Agent-based computational model of the prevalence of gonococcal infections after the implementation of HIV pre-exposure prophylaxis guidelines

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Abstract

Recently, the first comprehensive guidelines were published for pre-exposure prophylaxis (PrEP) for the prevention of HIV infection in populations with substantial risk of infection. Guidelines include a daily regimen of emtricitabine/tenofovir disoproxil fumarate (TDF/FTC) as well as condom usage during sexual activity. The relationship between the TDF/FTC intake regimen and condom usage is not yet fully understood. If men who have sex with men (MSM,) engage in high-risk sexual activities without using condoms when prescribed TDF/FTC they might be at an increased risk for other sexually transmitted diseases (STD). Our study focuses on the possible occurrence of behavioral changes among MSM in the United States over time with regard to condom usage. In particular, we were interested in creating a model of how increased uptake of TDF/FTC might cause a decline in condom usage, causing significant increases in non-HIV STD incidence, using gonococcal infection incidence as a biological endpoint. We used the agent-based modeling software NetLogo, building upon an existing model of HIV infection. We found no significant evidence for increased gonorrhea prevalence due to increased PrEP usage at any level of sample-wide usage, with a range of 0-90% PrEP usage. However, we did find significant evidence for decreased prevalence of HIV, with a maximal effect being reached when 5% to 10% of the MSM population used PrEP. Our findings appear to indicate that attitudes of aversion, within the medical community, toward the promotion of PrEP due to the potential risk of increased STD transmission are unfounded.

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Introduction

The Centers for Disease Control and Prevention (CDC) and US Public Health Service recently published the first comprehensive guidelines for the use of emtricitabine/tenofovir disoproxil difumate (TDF/FTC; brand name Truvada®) as a pre-exposure prophylactic (PrEP) for the prevention of HIV infection in populations with substantial risk, such as men who have sex with men (MSM) [1]. Guidelines for PrEP include a daily regimen of TDF/FTC as well as condom usage during sexual activity. Studies have been conducted to determine patient compliance regarding the drug intake regimen. However, the relationship between the TDF/FTC intake regimen and condom usage is not yet fully understood. It has been suggested that PrEP usage among some members of high risk populations, such as MSM, might engage in high risk sexual activities more frequently if prescribed TDF/FTC, placing PrEP users who are not wholly compliant with CDC guidelines (i.e., do not use condoms) at an increased risk for sexually transmitted diseases (STD) other than HIV.

In October of 2013, the CDC estimated that there were 1,144,500 persons aged 13 or older in in the United States (US) living with HIV with an estimated 50,000 new infections occurring per year [2,3]. MSM have been identified as having the highest risk of becoming infected, with data from 2011 estimating that 79% of all persons in the US living with HIV were MSM [1]. In 2011, MSM accounted for 63% of all new HIV infections in the US and from 2008 to 2010 this group saw a 12% increase in new HIV infections [1].

For numerous reasons, MSM are at a substantially higher risk for HIV infection. Prevalence of HIV in the US is higher among MSM than other men, with an estimated prevalence rate of 672 per 100,000 for MSM compared to 10.1 per 100,000 for other men [2]. Incidence of HIV among MSM has also been shown to be higher among young MSM (age 13-24) and MSM of color [1,2]. Analysis of high-risk behaviors among MSM in the US has shown that a substantial number of MSM engage in sexual activity with casual partners of unknown serostatus [3]. Additional factors that might affect an individual's risk of HIV infection include having a higher number of sexual partners, increased alcohol or recreational drug use, injection drug use, frequency of routine HIV testing and awareness of one's serostatus, income, and other complex social and behavioral factors [3,4]. However, the greatest behavioral influences of one's risk are one's choice of partner, sex act, and condom usage, with one's risk of HIV infection increasing as one engages in more high-risk sexual activities such as unprotected sex with a partner of unknown or positive serostatus [5].

Similarly, MSM are also at increased risk of non-HIV STDs due to similar modes of disease transmission as well as the increased prevalence of STDs within the MSM population when compared to the general population [4]. The CDC reports that the prevalence rate of gonococcal infection in the year 2012 for all people in the US was 107.5 cases per 100,000 [6]. A study of STD prevalence among MSM visiting Fenway Community Health, the largest clinical care provider for MSM in New England, found that gonococcal infections had a prevalence of 125.8 cases per 100,000 [7].

As changes in mainstream behaviors began to occur during the 1980's when public health initiatives promoted condom usage to lower HIV/AIDS incidence, a similar decline in the incidence of other STDs was also seen [4]. However, over time the incidence of STDs among MSM has increased, possibly due to changes in the mainstream perception of HIV infection and the need for condom usage [4,8]. As PrEP gains in notoriety and popularity, there has been some speculation within the medical community that it might normalize behavioral disinhibition, and increase the incidence and prevalence of HIV and other STDs [5,9].

Our study focuses on the possible occurrence of behavioral changes among MSM in the US over time with regard to condom usage. In particular, we were interested in creating a model of how increased uptake of TDF/FTC might cause a decline in condom usage, causing significant increases in non-HIV STD prevalence, using gonococcal infection prevalence as a biological endpoint. Since not all STDs are reportable to the CDC, there is some difficulty in measuring and estimating the incidence and prevalence of each disease. We chose to use gonorrhea prevalence as a biological endpoint that might elucidate potential trends in the incidence of other STDs should PrEP become widely implemented due to more readily available reported data. We built an innovative agent-based model to assess the potential impacts of PrEP administration on STD and HIV infection rates [10]. We hypothesized that increased usage of PrEP would be associated with decreases in condom usage among MSM and would correspond with increased prevalence of STDs within the overall population.

Methods

We used the agent-based, open-source modeling software NetLogo to design a computational epidemiological model of HIV and gonorrhea prevalence attributed to varying degrees of PrEP usage (and decreased condom usage) among MSM in the US. We customized the model from a previously existing model (NetLogo: AIDS) [https://ccl.northwestern.edu/netlogo/download.shtml] to fit the purposes of this study [10].

The model begins by assigning values to four global variables: average relationship commitment (duration in weeks), average coupling tendency (likelihood in percent), average condom use (likelihood in percent), and average test frequency (times per year). Values for these characteristics are assigned to each agent (individual member of the simulated population), assuming a normal distribution. The percent of agents living with HIV and/or gonorrhea (10.2% and 16.3%, respectively), based upon known prevalence rates for each disease [4,9], are hard-coded into the program. The likelihood of discontinuing condom usage given PREP usage is entered at the beginning of the population generation, using an adjustable slider in the user interface of NetLogo, before the simulation starts.

The program then generates the population by proceeding in 1-week cycles, until a user-determined number of weeks has been reached. Couples form and break up according to coupling tendency and commitment duration, respectively. For couples with a sexual encounter (on average once per week) HIV/gonorrhea infection occurs with different

likelihood according to published values for different types of sex acts, with each sex act conservatively set to be occurring with a 25% likelihood [11,12]. Each week, the model also simulates HIV testing and post-exposure prophylaxis. Once an agent tests positive for HIV, the weekly likelihood for having a sexual encounter is reduced from 100% down to a reduced percentage as preset using a slider, and the likelihood of condom usage is increased by 10% (hard-coded value). One example of the interface screen in NetLogo, with our model parameters, is illustrated in Figure 1.

We created a model that allows for the manipulation of multiple parameters that may play a role in HIV and gonorrhea transmission using agents acting as human individuals by proxy. The parameters selected were obtained from the scientific literature and all values for each parameter remained the same in all treatments, with the exception of the parameter denoting the percentage of the sample using PrEP routinely ('PrEP Uptake'). The independent variable 'PrEP Uptake' was varied to create nineteen independent treatment groups. Levels of PrEP Uptake for these groups, represented by the percent of usage within the MSM population, were: 0.0 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 20.0, 30.0, 40.0, 50.0, 60.0, 70.0, 80.0, 90.0 percent.

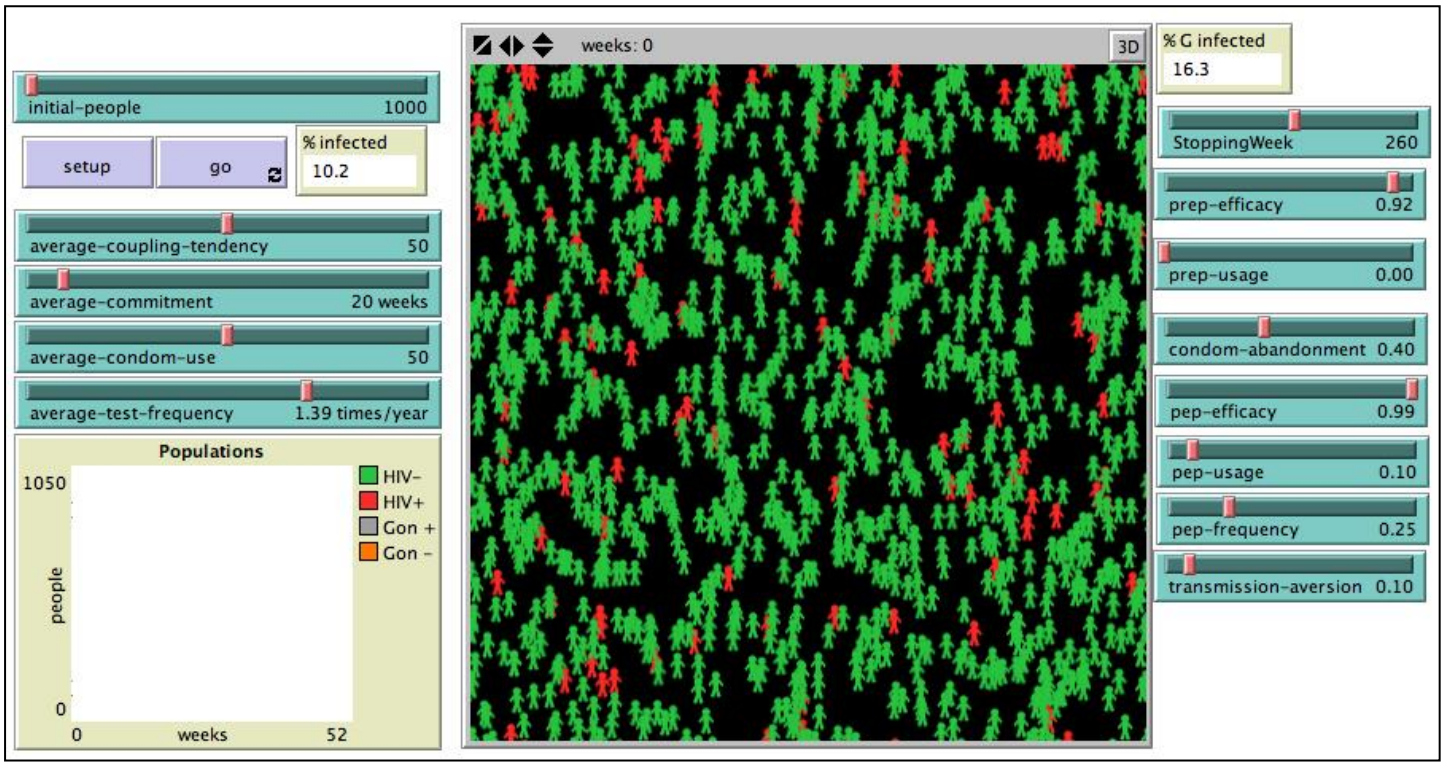

Figure 1: NetLogo interface screen (PrEP Uptake 0.0%). Depicted is an example of an interface screen for NetLogo when used to conduct simulations of population-wide PrEP usage at 0.0%. All parameters depicted in this screen remained constant through all simulations, with the exception of "PrEP-Usage,"

which was increased incrementally as an independent variable. Parameters may be adjusted on a sliding scale, with each parameter adjusting the number of agents used in the simulation (Initial People), the length of the simulation in weeks (Stopping Week), or efficacy of PrEP or PEP at preventing seroconversion (PrEP Efficacy and PEP Efficacy). Additional parameters depict the likelihood of agent coupling with another agent when single (Average Coupling Tendency) and the average length of each mutually monogamous coupling (Average Commitment). Parameters governing sexual behavior include "Average Condom Use" and "Average Test Frequency," which control the likelihood of condom use per sexual engagement and the annual frequency of an agent being tested for HIV. "PrEP Usage" and "PEP Usage" control the population-wide percentage of agents that use either prophylactic, respectively. "PEP Frequency" depicts the likelihood that the subset of MSM using PEP will use the prophylactic per sexual engagement. "Transmission Aversion" depicts the reduction in likelihood that a known HIV-positive agent will forgo sexual engagement. Additional parameters not depicted but modified in the source code, include the frequency of sexual engagement, the likelihood of engaging in any particular sexual act, the infection risk factors for each act, and the initial prevalence of HIV and gonorrhea at week 0.

Our modeled program began at week 0, generating an independent sample with the initial prevalence of HIV and gonorrhea infections within the population (10.2% and 16.7%, respectively) based upon known prevalence rates for each disease [4,9]. Agents within the model exhibit monogamous coupling behaviors governed by parameters 'Length of Commitment,' which designates the average length of time in weeks that the monogamous coupling will last before separation occurs due to a generated maximum commitment time for each partner based on the value assigned to this parameter, and 'Coupling Tendency,' which designates the average likelihood that a noncommittal agent will pair with the nearest unpaired agent. Parameters for 'Average Commitment' and 'Coupling Tendency' were set at 20 weeks and 50%, respectively.

Sexual acts encoded in the program are insertive and receptive anal and oral sexual intercourse. Likelihoods for any one act occurring within the time intervals of the model are 25% each [13]. The parameter 'Condom Usage' denotes the likelihood that the agents will choose to use a condom after deciding on whether or not to engage in a sexual act or after choosing the sexual act in which to engage. 'Condom Usage' was set at 50.0%. Should a condom be chosen, the likelihood of breakage, delayed application, or improper use while engaging in any act was set at 18.1% [14]. Per contact risk likelihoods for HIV infection for multiple combinations of PrEP and condom use were used in the program (Table1). Although it has been documented that STD infection carries a degree of influence over risk likelihoods for contracting HIV, infection risk likelihoods for HIV were calculated independently of gonorrheal infection, with risk likelihoods for gonorrhea being equal among PrEP users and non-users [9,12].

HIV testing and agent knowledge of personal serostatus were accounted for within the model by allowing agents to be tested with an average annual frequency for the entire

population. The parameter 'Testing Frequency' allows agents to be tested based on an annualized average frequency for the entire sample. Agents in the model received an HIV test 1.39 times per year on average [15]. Those who knew their serostatus as HIV positive were 10% more likely to use a condom before engaging in sexual activity. In addition, the parameter 'Transmission Aversion' reduces the likelihood that an agent of known HIV positive serostatus will engage in any sexual activity. 'Transmission Aversion' was conservatively set at 10% [16].

Post-exposure antiretroviral prophylaxis (PEP) was accounted for in the model as well. PEP is an antiretroviral prophylactic used shortly after one thinks they may have been exposed to HIV to prevent seroconversion. The parameter 'PEP Usage' denotes the percentage of the sample that will use PEP. 'PEP Usage' was conservatively set at 15% in all trials, based on limited surveys of MSM awareness and interest in PEP [17]. In addition, 'PEP Frequency' denotes how frequently those who may use PEP will actually do so. 'PEP Frequency' was set at 10% for all trials, equivalent to PEP being used once per 10 sexual acts, among those who may use it. The parameter "PEP efficacy" denotes the reduction in likelihood that seroconversion will occur if an HIV negative agent engages with an HIV positive agent. "PEP Efficacy" was set at 99% [18].

PrEP usage within the sample was accounted for by 'PrEP Uptake' or the percentage of the sample that consistently used PrEP for the duration of the trial. As stated, 'PrEP Uptake' ranged from 0% to 90% creating 19 independent treatment groups. 'PrEP efficacy' denotes the reduction in contact risk that one receives by using PrEP (Table 1). 'PrEP Efficacy' was set at 92% [19]. The parameter 'Condom Abandonment' denotes the likelihood that those using PrEP will forgo condom use due to PrEP usage. This parameter was set at 40%, as a pessimistic estimate higher than previous studies suggest may occur due to widespread PrEP use [20-22].

The parameters 'Initial People' and 'Stopping Week' denote the number of initial agents used in the model for the duration of the test and the length of the trial in weeks, respectively. All trials contained 1,000 agents and had duration of 260 weeks (5 years) in an attempt to limit the number of agents used within our trials and simulate the number of participants that may be found in a realistically possible large cohort study. We chose to limit the length of the model to five years or 260 weeks to elucidate possible short-term trends in HIV and gonococcal prevalence.

We collected data by executing multiple simulations with the model for each treatment group (n_i=19), with a total of 19 independent treatment groups tested. As stated, all parameters for the model were identical with the exception of 'PrEP Uptake.' Data for cumulative HIV and gonococcal infection were analyzed at each level of PrEP uptake. Cumulative infection data for each disease was gathered from the final week of each trial and used to create a sampling distribution for all treatment groups. Data were then analyzed to determine if they satisfied the assumptions of Kruskal-Wallis' non-parametric analysis of variance (ANOVA). Data analyzed via non-parametric ANOVA also underwent post-hoc pairwise comparative analysis via Dunn's test if warranted by the initial ANOVA. Our decision to use the non-parametric version of this test was motivated by previous pilot studies conducted by our lab finding repetitious violations of

the assumptions of the parametric ANOVA, specifically, heteroscedasticity between HIV and gonorrhea data that was not corrected by repeated increases of sample size.

Table 1: Assumed per-contact gonococcal and HIV risk percentages among sexually active MSM community members based on PrEP and condom usage.

	Sex Act[1]	PrEP Usage	Condom Usage	Per-Contact Non-HIV STD Risk[3] (%)	Per-Contact HIV Risk[2] (%)
Healthy, Susceptible MSM	Receptive Anal Sex	+	+	18.00	1.44
			-	27.00	2.16
		-	+	18.00	18.00
			-	27.00	27.00
	Insertive Anal Sex	+	+	04.00	0.32
			-	06.00	0.48
		-	+	04.00	04.00
			-	06.00	06.00
	Receptive Oral Sex	+	+	02.00	0.16
			-	04.00	0.32
		-	+	02.00	02.00
			-	04.00	04.00
	Insertive Oral Sex	+	+	00.10	0.008
			-	01.00	0.08
		-	+	00.10	00.10
			-	01.00	01.00

[1]All per contact risks calculated for sex acts with unknown serostatus partner [12].

[2]PrEP efficacy assumed to lower per contact risk of HIV transmission by 92% [12,27,28].

[3]All per contact risk percentages for gonococcal infection assumed to be equal to their non-PrEP HIV counterparts.

Results

After initial analysis of the response data to determine the appropriateness of using the non-parametric ANOVA, we found that both sets of data satisfied the test's assumptions. Data for all treatment groups for each disease was plotted to illustrate any potential trends that may be found statistically (Figure 2-3). In analysis of HIV data via non-parametric ANOVA, we found a significant difference between the median infection rate of at least one treatment group and all others ($p<0.001$), providing substantial evidence to reject the test's null hypothesis that all medians were equal. We conducted post-hoc analyses of the mean ranks generated by the non-parametric ANOVA via Dunn's test to determine

significant differences between treatment groups (Table 2). Through comparative pairwise analysis, we found multiple significant differences between HIV prevalence, with one percentage representing initial PrEP Uptake, and the corresponding paired percentage representing subsequent PrEP uptake. The significant differences we identified represented significant decreases in HIV prevalence at week 260 with a maximal effect being reached when 5% to 10% of the MSM population used PrEP.

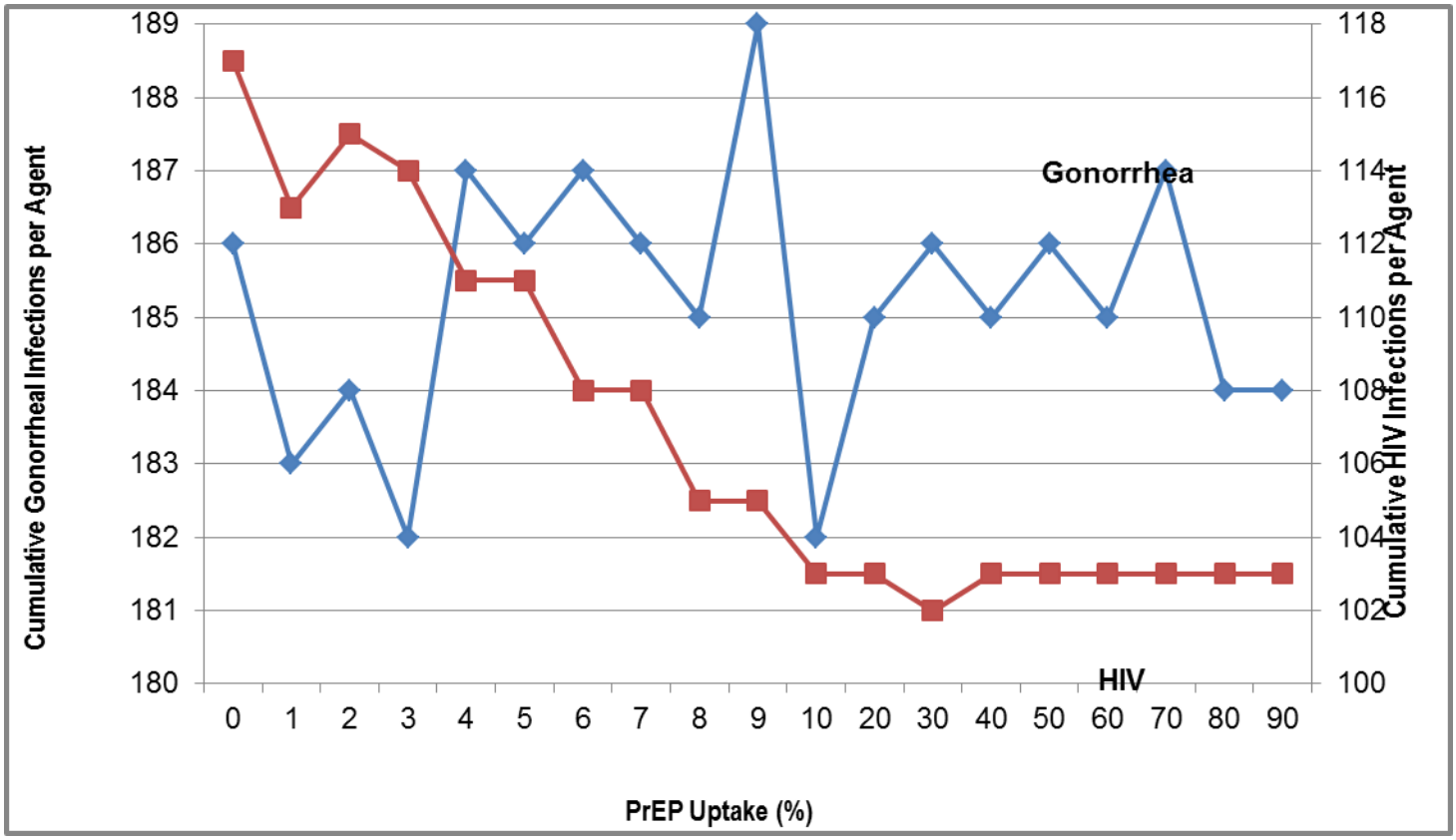

Figure 2: Line plot of median cumulative gonococcal and HIV infections per percent PrEP Uptake at 260 weeks. Prevalence results for all treatment groups of PrEP uptake at week 260 were aggregated and organized for visual aid. Depicted in blue is the prevalence for gonorrhea and depicted in red is HIV.

In results from the non-parametric ANOVA for gonorrheal data, we found no significant difference between the median infection rates of all treatment groups ($p=0.387$). That is to say, we found no significant evidence for increased gonorrhea prevalence due to increased PrEP usage at any level of sample-wide usage, with a range of 0-90% PrEP usage. We therefore did not conduct post-hoc analysis.

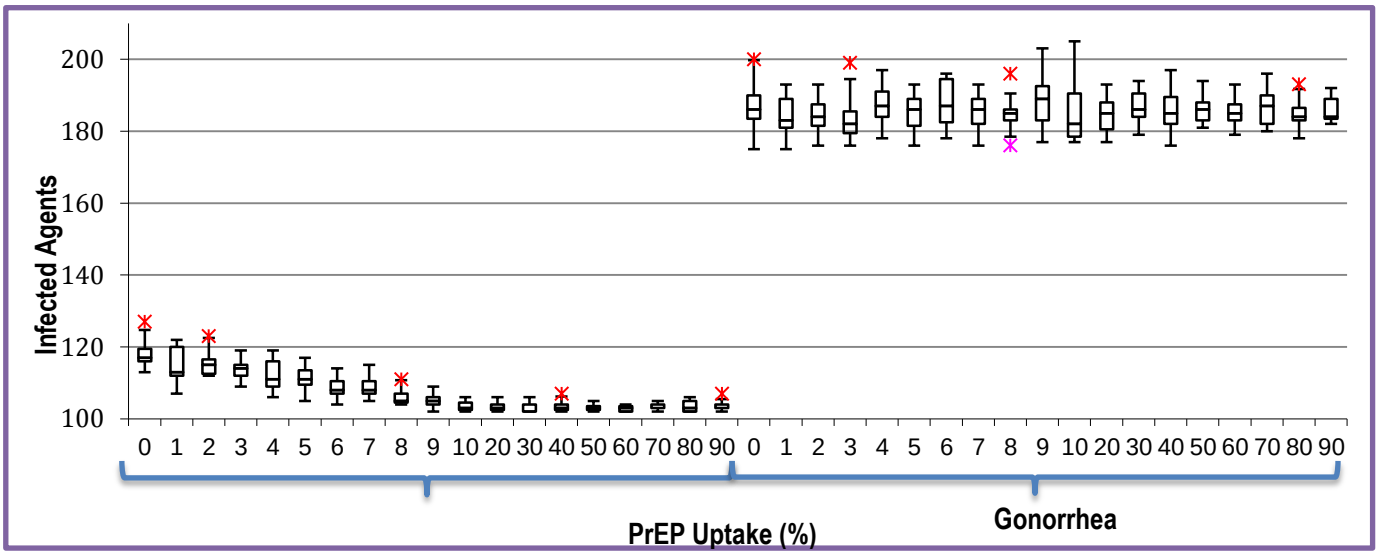

Figure 3: Boxplot of cumulative gonococcal and HIV infections per percent PrEP Uptake at week 260. The number of gonorrhea and HIV infected agents for all simulations were aggregated at each population-wide PrEP usage level and organized via boxplot.

Table 2: Post-hoc pairwise comparisons of cumulative HIV infection per percent PrEP uptake at week 260.

Subsequent PrEP Uptake (%) \ Initial PrEP Uptake (%)	0.0	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0	20.0	30.0	40.0	50.0	60.0	70.0	80.0
1.0	0.44750																	
2.0	0.56323	0.85594																
3.0	0.37591	0.89985	0.75854															
4.0	0.14121	0.47665	0.37173	0.55798														
5.0	0.09153	0.35353	0.26729	0.42260	0.82893													
6.0	0.00767	0.05655	0.03677	0.07493	0.23206	0.32758												
7.0	0.01296	0.08449	0.05655	0.10974	0.31081	0.42518	0.85594											
8.0	0.00018	0.00282	0.00153	0.00422	0.02288	0.03946	0.27998	0.20698										
9.0	0.00001	0.00015	0.00007	0.00024	0.00202	0.00409	0.05845	0.03898	0.41683									
10.0	0.00000	0.00000	0.00000	0.00000	0.00001	0.00002	0.00097	0.00050	0.02651	0.15952								
20.0	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00025	0.00012	0.00989	0.07713	0.71820							
30.0	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00004	0.00002	0.00235	0.02576	0.41046	0.64393						
40.0	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00037	0.00018	0.01308	0.09501	0.79267	0.92192	0.57532					
50.0	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00011	0.00005	0.00544	0.04906	0.57456	0.84111	0.79352	0.76533				
60.0	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00006	0.00003	0.00323	0.03294	0.46773	0.71487	0.92281	0.64313	0.86907			
70.0	0.00000	0.00000	0.00000	0.00000	0.00000	0.00001	0.00046	0.00023	0.01546	0.10753	0.83936	0.87433	0.53501	0.95204	0.71987	0.60065		
80.0	0.00000	0.00000	0.00000	0.00000	0.00000	0.00002	0.00086	0.00044	0.02432	0.14984	0.97335	0.74333	0.42972	0.81853	0.59755	0.48846	0.86557	
90.0	0.00000	0.00000	0.00000	0.00000	0.00000	0.00003	0.00137	0.00072	0.03395	0.19064	0.92192	0.64632	0.35700	0.71820	0.50967	0.40983	0.76363	0.89544

Pairwise Corrected Alpha = 0.00029

Numerical values indicate p-values for pairwise comparisons of initial and subsequent PrEP uptake treatments; values lower than the corrected alpha level indicated were deemed significant. Family alpha level was 0.05. Subsequent PrEP uptake indicates population-wide PrEP usage for the duration of the 5 year simulated period in comparison to the initial level of PrEP usage.

Discussion

Our findings indicate that daily PrEP usage may achieve herd immunity at a relatively low threshold among those at risk of infection. Though it is not currently known how many MSM in the US are using PrEP, our results may be used to indicate the particular threshold at which herd immunity to HIV may be conferred, and the threshold at which statistically significant decreases in HIV prevalence may be found. Additionally, our findings indicate that PrEP uptake does not cause a significant increase in gonorrheal prevalence. Our results appear to concur with the findings of recent studies analyzing the medical history and sexual behaviors of MSM using PrEP, indicating that PrEP usage does not seem to have an effect on the prevalence of other STDs, such as gonorrhea [23].

The annual incidence rate of new HIV infections among all people in the US has been estimated at 22.8 new infections per 100,000 [4]. Meta-analysis of the EXPLORE, 1999-2001 study, a randomized trial conducted among MSM in the US to test the efficacy of a behavioral intervention to prevent high-risk behaviors related to HIV acquisition, found that 78.2% of all study participants had engaged in some form of unprotected sex in the six month period prior to the baseline interview [3]. Through the current study, we attempt to aid in combatting the ongoing HIV epidemic in the US, providing additional findings to inform appropriate target thresholds for PrEP, and potentially decreasing physicians' and the public's aversions to PrEP usage related to concerns that it might place target populations at increased risk for non-HIV STDs.

HIV Prevention

Until recently, methods of HIV prophylaxis were limited to behavioral methods of prevention, such as condom usage, sexual abstinence, knowing the serostatus of one's sexual partners, and avoidance of high-risk behaviors, with effective methods of biochemical prophylaxis limited to Post-Exposure Prophylaxis (PEP) used in uncommon circumstances in which a patient might have been exposed to HIV [24].

Though condoms have been well documented and long recommended as the best prevention for sexually acquired HIV infection besides abstinence, some MSM continue to engage in unprotected sexual activity. Metadata analysis of male-to-female transmission estimates the efficacy of regular condom usage at preventing HIV acquisition at 94% [25]. Data from this same analysis also suggests that inconsistent condom usage can be 79% effective at preventing HIV transmission compared to using no condom during sexual activity [25]. Additional studies on "user failure" and condom breakage among MSM have estimated that 7.5% of all condoms will break or fail during intercourse and 10.6% will be used partially, or have a delayed application during sex [26].

As an additional protection against HIV infection, PrEP is now being recommended to HIV-negative people who are at substantial risk for HIV acquisition. Those at substantial risk of sexual acquisition of HIV include: serodiscordant couples, men or women with non-mutually monogamous sexual partners, MSM that engage in sexual activity with partners of unknown HIV infection status, men or women who regularly engage in sexual activity without a condom with partners of unknown HIV serostatus or who are also at

substantial risk of HIV infection [13]. The comprehensive clinical practice guidelines released by the US Public Health service for PrEP usage outline PrEP as a daily dosing of TDF/FTC and condom use when engaging in sexual activity, as well as regular HIV testing, STD testing, and regular clinical visits by the patient to evaluate the continued need for PrEP, and assess acquired risk behaviors and adherence [13].

Multiple trials to test the efficacy of PrEP have seen that TDF/FTC usage may reduce one's risk of HIV infection between 44% and 75% with the variation in efficacy believed to arise from differences in dosing adherence and behaviors between the populations under study [10,11]. However, data from the iPrEX study has shown that given the efficacy of TDF/FTC for MSM in the US and the elevated risk of HIV acquisition within this subpopulation, PrEP may be an effective, targeted solution for slowing the US HIV epidemic [12].

Controversy Surrounding PrEP

Despite the possible benefits that increased knowledge, availability, and usage of PrEP may bring to MSM, there has been some speculation that increased PrEP usage may place MSM at greater risk of contracting other STD's due to behaviors known as "risk compensation", or the belief that engaging one protective behavior will nullify the risk posed by a separate, risky behavior [14]. Since the discovery of HIV in the early 1980's, there have been numerous health campaigns which helped effectively change or influence the decisions and behaviors of the sexually active to help slow the growth of the HIV epidemic [3,15]. However, since the 1990's there has been an observed increase in the incidence of HIV infection among MSM which might be due in part to changing attitudes towards safer sex and HIV infection [3,15]. Observed behavioral trends that may be influencing this increase include "safe sex fatigue" and "treatment optimism", which might contribute to risk compensation among those who might otherwise engage in safer alternatives to their chosen behaviors in the context of HIV and non-HIV STD prevention. [15] "Safe sex fatigue" has been defined as an agreement to the phrase, "I find it difficult to maintain sexual safety," implying difficulty in maintaining consistent condom use [15]. Similarly, "treatment optimism" describes the abandonment of safer sexual practices due to the belief that one feels less concerned about acquiring HIV because medical advances, such as antiretroviral therapy, have reduced HIV-related morbidity and mortality [15]. Several surveys conducted to identify attitudes toward PrEP interest and safer sexual practices among MSM found that the majority of men surveyed were interested in PrEP usage depending on variations in reported efficacy, however, a substantial number of those interested also expressed that they would likely decrease their frequency of condom usage if they were to use PrEP [20], [12,16-18].

Previous studies have linked changes in behavior among MSM due to prevention fatigue or treatment optimism with increases in HIV and non-HIV STD incidence [5,9]. However, these studies are not directly analogous to the current issues surrounding PrEP usage. A study of the likelihood of PrEP users to engage in risk compensation based on data gathered in the iPrEx trial found that users were less likely to engage in risk compensation at the end of the trial than at baseline interviews [19]. It should be noted though that data collected in these interviews were self-reported and possibly biased.

Additionally, trial participants were provided counseling services to discourage increases in risk compensation behaviors, a service that might not be as widely available to non-trial PrEP users.

Our study findings should be considered in light of several limitations. Our model assumptions of monogamy, condom usage, agent knowledge of gonorrheal infection status, and correct PrEP/ PEP usage, while based on the scientific literature, may not apply to all MSM populations. Currently, our model assumes that all agents will engage exclusively in mutually monogamous relationships, which may not hold true in local communities. In addition, due to lack of available data, our model assumes that the likelihood of condom usage is equal for all sex acts, whether an agent is engaging in oral or anal sexual intercourse. Adjustments may be made to the model to adjust these limiting assumptions, both by adding additional parameters for simultaneous sexual partners and adjusting the likelihood of engagement in types of sexual acts based on available data. However, implementing these modifications may require additional parameters in the case of multiple sexual partners, ascribing partners as primary or secondary, accounting for frequency of sexual engagement with each partner type, and likelihood of condom usage and type of sexual act with each partner. The model also lacks parameters for how frequently an agent will be tested for gonorrhea and, as such, all cases of gonorrhea used in this version of the model should be regarded as asymptomatic. Though we found no significant relationship between PrEP and gonorrhea prevalence, future versions of this model should account for both testing and treatment of gonorrhea among agents to better determine the cumulative prevalence of gonorrhea to allow for a more accurate result. This model also assumes that all agents use PrEP/PEP correctly, adhering to the daily dosage of medication without any lapses, which has not been supported by initial studies of PrEP/PEP efficacy. Parameters may be added for each prophylactic regimen, but would require accurate survey data to determine the number of MSM who use each intermittently rather than as prescribed. Thus far, we have not been able to test the robustness of the model or the sensitivity of each parameter. This is due to the parameters of the model working both synchronistically and asynchronistically, preventing us from accurately testing the effects of any single parameter on our results.

Despite these limitations, our model provides a basis for future studies in which the model may be updated and modified as future, more accurate data become available. It should also be noted that although agent-based models are particularly useful in simulating the relationships between social interactions, behaviors, culture, and the spread of disease due to their potential for increased model complexity, the agents presented in such models are merely proxies for real people currently living with disease or the potential for disease. As such, it should be remembered that there are various levels and forms of relationships and commitment that are shared between romantic and sexual partners, and numerous social and behavioral factors that can vary across subgroups and individuals.

Conclusion

Though there is increasing evidence to support the use of PrEP in targeted populations, such as MSM, to better control the ongoing HIV epidemic, there has been concern that

widespread PrEP usage could lead to widespread behavioral disinhibition. Our findings do not support such hypotheses, however, and have found that, even with a rate of condom abandonment of 40.0% among PrEP users, there were no significant differences among gonorrhea prevalence across all PrEP usage levels. In addition we have found that the threshold of subsequent PrEP usage at which maximal decreases in HIV prevalence among MSM depends primarily on the initial percentage of the population using PrEP.

Future studies may build upon our model to better simulate the relationships we have elucidated. Future iterations of this model may better address the impact of PrEP, and additional or forthcoming HIV treatments, to improve our understanding of sexually transmitted disease transmission and prevention.

Conflict of Interest

All authors involved in this work have declared no conflict of interest. This research was conducted at Tufts University Sackler School of Graduate Biomedical Sciences, and funded by NIH grant R25 HL007785.

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