Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness

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Background and objective: HIV chemoprophylaxis may be a future prevention strategy to help control the global epidemic of HIV/AIDS. Safety and efficacy trials of two agents are currently underway. We assess the expected number of HIV cases prevented and cost-effectiveness of a hypothetical HIV chemoprophylaxis program among men who have sex with men in a large US city.

Design and methods: We developed a stochastic compartmental mathematical model using HIV/AIDS surveillance data to simulate the HIV epidemic and the impact of a 5-year chemoprophylaxis program under varying assumptions for epidemiological, behavioral, programmatic and cost parameters. We estimated program effectiveness and costs from the perspective of the US healthcare system compared with current HIV prevention practices. The main outcome measures were number of HIV infections prevented and incremental cost per quality-adjusted life-years saved.

Results: A chemoprophylaxis program targeting 25% of high-risk men who have sex with men in New York City could prevent 780 (4%) to 4510 (23%) of the 19 510 HIV infections predicted to occur among all men who have sex with men in New York City in 5 years. More than half of prevented infections would be among those not taking chemoprophylaxis but who benefit from reduced HIV prevalence in the community. Under base-case assumptions, incremental cost was US$ 31 970 per quality-adjusted life-years saved. The program was cost-effective under most variations in efficacy, mechanism of protection and adherence.

Conclusion: HIV chemoprophylaxis among high-risk men who have sex with men in a major US city could prevent a significant number of HIV infections and be cost-effective.

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Introduction

HIV affects approximately 33 million individuals worldwide, and an estimated 6800 new infections occur daily [1]. In the United States, an estimated 984 155 AIDS cases were diagnosed by the end of 2005, and one million persons were estimated to be living with HIV/AIDS (LWHA), including approximately 45% men who have sex with men (MSM) [2,3]. There is an urgent need for new HIV prevention interventions in the United States and worldwide. One promising new approach is antiretroviral chemoprophylaxis [4–7].

For numerous infectious diseases, chemoprophylaxis is an established primary prevention strategy for protecting uninfected persons before, during, or after a window of exposure time to a particular pathogen [8]. For HIV/AIDS, preexposure and postexposure use of an antiretroviral agent has been proven effective in the prevention of mother-to-child transmission [9,10], and evidence suggests its efficacy following occupational and nonoccupational exposures [11,12]. Now, daily chemoprophylaxis is being considered for prevention of HIV infection for persons experiencing repeated, high-risk nonoccupational exposures [5,6,13].

Two agents currently under consideration for use as HIV chemoprophylaxis are tenofovir disoproxil fumarate (TDF) and a combination tablet of emtricitabine (FTC)/TDF, nucleotide and nucleoside reverse transcriptase inhibitors, respectively, used currently as part of combination therapy for HIV-infected persons. Both have favorable safety profiles, good tolerability, long intracellular pharmacokinetic half-life, high barriers to development of drug resistance, and a demonstrated potential for chemoprophylactic efficacy [6,7,14–16]. Consequently, several clinical trials are planned or currently evaluating their use as a once-daily, oral chemoprophylactic agent among high-risk populations in several countries, including the United States [5,17,18]. If chemoprophylaxis trials are successful, public health decisions on implementing chemoprophylaxis for HIV prevention will depend on its potential impact and cost-effectiveness by community [19]. To understand the potential epidemiological and economic implications of an efficacious chemoprophylactic agent, we developed mathematical models to simulate HIV transmission and the use of chemoprophylaxis among MSM in a large US metropolitan area. We have focused on the MSM population because of the importance of this risk group in the United States and in many other parts of the world.

Methods

We present a framework for epidemiological and economic evaluation of a once-daily, self-administered oral chemoprophylaxis regimen among high-risk HIV-negative MSM. Epidemiological projections are derived from dynamic mathematical modeling; economic analysis is constructed from the perspective of US healthcare system and includes the costs of chemoprophylaxis program and savings in HIV/AIDS care.

Dynamic transmission model description

We developed a compartmental model simulating acquisition of HIV infection and progression, and effects of HIV/AIDS care on survival and HIV transmission. The model examines the effectiveness of chemoprophylaxis for preventing HIV infection. To represent a large metropolitan city in our model development, we used published epidemiological and survey data from New York City (NYC). We stratified an estimated population of high-risk MSM into four age and four sexual risk classes (defined according to annual number of new sex partners). The model's compartmental flows, choice of parameter values, and mathematical details are provided at http://www.aidsonline.com. In particular, the HIV-infection rate is calculated by age and sexual risk class and depends on annual number of new sex partners, HIV-infection status in the chosen partner and HIV transmission probabilities, which vary according to the partner's HIV-infection stage and duration of the partnership. Long-duration sero-discordant partnerships are associated with higher per-partnership HIV transmission probabilities than short-duration partnerships but higher risk classes are more likely to transmit HIV within a given timeframe because of their greater number of partners. Base-case values and ranges for model parameters came from the published literature, wherever available [6,7,20–53] (http://www.aidsonline.com). These values were validated by comparing the model-generated HIV prevalence, incidence, and absolute number of MSM LWHA, stratified by age category, to available surveillance data from the Centers for Disease Control and Prevention and the New York City Department of Health and Mental Hygiene [2,54–59]. More details on validation are given at http://www.aidsonline.com. The number of HIV infections prevented is derived from comparison of the model-generated HIV incidence in the absence and presence of chemoprophylaxis programs.

Program parameters

Given current uncertainty in key parameters related to chemoprophylaxis programs, we considered 36 hypothetical scenarios, including different combinations of mechanism of protection, efficacy, adherence (program and individual), and population coverage. We defined program adherence as the proportion of all MSM who adhered completely to a daily chemoprophylaxis regimen. Within a fixed scenario, we varied behavioral (annual number of new sexual partners) and epidemiological parameters (e.g., HIV transmission probabilities, rate of HIV disease progression) using Latin-hypercube sampling [60,61] 200 times to generate expected, low and high estimates of cases prevented (equal to the 50th, 5th

and 95th percentiles), summing to 7200 simulations. We refer to the 5th to 95th percentile range as a 90% credibility interval (90% CI).

We considered three protection mechanisms for HIV chemoprophylaxis. Under all mechanisms, efficacy is defined as the reduction in susceptibility to HIV infection upon exposure to an HIV-infected partner. Our basic mechanism of protection assumes that a patient's daily drug use confers either 50 or 70% efficacy, but partial individual adherence (e.g., drug is not taken every day) confers zero efficacy. A second, 'adherence-dependent' mechanism confers some protection upon partial individual adherence. Persons with complete adherence experience either 50 or 70% efficacy (as under the basic mechanism), whereas those with partial adherence experience a reduced efficacy of 30 or 50%. Under a third 'exposure-dependent' mechanism, higher levels of viral exposure reduce the agent's protective efficacy. We assume complete individual adherence confers an expected efficacy of 50 or 70% at moderate levels of HIV exposure and 30 or 50% at high and sustained levels of exposure. Circumstances under which the high and sustained levels of HIV exposure might occur include multiple unprotected sexual or needle-sharing encounters with an infected partner in the primary phase of infection, commercial sex workers in high prevalence areas, or persons engaging in high-risk behavior with multiple, high-risk partners [62,63].

We examined implementation of a chemoprophylaxis program among uninfected MSM at very high risk of HIV infection, assuming MSM could be reached for enrollment in a chemoprophylaxis program through local HIV prevention programs and through venues and publications whose primary audience is MSM. Focusing on a very high-risk population improves the opportunity to achieve a potentially large public health impact. We define very high-risk individuals as those who in the past 6 months reported unprotected sex with an HIV-infected person, unprotected sex in exchange for money or drugs, anonymous sex, five or more sexual or needle-sharing partners, or were diagnosed with a sexually transmitted infection. Very high-risk MSM are thought to be 30% of the general MSM population [22–27]. In all simulations we modeled the participation of either 1500 or 15 000 individuals, corresponding to coverage rates of 2.5 and 25% of the very high-risk MSM population of NYC. Based on our assumptions, 15 000 high-risk MSM comprise just over 5% (5.2%) of the entire susceptible MSM population in NYC. We also considered three levels of program adherence by the targeted population: 95, 50 and 33% (i.e., the proportion of the enrolled population who maintain full individual adherence). All simulated interventions began in 2008 and continued until 2013.

Economic analyses

The economic analysis was conducted from the perspective of the US healthcare system. We included costs for chemoprophylaxis administration and monitoring and savings associated with prevented HIV treatment [46–50] (http://www.aidsonline.com). The outcome was incremental cost per quality-adjusted life years (QALY) saved for each HIV infection prevented. We selected one plausible set of assumptions for our base-case scenario to demonstrate cost-effectiveness, as recommended by Gold *et al.* [53]. Those assumptions were 50% efficacy under a basic mechanism of protection, with 15 000 coverage, and 50% adherence.

Drug costs, medical screening, monitoring and HIV/AIDS care

The agent that would be used for chemoprophylaxis, and thus its cost, is uncertain. In our analysis we used the 2007 US average wholesale price from the producer of FTC/TDF of US$ 31 per 500 mg tablet [46]. We also estimated the daily threshold price of the chemoprophylactic agent above which the incremental cost-effectiveness ratio (ICER) would exceed US$ 50 000 and US$ 100 000 per QALY saved. Costs for medical screening to determine eligibility of potential chemoprophylaxis candidates, followed by ongoing medical monitoring and adherence promotion (1 month after chemoprophylaxis initiation and at 3-month intervals thereafter) were calculated to be US$ 1300 per participant in the first year and US$ 1020 each year thereafter [47–49] (http://www.aidsonline.com). To approximate the true cost of service provision rather than charges, costs for medical services were based on Medicare reimbursement rates. We assumed an annual dropout rate of 40% equal to the recruitment rate, keeping the total enrollment of high-risk MSM constant. The average 5-year per-participant program cost was US$ 5370 (discounted at 3%). We assumed that all participants incurred these costs, regardless of their actual adherence to chemoprophylaxis or participation in medical monitoring. The average 5-year combined cost for drug and support services was US$ 58 700 per participant, of which 91% was for chemoprophylaxis agents.

To assess the value of infections prevented, we used a base-case HIV-related lifetime treatment cost of US$ 343 130 and 6.95 QALYs saved [50–52]. In sensitivity analyses we adjusted the lifetime treatment cost by 30%. Both costs and QALYs were discounted at 3% in the analysis. We calculated net costs as program costs, for chemoprophylaxis and monitoring, less lifetime treatment costs among those in whom HIV infection was prevented. We divided net costs by the number of QALYs saved to estimate the ICER.

Sensitivity/uncertainty analyses

For the epidemiological analysis, we assessed 36 intervention scenarios varying efficacy, mechanism of protection, coverage, and adherence. We varied behavioral and epidemiological parameters using Latin-hypercube sampling 200 times within each scenario. For the economic analysis, we estimated ICERs and daily

chemoprophylactic threshold prices for all combinations of program parameters and the three estimates of lifetime treatment costs, as well as for the low and high limits of the 90% CI around expected number of cases prevented.

In supplementary analyses, we examined the combined effect of chemoprophylaxis efficacy and increases in risk behavior on the number of cases of HIV prevented under base-case assumptions. In these simulations, chemoprophylaxis efficacy varied between 10 and 90%. Changes in risk behavior were modeled by assuming a hypothetical population-wide increase of 0–20% in annual number of sexual partners as a consequence of introducing a chemoprophylaxis intervention.

Results

Baseline model prevalence and incidence

Figure 1a illustrates model predictions of the number of MSM LWHA in NYC between 1975 and 2020 generated from base-case parameter assumptions and sensitivity analyses. The model predicts a total of 48 380 MSM LWHA (90% CI: 28 910–58 730) who are HIV-infected (diagnosed or undiagnosed) living in 2008, corresponding to the model's HIV prevalence of 14.6% (90% CI: 8.1–18.4%). Average prevalence by age from our model is 6.4, 13.1, 18.3 and 16.2% for 13–24, 25–34, 35–44 and over 45 years, respectively, corresponding roughly with data from the National HIV Behavioral Surveillance system [54,55]. Figure 1b illustrates the model predictions of the number of new infections per year among MSM. The model predicts 3880 new infections (90% CI: 3000–4840) in 2008 equivalent to a 1.35% annual incidence rate in MSM (90% CI: 0.92–1.87%). By age group, our model predicts 380, 1740, 1210 and 520 new infections in the age groups 13–24, 25–34, 35–44 and over 45 years, respectively, in year 2008. Incidence rates by age group are 0.84, 1.85, 1.58 and 0.75%. This trend in which HIV incidence is highest in middle age groups is consistent with age-specific estimates of HIV incidence in all men in NYC [56] and estimates from MSM in Texas and Louisiana [57]. More model predictions for prevalence and incidence by age are given at http://www.aidsonline.com in which they are compared with surveillance data.

During the 5-year period from 2008 to 2013, we predict that a total of 19 510 (90% CI: 14 700–24 560) new infections are projected to occur in the absence of additional effective interventions. Of these new infections, over half (10 740 infections) will occur in the highest risk sexual activity classes.

Cases prevented for base-case scenario

In this scenario, with coverage of 15 000 high-risk MSM, the basic mechanism of protection, an efficacy of 50% and program adherence of 50%, 1710 new cases of HIV could be prevented, or 8.7% of the 19 510 new cases of HIV predicted by current incidence rates. Among the 1710 cases prevented, 700 are directly prevented through participation in the chemoprophylaxis program, whereas the remaining 1010 cases are secondary cases prevented indirectly by reducing HIV prevalence in the community. Specifically, it is the prevalence of sexually active individuals in the short primary stage of infection (in which most HIV transmissions occur under our parameter assumptions) that declines rapidly with chemoprophylaxis and leads to a large number of indirectly prevented cases.

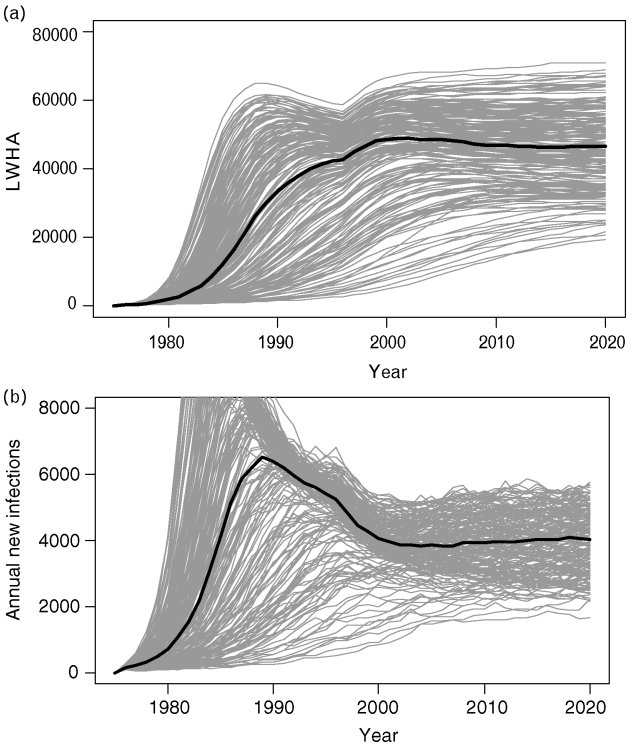

Fig. 1. Baseline model prevalence and incidence. (a) Model projections of the total number of MSM living with HIV/AIDS (LWHA) in New York City obtained over 200 simulations. The black line is the average number of MSM LWHA over the 200 simulations. (b) Model projections of total number of new HIV infections per year in MSM in NYC obtained over 200 simulations. MSM, men who have sex with men; NYC, New York City.

Alternative scenarios

Table 1 provides the number and proportion of HIV cases prevented during the 5-year chemoprophylaxis intervention period from 2008 to 2013 under different assumptions of mechanism of protection, efficacy, adherence, and coverage. The proportion ranges from 0.3 to 23.1%. Low and high values for expected cases prevented correspond to the 90% CI from 200 repetitions of a given scenario.

Within a given scenario, the uncertainty in number of sexual partners and epidemiological parameters imply that

Table 1. Total undiscounted direct and indirect cases of HIV infections prevented between 2008 and 2013 in men who have sex with men in New York City in 36 different scenarios of chemoprophylaxis.

Mechanism	Efficacy	Coverage of high-risk MSM number (percentage)	Program adherence (%)[a]	Expected cases prevented (%)	Lower limit of cases prevented	Upper limit of cases prevented
Basic[b]	50% fully adherent; 0% otherwise	15 000 (25%)	95	2793 (14.3)	1571	4122
			50	**1705 (8.7)**	**306**	**2947**
			33	1058 (5.4)	0	2442
		1500 (2.5%)	95	244 (1.3)	0	1595
			50	190 (1.0)	0	1480
			33	114 (0.6)	0	1405
	70% fully adherent; 0% otherwise	15 000 (25%)	95	3900 (20.0)	2628	5247
			50	2203 (11.3)	927	3541
			33	1358 (7.0)	60	2813
		1500 (2.5%)	95	408 (2.1)	0	1755
			50	259 (1.3)	0	1482
			33	179 (0.9)	0	1423
Exposure-dependent[c]	50% at moderate exposure and full adherence; 30% at high exposure and full adherence	15 000 (25%)	95	1958 (10.9)	721	3250
			50	1162 (6.0)	0	2426
			33	780 (4.0)	0	2140
		1500 (2.5%)	95	214 (1.1)	0	1513
			50	174 (0.9)	0	1468
			33	108 (0.6)	0	1328
	70% at moderate exposure and full adherence; 50% at high exposure and full adherence	15 000 (25%)	95	3118 (16.0)	1804	4889
			50	1790 (9.2)	411	3022
			33	1253 (6.4)	0	2506
		1500 (2.5%)	95	188 (1.0)	0	1625
			50	108 (0.6)	0	1575
			33	56 (0.3)	0	1355
Adherence-dependent[d]	50% for fully adherent; 30% for partially adherent	15 000 (25%)	95	3247 (16.6)	1862	4517
			50	3090 (15.8)	1689	4360
			33	2886 (14.8)	1637	4337
		1500 (2.5%)	95	443 (2.3)	0	1796
			50	282 (1.4)	0	1716
			33	266 (1.4)	0	1600
	70 for fully adherent; 50% for partially adherent	15 000 (25%)	95	4512 (23.1)	3144	6129
			50	4384 (22.5)	3133	5856
			33	4266 (21.9)	2953	5739
		1500 (2.5%)	95	546 (2.8)	0	1842
			50	358 (1.8)	0	1782
			33	312 (1.6)	0	1644

Expected, lower and upper limits of cases prevented are the 50th, 5th and 95th percentiles, respectively, over 200 simulations within a scenario. Values in bold correspond to base-case programmatic assumptions. Values in parentheses under expected cases prevented show the percentage of all cases prevented over 5 years. MSM, men who have sex with men.

[a]Program adherence refers to the percentage of individuals enrolled in the chemoprophylaxis whose individual adherence is full (i.e., the drug is taken every day).

[b]Basic mechanism assumes that a patient's daily use confers either 50 or 70% efficacy, but that partial individual adherence (e.g., the drug is not taken every day) confers zero efficacy.

[c]Exposure-dependent mechanism assumes complete individual adherence confers an expected efficacy of 50 or 70% at moderate levels of HIV exposure and reduced efficacy (30 or 50%) at high and sustained levels of exposure.

[d]Adherence-dependent mechanism assumes persons with complete adherence experience either 50 or 70% efficacy (as under the basic mechanism), whereas those with partial individual adherence experience a reduced efficacy of 30 or 50%.

the expected number of cases of HIV infections prevented will vary by approximately plus or minus 1300 cases. Therefore, when coverage is 2.5% and the expected number of HIV infections prevented is less than 1300, it is possible that no population-wide benefit will be achieved. This is reflected in zero values for the lower limit of cases prevented in some scenarios.

Figure 2 illustrates the effect of chemoprophylaxis efficacy and increases in risky behavior on the number of HIV cases prevented in the base-case scenario. The contour '0' represents the level at which a population-wide increase in annual number of new sexual partners will counterbalance any expected benefit of a chemoprophylactic agent of given efficacy. In particular, if

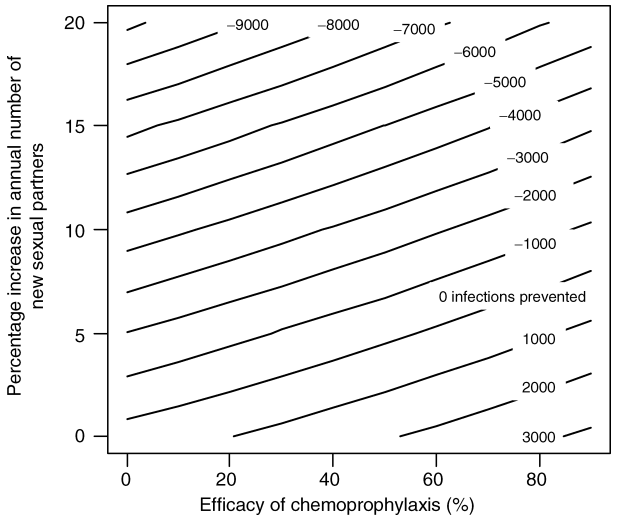

Fig. 2. HIV infections prevented among men who have sex with men at different levels of chemoprophylactic efficacy and risky behavior. Contour lines show equivalent numbers of HIV infections prevented at different combinations of chemoprophylaxis efficacy (*x*-axis) and increase in annual number of sex partners (*y*-axis) over a 5-year period in NYC or large metropolitan area. The contour labelled '0 infections prevented' indicates the percentage increase in sexual partners population-wide (enrolled on chemoprophylaxis or not) offsets the benefits of a chemoprophylaxis program at a given drug efficacy. Negative values refer to an increase in HIV infections due to large increases in risky behavior. Chemoprophylaxis mechanism is 'basic', coverage of high-risk MSM is 25% and adherence is 50%. NYC, New York City.

chemoprophylaxis efficacy is 50%, then a 4.1% increase in annual number of new sexual partners will offset the 1710 new cases of HIV infection, which would otherwise be expected.

Costs, effectiveness, and cost-effectiveness of HIV chemoprophylaxis

At US$ 31 per daily dose, the present value cost of the 5-year chemoprophylaxis intervention for 15 000 MSM is US$ 900 million. The present value of HIV/AIDS costs avoided total US$ 546 million. Thus, net incremental costs of the intervention are US$ 354 million for the base-case scenario. Net QALYs saved through the intervention are estimated at 11 000.

Table 2 indicates the ICERs for variations in program parameters, including the programmatic base-case assumptions, and for low and high HIV care costs. It provides the US$ 50 000 threshold daily chemoprophylaxis cost associated with the base-case cost of lifetime HIV care. We omitted the analysis for 2.5% coverage in Tables 2 and 3 because this level of coverage did not consistently achieve the minimum number of cases prevented. Under base-case programmatic assumptions, a chemoprophylaxis program cost US$ 31 970 per QALY saved, and the daily chemoprophylaxis cost would have to be greater than US$ 39 before the US$ 50 000 willingness-to-pay threshold was exceeded.

Table 3 provides the ICERs and daily chemoprophylactic threshold prices where the number of cases prevented corresponds to the upper and lower limits generated by the epidemiological model. Based on results in Tables 2 and 3, the ICER fell below the US$ 50 000 cost-effectiveness threshold in 75% of 80 scenarios, and below the US$ 100 000 threshold in 87.5% of the scenarios. Higher ICERs were associated with lower adherence under the basic and exposure-dependent mechanisms.

Discussion

Our analyses show the use of HIV chemoprophylaxis among high-risk MSM in large metropolitan areas could result in significant numbers of HIV infections prevented and be cost-effective under many of the combinations of program parameters and costs of chemoprophylaxis and HIV care. Under base-case assumptions, chemoprophylaxis prevented 8.7% of expected HIV cases over 5 years, and from 0.3 to 23.1% over a broad range of programmatic assumptions. Across all assumptions and the 90% CI for cases prevented, chemoprophylaxis was cost-effective 75% of the time at a threshold of US$ 50 000 per QALY saved and 87.5% of the time at a US$ 100 000 threshold.

The present model not only indicates expected cases of HIV prevented among those taking chemoprophylaxis, but also infections prevented indirectly through herd effects. Our base-case analysis shows that indirectly prevented infections represent 59% of all HIV cases prevented.

The safety and efficacy of TDF or FTC/TDF prophylaxis is being evaluated currently among heterosexual, homosexual and injection drug users (IDU) in trials in North and South America, Asia, and Africa [18]. Trial completion is expected as early as 2008 among IDU in Thailand, whereas the completion date for several other trials has not yet been announced. In our model, we allowed efficacy to vary between 30 and 70% depending on the mechanism of protection. We did not explore very low levels of efficacy based on an assumption that an agent would have to achieve 30–50% efficacy to be adopted by providers and consumers. Early primate and human studies suggest that efficacies around 50% or more could be possible [6,7].

Chemoprophylactic coverage among MSM was important to the results. We found that when 2.5% of high-risk

Table 2. Incremental cost per quality-adjusted life-years gained (US$/QALY) at three levels of lifetime HIV care costs.

Mechanism	Efficacy	Program adherence (%)	Base-case cost of HIV care		Low-cost HIV care (US$/QALY)	High-cost of HIV care (US$/QALY)
			US$ per QALY	Threshold daily drug price[a]		
Basic[b]	50% fully adherent; 0% otherwise	95	295	65	15 099	CS[c]
		50	**31 972**	**39**	**46 775**	**17 168**
		33	81 699	23	96 502	66 896
	70% fully adherent; 0% otherwise	95	CS	92	1009	CS
		50	13 590	51	28 393	CS
		33	52 750	30	67 553	37 947
Exposure-dependent[d]	50% at moderate exposure, full adherence; 30% at high exposure, full adherence	95	21 465	45	36 268	6661
		50	69 971	25	84 774	55 167
		33	128 404	16	143 208	113 601
	70% at moderate exposure, full adherence; 50% at high exposure, full adherence	95	CS	73	9925	CS
		50	28 110	41	42 914	13 307
		33	61 305	28	76 109	46 502
Adherence-dependent[e]	50% for fully adherent; 30% for partially adherent	95	CS	76	8158	CS
		50	CS	73	10 327	CS
		33	CS	68	13 499	CS
	70 for fully adherent; 50% for partially adherent	95	CS	107	CS	CS
		50	CS	104	CS	CS
		33	CS	101	CS	CS

Coverage is 25% of high-risk MSM. Values in bold correspond to base-case programmatic assumptions. MSM, men who have sex with men; QALY, quality-adjusted life-years.
[a]Daily chemoprophlaxis threshold price is the price above which net program costs per QALY saved exceeds US$ 50 000 per year.
[b]Basic mechanism assumes that a patient's daily use confers either 50 or 70% efficacy, but that partial adherence (e.g., the drug is not taken every day) confers zero efficacy.
[c]CS indicates net cost savings, resulting when HIV/AIDS care costs saved exceed costs for chemoprophylaxis provision.
[d]Exposure-dependent mechanism assumes complete adherence confers an expected efficacy of 50 or 70% at moderate levels of HIV exposure and reduced efficacy (30 or 50%) at high and sustained levels of exposure.
[e]Adherence-dependent mechanism assumes persons with complete adherence experience either 50 or 70% efficacy (as under the basic mechanism), whereas those with partial adherence experience a reduced efficacy of 30 or 50%.

MSM were enrolled, chemoprophylaxis did not prevent enough HIV infections to justify the intervention. Coverage of 25% of high-risk MSM led to expected reductions in HIV infections of 4–23%, depending on assumptions about efficacy, mechanism of protection, and coverage. Assumptions about lifetime HIV treatment costs generally did not affect whether cost-effectiveness ratios fell within thresholds of interest.

In our model, we used the average wholesale price of FTC/TDF. Our analyses show that under many scenarios the daily cost could be substantially higher than that price before the US$ 50 000 cost/QALY saved threshold was exceeded. On the contrary, use of less costly agents (e.g., TDF) may also be cost-effective at lower efficacy if coverage of high-risk MSM is 25% or higher and program adherence is 50% or higher. In our analyses, use of TDF (US$ 17 per 300 mg tablet) as a chemoprophylactic agent instead of FTC/TDF reduced program costs by 39%.
Three key concerns have been raised about the use of antiretroviral drugs to prevent HIV infection. Those are the possibility that chemoprophylaxis could lead to increases in risk behavior that offset the benefits, antiretroviral drug resistance among those who experience breakthrough HIV infections, and renal impairment related to prolonged use of TDF.

We examined the effect of increases in risk behavior that might stem from a greater sense of protection while using HIV chemoprophylaxis, resulting in fewer cases prevented or potentially, higher HIV incidence. Increases in risk behavior have been documented in some populations following the widespread introduction of highly active antiretroviral therapy [64,65]. One model showed that even a 10% increase in risk behavior would offset antiretroviral therapy's benefits in decreasing transmission [66]. We found that under our base-case assumptions, only a 4.1% increase in sexual partners (among enrolled and not enrolled in chemoprophylaxis) was sufficient to fully offset the number of infections prevented. Ongoing reinforcement of risk-reduction measures for persons receiving chemoprophylaxis, and improved behavioral surveillance to detect increases in risk behaviors will be vital to an HIV chemoprophylaxis program.

The development of antiretroviral drug resistance could limit future HIV treatment choices for individuals who

Table 3. Incremental cost per quality-adjusted life-years gained (US$ per QALY) at lower and upper limits of cases prevented.

Mechanism	Efficacy	Program adherence (%)	Lower limit of cases prevented		Upper limit of cases prevented	
			US$ per QALY	Threshold daily drug price[a]	US$ per QALY	Threshold daily drug price[a]
Basic[b]	50% fully adherent; 0% otherwise	95	38 908	35	CS[c]	98
		50	**403 741**	**5**	**CS**	**69**
		33	Zero cases averted		7430	57
	70% fully adherent; 0% otherwise	95	3412	61	CS	125
		50	100 218	20	CS	84
		33	2 261 390	−1	CS	66
Exposure-dependent[d]	50% at moderate exposure, full adherence; 30% at high exposure, full adherence	95	142 950	15	CS	76
		50	Zero cases averted		7805	56
		33	Zero cases averted		15 442	49
	70% at moderate exposure, full adherence; 50% at high exposure, full adherence	95	27 509	41	CS	117
		50	287 989	7	CS	71
		33	Zero cases averted		5980	58
Adherence-dependent[e]	50% for fully adherent; 30% for partially adherent	95	25 115	43	CS	107
		50	32 742	38	CS	104
		33	35 350	37	CS	103
	70 for fully adherent; 50% for partially adherent	95	CS	74	CS	147
		50	CS	74	CS	140
		33	CS	69	CS	137

Coverage is 25% of high-risk MSM. Values in bold correspond to base-case programmatic assumptions. MSM, men who have sex with men; QALY, quality-adjusted life-years.
[a]Daily chemoprophlaxis threshold price is the price above which net program costs per QALY saved exceeds US$ 50 000 per year.
[b]Basic mechanism assumes that a patient's daily use confers either 50 or 70% efficacy, but that partial adherence (e.g., the drug is not taken every day) confers zero efficacy.
[c]CS indicates net cost savings, resulting when HIV/AIDS care costs saved exceed costs for chemoprophylaxis provision.
[d]Exposure-dependent mechanism assumes complete adherence confers an expected efficacy of 50 or 70% at moderate levels of HIV exposure and reduced efficacy (30 or 50%) at high and sustained levels of exposure.
[e]Adherence-dependent mechanism assumes persons with complete adherence experience either 50 or 70% efficacy (as under the basic mechanism), whereas those with partial adherence experience a reduced efficacy of 30 or 50%.

experience breakthrough HIV infections while taking chemoprophylaxis, and the HIV drug-resistant viral strain could be transmitted to others. However, the risk of drug resistance emergence in persons who fail chemoprophylaxis is currently unknown and will likely depend on several factors, including the potency of the chemoprophylaxis, adherence, and the duration of drug exposure following infection. Data from primate models suggest that drug resistance emergence in breakthrough infections in the presence of either TDF, FTC, or TDF/FTC was less frequent than anticipated and underscored potential differences in drug resistance dynamics during chemoprophylaxis failures from those in single-drug or dual-drug therapy of established infections [7,45]. We, therefore, decided not to include the development of antiretroviral drug resistance in our model until more data become available. One modeling study [67] that explored the impact of antiretroviral drug resistance during breakthrough infections found that assumptions about the emergence of drug resistance had little impact on QALYs saved. Another reported that the development of drug resistance could be minimized by targeting chemoprophylaxis to high-risk populations, optimizing high efficacy and high adherence, and decreasing the amount of time infected persons remain on chemoprophylaxis [68]. Ongoing adherence support for participants, frequent HIV screening to detect breakthrough infections early, and genotypic resistance testing for those who become HIV-infected may be important.

In our analyses, we assumed no significant renal impairment associated with chemoprophylaxis given our inclusion of initial and quarterly medical screening to exclude patients at risk of or developing the condition. The established safety profile of FTC/TDF [69] indicates little evidence of renal impairment among patients receiving the drug to treat HIV. A study of TDF chemoprophylaxis among African women found no indication of renal impairment in 210.2 person-years of follow-up [6].

In summary, although effectiveness and cost-effectiveness of an HIV chemoprophylaxis program for high-risk MSM in the United States are subject to a number of important, inter-related and still largely undetermined variables, we found such a program could be reasonably effective at reducing the number of new HIV infections and quite cost-effective over a broad range of epidemiological, programmatic, and cost variables. This analysis should give strong impetus to the ongoing chemoprophylaxis trials as well as to research on potential program implementation.

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