4 (3.1–3.8)	82.0 (81.1–83.0)
3.0	2.0	11.1 (10.7–11.4)	6.8 (6.5–7.2)	5.0 (4.7–5.3)	77.1 (76.1–78.1)
3.0	3.0	13.0 (12.8–13.3)	7.9 (7.7–8.2)	6.6 (6.4–7.0)	72.4 (71.4–73.2)

RR of HIV acquisition by STI anatomic site		Anatomic sites of sexual activity with prevalent STI			
Rectal	Urethral	Median (IQR) proportion of transmission events			
		Rectal and Urethral	Rectal Only	Urethral Only	Neither
1.97	1.48	7.4 (7.1–7.7)	5.4 (5.0–5.7)	3.0 (2.8–3.3)	84.2 (83.3–85.1)
1.0	1.0	4.7 (4.3–5.0)	3.6 (3.2–3.9)	2.9 (2.5–3.2)	88.8 (87.9–89.9)
1.0	2.0	5.2 (4.8–5.5)	4.0 (3.6–4.2)	3.3 (2.9–3.6)	87.6 (86.6–88.6)
1.0	3.0	5.9 (5.6–6.2)	4.5 (4.1–4.8)	3.7 (3.3–4.0)	85.9 (85.0–86.9)
2.0	1.0	6.8 (6.6–7.2)	5.0 (4.6–5.3)	2.8 (2.5–3.1)	85.4 (84.3–86.3)
2.0	2.0	7.8 (7.5–8.1)	5.6 (5.3–5.9)	3.3 (3.0–3.6)	83.3 (82.4–84.3)
2.0	3.0	8.3 (7.9–8.6)	6.0 (5.6–6.3)	3.6 (3.3–3.8)	82.2 (81.2–83.2)
3.0	1.0	8.5 (8.2–8.8)	6.1 (5.8–6.4)	2.8 (2.6–3.1)	82.6 (81.6–83.3)
3.0	2.0	9.4 (9.1–9.8)	6.7 (6.3–7.0)	3.2 (2.9–3.4)	80.6 (79.8–81.7)
3.0	3.0	10.2 (9.7–10.5)	7.3 (7.1–7.5)	3.6 (3.3–3.8)	79.0 (78.2–79.9)

TABLE 5. Proportion of Transmission Events in Which the Newly HIV-Infected Partner Had Site- and Role-Specific Gonorrhea or Chlamydia

RR of HIV Transmission by STI		STI Status of Newly HIV-Infected Partner			
		Median (IQR) Proportion of Transmission Events			
Gonorrhea	Chlamydia	Gonorrhea and Chlamydia	Gonorrhea Only	Chlamydia Only	Neither
1.0	1.0	0.3 (0.2–0.6)	3.0 (2.7–3.3)	7.9 (7.5–8.3)	88.7 (87.8–89.5)
1.0	2.0	0.4 (0.3–0.6)	3.1 (2.8–3.4)	9.8 (9.3–10.2)	86.7 (85.7–87.6)
1.0	3.0	0.5 (0.4–0.7)	3.3 (3.0–3.6)	10.9 (10.5–11.3)	85.2 (84.4–86.1)
2.0	1.0	0.4 (0.3–0.7)	4.0 (3.7–4.3)	7.6 (7.2–8.0)	87.9 (87.0–88.7)
2.0	2.0	0.6 (0.6–0.9)	4.5 (4.1–4.8)	9.6 (9.3–10.0)	85.3 (84.3–86.1)
2.0	3.0	0.9 (0.7–1.1)	4.8 (4.5–5.1)	11.2 (10.8–11.6)	83.1 (82.3–84.0)
3.0	1.0	0.6 (0.3–0.7)	4.9 (4.4–5.1)	7.8 (7.6–8.3)	86.7 (85.8–87.7)
3.0	2.0	0.8 (0.6–1.0)	5.3 (5.0–5.7)	9.8 (9.5–10.1)	84.0 (83.2–84.9)
3.0	3.0	1.0 (0.8–1.2)	5.9 (5.6–6.3)	11.4 (11.0–11.7)	81.7 (80.8–82.7)

RR of HIV acquisition by STI anatomic site		Median (IQR) proportion of transmission events			
Rectal	Urethral	Gonorrhea and Chlamydia	Gonorrhea Only	Chlamydia Only	Neither
1.97	1.48	0.4 (0.2–0.5)	3.4 (3.0–3.7)	8.0 (7.7–8.3)	88.2 (87.4–89.1)
1.0	1.0	0.2 (0.1–0.3)	2.2 (1.9–2.4)	5.1 (4.7–5.5)	92.5 (91.8–93.3)
1.0	2.0	0.2 (0.1–0.3)	2.2 (2.0–2.5)	5.8 (5.4–6.2)	91.7 (91–92.5)
1.0	3.0	0.4 (0.2–0.5)	2.7 (2.3–2.9)	6.4 (6.2–6.9)	90.5 (89.7–91.3)
2.0	1.0	0.3 (0.2–0.4)	3.1 (2.7–3.3)	7.7 (7.3–8.0)	88.9 (88.3–89.8)
2.0	2.0	0.4 (0.3–0.6)	3.5 (3.1–3.8)	8.6 (8.2–8.9)	87.5 (86.7–88.4)
2.0	3.0	0.4 (0.3–0.6)	3.6 (3.3–3.9)	9.1 (8.7–9.5)	86.8 (86–87.7)
3.0	1.0	0.4 (0.3–0.5)	3.7 (3.4–4.1)	9.6 (9.2–9.9)	86.3 (85.5–87.0)
3.0	2.0	0.5 (0.3–0.6)	4.2 (3.9–4.4)	10.4 (10.1–10.9)	84.9 (84.1–85.7)
3.0	3.0	0.5 (0.4–0.7)	4.5 (4.2–4.8)	11.3 (10.8–11.7)	83.7 (82.8–84.5)

attributable to NG/CT. This represents an estimate of the causal effect of NG/CT on HIV incidence, and therefore might represent the potential effect of a maximally efficient STI control intervention on HIV incidence in this population.

A difficult task in empirical studies²⁸ has been to isolate the effects of NG/CT on HIV transmission versus acquisition, as we did using a simulation-based approach. Disentangling these is critical from a public health perspective because it implies either a targeting of STI screening and treatment for HIV-infected versus HIV-uninfected MSM. For example, if prevalent STI has a stronger effect on HIV acquisition then this would indicate that, from a HIV prevention perspective, that screening of HIV-uninfected MSM would be most effective.

Few modeling studies of MSM have simulated the cocirculation of HIV and STIs among MSM, and ours may be the first that does so to explicitly investigate the population-level impact of prevalent NG/CT on HIV incidence in this population. Other modeling studies have assumed a fixed set of RR parameters, despite the major uncertainty of these parameter values.¹¹ There is little empirical evidence to inform these parameters, and yet, as our analysis shows, they have a substantial impact on the predicted HIV outcomes in modeling. Further, we were able to rigorously estimate the population-level effects of NG/CT by isolating the effects of these STIs based on sexual role and site of NG/CT infection. This type of data has proven to be very challenging to measure empirically because this requires identifying the sexual encounter that resulted in HIV infection, the sexual role(s) of each partner during that encounter, and the site-specific STI status of each partner. Sexual roles are critical for understanding the complex epidemiology of HIV/STI among MSM given the potential for bidirectional transmission in versatile partnerships. This concept of bidirectional transmission can facilitate the speed of transmission compared with fixed-role heterosexual partnerships.²⁹ Because NG and CT are typically site-specific rather than systemic infections, dynamic sexual roles remains a critical area for future epidemiological research.

Empirical data on the individual- and population-level effects of STI on HIV transmission and acquisition are limited. Trials and cohort studies conducted among heterosexuals in Africa have generally observed high prevalence of ulcerative STI.^{24,30,31} Different classes of STIs present with symptoms (eg, ulceration) that likely affect the transmission and acquisition of HIV differently. Further, sexual behaviors differ markedly between heterosexuals and MSM, and anal sex is more prevalent among the MSM population compared to heterosexuals.³² Given the increased HIV transmission probabilities in rectal compared to vaginal sex,^{33,34} it is likely that the effects of STI differ between heterosexual and MSM populations. Sexual role versatility²⁹ and the anatomic site of the STI might affect the dynamics of the interaction between STI and HIV.

These estimates have critical importance for both epidemiology science and public health efforts aimed at disease control. For the latter, our study contributes to the evidence base supporting interventions for STI screening and treatment as a mechanism toward prevention programs on HIV incidence. We estimate the PAF of STI on HIV acquisition to be between 2% and 14% and HIV transmission to be between 3% and 20%. It is important to note that in our sensitivity analyses we held the effect of NG/CT on HIV transmission constant when examining RRs for HIV acquisition (and vice versa). Thus, these ranges might underestimate the true effect of NG/CT on HIV incidence if the effects we modeled underestimate the true RRs. Separately examining the effects of NG/CT on HIV acquisition and transmission can inform the potential impact of STI detection and treatment among HIV-uninfected and HIV-infected MSM on HIV incidence, respectively. Our overall estimate, comparing the scenario with acquisition and transmission RRs with the strongest evidence to a null scenario in which NG/CT do not affect HIV transmission or acquisition, indicates that approximately 10% of HIV incidence is due to NG/CT infection. This estimate corresponds to approximately 2600 HIV infections that could be averted annually in the United States with the immediate and

universal elimination of NG/CT through an idealized STI control intervention.³⁵ This sets the optimistic estimate sets the benchmark against which real-world interventions could be compared.

Limitations

First, we estimated the PAF of NG/CT on HIV incidence using experimental scenarios with different prevailing RRs for HIV transmission or acquisition that were all modeled using the same calibrated model. This resulted in increasing population-level HIV incidence as the RRs increased due to increasing HIV transmission. An alternative approach would be to generate separate burn-in models for each of the RR combinations with the same targeted equilibrium HIV prevalence. However, this method would also require adjustment of other behavioral or biological parameters (eg, frequency of sex acts), to achieve the same HIV prevalence across different RR scenarios. The counterfactual scenarios presented in this analysis provide an estimate of the proportion of HIV incidence attributable to NG and CT when all other variables are held constant, analogous to an idealized STI control intervention. Second, the PAF values obtained in this analysis are inextricably linked to biological and behavioral factors. The prevalence of NG/CT, specifically the prevalence of NG/CT in HIV-discordant partnerships, has a direct impact on the PAF. Sexual networks with higher prevalence of NG/CT will have a greater proportion of HIV incidence attributable to NG/CT. Different levels of assortativeness, by degree or HIV/STI status, would also result in different PAF values, but we used a rigorous statistical analysis of empirical data on sexual network structure and behavior within partnerships to guide our base model. Our model was calibrated to national prevalence estimates of HIV. Nationally representative incidence rates for NG and CT are not available, so we estimated these rates from a cohort of MSM in Atlanta, Georgia.^{26,27} Third, our model did not include other STIs that may impact HIV transmission, such as syphilis and herpes simplex virus, which also share the site-specific transmission characteristics of NG and CT. Finally, the model only estimates the effect of anal sex. Although oral sex is negligible in estimating HIV risk, it does play a role in STI transmission.³⁶ However, given our focus on the effect of NG and CT on HIV transmission and acquisition, the exclusion of oral sex from the model is unlikely to bias our results.

In conclusion, this study suggests that approximately 10% of HIV infections among MSM are attributable to NG/CT infection. In sensitivity analyses, we found that prevalent NG and CT contribute to between 2% and 14% of HIV acquisition and 3% and 20% of HIV transmissions among MSM. Public health strategies designed to detect and treat NG and CT among MSM in the United States might result in a meaningful reduction of HIV incidence among this high-risk population, although they must be part of a broader comprehensive strategy for HIV prevention that may also include consistent and correct condom use, choosing less risky sexual behaviors, routine testing for high-risk behaviors, drug treatment programs and using sterile equipment (for people who inject drugs), HIV preexposure prophylaxis³⁷ for uninfected MSM, and treatment as prevention³⁸⁻⁴⁰ for HIV-infected MSM.

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