The Potential Impact of a Gel-Based Point-of-Sex Intervention in Reducing Gonorrhea Incidence Among Gay and Bisexual Men: A Modeling Study

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Background: Increases in sexually transmitted infections among gay and bisexual men (GBM) over the past decade have coincided with declines in condom use and rapid uptake of HIV preexposure prophylaxis (PrEP). We explored the impact of an antimicrobial gel-based point-of-sex intervention (gel-PSI) with a lower efficacy for reducing gonorrhea transmission risk than condoms on population-level gonorrhea incidence among GBM in Victoria, Australia.

Methods: A deterministic compartmental model of HIV and gonorrhea transmission was used to project annual gonorrhea incidence from 2020 to 2025. Individuals were classified as HIV-negative (PrEP or non-PrEP users) or HIV-positive, and further stratified by gonorrhoea risk (high/low). All possible scenarios where between 0% and 100% of GBM using condoms transitioned to gel-PSI (considered a downgrade in protection) and 0% and 100% of GBM not using condoms transitioned to gel-PSI (considered an upgrade in protection), with gel-PSI efficacy ranging from 20% to 50%, were run.

Results: The baseline scenario of no gel-PSI uptake (status quo) projected 94,367 gonorrhea infections between 2020 and 2025, with an exponentially increasing trend in annual infections. For a gel-PSI efficacy of 30%, a net reduction in cumulative gonorrhea incidence was projected, relative to the status quo, for any ratio of proportion of condom users "downgrading" to proportion of noncondom users "upgrading" to gel-PSI use of less than 2.6. Under the supposition of equal proportions of condom users and noncondom users switching to gel-PSI, a relative reduction was projected for any gel-PSI efficacy greater than 16%.

Conclusions: Our model suggests that the introduction of a gel-PSI could have benefits for controlling gonorrhea transmission among GBM, even in scenarios where the gel-PSI is considerably less efficacious than condoms and when gel-PSI uptake leads to consequent reductions in consistent condom use.

Globally, gay and bisexual men (GBM) are disproportionately affected by sexually transmitted infections (STIs), with recent data showing sharp increases in gonorrhea, chlamydia, and syphilis infections in recent years among GBM in Australia, the United States, and across Europe.[1–3] Although the introduction of highly sensitive nucleic acid amplification tests and increases in testing among GBM[1,4] have likely contributed to rising STI notifications, declining condom use among GBM,[5,6] coinciding with wide-scale implementation of multiple HIV biomedical interventions, including treatment as prevention for HIV[7] and HIV preexposure prophylaxis (PrEP),[8,9] is also considered a key factor driving increased STI transmission risk.

Mathematical modeling has suggested that the high frequency of STI testing associated with PrEP uptake among GBM may help reduce STI incidence in the years after PrEP implementation.[10] However, there is little real-world evidence showing reduced STI incidence as a result of increased STI testing frequency among PrEP users, and findings from a recent modeling study of various testing scenarios on syphilis epidemiology suggest that despite having overall benefits, increased testing due to PrEP implementation alone is unlikely to reverse the background trend of increasing syphilis transmission.[11]

In contrast to efforts to increase testing, interventions used at the time of sex may offer a more affordable and acceptable method of STI prevention for GBM, and be more effective in preventing transmission. Various point-of-sex interventions aimed at reducing STI transmission risk have been suggested, such as antimicrobial lubricants, rectal gels, and creams.[12–14] Microbicidal products to prevent HIV transmission have also been explored; however, there has been limited success in developing a highly efficacious product,[15] and there are limited data on efficacy of microbicidal interventions on STI transmission. In addition, acceptability and willingness to use antimicrobial products vary among GBM, depending on availability, effectiveness, cost, and perceived risk.[12,16,17]

Antimicrobial gel-based products may not reduce the risk of STI transmission as much as condoms, but even a product used during sex with modest efficacy would provide individual-level

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benefits for GBM who are currently not using condoms or using them infrequently. However, the population-level impact of a partially effective, point-of-sex intervention on STI transmission will be influenced by a number of factors, including product efficacy and acceptability. Another important consideration is how risk reduction practices used by GBM may alter with the availability of a new product that is less effective at preventing STIs but has less of an impact on sexual pleasure compared with condoms. Importantly, reductions in STI transmission resulting from uptake of such an intervention by some GBM may be counteracted by increases in STI risk among GBM who transition from using condoms to using the less effective product. In other words, GBM who transition from no condom use to using the new intervention will experience an "upgrade" in protection from STI acquisition, whereas GBM who transition from condom use to using the new intervention will experience a "downgrade" in protection. Alongside product effectiveness, the population-level benefits of such a product are dependent on the level of uptake among GBM who do and do not engage in more efficacious STI prevention strategies.

Given concerns around increasing gonorrhea incidence among Australian GBM,[18] including in the context of the rapid uptake of PrEP,[19] we used a mathematical model of HIV and gonorrhea transmission among GBM in the state of Victoria to evaluate the population-level effectiveness of differential uptake of a new antimicrobial gel-based point-of-sex intervention (gel-PSI) in reducing gonorrhea incidence among GBM. We estimated the threshold of uptake among noncondom users and condom users required for an overall reduction in gonorrhea incidence based on varying hypothetical levels of product efficacy.

METHODS

We used a population-level, deterministic, compartmental model of HIV and gonorrhea transmission among GBM in Victoria, Australia (Fig. 1). The model used a series of ordinary differential equations representing compartment transition rates; individual sex acts were not explicitly modeled. Estimates and

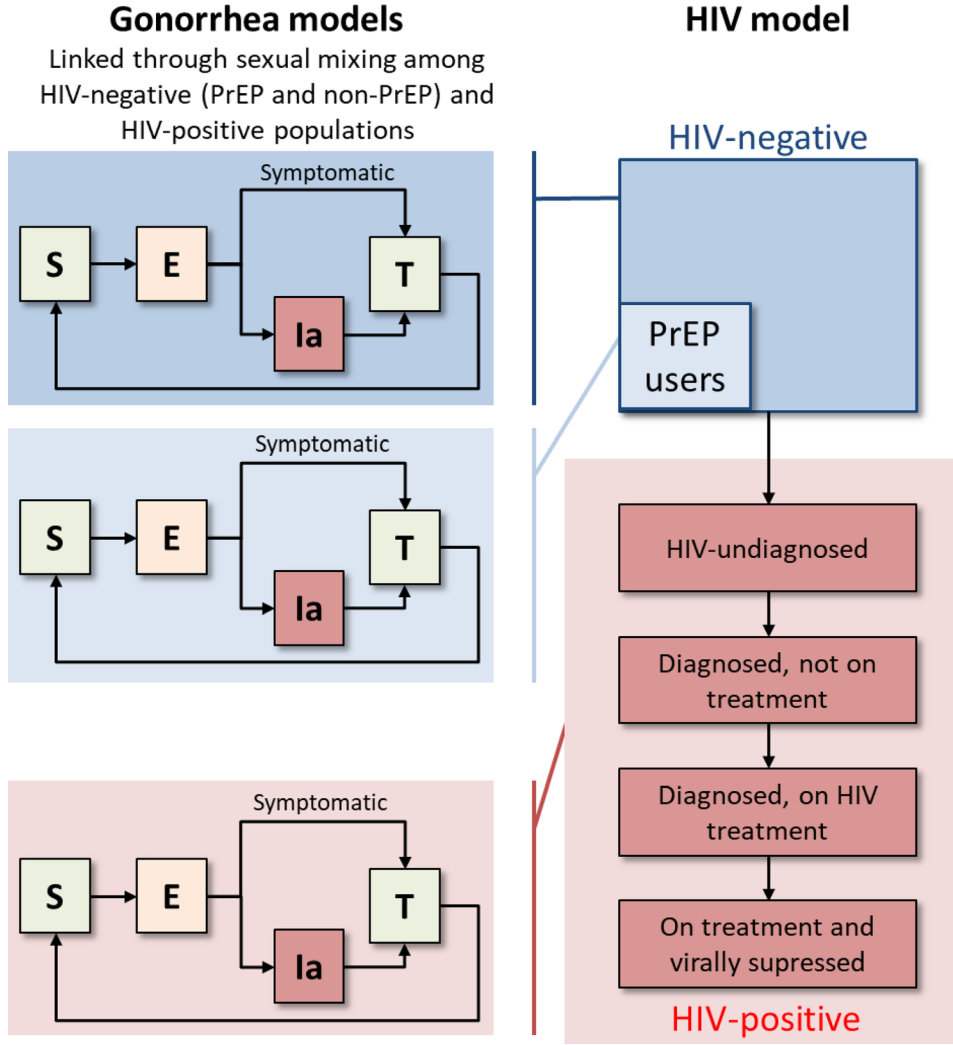

Figure 1. Model schematic. An HIV transmission and care cascade progression model was coupled with a gonorrhea model for 3 subpopulations of GBM: HIV-positive, HIV-negative not using PrEP, and HIV-negative using PrEP. The gonorrhea models are linked through sexual mixing among the 3 subpopulations. Gonorrhea model compartments represent susceptible (S), exposed (E), infected and asymptomatic (Ia), and treatment (T; GBM with symptomatic gonorrhea were model to commence treatment immediately). Each subpopulation was further stratified so that a fraction was at higher risk of gonorrhea (not shown).

sources for model parameters described hereinafter are provided in Table 1. Analysis was conducted using R (version 3.5).

HIV Model Dynamics

The model population was classified into 3 subpopulations; HIV-negative GBM using PrEP, HIV-negative GBM not using PrEP, and HIV-positive GBM. HIV-positive individuals were stratified by current stage in the HIV care cascade (undiagnosed, diagnosed but not on treatment, on HIV treatment and not virally suppressed, or on HIV treatment and virally suppressed) and were able to progress through the cascade. During each time step, HIV-negative individuals seroconverted to HIV-positive, moving to the HIV-positive undiagnosed compartment, at a rate dependent on (1) average condom use in the population, (2) PrEP coverage among HIV-negative individuals, (3) the dynamic prevalence of HIV in the model (weighted to account for a removal of infectiousness among HIV-positive people who were virally suppressed), and (4) a force of infection constant that was used to fit the model to observed HIV notification data over time in Victoria. Calibration parameters, such as the force of infection constant above, are used in population-level models to fit to data without explicitly modeling individual behaviors, which influence transmission risk, such as rate of partner change and sexual positioning, for which data are limited.

Gonorrhea Model Dynamics

A gonorrhea model was included for each HIV subpopulation (Fig. 1). The gonorrhea models classified individuals as being susceptible (S), exposed (E), infected and asymptomatic (Ia), or undergoing treatment (T). Gay and bisexual men with symptomatic gonorrhea were assumed to commence treatment immediately. In the model, susceptible individuals could become infected with gonorrhea at a rate that was dependent on (1) average condom use in the subpopulation, (2) the dynamic gonorrhea prevalence among each of the subpopulations and their level of sexual mixing between subpopulations, and (3) a force of infection constant that was used to fit the model to observed gonorrhea notification data among HIV-negative (PrEP and non-PrEP users combined) and HIV-positive GBM over time in Victoria. Individuals who became infected with gonorrhea moved from susceptible (S) to exposed (E), and after an incubatory period of 5 days, a proportion became symptomatic and were assumed to commence gonorrhea treatment (T), whereas the remaining proportion became infected and asymptomatic (Ia). Individuals in the exposed or asymptomatic gonorrhea infection stages were only treated after a test (testing rates described hereinafter). After gonorrhea treatment, individuals returned to the susceptible compartment after 7 days, the recommended period of abstinence after receiving treatment. To capture heterogeneous levels of risk among the GBM population, each gonorrhea model (i.e., among the subpopulations HIV-negative on PrEP, HIV-negative not on PrEP, and HIV-positive) included a stratification for gonorrhea infection risk (high risk vs. low risk for gonorrhea infection).

Model Parameters

Annual Victorian GBM population size, PrEP coverage, and HIV prevalence were estimated using Australian notification and surveillance data (Supplementary Methods 1, http://links.lww.com/OLQ/A523). For each subpopulation (HIV-negative on PrEP, HIV-negative not on PrEP, and HIV-positive), gonorrhea testing rate was modeled as a constant parameter, estimated using surveillance data from the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Blood-borne Viruses

TABLE 1. Model Parameters

Parameter	Value	Reference/Comment
HIV parameters		
Effectiveness of latex condoms at preventing HIV	91%	Estimated condom effectiveness during anal sex between men in 2 prospective cohort studies [S1]
Effectiveness of latex condoms at preventing gonorrhea	75%	Conservative estimate (Supplementary Methods 4, http://links.lww.com/OLQ/A523)
Effectiveness of PrEP at preventing HIV transmission	99%	US CDC PrEP effectiveness estimate [S2]
Reduction in HIV infectiousness when on treatment	100%	Reduction in HIV transmission from Opposites Attract study [S3]
Gonorrhea parameters		
Duration of exposed stage for symptomatic individuals	5 d	[S4]
Duration of treatment	7 d	Australian STI guidelines recommend abstaining from sex for 7 d after treatment [S5]
Proportion of GBM with gonorrhea who are symptomatic	29%	Calculated from ACCESS study data. Proportion diagnosed with either rectal infection only or including urethral infection, and corresponding probabilities of being symptomatic (Supplementary Methods 4, http://links.lww.com/OLQ/A523)
Increased gonorrhea risk for high-risk GBM	7.5	Estimated from the PrEPX study [S6] (Supplementary Methods 6, http://links.lww.com/OLQ/A523)
Proportion of GBM at high risk of gonorrhea	13%	
Gonorrhea testing frequency		
HIV-negative GBM on PrEP	1/90 d	Australian PrEP guidelines recommend quarterly testing [S7]
HIV-negative GBM not on PrEP	1/224 d	Previous analysis of Victorian GBM in ACCESS data [S8]
HIV-positive GBM	1/133 d	Previous analysis of Victorian GBM in ACCESS data [S8]
Sexual risk parameters		
Proportion of sex acts that are HIV serodiscordant (HIV-negative non-PrEP users)	10%	Estimated from large cross-sectional survey of GBM [S9]
Proportion of sex acts that are HIV serodiscordant (HIV-negative PrEP users)	17%	
Proportion of sex acts that are HIV serodiscordant (HIV-positive GBM)	34%	
Relative condom use of GBM on PrEP and HIV-positive GBM compared with HIV-negative GBM not on PrEP	0.3	Estimated from Melbourne Gay Community Period Survey 2019 [S10]

and Sexually Transmitted Infections (ACCESS) surveillance project (Supplementary Methods 2, http://links.lww.com/OLQ/A523). Condom use was included as a time-varying parameter for each subpopulation, reflecting average condom use in that population, and was estimated using Victorian biobehavioral surveillance data (Supplementary Methods 3, http://links.lww.com/OLQ/A523). Condom effectiveness, gonorrhea symptomatic rate, and sexual mixing were estimated from the literature (Supplementary Methods 4, http://links.lww.com/OLQ/A523) and the proportion of individuals across each subpopulation classified as "high risk" for gonorrhea and the relative increase in gonorrhea acquisition risk were calculated from previously reported STI data from GBM enrolled in a Victorian PrEP study (Supplementary Methods 5, http://links.lww.com/OLQ/A523).

Model Calibration

The force of infection constant for HIV and the diagnosis rate for HIV in the model were calibrated to best-fit time-series data for the estimated number of HIV-positive GBM in Victoria and Victorian HIV notifications attributed to male-to-male sex. Among people diagnosed with HIV, the proportion who were on treatment and the proportion who were virally suppressed in the model were fitted to time series data from Victoria (Supplementary Table 2, http://links.lww.com/OLQ/A523). For all forward projections, the HIV care cascade was modeled to continue to follow Australian trends toward achieving and maintaining 95% of people living with HIV diagnosed, 95% of people diagnosed started on treatment, and 95% of people on treatment virally suppressed by 2030 (Supplementary Fig. 1, http://links.lww.com/OLQ/A523).

Once the HIV model was calibrated, the force of infection constants for gonorrhea among HIV-negative and HIV-positive GBM was calibrated to best-fit time-series data for gonorrhea notifications (Supplementary Table 4, http://links.lww.com/OLQ/A523). Both the HIV and gonorrhea models were calibrated by minimizing the sum of squares between the model and data using the Nelder-Mead method. A sensitivity analysis was conducted in which the gonorrhea force of infection was held constant from 2018 onward, rather than dynamic and dependent on gonorrhea prevalence, to test the impact of gel-PSI if background exponential growth trends in gonorrhea incidence became more linear in the projected years.

Introduction of a Gel-PSI and Model Outcomes

Uptake Threshold Ratios for Net Benefit

The main model outcome was cumulative gonorrhea incidence between 2020 and 2025 (inclusive). Each subpopulation (HIV-positive PrEP, HIV-negative PrEP, and HIV-negative non-PrEP) consisted of GBM whose primary method of gonorrhea prevention was no STI prevention, using condoms, or using the gel-PSI. As the coverage of different prevention methods changed among each subpopulation, this was modeled to scale the force of infection according to an effectiveness-weighted prevention factor (i.e., the sum of prevention methods of coverage multiplied by their effectiveness).

First, differential levels of gel-PSI uptake by current condom use were explored, with no differential uptake by HIV or PrEP status. Scenarios were run where between 0% and 100% of GBM currently using no prevention (across HIV-positive PrEP, HIV-negative PrEP, and HIV-negative non-PrEP) upgraded to gel-PSI and 0% and 100% of GBM using condoms downgraded to gel-PSI. These changes were implemented to be phased in over a 2-year period (2020–2022) and held constant out to 2025. The threshold ratio of percentage "downgrading" (from condoms to gel-PSI) to "upgrading" (from no prevention to gel-PSI) for a net reduction in cumulative gonorrhea incidence from 2020 to 2025 was calculated. This was repeated for theoretical levels of gel-PSI effectiveness for preventing gonorrhea of 20%, 30%, 40%, or 50%. In all of these scenarios, the effectiveness of the gel-PSI was assumed to be lower than the effectiveness of condoms in reducing gonorrhea transmission risk.

Differential Uptake Among Subpopulations

Several specific scenarios of gel-PSI uptake were then explored with differential uptake across the 3 subpopulations (HIV-negative on PrEP, HIV-negative not on PrEP, and HIV-positive) and across those already using or not using condoms before gel-PSI introduction. In these scenarios, we used a gel-PSI efficacy of 30% for reducing gonorrhea transmission-risk.

- Scenario a: use of the gel-PSI increased to a threshold of 50% of each subpopulation (HIV-positive, HIV-negative not on PrEP, HIV-negative on PrEP), with only those not using condoms upgrading to gel-PSI and condom users remaining as condom users
- Scenario b: 50% of condom users downgrade to gel-PSI and 50% of noncondom users upgrade to gel-PSI
- Scenario c: all condoms users across each subpopulation downgrade to gel-PSI
- Scenario d: all PrEP users (condom and noncondom users) switch to gel-PSI

Given that the uptake of the gel-PSI among individuals at risk of HIV (HIV-negative not on PrEP) would likely depend on the gel-PSI's effectiveness at also reducing HIV, we then explored scenarios with differential levels of uptake between those at risk of HIV (HIV-negative not on PrEP) and those not at risk of HIV (HIV-negative on PrEP and HIV-positive):

- Scenario e: 50% of PrEP users and HIV-positive GBM (both condom users and noncondom users) switch to gel-PSI, whereas non-PrEP users have no gel-PSI uptake.
- Scenario f: 50% of GBM not on PrEP (condom users and noncondom users) switch to gel-PSI, whereas PrEP users and HIV-positive GBM have no gel-PSI uptake.

We report the net absolute difference and relative difference in cumulative gonorrhea infections from 2020 to 2025 (inclusive) between each scenario and the baseline scenario of no gel-PSI uptake (status quo).

Sensitivity Analyses

Sensitivity analyses were run to examine the influence of key assumptions in model parameters. Using scenario b (50% upgrade and 50% downgrade in STI prevention among noncondom users and condom users, respectively, and a gel-PSI efficacy of 30%), we explored the effect of varying the following parameters on cumulative gonorrhea incidence from 2020 to 2025 and the relative reduction between scenario b and no gel-PSI uptake: the effectiveness of condoms at reducing gonorrhea transmission risk from 75% to 50% and 100%; sexual mixing by changing the proportion of serodiscordant sex acts to 0% (complete serosorting), 50% of sex acts serodiscordant and mixing at random (no serosorting); increasing PrEP uptake post-2020 to reach 50% and 75% of HIV-negative GBM by 2025; proportion of gonorrhea

cases (any anatomical site), which were symptomatic from 45% to 25% and 75%; increased risk factor for the high risk for the gonorrhea group from 7.5 to 2, 10, and 20; condom use among HIV-negative GBM from the remaining stable at 29% to 2025 to reducing to 15% and 5% by 2025 (with condom use among PrEP users and HIV-positive GBM 0.3 times that of non-PrEP users); and increased gonorrhea testing rates among non-PrEP users by reducing mean number of days between tests by 25% and 50% by 2025.

RESULTS

Projected Gonorrhea Notifications to 2025

Calibration of the gonorrhea model to notification data was fairly accurate among both HIV-negative and HIV-positive populations (Fig. 2; see Supplementary Fig. 2, http://links.lww.com/OLQ/A523 for calibration of the HIV model to HIV notification data). In the baseline scenario of no gel-PSI uptake (status quo), projected annual gonorrhea incidence increased exponentially, reaching approximately 23,848 infections among Victorian GBM in the year 2025 (Fig. 3) equating to a cumulative incidence of 94,367 gonorrhea infections from 2020 to 2025. Supplementary Figure 3, http://links.lww.com/OLQ/A523 shows projected annual incidence attributable to each subpopulation (HIV-positive PrEP, HIV negative on PrEP, and HIV negative not on PrEP).

Prevention Upgrade and Downgrade Thresholds

After the introduction of a gel-PSI with an efficacy of 30%, compared with the baseline scenario of no gel uptake among the population, a relative reduction in cumulative gonorrhea incidence from 2020 to 2025 was observed for any ratio of proportion of condom users downgrading to proportion of noncondom users upgrading to gel-PSI use of less than 2.6 (Fig. 4). For example, if 50% of condom users downgraded to gel-PSI, provided that at least 20% of noncondom users upgraded, a relative reduction in gonorrhea incidence was observed for a gel efficacy of 30%. If 50% of condom users downgraded to gel-PSI under a gel efficacy of 50%, a net benefit was observed provided at least 7% on noncondom users upgraded, with the threshold ratio of proportion of condom users downgrading to proportion of noncondom users upgrading to gel-PSI use equal to 7.4 (Fig. 4). If the proportion of condom users downgrading to gel-PSI was equal to the proportion of noncondom users upgrading to gel-PSI, a net reduction in gonorrhea notifications was projected for a gel-PSI with efficacy of 16% or higher.

Intervention Uptake Scenarios

Change in cumulative gonorrhea incidence across each scenario relative to the baseline scenario of no gel-PSI uptake is shown in Table 2. All but one scenario (scenario c, only condom users downgrading to gel-PSI) projected a relative reduction in cumulative gonorrhea incidence from 2020 to 2025 (Fig. 4). All scenarios project an increasing trend in annual gonorrhea incidence among GBM to 2025 and beyond.

Sensitivity Analyses

Having a constant force of infection from 2018 onward led to a moderate reduction in both the cumulative gonorrhea incidence and relative reductions after gel-PSI uptake scenarios (Supplementary Fig. 5, http://links.lww.com/OLQ/A523); however, benefits were still observed across most scenarios (Supplementary Table 5, http://links.lww.com/OLQ/A523). Altering the specified model parameters moderately affected the cumulative gonorrhea incidence projected to 2025 (Supplementary Fig. 6, http://links.lww.com/OLQ/A523); however, altering these parameters only had small effects on the relative impact of the gel-PSI intervention (under scenario b; 50% uptake among condom users and 50% uptake among noncondom users, assuming a gel-PSI efficacy of 30%; Supplementary Fig. 7, hhttp://links.lww.com/OLQ/A523). All sensitivity scenarios returned a relative reduction in cumulative gonorrhea incidence from 2020 to 2025 of between 19%

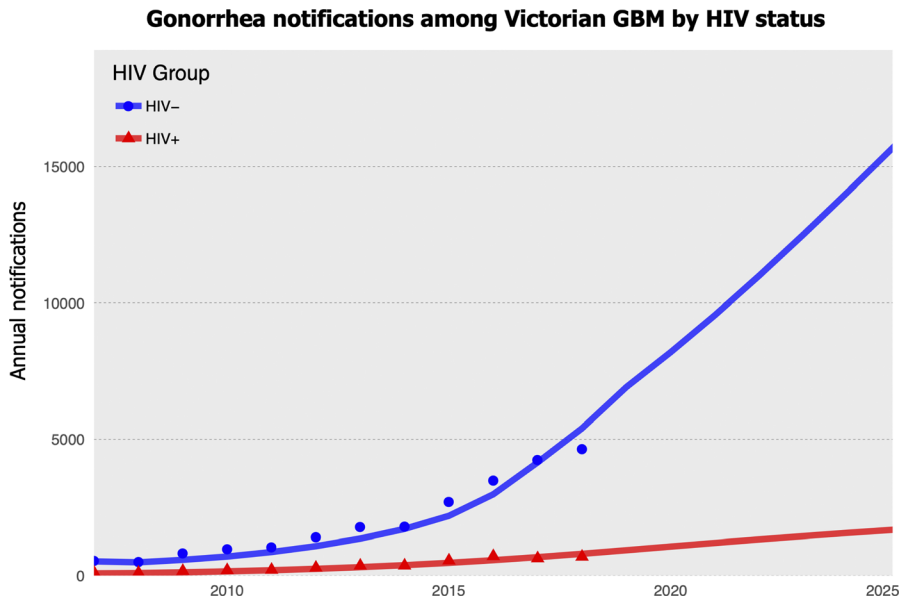

Figure 2. Annual gonorrhea notifications among GBM in Victoria (dots) versus calibrated model projections (lines) for HIV-negative (blue) and HIV-positive (red) GBM.

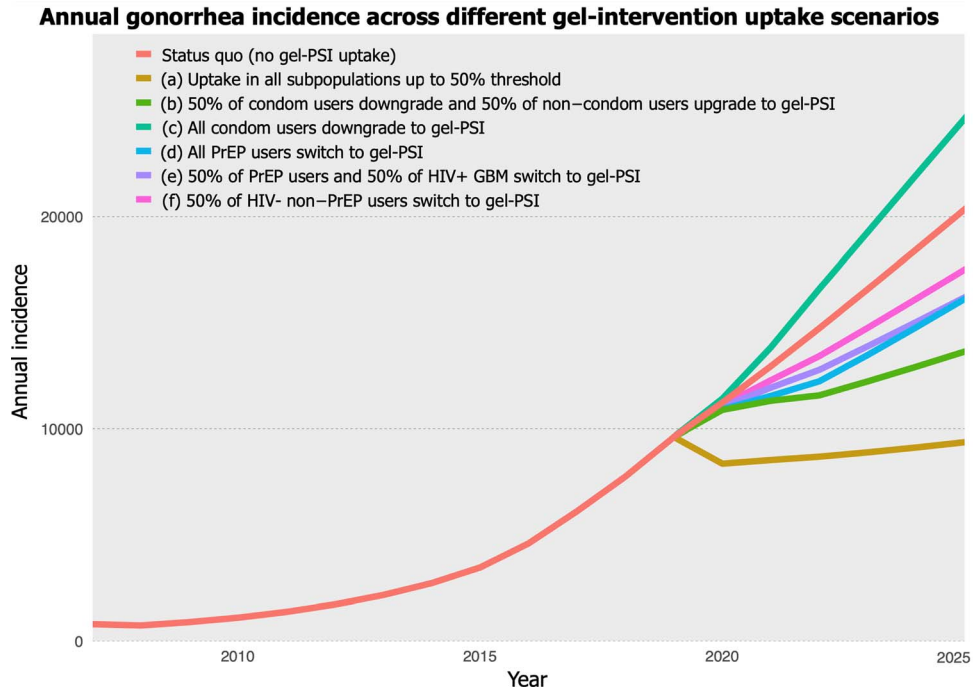

Figure 3. Projected annual gonorrhea incidence among Victorian GBM from 2007 to 2025 for different model scenarios of uptake of a gel-PSI according to HIV status, PrEP use, and condom use.

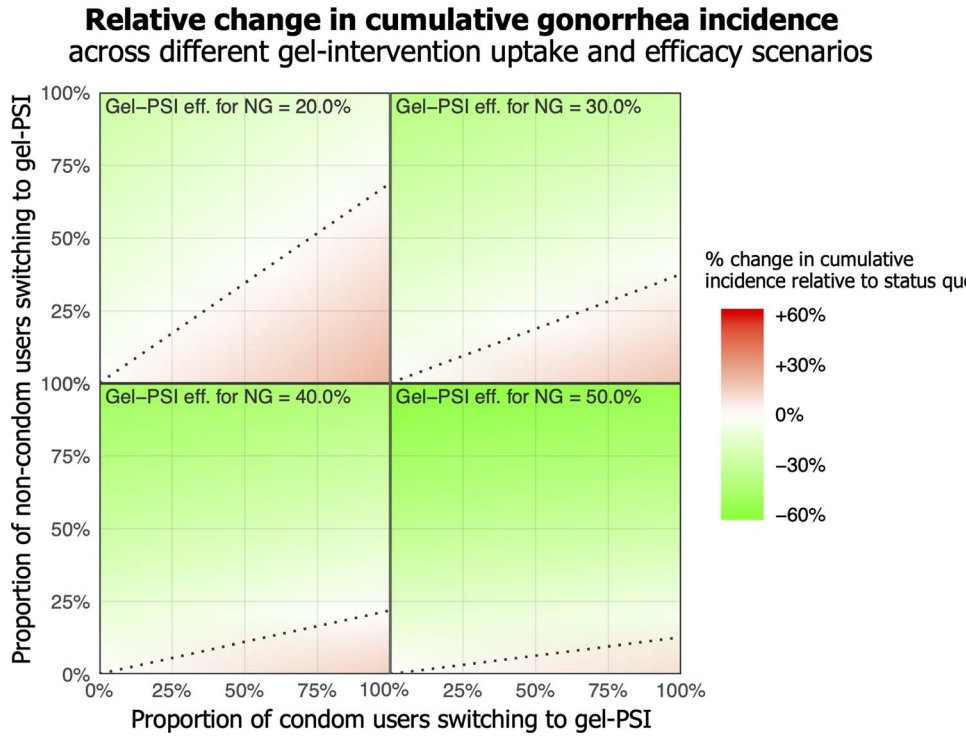

Figure 4. Population-level impact of gel-based intervention according to gel efficacy, intervention uptake among noncondom users, and intervention uptake among condom users. Compared with the status-quo scenario of no gel-PSI, heat maps show the difference in cumulative gonorrhea incidence from 2020 to 2025 among GBM in Victoria according to the proportion of condom users who "downgrade" to gel prevention (*x* axes), the proportion of noncondom users who "upgrade" to gel prevention (*y* axes), and the effectiveness of the intervention for reducing gonorrhea transmission (panels for 20%, 30%, 40%, or 50% efficacy). Green and red shadings represent positive and negative population-level benefits, respectively, with the dotted line representing zero net effect on cumulative gonorrhea incidence.

TABLE 2. Cumulative Gonorrhea Incidence Among Victorian GBM From 2020 to 2025 Across Different Model Scenarios of Uptake of a Gel-PSI According to HIV Status, PrEP Use, and Condom Use

	Scenario	Cumulative Incidence 2020–2025	Difference in Cumulative Incidence to Status Quo	Relative Reduction in Cumulative Incidence, %
	Status quo (no gel-PSI uptake)	94,367		
a	Uptake in all subpopulations up to 50% threshold*	52,988	−41,379	−44
b	50% of condom users downgrade and 50% of noncondom users upgrade	72,559	−21,808	−23
c	All condom users downgrade to gel-PSI	107,720	13,353	14
d	All PrEP users switch to gel-PSI	79,081	−15,286	−16
e	50% of PrEP users and HIV-positive GBM switch to gel-PSI	80,860	−13,507	−14
f	50% of non-PrEP users switch to gel-PSI	85,203	−9164	−10

*Fifty percent of each population upgrade to using the gel-PSI, assuming no change to those already using condoms.

and 28% compared with no gel-PSI uptake (Supplementary Table 6, http://links.lww.com/OLQ/A523).

DISCUSSION

Our model demonstrated that the introduction of a hypothetical gel-PSI, which is less efficacious than latex condoms in reducing gonorrhea acquisition risk per sex act, led to a population-level decrease in gonorrhea incidence among GBM relative to the status quo in most uptake scenarios. Intuitively, greater reductions in gonorrhea incidence were projected with greater uptake of the intervention among those not already using condoms.

The rate of uptake of such a point-of-sex intervention among GBM already using and not using condoms will depend on a range of factors including efficacy, product availability, acceptability, cost, safety, and effect on sexual pleasure. The proportion of HIV-negative GBM not using PrEP who would transition from using condoms to using the gel-PSI would also likely depend on the product's efficacy in reducing HIV transmission risk and gonorrhea risk. However, among HIV-negative GBM on PrEP and HIV-positive GBM, reduction in HIV transmission risk would not have a substantial impact on the likelihood of uptake, given the negligible risk of HIV acquisition or transmission in these groups.

A key factor in determining the impact of the gel-based intervention is estimating the negative effects of reduced condom use among GBM who switch to the lower-efficacy gel-based intervention. In our model, we explored this trade-off in protection and found that, in most scenarios, it was outweighed by the benefits of noncondom users upgrading to gel-based prevention. In scenarios where all condom users downgraded to using the less-efficacious gel-based intervention, even with an intervention that reduces gonorrhea transmission risk per sex act by only 50%, net benefits were observed provided 12% or more of noncondom users started using the gel-PSI.

The likelihood of overall benefits is further enhanced by the different risk profiles of condom users who may downgrade to gel-based prevention compared with noncondom users who may upgrade to gel-based prevention. Given the risk-based eligibility criteria for PrEP in Australia[20] and the estimated high level of PrEP coverage among those eligible for PrEP,[21,22] it is reasonable to suggest that HIV-negative GBM not using PrEP are a population at reduced risk of gonorrhea infection. Therefore, reductions in condom use among this population will likely have a modest effect on gonorrhea transmission when compared with the beneficial effects of uptake of the gel intervention among PrEP users. It is also reasonable to suggest that an intervention with minimal effect on sexual pleasure would have a high uptake among those who do not use condoms, as reduced sexual pleasure is a well-established barrier to condom use among GBM.[23] In considering these factors, our model suggests that in the Australian context, a new intervention with minimal impact on sexual pleasure would likely lead to a net reduction in gonorrhea incidence among GBM.

Although we did not explicitly model sexual network dynamics in our study, it is likely that the population-level impact of a new point-of-sex intervention would be maximized through high uptake among sexual networks of high STI transmission. Recent data from Victoria show that STIs among PrEP users are highly concentrated among GBM experiencing repeat infections, and that increased partner numbers and participation in group sex are associated with increased STI risk in the context of PrEP, suggesting that networks of high STI transmission exist within populations of PrEP users.[19] Interventions targeted toward a relatively small proportion of GBM at increased risk of STIs could have a substantial impact on interrupting STI transmission.

Despite previous research showing the high acceptability of hypothetical antimicrobial products among GBM,[17,24] early research showing the potential for such products in reducing STI acquisition risk,[25] and our findings that antimicrobial products with low efficacies could still be beneficial at the population level, there remain no such products with regulatory approval or commercial availability in any country. A barrier to the promotion and uptake of such products is the potential for antimicrobial resistance, a growing concern for gonorrhea. More recent qualitative research reports that, although some GBM show interest in antimicrobial interventions, including the use of antibiotics for STI prophylaxis, many have concerns around the potential for antimicrobial resistance and adverse health effects and show hesitance toward the widespread use of antibiotics for such purposes.[26] Although such attitudes may hinder community-level uptake of a gel-based antimicrobial intervention, our projections suggest that even relatively low levels of uptake may have population-level benefits. To offset the potential threat posed by increased antibiotic resistance after uptake, it would be important to couple the antimicrobial-based intervention with regular screening and comprehensive resistance testing. In addition, further research would be required to asses any adverse effects of the regular use of microbicides on the rectal microbiome.

Despite the introduction of the gel-PSI leading to a net reduction in gonorrhea incidence in most scenarios, almost all scenarios projected an increasing trend in gonorrhea incidence to the year 2025 and beyond. These findings highlight that even with a fairly efficacious product and reasonable uptake among the GBM population, a point-of-sex intervention that reduces gonorrhea acquisition risk will likely not be enough to curtail the rise in incidence of gonorrhea. A combination of preventive measures,

including high rates of asymptomatic screening and a gonorrhea vaccine, will likely be required to reverse the trend of increasing gonorrhea transmission. Although we have explored a hypothetical gel-based product, many interventions could be used to partially reduce the risk of gonorrhea transmission. The implications of our findings could be applicable to other novel prevention strategies, such as using mouthwash before or after oral sex to reduce risk of pharyngeal gonorrhea,[27] microbicidal rectal enemas used before or after receptive sex, or antibiotic preexposure or postexposure prophylaxis for the prevention of STIs.[28,29] Furthermore, an antimicrobial intervention would likely have concurrent benefits for other infections not explored in this model, such as chlamydia and syphilis.

There are several limitations to our analysis. First, we did not model anatomical site-specific gonorrhea transmission. Recent evidence suggests that oral transmission of gonorrhea may account for a large proportion of new infections,[30] and this would not have been captured in our model. Second, although we were able to add parameters for sexual mixing between populations, these were based on behavioral surveys conducted among a select sample of GBM, and data were aggregated rather than event level. The lack of setting-specific, individual-level sexual partnership data precluded accurate estimates of sexual mixing patterns between subpopulations of GBM, including mixing based on HIV status, PrEP status, and STI risk. Furthermore, it is possible that after the introduction of such a product, sexual networks may change as individuals' use of the product may influence partner selection. However, altering our sexual mixing parameters in sensitivity analysis had little effect on model projections. Third, we were not able to incorporate more complex network dynamics, such as heterogeneity in partner turnover across groups of GBM, differentiation of casual and regular partnerships, or overlap of concurrent partnerships, all of which would have important implications for gonorrhea transmission. Fourth, although our model projects an exponentially increasing annual incidence of gonorrhea among the population, it is important to note that this is in the scenario of no other interventions being introduced or additional behavior changes in response to increasing transmissions. In reality, it is likely that some other limiting factor or factors would curtail the exponential growth in gonorrhea incidence. Finally, there is also uncertainty associated with recency and representativeness of data and parameter estimates; however, sensitivity analyses indicated that these were unlikely to alter our main conclusions.

Our study shows that interventions used at the point-of-sex that may only have a modest effect in reducing individual STI acquisition risk, such as gel-based antimicrobial lubricant, are likely to provide population-level benefits among GBM. Commercial development and regulatory approval of these products should be expedited. Despite potential benefits, such interventions are alone unlikely to reverse the increasing trend of increasing STIs, and additional interventions will be required.

REFERENCES

1. HIV, Viral Hepatitis and Sexually Transmissible Infections in Australia: Annual Surveillance Report 2018. Sydney: Kirby Institute, University of New South Wales, 2018.
2. Stenger MR, Pathela P, Anschuetz G, et al. Increases in the rate of *Neisseria gonorrhoeae* among gay, bisexual and other men who have sex with men—Findings from the Sexually Transmitted Disease Surveillance Network 2010–2015. Sex Transm Dis 2017; 44:393–397.
3. van Bilsen WPH, Boyd A, van der Loeff MFS, et al. Diverging trends in incidence of HIV versus other sexually transmitted infections in HIV-negative MSM in Amsterdam. AIDS 2020; 34:301–309.
4. An Q, Wejnert C, Bernstein K, et al. Syphilis screening and diagnosis among men who have sex with men, 2008–2014, 20 U.S. cities. J Acquir Immune Defic Syndr 2017; 75(Suppl 3):S363–S369.
5. Broady T, Mao L, Bavinton B, et al. Gay Community Periodic Survey: Melbourne 2019. Sydney: Centre for Social Research in Health, UNSW Sydney.
6. Chen Y-H, Guigayoma J, McFarland W, et al. Increases in pre-exposure prophylaxis use and decreases in condom use: Behavioral patterns among HIV-negative San Francisco men who have sex with men, 2004–2017. AIDS Behav 2019; 23:1841–1845.
7. Bavinton BR, Pinto AN, Phanuphak N, et al. Viral suppression and HIV transmission in serodiscordant male couples: An international, prospective, observational, cohort study. Lancet HIV 2018; 5: e438–e447.
8. Holt M, Lea T, Mao L, et al. Community-level changes in condom use and uptake of HIV pre-exposure prophylaxis by gay and bisexual men in Melbourne and Sydney, Australia: Results of repeated behavioural surveillance in 2013–17. Lancet HIV 2018; 5:e448–e456.
9. Traeger MW, Schroeder SE, Wright EJ, et al. Effects of pre-exposure prophylaxis for the prevention of human immunodeficiency virus infection on sexual risk behavior in men who have sex with men: A systematic review and meta-analysis. Clin Infect Dis 2018; 67:676–686.
10. Jenness SM, Weiss KM, Goodreau SM, et al. Incidence of gonorrhea and chlamydia following human immunodeficiency virus preexposure prophylaxis among men who have sex with men: A modeling study. Clin Infect Dis 2017; 65:712–718.
11. Wilkinson AL, Scott N, Tidhar T, et al. Estimating the syphilis epidemic among gay, bisexual and other men who have sex with men in Australia following changes in HIV care and prevention. Sex Health 2019; 16:254–262.
12. Carballo-Dieguez A, Stein Z, Saez H, et al. Frequent use of lubricants for anal sex among men who have sex with men: The HIV prevention potential of a microbicidal gel. Am J Public Health 2000; 90: 1117–1121.
13. Carballo-Diéguez A, Exner T, Dolezal C, et al. Rectal microbicide acceptability: Results of a volume escalation trial. Sex Transm Dis 2007; 34:224–229.
14. McGowan I. Rectal microbicide development. Curr Opin HIV AIDS 2012; 7:526–533.
15. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 2010; 329:1168–1174.
16. Zhang G, Zhang H, Yu H, et al. Hypothetical rectal microbicide acceptability and factors influencing it among men who have sex with men in Tianjin, China. PLoS One 2016; 11:e0156561.
17. Murphy DA, Lea T, de Wit JB, et al. Interest in using rectal microbicides among Australian gay men is associated with perceived HIV vulnerability and engaging in condomless sex with casual partners: Results from a national survey. Sex Transm Infect 2015; 91:266–268.
18. Callander D, Guy R, Fairley CK, et al. Gonorrhoea gone wild: Rising incidence of gonorrhoea and associated risk factors among gay and bisexual men attending Australian sexual health clinics. Sex Health 2019; 16:457–463.
19. Traeger MW, Cornelisse VJ, Asselin J, et al. Association of HIV preexposure prophylaxis with incidence of sexually transmitted infections among individuals at high risk of HIV infection. JAMA 2019; 321:1380–1390.
20. Wright E, Grulich A, Roy K, et al. Australasian society for HIV, viral hepatitis and sexual health medicine HIV pre-exposure prophylaxis: clinical guidelines. J Virus Erad 2017; 3:168–184.
21. Zablotska IB, Gray R, Whittaker B, et al. The estimated number of potential PrEP users among gay-identifying men who have sex with men in Australia. PLoS One 2018; 13:e0204138.
22. Monitoring HIV Pre-exposure Prophylaxis Uptake in Australia. Sydney, New South Wales: The Kirby Institute, UNSW Sydney, 2019.
23. Golub SA, Gamarel KE. Psychometric evaluation of the Condom Barriers and Motivations Scale (CBMS). J Behav Med 2017; 40:494–505.
24. Frasca T, Giguere R, Ibitoye M, et al. Lessons for rectal microbicide development from an acceptability trial of a placebo gel applied prior to receptive anal intercourse. Arch Sex Behav 2017; 46:1101–1109.

25. Fernandez-Romero JA, Deal C, Herold BC, et al. Multipurpose prevention technologies: The future of HIV and STI protection. Trends Microbiol 2015; 23:429–436.
26. Callander D, Philpot S, Mao L, et al. 'My Sex, My Sexual Health': A Social Study of Sexually Transmissible Infections Among Gay and Bisexual Men. Sydney, New South Wales: The Kirby Institute, UNSW Sydney, 2019.
27. Chow EPF, Walker S, Hocking JS, et al. A multicentre double-blind randomised controlled trial evaluating the efficacy of daily use of antibacterial mouthwash against oropharyngeal gonorrhoea among men who have sex with men: The OMEGA (Oral Mouthwash use to Eradicate GonorrhoeA) study protocol. BMC Infect Dis 2017; 17:456.
28. Molina J-M, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: An open-label randomised substudy of the ANRS IPERGAY trial. Lancet Infect Dis 2018; 18: 308–317.
29. Bolan RK, Beymer MR, Weiss RE, et al. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: A randomized, controlled pilot study. Sex Transm Dis 2015; 42:98–103.
30. Fairley CK, Cornelisse VJ, Hocking JS, et al. Models of gonorrhoea transmission from the mouth and saliva. Lancet Infect Dis 2019; 19: e360–e366.