Annals of Internal Medicine | ORIGINAL RESEARCH

The Cost-Effectiveness of Preexposure Prophylaxis for HIV Prevention in the United States in Men Who Have Sex With Men

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Background: A recent randomized, controlled trial showed that daily oral preexposure chemoprophylaxis (PrEP) was effective for HIV prevention in men who have sex with men (MSM). The Centers for Disease Control and Prevention recently provided interim guidance for PrEP in MSM at high risk for HIV. Previous studies did not reach a consistent estimate of its cost-effectiveness.

Objective: To estimate the effectiveness and cost-effectiveness of PrEP in MSM in the United States.

Design: Dynamic model of HIV transmission and progression combined with a detailed economic analysis.

Data Sources: Published literature.

Target Population: MSM aged 13 to 64 years in the United States.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: PrEP was evaluated in both the general MSM population and in high-risk MSM and was assumed to reduce infection risk by 44% on the basis of clinical trial results.

Outcome Measures: New HIV infections, discounted quality-adjusted life-years (QALYs) and costs, and incremental cost-effectiveness ratios.

Results of Base-Case Analysis: Initiating PrEP in 20% of MSM in the United States would reduce new HIV infections by an estimated 13% and result in a gain of 550 166 QALYs over 20 years at a cost of $172 091 per QALY gained. Initiating PrEP in a larger proportion of MSM would prevent more infections but at an increasing cost per QALY gained (up to $216 480 if all MSM receive PrEP). Preexposure chemoprophylaxis in only high-risk MSM can improve cost-effectiveness. For MSM with an average of 5 partners per year, PrEP costs approximately $50 000 per QALY gained. Providing PrEP to all high-risk MSM for 20 years would cost $75 billion more in health care–related costs than the status quo and $600 000 per HIV infection prevented, compared with incremental costs of $95 billion and $2 million per infection prevented for 20% coverage of all MSM.

Results of Sensitivity Analysis: PrEP in the general MSM population would cost less than $100 000 per QALY gained if the daily cost of antiretroviral drugs for PrEP was less than $15 or if PrEP efficacy was greater than 75%.

Limitation: When examining PrEP in high-risk MSM, the investigators did not model a mix of low- and high-risk MSM because of lack of data on mixing patterns.

Conclusion: PrEP in the general MSM population could prevent a substantial number of HIV infections, but it is expensive. Use in high-risk MSM compares favorably with other interventions that are considered cost-effective but could result in annual PrEP expenditures of more than $4 billion.

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Men who have sex with men (MSM) are an important group to reach with programs to prevent HIV infection. Of the estimated 48 000 to 56 000 new HIV infections per year in the United States, 56% to 61% occur among MSM (1, 2). In 2010, results of a clinical trial (3) suggested that antiretroviral drugs (ARVs) are effective as preexposure chemoprophylaxis (PrEP) for HIV prevention in uninfected MSM. The iPrEx (Preexposure Prophylaxis Initiative) study (3) showed that in MSM, daily tenofovir–emtricitabine therapy reduced HIV incidence by 44% overall and by 73% among MSM who reported high adherence. In 2011, the Centers for Disease Control and Prevention (CDC) published interim guidance (4) for prescribing tenofovir–emtricitabine as PrEP for MSM. This guidance highlights the importance of regular monitoring for adverse effects from PrEP, HIV testing, and counseling to encourage adherence and risk reduction.

Although PrEP has proven to be effective at preventing HIV infection, its costs are considerable. Previous studies (5, 6) on the cost-effectiveness of PrEP in MSM in the United States have reached inconsistent conclusions. Paltiel and colleagues (5) estimated that PrEP costs $298 000 per quality-adjusted life-year (QALY) gained in high-risk MSM, whereas Desai and colleagues (6) estimated that a PrEP program targeting high-risk MSM in New York City would cost $32 000 per QALY gained. We examined the effectiveness and cost-effectiveness of PrEP strategies for MSM in the United States by using the newly available clinical trial data, CDC interim guidance, and an epidemic

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Context

In clinical trials, preexposure chemoprophylaxis (PrEP) with antiretroviral drugs significantly reduced the risk for HIV infection in HIV-negative men who have sex with men (MSM). The cost-effectiveness of PrEP is debated.

Contribution

In a model, a strategy that targeted PrEP to the 20% of MSM considered to be at highest risk for HIV prevented twice as many infections over the long term, and at better economic value, than a strategy that provided PrEP to 20% of all HIV-negative MSM.

Caution

Assumptions were made about adherence, behavior, and sexual networking.

Implication

Targeted PrEP could have a substantial impact on the U.S. HIV epidemic at an acceptable cost.

—The Editors

modeling framework combined with a detailed economic analysis.

METHODS

We adapted a deterministic dynamic compartmental model of HIV transmission and progression (7) to assess the effectiveness and cost-effectiveness of PrEP for HIV prevention in MSM. We calibrated the model to estimates of HIV incidence among MSM aged 13 to 64 years in the United States (**Appendix**, available at www.annals.org) (1, 2) and estimated HIV prevalence and incidence, QALYs, and health care costs with various PrEP strategies over a 20-year time horizon. We assumed a societal perspective and discounted costs and QALYs at 3% annually (8). **Table 1** (9–61) presents key model parameters, and the **Appendix** provides additional model details.

We divided the population by HIV infection status, awareness of HIV status, and PrEP use. Infected persons were also defined by HIV disease stage and treatment status (**Appendix Figure 1**, available at www.annals.org). Initial HIV prevalence was 12.3% and annual incidence was 0.8%, representing an average across the United States (2, 9–12). Persons entered the model at age 13 and were followed for 20 years or until age 65 years. Modeling MSM aged 13 to 64 years is consistent with CDC recommendations for routine HIV screening (62). Mortality comprised HIV- and non–HIV-related deaths.

HIV Transmission

We modeled HIV transmission via homosexual contact on the basis of number of male sexual partners (28, 29) and average condom use (31). We assumed proportional mixing in selecting an HIV-infected partner; that is, persons were more likely to partner with MSM who had many partners than with those who had few partners. The probability of HIV transmission between serodiscordant partners depended on the infected person's disease stage and use of antiretroviral therapy (ART), as well as the PrEP status of the uninfected person (25, 26).

HIV Disease Progression and Treatment

Disease progression was based on the average time in each of 4 disease stages: acute infection, asymptomatic HIV, symptomatic HIV, and AIDS. Progression rates were based on HIV natural history and ART status (20–22, 35).

We assumed that HIV-infected persons with a CD4 cell count of 0.350×10^9 cells/L or lower were offered ART (63). Given recent guidelines (64) that recommend ART initiation at CD4 cell counts greater than 0.350×10^9 cells/L, we examined the effects of earlier ART initiation in a sensitivity analysis. The benefits of ART and suppression of viral replication included improved quality of life and reduced disease transmission, disease progression, and mortality (22, 35). We assumed a 90% reduction in sexual infectivity due to ART used to treat HIV infection in our base case and varied this in sensitivity analyses (22, 26, 37, 38).

To be treated, HIV-infected persons must be identified as infected. We estimated that 67% of MSM are screened annually with antibody testing (28, 45). Providing counseling with HIV testing has been found to reduce risky sexual behavior (49); thus, we assumed a 20% reduction in risky behavior for both infected and uninfected persons after HIV screening (22, 35, 49).

PrEP Strategies

We considered 2 strategies: PrEP for the general MSM population and PrEP for high-risk MSM. We chose a representative example of a high-risk population and varied risk levels in sensitivity analyses. We compared PrEP strategies with the status quo of no PrEP. We assumed that MSM would immediately begin receiving PrEP and would continue for the 20-year time horizon or until they aged out of the model.

We based our PrEP protocol on the CDC interim guidance on PrEP in uninfected MSM (4). Before initiating PrEP, MSM had to have negative results on an HIV antibody test, have adequate calculated creatinine clearance, and be tested for sexually transmitted infections. The PrEP regimen included daily tenofovir–emtricitabine and physician visits 5 times per year (every 2 to 3 months), at which HIV-negative status was confirmed with an antibody test and risk-reduction counseling and condoms were provided. In addition, MSM were tested for sexually transmitted infections every 6 months and renal function was tested annually. Persons who became infected with HIV while receiving PrEP were provided with appropriate counseling and discontinued the treatment once infection was detected.

Table 1. **Summary of Key Model Parameters***

Parameter	Value (Range)	Source (Reference)
Demographic		
Total MSM population aged 13 to 64 y, *n*	4 343 741 (2.2 to 7.5 million)	Calculated (9, 10)
HIV prevalence in MSM, %	12.3 (1 to 20)	Calculated (9–12)
Male mortality rate	0.0043 (0.003 to 0.005)	Calculated (13)
Average disease duration, *y*		
Acute HIV	0.25 (0.08 to 0.40)	(14–18)
Asymptomatic HIV	7 (6 to 10)	(19–22)
Symptomatic HIV	3 (1 to 4)	(19–22)
Symptomatic HIV treated with ART	18 (12 to 30)	(19, 22–24)
AIDS	2 (1 to 3)	(19–22)
AIDS treated with ART	5 (2 to 15)	(19, 22–24)
Sexual behavior		
Probability of transmission per MSM partnership†		
Acute HIV	0.210 (0.10 to 0.40)	(25–27)
Asymptomatic HIV	0.039 (0.02 to 0.08)	(19, 25–27)
Symptomatic HIV	0.039 (0.02 to 0.08)	(19, 25–27)
AIDS	0.160 (0.08 to 0.30)	(19, 25–27)
Male partners, *n*	3.0 (2.0 to 5.0)	(19, 28–30)
Condom use with male partners, %	40 (30 to 60)	(19, 31–34)
Treatment		
ART started at a CD4 cell count of 0.350×10^9 cells/L for those with known HIV status, %	50 (25 to 75)	Estimated (19, 22, 35, 36)
Rate of initiating ART at CD4 cell count $<0.350 \times 10^9$ cells/L	0.05 (0 to 0.10)	Estimated (19, 22, 35)
Reduction in sexual infectivity due to ART, %	90 (50 to 99)	(19, 22, 26, 35, 37–44)
Screening		
Population tested annually, %	67 (30 to 90)	(28, 45, 46)
Reduction in sexual behavior (number of male partners) due to testing and counseling, %	20 (0 to 50)	(19, 35, 47–49)
PrEP		
Reduction in risk for infection due to PrEP, %	44 (10 to 92)	(3)
Time receiving PrEP, *y*	20 (1 to 20)	Assumed
Change in number of male partners due to PrEP, %	0 (−20 to 20)	Assumed
Change in condom use with male partners due to PrEP, %	0 (−20 to 20)	Assumed
Cost‡		
Annual HIV-related health care costs, $		
Acute HIV	30 (10 to 500)	Calculated (7, 15, 50, 51)
Untreated asymptomatic HIV	4130 (3000 to 6000)	(19, 52–54)
Untreated symptomatic HIV	6934 (5000 to 9000)	(19, 52–54)
Symptomatic HIV treated with ART§	6181 (5000 to 7000)	(19, 52–54)
Untreated AIDS	21 863 (15 000 to 26 000)	(19, 52–56)
AIDS treated with ART§	9950 (6000 to 17 000)	(19, 35, 53, 54)
Annual non–HIV-related health care costs for uninfected and infected persons, $	4061 (3000 to 6000)	(57)
Annual cost of ART, $	15 589 (12 500 to 19 000)	(19, 35, 53, 56)
Cost of PrEP, $		
30-d supply of tenofovir–emtricitabine	776 (300 to 1118)	(5, 58)
Testing for sexually transmitted infection	54 (25 to 75)	(59)
Measurement of blood urea nitrogen and serum creatinine levels	23 (10 to 40)	(59)
Physician visit	100 (10 to 200)	(59)
Cost of antibody testing for HIV, $		
Uninfected	13 (5 to 25)	(59)
HIV-infected	66 (50 to 100)	(59)
Cost of counseling		
Pretest counseling	13 (0 to 100)	(60, 61)
Posttest counseling for HIV-negative persons	7 (0 to 50)	(60, 61)
Posttest linkage and counseling for HIV-positive persons	14 (0 to 100)	(60, 61)
Cost of HIV diagnosis, $	491 (125 to 1200)	(59)
Annual discount rate, %	3 (0 to 5)	(8)

ART = antiretroviral treatment; MSM = men who have sex with men; PrEP = preexposure chemoprophylaxis.
* All rates are annual.
† From HIV-positive to HIV-negative men.
‡ In 2010 U.S. dollars.
§ Excludes ART costs.

Table 2. **Benefits and Costs of PrEP Strategies Over 20 Years in the General MSM Population**

Strategy	HIV Infection*		HIV Prevalence at 20 Years, %	Total Cost of PrEP, *billion $*†‡	Total Cost, *billion $*†	Total QALYs†	Incremental Cost, *billion $*†§	Incremental QALYs†§	ICER, *$/QALY*	
	New Cases, *n*	Prevented Cases, *n (%)*							Relative to No PrEP	Relative to the Next Lower Level of PrEP
100% start PrEP	242 627	249 156 (51)	6.4	495	1366	117 488 043	480	2 217 732	216 480	253 645
50% start PrEP	348 492	143 291 (29)	7.9	247	1124	116 533 983	238	1 263 673	188 421	201 012
20% start PrEP	429 025	62 759 (13)	9.0	98	980	115 820 477	95	550 166	172 091	172 091
Status quo (no PrEP)	491 784	–	9.9	–	886	115 270 310	–	–	–	–

ICER = incremental cost-effectiveness ratio; PrEP = preexposure chemoprophylaxis; QALY = quality-adjusted life-year.
* Undiscounted totals. Discounting infections at 3% annually reduces the number of infections averted for each strategy by approximately 22%.
† Costs and QALYs are net present values (3% annual discount rate) over 20 y.
‡ Includes the costs of antiretroviral drugs for PrEP, monitoring tests and physician visits, and initiating and discontinuing therapy.
§ Incremental costs and QALYs are relative to the status quo.

We assumed that tenofovir–emtricitabine therapy reduces the probability of acquiring HIV by 44% on the basis of the overall reduction in incidence seen in patients in the iPrEx study (3). Preexposure chemoprophylaxis was more effective in preventing HIV infection in iPrEx subgroups with greater adherence, and incidence reduction was 73% in study patients who reported or exhibited pill use on at least 90% of days (3). We therefore varied PrEP efficacy in sensitivity analyses. Although behavioral disinhibition is a concern with PrEP, no conclusive evidence exists about the effect of PrEP on sexual risk behavior (65, 66). Hence, we assumed no change in risky behavior from counseling or risk compensation in our base case. In sensitivity analyses, we examined the effect of changes in number of sexual partners and condom use as a result of PrEP.

Various studies (67–70) have assessed willingness and likelihood to use PrEP in surveyed MSM populations, and conclusions have varied. The percentage of MSM who ultimately use PrEP is unknown and will depend on such factors as public health campaigns and access to health care. We evaluated initiating PrEP in 5% to 100% of the HIV-negative MSM population (**Appendix**), but we focus here on the results of initiating PrEP in 20%, 50%, and 100% of uninfected MSM to illustrate the differences in effectiveness and cost-effectiveness as the percentage of MSM receiving PrEP increases.

Health Outcomes and Costs

We simulated the population over time and calculated discounted costs and QALYs for each PrEP scenario. We estimated quality of life for each health state and adjusted the utilities on the basis of the average age of the modeled population (22, 35, 71). We assumed no reduction in quality of life from PrEP, because clinical trials have shown minimal side effects from tenofovir–emtricitabine therapy (3, 72). In sensitivity analyses, we evaluated the effect of decreased quality of life while receiving PrEP, because study participants receiving PrEP were more likely than those receiving placebo to have minor side effects, such as nausea (3, 72).

We included costs associated with medical care in each health state, as well as costs of PrEP and HIV testing, counseling, and diagnosis, to calculate total health-related costs. Baseline medical costs, HIV-related health care costs (including costs of associated comorbid conditions), the cost of ART, and the cost of counseling were estimated from the published literature (22, 53). The costs of ARVs for PrEP were estimated by adjusting the average monthly wholesale price of tenofovir–emtricitabine to reflect rebates and retail pharmacy dispensing fees (5). Costs of non-ARV components of the PrEP protocol and the HIV testing protocol were obtained from the Centers for Medicare & Medicaid Services 2010 fee schedules (59). Our model also included discounted health-related costs and QALYs for the remaining lifetime of the population at the end of the time horizon and for persons who aged out of the modeled population.

Role of the Funding Source

Our study was funded by the National Institute on Drug Abuse, the Department of Veterans Affairs, the National Institute of Allergy and Infections Disease, and Stanford University. None of the funding sources had any role in the design, conduct, or reporting of the study.

RESULTS

PrEP for the General MSM Population

In the absence of PrEP, we estimate that 491 784 new HIV infections will occur among MSM in the United States in the next 20 years (**Table 2**). Use of PrEP could substantially reduce this incidence. Preexposure chemoprophylaxis in 20% of the U.S. MSM population would reduce the number of infections over 20 years by 62 759 (13% of the projected total) and yield 550 166 incremental QALYs (**Table 2**). Initiating PrEP in a greater proportion of the MSM population would yield greater health benefits. If 50% of MSM receive PrEP, 143 291 new infections (29%) would be prevented and 1.3 million QALYs would be gained compared with the status quo. If all MSM re-

ceive PrEP, 249 156 infections (51%) would be prevented, HIV prevalence in MSM would decrease to 6.4% after 20 years (**Appendix Figure 2**, *top*, available at www.annals.org), and more than 2 million QALYs would be gained.

In the first year of PrEP, the percentage reduction in annual HIV incidence would be similar to the efficacy of PrEP scaled by the percentage of MSM receiving PrEP. For example, if 20% of MSM receive PrEP, incidence of HIV would be reduced by 10% in the first year, approximately equal to 44% efficacy multiplied by 20% receiving PrEP (**Appendix Figure 2**, *bottom*). If 50% or 100% of MSM receive PrEP, incidence would be reduced by 24% and 45% in the first year, respectively. However, preventing secondary transmission causes the percentage reduction in HIV incidence to increase over time. After 20 years, annual HIV incidence would be reduced by 17% if 20% of MSM receive PrEP, by 37% if 50% of MSM receive PrEP, and by 60% if all MSM receive PrEP.

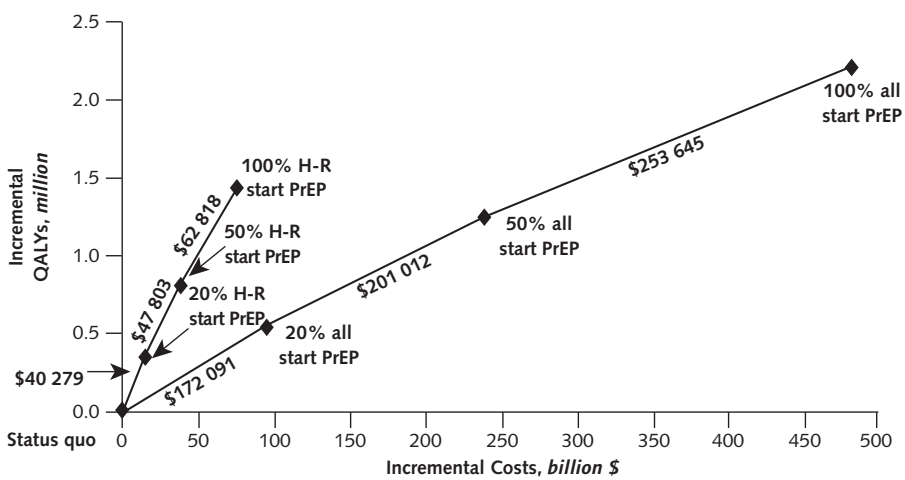
Although PrEP is effective at preventing HIV in MSM, it is expensive. Initiating PrEP in 20% of MSM would have an incremental cost-effectiveness ratio of $172 091 per QALY gained compared with the status quo (**Table 2** and **Figure 1**). Increasing the percentage of MSM who initiate PrEP also increases the incremental cost-effectiveness ratio because of diminishing benefits from additional PrEP. Initiating PrEP in 50% of MSM would cost $188 421 per QALY gained compared with the status quo, or $201 012 compared with initiating PrEP in 20% of MSM, whereas initiating PrEP in all MSM would cost $216 480 per QALY gained, or $253 645 compared with initiating PrEP in 50% of MSM.

The costs associated with PrEP are substantial. Use in 20% of MSM over 20 years generates an additional $95 billion in health care–related costs compared with the status quo ($98 billion for PrEP minus $3 billion in savings in HIV care), or nearly $2 million per HIV infection prevented (**Table 2**). These costs include all medical costs (HIV- and non–HIV-related) over the lifetime of the cohort. The ARVs and monitoring associated with PrEP for 20% of MSM would cost $98 billion over 20 years, or an average of $4.9 billion per year (**Appendix Figure 3**, *top*, available at www.annals.org). Costs increase as a higher percentage of MSM begin PrEP. If all MSM receive PrEP for 20 years, health care–related costs would increase by $480 billion.

PrEP for High-Risk MSM

Targeting high-risk MSM, rather than offering PrEP to the general MSM population, can improve cost-effectiveness. We estimated that 20% of MSM are at high risk, with a representative high-risk population having an average of 5 annual partners each, an initial HIV prevalence of 20%, and an initial annual incidence of 2.3% (28, 31, 45). Preexposure chemoprophylaxis in all of these high-risk MSM would cost $52 443 per QALY gained compared with the status quo (**Table 3**). As with the general MSM population, increasing the percentage of high-risk MSM who receive PrEP leads to diminishing returns: If 20% of high-risk MSM receive PrEP, the intervention costs $40 279 per QALY gained compared with the status quo (**Figure 1**); with 50% coverage, PrEP costs $44 556 per QALY gained compared with the status quo. In these

Figure 1. **Cost-effectiveness of PrEP for HIV prevention.**



Incremental costs and QALYs are plotted for each PrEP scenario in the general MSM population and in high-risk MSM, with the origin corresponding to the status quo of no PrEP. The lines show the incremental cost-effectiveness ratio relative to the next lower level of PrEP (the preceding scenario with a lower percentage of MSM starting PrEP). Under each PrEP scenario, persons initiate PrEP immediately and continue PrEP for the 20-y time horizon or until they reach age 65 years, and PrEP is 44% effective and costs $10 083 per year, inclusive of monitoring costs. Incremental costs and QALYs are calculated over a 20-y time horizon and are discounted to the present at 3% annually. H-R = high-risk; MSM = men who have sex with men; PrEP = preexposure chemoprophylaxis; QALY = quality-adjusted life-year.

Table 3. **Benefits and Costs of PrEP Strategies Over 20 Years in High-Risk MSM***

Strategy	HIV Infection†		HIV Prevalence at 20 Years, %	Total Cost of PrEP, *billion* $‡§	Total Cost, *billion* $‡	Total QALYs‡	Incremental Cost, *billion* $‡‖	Incremental QALYs‡‖	ICER, *$/QALY*	
	New Cases, *n*	Prevented Cases, *n (%)*							Relative to No PrEP	Relative to the Next Lower Level of PrEP
100% start PrEP	155 728	167 143 (52)	17	85	272	21 628 307	75	1 439 261	52 443	62 818
50% start PrEP	227 686	95 185 (29)	23	42	233	21 006 700	36	817 655	44 556	47 803
20% start PrEP	281 809	41 061 (13)	28	17	210	20 541 886	14	352 840	40 279	40 279
Status quo (no PrEP)	322 871	–	31	–	196	20 189 046	–	–	–	–

ICER = incremental cost-effectiveness ratio; PrEP = preexposure chemoprophylaxis; QALY = quality-adjusted life-year.
* Strategies do not include any benefits to low-risk MSM, because we did not model mixing between high- and low-risk MSM in our high-risk analysis.
† Undiscounted totals. Discounting infections at 3% annually reduces the number of infections averted for each strategy by approximately 24%.
‡ Costs and QALYs are net present values (3% annual discount rate) over 20 y.
§ Includes the costs of antiretroviral drugs for PrEP, monitoring tests and physician visits, and initiating and discontinuing therapy.
‖ Incremental costs and QALYs are relative to the status quo.

scenarios, PrEP is effective at preventing HIV infection, with 13%, 29%, and 52% of new infections prevented in high-risk MSM at 20%, 50%, and 100% coverage, respectively (**Table 3**).

Providing PrEP to high-risk MSM costs less than doing so for all MSM. If all high-risk MSM receive PrEP for 20 years, total health care–related costs would increase by $75.5 billion compared with the status quo, or approximately $600 000 per HIV infection prevented. Providing ARVs and monitoring for PrEP would cost $85.2 billion over 20 years, or an average of $4.3 billion per year, whereas HIV treatment and care are associated with savings of nearly $10 billion because of fewer future infections (**Table 3** and **Appendix Figure 3**, *bottom*). If fewer high-risk MSM receive PrEP, as probably would occur in practice, costs would be lower. If 50% of high-risk MSM initiate PrEP, the costs of PrEP over 20 years would be $41.9 billion and total health care–related costs compared with the status quo would be $36.4 billion. If only 20% of high-risk MSM initiate PrEP, the costs over 20 years would be $16.6 billion, or an average of $828 million per year, and total health care–related costs compared with the status quo would be $14.2 billion. The cost per infection prevented decreases at lower coverage levels of high-risk MSM—for example, it would be $460 000 per infection prevented at 20% coverage of high-risk MSM.

Sensitivity Analysis

In sensitivity analyses, we found that PrEP cost, efficacy, and effect on quality of life considerably affected cost-effectiveness. One common concern with PrEP is behavioral disinhibition (65, 66), but we found that the effectiveness and cost-effectiveness of PrEP are not substantially affected by moderate changes in the number of sexual partners or in condom use induced by PrEP (**Appendix**). We also found that initiating ART at CD4 cell counts of 0.500×10^9 cells/L, as opposed to 0.350×10^9 cells/L as in our base case, did not qualitatively change the effectiveness or cost-effectiveness of PrEP (**Appendix**). The daily cost of tenofovir–emtricitabine and its efficacy are key drivers of the cost-effectiveness of PrEP. Preexposure chemoprophylaxis in 20% of the general MSM population costs less than $100 000 per QALY gained if the daily cost decreases below $15 or if it is more than 75% effective at reducing risk for HIV infection, which may be possible in highly adherent persons. The daily cost would have to nearly double for PrEP in high-risk MSM to cost more than $100 000 per QALY gained. Although we assumed in our base case that PrEP had no effect on quality of life, some persons may experience side effects. We found that, on average, PrEP must reduce the quality of life by more than 8% for the cost of treating all high-risk MSM to exceed $100 000 per QALY gained.

Because risk behaviors and HIV prevalence vary across subpopulations of MSM, we examined a range of risk levels in sensitivity analyses (**Appendix**). In a high-risk group with an average of 5 annual partners, PrEP for all high-risk MSM would cost less than $100 000 per QALY gained as long as initial prevalence in the group was 8% or higher. For a medium-risk group with an initial prevalence of 15% and an average of 4 annual partners, PrEP for the entire group would cost approximately $100 000 per QALY gained.

The cost and efficacy of PrEP, and thus its cost-effectiveness, depend on adherence. The iPrEx study finding of 44% efficacy corresponded to approximately half of the study patients reporting or exhibiting high adherence, defined as pill use on at least 90% of days; however, average adherence is unknown (3). The cost of PrEP would probably be lower for MSM with lower adherence than in our base case (which includes the costs of daily pills), because nonadherent MSM would refill their ARV prescriptions less often. If MSM receiving PrEP take their daily pills only 50% of the time on average, and efficacy is still 44%, then the cost for high-risk MSM would be $25 165 per QALY gained, compared with $52 443 per QALY gained with the full daily pill cost. If average pill use is

75%, the cost would be $38 804 per QALY gained. If all MSM are highly adherent to PrEP, such that efficacy is 73% and the full daily pill cost is realized, the cost would be $35 080 per QALY gained. **Figure 2** (*bottom*) illustrates how the cost-effectiveness of PrEP for high-risk MSM varies as a function of cost and efficacy. Because average pill use would probably be less than daily in practice, PrEP in high-risk MSM would probably cost less than $50 000 per QALY gained. **Figure 2** (*top*) illustrates this relationship for the general MSM population.

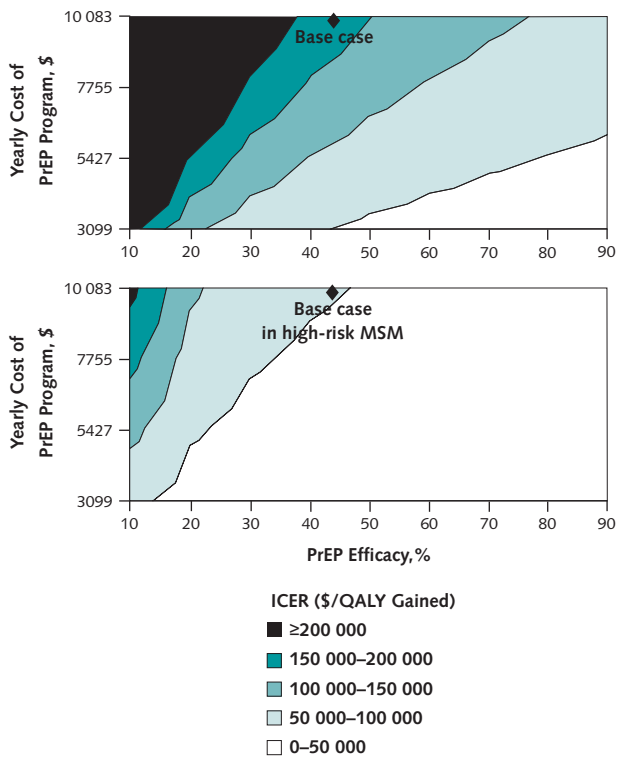
DISCUSSION

Our analysis demonstrates that PrEP for HIV prevention in MSM could have an important impact on the HIV epidemic in the United States. We show that even if only 20% of the U.S. MSM population were to initiate PrEP, more than 60 000 new HIV infections could be prevented over the next 20 years. However, PrEP is expensive, and limiting it to high-risk MSM would be integral to producing health benefits in an economically efficient manner (73). Initiating PrEP in 20% of the overall MSM population would cost $172 091 per QALY gained. In contrast, targeting PrEP to all high-risk MSM, who we estimate make up 20% of the overall MSM population, would cost approximately $50 000 per QALY gained and prevent more infections. If the daily cost of ARVs decreased to $15, PrEP could be more cost-effective in a broader population of MSM, but use only in high-risk MSM is attractive at current costs. Although the cost per QALY gained in high-risk MSM is similar to other interventions considered to be cost-effective, initiating PrEP in all high-risk MSM would cost more than $4 billion per year for ARVs and monitoring.

Despite the good value provided by PrEP in high-risk MSM, the budgetary effect will be large. Affordability is uncertain, particularly in view of competing priorities, such as providing ART to infected persons or developing new prevention technologies. Other interventions for MSM, such as symptom-based viral load testing for acute HIV infection (7), also provide good value but at a lower cost. In addition, many practical issues must be resolved before PrEP can be implemented, such as who would prescribe and who would pay for PrEP.

Because PrEP provides the most value in reducing HIV transmission when used in high-risk MSM, efficient clinical PrEP will depend on a clinician's ability to identify high-risk MSM. The number of partners and consistency of condom use are 2 key drivers of risk for HIV infection in MSM, and our results suggest that PrEP in MSM who have multiple sexual partners can be cost-effective. To stratify patients by risk, a clinician can ask a patient how many partners he had in the past year. Asking about condom use with nonprimary partners could strengthen the risk assessment and inform the decision to offer PrEP. Assessing risk from these variables is not uncommon in HIV prevention interventions (42, 62). Future studies on risk stratification of MSM could provide further guidance to clinicians in identifying high-risk MSM.

Figure 2. **Cost-effectiveness of PrEP for HIV prevention as a function of PrEP efficacy and cost.**



This 2-way sensitivity analysis shows ranges of the ICER for initiating PrEP in 20% of the general MSM population (*top*) and in all high-risk MSM (*bottom*) as a function of PrEP efficacy and cost. Costs depicted on the vertical axes are annual and include all antiretroviral drug and monitoring costs. Incremental costs and QALYs used to calculate the ICERs are calculated over a 20-y time horizon and are discounted to the present at 3% annually. ICER = incremental cost-effectiveness ratio; MSM = men who have sex with men; PrEP = preexposure chemoprophylaxis; QALY = quality-adjusted life-year.

Our analysis finds that PrEP provides better value (73) when fewer MSM initiate the treatment than when all MSM receive it. This phenomenon of diminishing returns is seen in other prevention programs as they are scaled up (74, 75). Secondary transmission benefits lead to substantial prevention of HIV infections, even at low PrEP coverage. Thus, it can have a clinically significant (and efficient) effect at relatively low coverage levels.

We studied daily oral PrEP. The efficacy of intermittent PrEP is being tested in clinical trials. If PrEP only before high-risk behavior is shown to be effective at preventing HIV infection, this could substantially lower the cost of the ARVs associated with PrEP. Our examination of the cost-effectiveness of daily PrEP as a function of cost and efficacy can help estimate the thresholds of cost and efficacy at which intermittent PrEP is cost-effective.

Previous studies reached different conclusions about the cost-effectiveness of PrEP in MSM. Paltiel and colleagues (5) found that PrEP cost $298 000 per QALY gained in a high-risk MSM population with an annual HIV incidence of 1.6%, whereas Desai and colleagues (6) found that it cost $32 000 per QALY gained for high-risk MSM in New York City with an annual incidence of 1.35%. Although Paltiel and colleagues suggest that PrEP is cost effective only in subgroups with very high–incidence, we find lower incremental cost-effectiveness ratios for high-risk MSM under a broader set of risk assumptions. Our results differ in part because of the extent to which each model captures the full benefits from reduced transmission due to PrEP and the length of time that MSM continue PrEP. Whereas Paltiel and colleagues modeled PrEP efficacy as a flat percentage of reduction in incidence and had MSM continue PrEP for their entire lifetime, we captured the dynamic effects of reduced transmission on incidence and assumed that MSM would discontinue the treatment after 20 years or at age 65 years. When we match Paltiel and colleagues' assumptions as closely as possible given our different modeling framework, we arrive at a similar conclusion—that PrEP is only cost-effective for the highest-risk subgroup of MSM. With our base-case model assumptions, our findings are more similar to those of Desai and colleagues (6). Both studies found that PrEP costs less than $100 000 per QALY gained for high-risk MSM with an annual incidence greater than 1.3%. A strength of our analysis is that we capture longer-term benefits of reduced transmission and incorporate a detailed economic analysis along with the epidemic modeling.

Our analysis has limitations. First, the cost-effectiveness of offering PrEP to all MSM depends on the propensity of MSM to use PrEP by risk level. For example, if high-risk MSM are more likely than low-risk MSM to use PrEP, offering it to all MSM may be cost-effective, because in practice it will be as if PrEP is targeted to high-risk MSM. However, if low-risk MSM are more likely than high-risk MSM to use PrEP, perhaps because they are more risk-averse, then PrEP for the general MSM population may be even less cost-effective than in our base case. Second, high-risk MSM may mix with low-risk MSM and have networks of sexual partners, which we did not model when examining PrEP for high-risk MSM because of lack of data on mixing patterns. Therefore, we cannot directly compare strategies of PrEP for all MSM with those for high-risk MSM. However, we can infer that PrEP for all MSM would be even less cost-effective when compared with PrEP for high-risk MSM than when compared with the status quo. With regard to sexual networks, to the extent that it could be targeted to MSM who are centrally located in such networks, PrEP would be even more cost-effective. Third, we did not include the possibility that PrEP facilitates the development of drug-resistant HIV in our model, because the iPrEx study found that no resistance developed in study patients who acquired HIV during the trial (3). In sensitivity analyses, we estimated the effects of resistance in terms of the efficacy and cost of future treatment of men who acquire HIV while receiving PrEP and found that resistance did not largely affect results. Fourth, we did not include potential renal impairment associated with PrEP. Because we assumed monitoring for elevated creatinine levels in persons receiving PrEP per CDC guidelines, and because tenofovir–emtricitabine was not found to cause long-term renal impairment in patients in the iPrEx study (3), we do not anticipate this exclusion to affect the results. Finally, we did not model HIV risk and benefits for MSM who also have female partners or who are injection drug users.

Our analysis demonstrates that PrEP in MSM could prevent a considerable number of new HIV infections. However, its use in the general MSM population would be expensive. Use in high-risk MSM would provide substantial health benefits at a lower cost, although the budgetary effect would still be sizeable. Preexposure chemoprophylaxis in the estimated 20% of MSM who are at high risk for HIV infection would prevent more than twice as many infections as PrEP in 20% of the general MSM population and would provide better value. These findings can help inform clinicians' decisions about whom to offer PrEP and policymakers' decisions about recommendations for PrEP.

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Appendix

We adapted a previously published deterministic dynamic compartmental model to assess the effectiveness and cost-effectiveness of PrEP for HIV prevention in MSM in the United States (7). **Appendix Figure 1** shows a schematic representation of the model, **Appendix Table 1** summarizes model notation, and **Appendix Table 2** (76–91) presents model parameters not included in **Table 1** in the main text. The model calculates $X_i(t)$, the number of persons in each compartment i at time t. Persons transition between compartments and age into or transition out of the population at rates defined by population demographic characteristics, disease progression parameters, screening and treatment interventions, and PrEP interventions. We implemented the model in Microsoft Office Excel 2007 (Microsoft, Redmond, Washington) with a weekly time step and considered a time horizon of 20 years. This time frame is long enough to capture most of the costs and benefits of PrEP in the modeled population of MSM but not long enough to allow future events in HIV care to undermine the believability of the results. We have discussed additional details on population dynamics, disease progression, and calculations of QALYs and costs elsewhere (7). Further details of the model are available by contacting the authors.

Model Compartments

We estimated that there are approximately 4.3 million MSM aged 13 to 64 years in the United States (9, 10). We subdivided this population into 15 compartments based on HIV infection status (uninfected or infected), screening status (unidentified or identified), PrEP status (receiving or not receiving PrEP), HIV disease stage if infected (acute infection, asymptomatic HIV [CD4 cell count $>0.350 \times 10^9$ cells/L], symptomatic HIV [CD4 cell count of 0.200 to 0.350×10^9 cells/L], or AIDS [CD4 cell count $<0.200 \times 10^9$ cells/L]), and treatment status if infected (receiving or not receiving ART).

PrEP Interventions

We modeled varying percentages of the uninfected population initiating PrEP at the start of the model time horizon. Because our protocol only required a negative result from an HIV antibody test for PrEP eligibility, we allowed for persons with acute HIV infection to initiate and use PrEP until an antibody test administered during monitoring returned a positive result.

We assumed in our base case that MSM receiving PrEP continued PrEP for the 20-year time horizon or until aging out of the model at age 65 years. Our model also allows for MSM to continue receiving PrEP for less time, on average. Because we modeled the average MSM population across the United States, our base-case results also apply to MSM initiating and discontinuing a daily PrEP regimen at rates that result in a similar percentage of MSM receiving PrEP over time as in our base case.

It is uncertain whether PrEP will induce changes in number of sexual partners or condom use (65, 66). Although risk-taking could increase as persons feel protected against HIV infection, it could also decrease because of the risk-reduction counseling and condoms that should be provided during visits to a physician for monitoring. In our base case, we assumed no risk compensation or reduction from PrEP; in our sensitivity analysis, we examined the effects of changes in number of partners and condom use. We examined both increases and decreases in number of sexual partners for persons receiving PrEP. We also modeled increases and decreases in condom use for those receiving PrEP and examined a corresponding change in condom use in the non-PrEP population, which was proportional to the size of the population receiving PrEP. Whereas other studies have assumed that risk compensation would occur population-wide (6), we assessed risk compensation in number of partners only in those using PrEP because it is reasonable to assume that choosing to partner with more people is directly tied to feeling biologically protected from PrEP. We examined changes in condom use for persons receiving and not receiving PrEP because condom use could change in existing partnerships or those that would have also formed under the status quo. If one member of a partnership initiates or is already receiving PrEP, the couple might use condoms less frequently.

HIV Transmission

We modeled HIV transmission resulting from homosexual contact. The total rate of contacts sufficient to transmit infection is the sum of the sufficient contact rates between an uninfected person in compartment i ($i = 1, 2, 13$) and an infected person in compartment j ($j = 3, \ldots, 12, 14, 15$) at time t, which we denote by $\beta_{i,j}(t)$.

The homosexual contact rate is a function of high-risk behavior, the probability of selecting an infected person as a partner, and the probability of HIV transmission per partnership. We modeled the chance of acquiring HIV infection as a binomial process, similar to Long and colleagues (19). A "success" is defined as transmission of HIV. Uninfected persons in compartment i select $n_i(1 - u_i\kappa)$ high-risk partners per year (that is, partnerships involving unprotected sexual contact), where n_i is the annual number of male partners, u_i is condom use with male partners, and κ is condom effectiveness in reducing HIV transmission, with the probability of transmission per partnership, $\sigma_{i,j}$, being the probability of success in a partnership with an infected person in compartment j. We assumed proportional mixing; thus, uninfected persons choose high-risk partners from infected compartment j on the basis of the number of high-risk partnerships that persons in compartment j have. The probability of selecting a high-risk partner from compartment j is:

$$P(selectj) = \frac{X_j(t)n_j(1 - u_j\kappa)}{\sum_k X_k(t)n_k(1 - u_k\kappa)} \quad (1)$$

Each contact rate $\beta_{i,j}(t)$ can then be calculated as follows:

$$\beta_{i,j}(t) = 1 - (1 - P(selectj)\sigma_{i,j})^{n_i(1-u_i\kappa)} \quad (2)$$

The annual probability of transmission in a partnership, $\sigma_{i,j}$, assuming no condom use or ineffective condom use, depends on the disease stage and ART status (receiving or not receiving) of the infected person and the PrEP status of the uninfected person. Uninfected persons receiving PrEP have a reduced chance of HIV infection, defined by the PrEP efficacy, ε_{pr}. Infected persons receiving ART have reduced sexual infectivity, given by the multiplier ε_{tx}. The annual probability of HIV transmission per unprotected sexual partnership between an uninfected male and an infected male with HIV status k, in the absence of ART or PrEP, is denoted as π_k. For example, the annual probability of transmission in a partnership between an uninfected person receiving PrEP and an infected person with AIDS receiving ART is:

$$\sigma_{13,12} = \pi_{AIDS}(1 - \varepsilon_{tx})(1 - \varepsilon_{pr}) \quad (3)$$

System of Equations

We modeled HIV transmission and progression with a system of 15 nonlinear differential equations. The equations describing the change in the number of persons in each compartment at each time step are listed here. We let X_i denote $X_i(t)$ for ease of notation. Change in number of unidentified uninfected persons (compartment 1):

$$\frac{dX_1}{dt} = \rho\sum_i X_i - \left(\sum_{2<j<13, j>13} \beta_{1,j}(t)\right)X_1 - \psi X_1 + \omega_{id}X_2 - \mu_1 X_1 - \delta_1 X_1 \quad (4)$$

Change in number of identified uninfected persons (compartment 2):

$$\frac{dX_2}{dt} = -\left(\sum_{2<j<13, j>13} \beta_{2,j}(t)\right)X_2 + \psi X_1 - \omega_{id}X_2 + \omega_{pr}X_{13} - \mu_2 X_2 - \delta_2 X_2 \quad (5)$$

Change in number of unidentified acutely infected persons (compartment 3):

$$\frac{dX_3}{dt} = \left(\sum_{2<j<13, j>13} \beta_{1,j}(t)\right)X_1 + \left(\sum_{2<j<13, j>13} \beta_{2,j}(t)\right)X_2 - (\psi + \nu_3)X_3 - \theta_3 X_3 - \mu_3 X_3 - \delta_3 X_3 \quad (6)$$

Change in number of identified acutely infected persons (compartment 4):

$$\frac{dX_4}{dt} = (\psi + \nu_3)X_3 - \theta_4 X_4 - \mu_4 X_4 - \delta_4 X_4 \quad (7)$$

Change in number of infected persons who are unidentified and asymptomatic (compartment 5):

$$\frac{dX_5}{dt} = \theta_3 X_3 - (\psi + \nu_5)X_5 - \theta_5 X_5 - \mu_5 X_5 - \delta_5 X_5 \quad (8)$$

Change in number of infected persons who are identified and asymptomatic (compartment 6):

$$\frac{dX_6}{dt} = \theta_4 X_4 + (\psi + \nu_5) X_5 + \omega_m X_{15} - \theta_6 X_6 - \mu_6 X_6 - \delta_6 X_6 \quad (9)$$

Change in number of infected persons who are unidentified and symptomatic (compartment 7):

$$\frac{dX_7}{dt} = \theta_5 X_5 - (\psi + \nu_7) X_7 - \theta_7 X_7 - \mu_7 X_7 - \delta_7 X_7 \quad (10)$$

Change in number of infected persons who are identified, untreated, and symptomatic (compartment 8):

$$\frac{dX_8}{dt} = \theta_6(1 - \phi_6) X_6 - (\psi + \nu_7)(1 - \phi_7) X_7 - \hat{\phi}_8 X_8 - \theta_8 X_8 - \mu_8 X_8 - \delta_8 X_8 \quad (11)$$

Change in number of unidentified persons with AIDS (compartment 9):

$$\frac{dX_9}{dt} = \theta_7 X_7 - (\psi + \nu_9) X_9 - \alpha_9 X_9 - \mu_9 X_9 - \delta_9 X_9 \quad (12)$$

Change in number of identified untreated persons with AIDS (compartment 10):

$$\frac{dX_{10}}{dt} = \theta_8 X_8 + (\psi + \nu_9)(1 - \phi_9) X_9 - \hat{\phi}_{10} X_{10} - \alpha_{10} X_{10} - \mu_{10} X_{10} - \delta_{10} X_{10} \quad (13)$$

Change in number of infected persons who are identified, treated, and symptomatic (compartment 11):

$$\frac{dX_{11}}{dt} = \theta_6 \phi_6 X_6 + (\psi + \nu_7) \phi_7 X_7 + \hat{\phi}_8 X_8 - \theta_{11} X_{11} - \mu_{11} X_{11} - \delta_{11} X_{11} \quad (14)$$

Change in number of identified treated persons with AIDS (compartment 12):

$$\frac{dX_{12}}{dt} = (\psi + \nu_9) \phi_9 X_9 + \hat{\phi}_{10} X_{10} + \theta_{11} X_{11} - \alpha_{12} X_{12} - \mu_{12} X_{12} - \delta_{12} X_{12} \quad (15)$$

Change in number of uninfected persons receiving PrEP (compartment 13):

$$\frac{dX_{13}}{dt} = -\left(\sum_{2<j<13, j>13} \beta_{13,j}(t) \right) X_{13} - \omega_{pr} X_{13} - \mu_{13} X_{13} - \delta_{13} X_{13} \quad (16)$$

Change in number of unidentified acutely infected persons receiving PrEP (compartment 14):

$$\frac{dX_{14}}{dt} = \left(\sum_{2<j<13, j>13} \beta_{13,j}(t) \right) X_{13} - \theta_{14} X_{14} - \mu_{14} X_{14} - \delta_{14} X_{14} \quad (17)$$

Change in number of infected persons receiving PrEP who are unidentified and asymptomatic (compartment 15):

$$\frac{dX_{15}}{dt} = \theta_{14} X_{14} - \omega_m X_{15} - \mu_{15} X_{15} - \delta_{15} X_{15} \quad (18)$$

Calibration and Validation

We instantiated the model by calculating the number of MSM in the United States aged 13 to 64 years (using census data and estimates from the CDC of the percentage of MSM) and HIV prevalence in MSM (using estimates from the CDC of the number of MSM living with HIV) (9–11). We then calibrated the model by comparing model-generated numbers of new infections per year with estimates from the CDC of the number of new infections in MSM per year (2). Prejean and colleagues (2) estimate that the number of new infections in MSM in the United States from 2006 to 2009 ranged from 26 900 to 32 300 annually. In comparison, our model estimates 30 395 new HIV infections in MSM in the first year. We also confirmed that the total number of MSM in our modeled population grew at a rate consistent with estimates from the U.S. Census Bureau of male population growth over the next 20 years.

Sensitivity Analysis

We performed sensitivity analyses on all model parameters and found that the results were not substantially affected by most parameters. For example, although increasing the time horizon to 30 years led to a small decrease in the cost-effectiveness ratios for PrEP strategies and considering a 5% discount rate led to a small increase, neither had a qualitative effect on the results. **Appendix Tables 3 to 5** and **Appendix Figure 4** show the results of the sensitivity analysis for those parameters discussed in the text. **Appendix Figure 5** shows a tornado diagram of the most influential 1-way sensitivity analyses for PrEP for all high-risk MSM.

Because behavioral disinhibition is a potential concern with PrEP, we analyzed the effect of changes in number of partners and condom use as a result of PrEP. As previously discussed, we assumed that changes in number of partners would affect only those receiving PrEP. A 20% increase or decrease in number of sexual partners for persons receiving PrEP did not appreciably change the effectiveness or cost-effectiveness of PrEP for all MSM or high-risk MSM. For the case of 20% of all MSM initiating PrEP, increasing or decreasing the number of partners for those receiving PrEP by 20% resulted in 12% to 14% of new HIV infections prevented, compared with the base-case result of 13% prevented. The cost of PrEP ranged from $157 401 to $192 861 per QALY gained, compared with $172 091 per QALY gained in the base case. In the behavioral disinhibition scenario, in which PrEP induces an increase in the number of partners, more infections are prevented and the cost per QALY

gained is lower than in the base case as long as PrEP coverage is less than 90%. The opposite is true if PrEP induces risk reduction: Fewer infections are prevented and cost per QALY gained is higher than in the base case. This counterintuitive finding is due to our assumptions of proportional mixing and is similar to Long and colleagues' findings (19) on the effects of behavioral disinhibition with a hypothetical HIV vaccine. When persons receiving PrEP increase their number of partners, they account for a larger proportion of the partnerships occurring in the MSM population. An HIV-infected person is then more likely to partner with a person receiving PrEP than with an unprotected, uninfected person compared with the base case, leading to less HIV transmission. Conversely, if persons receiving PrEP reduce their number of partners, an infected person is more likely to select an unprotected, uninfected person as a partner, leading to more HIV transmission. As would be expected, this effect disappears if almost all of the modeled population is using PrEP.

As discussed previously, behavioral disinhibition with condom use is likely to affect both those receiving and those not receiving PrEP. The degree of change in the non-PrEP population probably would be relative to the size of the population receiving PrEP. For example, if 20% of all MSM initiate PrEP and reduce condom use by 20%, a small fraction of the non-PrEP population could be expected to also reduce condom use by 20%. If 10% of the non-PrEP population reduces condom use by 20%, 12% of new HIV infections are prevented, compared with 13% in the base case, and PrEP costs $186 251 per QALY gained, compared with $172 091 per QALY gained in the base case. If all uninfected, high-risk MSM initiate PrEP and reduce condom use by 20%, all other high-risk MSM could be expected to reduce condom use as well. In this scenario, 43% of infections would be prevented, compared with 52% in the base case, and PrEP would cost $63 521 per QALY gained compared with the status quo, versus $52 443 per QALY gained in the base case. As these results show, if the reduction in condom use caused by PrEP is proportional to the size of the population using PrEP, behavioral disinhibition does not have a considerable effect on the results. However, if 20% of all MSM initiate PrEP and decrease condom use by 20% and all other MSM decrease condom use as well, the results change dramatically: PrEP would then lead to a 4% increase in new infections and to fewer QALYs than in the status quo. Because this scenario is unlikely, we conclude that behavioral disinhibition with condom use will not have a substantial effect on the effectiveness and cost-effectiveness of PrEP.

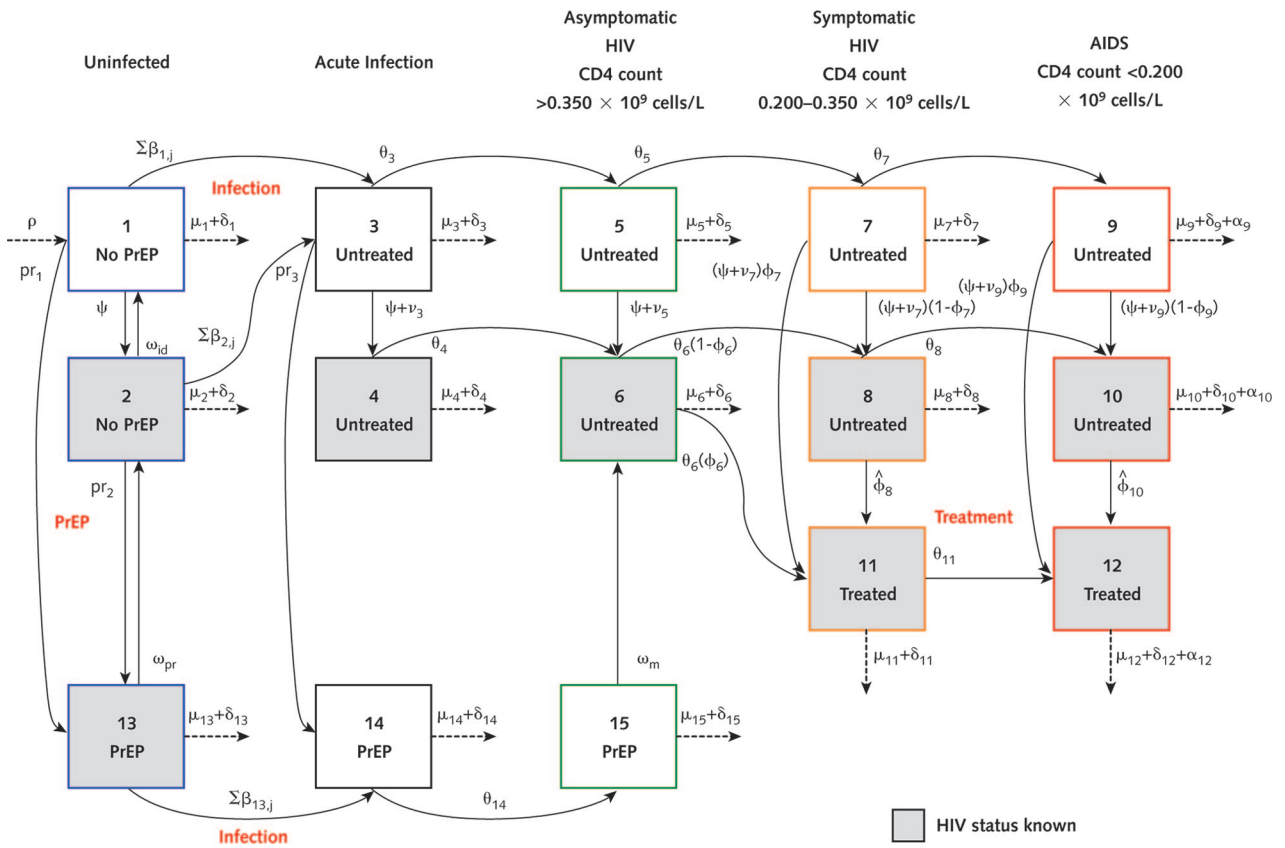
Although we assumed ART initiation at CD4 cell counts of 0.350×10^9 cells/L in our base case, recent guidelines recommend earlier treatment (64). In sensitivity analyses, we examined initiating ART at CD4 cell counts of 0.500×10^9 cells/L. The effectiveness and cost-effectiveness of PrEP remained qualitatively similar with earlier ART initiation and an associated survival gain in the status quo. Preexposure prophylaxis for all MSM remained prohibitively expensive, and PrEP for high-risk MSM still cost approximately $50 000 per QALY gained.

Comparison With Other Studies

Paltiel and colleagues (5) found that PrEP for MSM would cost $298 000 per QALY gained in a high-risk population with 1.6% annual HIV incidence, assuming PrEP efficacy of 50%. In contrast, we find that PrEP in high-risk MSM with 2.3% annual HIV incidence would cost approximately $50 000 per QALY gained. The results differ for 2 key reasons. Paltiel and colleagues modeled PrEP efficacy as a flat percentage reduction in HIV incidence and, as the authors note, their model did not capture secondary transmissions prevented and as such did not capture the full benefits from reduced transmission due to PrEP. In contrast, our model captures both primary and secondary transmissions prevented, which leads to a cumulative effect on incidence reduction from PrEP. The percentage reduction in incidence increases over time because of secondary transmission benefits (**Appendix Figure 2**, *bottom*). In addition, Paltiel and colleagues assumed that patients received PrEP for their entire lifetime, even though the benefits of PrEP likely diminish or disappear as a person ages and changes behavior. We assumed that patients received PrEP either for the 20-year model time horizon or until they aged out of the model at age 65 years. We recognize, as do Paltiel and colleagues, that it would be most efficient for MSM to use PrEP only during periods of their life when they exhibit risk behaviors, and we note this as a limitation of our model. When we match the assumptions of Paltiel and colleagues as closely as possible given our different modeling frameworks, we arrive at a similar conclusion—that PrEP is only cost-effective for the highest-risk subgroup of MSM.

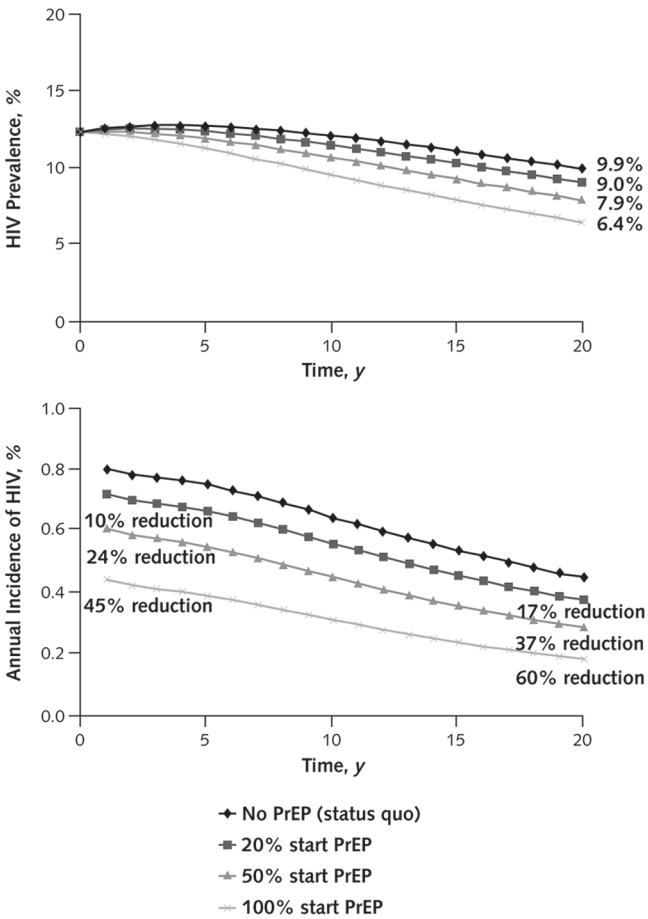
Our findings are similar to those of Desai and colleagues (6), who found that PrEP is cost-effective by conventional standards for high-risk MSM. Our analysis strengthens and builds on this conclusion. Desai and colleagues examined the effects of a 5-year PrEP program, whereas our 20-year time horizon captures the long-term benefits of reduced transmission. In addition, Desai and colleagues calculated the incremental cost-effectiveness of PrEP by using a static estimate of savings in lifetime treatment costs and QALYs for persons in whom HIV infection was prevented. However, the savings in treatment costs used in their analysis is not the marginal cost of treating an HIV-infected person, so the costs saved from preventing an infection were likely overestimated. We sought to accurately model the costs associated with a PrEP program by accounting for all health care–related costs incurred in the population in each scenario and then comparing PrEP scenarios with the status quo.

Appendix Figure 1. **Model schematic.**



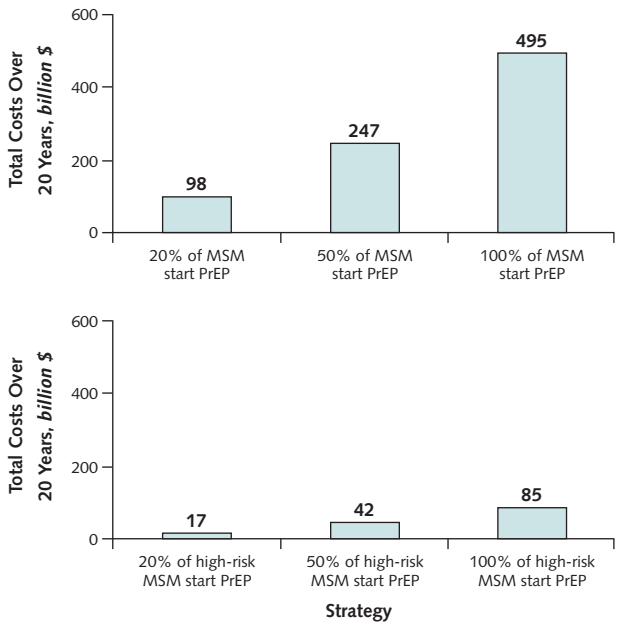
This schematic presents our deterministic dynamic compartmental model. Each box represents a compartment of the population of men who have sex with men, identified by HIV infection status; screening status; PrEP status; and, if infected, HIV disease stage and treatment status. The number within each square denotes the index number of that compartment. The arrows depict population movement from 1 compartment to another and into or out of the population, with the associated variables representing the rates of change. **Appendix Table 1** describes the variables. PrEP = preexposure chemoprophylaxis.

Appendix Figure 2. **Prevalence and incidence of HIV with and without PrEP for HIV prevention.**



Under each PrEP scenario, persons initiate PrEP immediately and continue PrEP for the 20-y time horizon or until they reach age 65 y, and PrEP is 44% effective. **Top.** Prevalence in the overall U.S. MSM population, as simulated by our model, for each scenario for the 20-y time horizon. **Bottom.** Annual HIV incidence in the susceptible U.S. MSM population, as simulated by our model, for each scenario for the 20-y time horizon. The percentage reduction in HIV incidence relative to the status quo is noted for the first and last years of the model time horizon for each scenario. MSM = men who have sex with men; PrEP = preexposure chemoprophylaxis.

Appendix Figure 3. **Costs of PrEP for HIV prevention as a function of the percentage of uninfected MSM receiving PrEP.**



Total costs of PrEP over 20 y are plotted for each use scenario in the general MSM population (*top*) and in high-risk MSM (*bottom*). Total costs of PrEP include the cost of antiretroviral drugs for PrEP, costs of monitoring tests and physician visits, and initiation and discontinuation costs. Under each PrEP scenario, persons initiate PrEP immediately and continue PrEP for the 20-y time horizon or until they reach age 65 y, and PrEP is assumed to be 44% effective and cost $10 083 per year. Costs are calculated over a 20-y time horizon and are discounted to the present at 3% annually. MSM = men who have sex with men; PrEP = preexposure chemoprophylaxis.

Appendix Table 1. Model Parameters and Notation

Parameter	Description
Demographic	
$X_i(t)$	Number of persons in compartment i at time t
ρ	Entry rate of persons into the model at age 13 y
μ_i	Maturation rate out of compartment i at age 65 y
δ_i	Non-AIDS death rate for compartment i
r	Annual discount rate
HIV progression	
θ_i	HIV disease progression rate for compartment i (i = 3–8, 11, 14)
α_i	AIDS death rate for compartment i (i = 9, 10, 12)
Sexual behavior	
n_i	Annual number of male partners of persons in compartment i
u_i	Condom use with male partners by persons in compartment i
κ	Condom effectiveness in reducing HIV transmission
Transmission	
$\sigma_{i,j}$	Annual probability of HIV transmission per unprotected sexual partnership between uninfected (compartment i, i = 1, 2, 13) and infected (compartment j, j = 3–12, 14–15) persons
π_k	Annual probability of HIV transmission per unprotected sexual partnership between an uninfected male and an infected male with HIV status k
$\beta_{i,j}(t)$	Sufficient contact rate at time t between uninfected (compartment i, i = 1, 2, 13) and infected (compartment j, j = 3–12, 14–15) persons
Treatment	
ϕ_i	Fraction of persons in compartment i (i = 6, 7, 9) starting ART at CD4 cell count of = 0.350×10^9 cells/L
$\hat{\phi}_i$	Rate of persons in compartment i (i = 8, 10) starting ART at CD4 cell count <0.350×10^9 cells/L
ε_{tx}	ART efficacy in reducing sexual infectivity in infected persons
Screening	
Ψ	Probability of screening
v_i	Probability of symptomatic testing or case detection for persons in compartment i (i = 3, 5, 7, 9)
$\frac{1}{\omega_{id}}$	Average duration of identification status for uninfected persons
p_{id}	Reduction in sexual behavior due to screening and counseling
PrEP	
pr_i	Fraction of persons in compartment i starting PrEP (i = 1–3)
$\frac{1}{\omega_{pr}}$	Average duration receiving PrEP
$\frac{1}{\omega_m}$	Average time between PrEP monitoring visits
ε_{pr}	PrEP efficacy in reducing the probability of an uninfected person acquiring HIV from homosexual contact with an infected person
p_{pr}	Change in number of sexual partners due to PrEP
c_{pr}	Change in condom use due to PrEP

ART = antiretroviral treatment; PrEP = preexposure chemoprophylaxis.

Appendix Table 2. **Summary of Additional Model Inputs**

Parameter	Value	Range	Source (Reference)
Demographic			
Male maturation rate	0.0106	0.005–0.02	Calculated (10, 76)
Male entry rate	0.022	0.01–0.04	Calculated (10, 76)
Disease—quality-of-life factors			
Uninfected, no PrEP	1.00	–	(19, 77)
Uninfected, receiving PrEP	1.00	0.90–1.00	(3, 72)
Acute HIV, unidentified	0.92	0.73–0.97	Calculated (15, 50, 51, 78–82)
Acute HIV, identified	0.86	0.68–0.91	Calculated (15, 35, 50, 51, 71, 78–82)
Asymptomatic HIV, unidentified	0.91	0.85–0.95	(35, 71)
Asymptomatic HIV, identified (year 1)	0.84	0.84–0.95	(35)
Asymptomatic HIV, identified (years ≥2)	0.89	0.85–0.95	(35)
Symptomatic HIV, unidentified	0.79	0.70–0.80	(35, 83, 84)
Symptomatic HIV, identified	0.72	0.70–0.80	(71)
Symptomatic HIV, treated with ART	0.83	0.82–0.87	(19, 35, 83)
AIDS, unidentified	0.72	0.60–0.75	(19, 35)
AIDS, identified	0.72	0.60–0.75	(19, 83, 84)
AIDS, treated with ART	0.82	0.82–0.87	(19, 83)
Age-specific multiplier	0.96	0.887–1.00	(77, 85, 86)
Sexual behavior, %			
Condom effectiveness	90	85–95	(87)
Screening			
Annual probability of symptom-based case finding, %			
Symptomatic HIV	10	0–30	(19, 35)
AIDS	20	10–60	(19, 35)
Identification duration if uninfected, *y*	1	0.5–3	Assumed
Postseroconversion sensitivity of antibody test, %	99.5	98.0–99.9	(35, 88–90)
Postseroconversion specificity of antibody test, %	99.9994	99–100	(35, 88–90)
Quality decrement for false-positive result (multiplier to above quality-of-life factors)	0.12	0–0.48	Calculated (35, 71, 91)

ART = antiretroviral treatment; PrEP = preexposure chemoprophylaxis.

Appendix Table 3. **Results of Key Sensitivity Analyses in the General MSM Population***

Strategy	HIV Infections Prevented, *n (%)*†	Incremental Cost, *billion $*‡	Incremental QALYs‡	ICER, *$/QALY*	
				Relative to No PrEP	Relative to the Next Lower Level of PrEP§
Base-case scenario					
100% start PrEP	249 156 (51)	480	2 217 732	216 480	253 645
50% start PrEP	143 291 (29)	238	1 263 673	188 421	201 012
20% start PrEP	62 759 (13)	95	550 166	172 091	172 091
Percentage of MSM initiating PrEP					
100%	249 156 (51)	480	2 217 732	216 480	284 567
90%	230 360 (47)	431	2 046 779	210 793	269 333
80%	210 462 (43)	383	1 866 586	205 142	254 651
70%	189 397 (39)	335	1 676 492	199 528	240 515
60%	167 021 (34)	286	1 475 781	193 954	226 918
50%	143 291 (29)	238	1 263 673	188 421	213 852
40%	118 083 (24)	190	1 039 325	182 931	201 310
30%	91 281 (19)	142	801 821	177 487	189 284
20%	62 759 (13)	95	550 166	172 091	177 765
10%	32 382 (7)	47	283 283	166 745	169 479
5%	16 451 (3)	24	143 769	164 092	164 092
Tenofovir–emtricitabine costs $15/d					
100% start PrEP	249 156 (51)	291	2 217 732	131 277	154 248
50% start PrEP	143 291 (29)	144	1 263 673	113 935	121 717
20% start PrEP	62 759 (13)	57	550 166	103 841	103 841
PrEP efficacy is 73%					
100% start PrEP	367 303 (75)	480	3 281 066	146 228	185 693
50% start PrEP	224 554 (46)	237	1 973 507	120 080	132 502
20% start PrEP	102 793 (21)	94	893 521	105 066	105 066
PrEP causes moderate resistance					
100% start PrEP	234 185 (48)	490	2 102 491	233 040	240 418
50% start PrEP	122 177 (25)	249	1 100 613	226 325	226 325‖
20% start PrEP	37 012 (8)	107	351 383	303 091	Dominated

ICER = incremental cost-effectiveness ratio; MSM = men who have sex with men; PrEP = preexposure prophylaxis; QALY = quality-adjusted life-year.

* In the base-case scenario, the daily cost of tenofovir–emtricitabine is $26, PrEP efficacy is 44%, and PrEP does not cause any resistance. In the resistance scenario, average efficacy of antiretroviral therapy in reducing HIV infectivity is 85% vs. 90% in the base case, and annual cost of antiretroviral therapy is $19 000 vs. $15 589 in the base case.

† Undiscounted totals.

‡ Costs and QALYs are net present values (3% annual discount rate) over 20 y. Incremental costs and QALYs are relative to the status quo.

§ Relative to the next lower level of PrEP use that is not dominated by another strategy. A dominated strategy is not an efficient use of resources; thus, the next level of PrEP use would be implemented.

‖ The ICER of 50% PrEP is calculated relative to the status quo of no PrEP because 20% PrEP is dominated.

Appendix Table 4. **Results of Key Sensitivity Analyses in High-Risk MSM***

Strategy	HIV Infections Prevented, *n (%)*†	Incremental Cost, *billion $*‡	Incremental QALYs‡	ICER, *$/QALY*	
				Relative to No PrEP	Relative to the Next Lower Level of PrEP§
Base-case scenario					
100% of high-risk start PrEP	167 143 (52)	75	1 439 261	52 443	62 818
50% of high-risk start PrEP	95 185 (29)	36	817 655	44 556	47 803
20% of high-risk start PrEP	41 061 (13)	14	352 840	40 279	40 279
Percentage of high-risk MSM initiating PrEP					
100%	167 143 (52)	75	1 439 261	52 443	72 225
90%	154 412 (48)	67	1 328 708	50 797	67 490
80%	140 890 (44)	60	1 211 615	49 184	63 036
70%	126 537 (39)	52	1 087 637	47 605	58 853
60%	111 313 (34)	44	956 429	46 062	54 933
50%	95 185 (29)	36	817 655	44 556	51 266
40%	78 117 (24)	29	670 993	43 090	47 843
30%	60 084 (19)	22	516 144	41 664	44 654
20%	41 061 (13)	14	352 840	40 279	41 689
10%	21 035 (7)	7	180 852	38 939	39 609
5%	10 644 (3)	4	91 543	38 285	38 285
Tenofovir–emtricitabine costs $50/d					
100% of high-risk start PrEP	167 143 (52)	150	1 439 261	104 516	124 060
50% of high-risk start PrEP	95 185 (29)	73	817 655	89 658	95 780
20% of high-risk start PrEP	41 061 (13)	29	352 840	81 593	81 593
Quality of life reduced by 8% while receiving PrEP					
100% of high-risk start PrEP	167 143 (52)	75	794 473	95 006	132 917
50% of high-risk start PrEP	95 185 (29)	36	500 698	72 762	81 374
20% of high-risk start PrEP	41 061 (13)	14	227 646	62 431	62 431
50% of ARV cost; PrEP efficacy, 44%					
100% of high-risk start PrEP	167 143 (52)	36	1 439 261	25 165	30 736
50% of high-risk start PrEP	95 185 (29)	17	817 655	20 930	22 670
20% of high-risk start PrEP	41 061 (13)	7	352 840	18 637	18 637
75% of ARV cost; PrEP efficacy, 44%					
100% of high-risk start PrEP	167 143 (52)	56	1 439 261	38 804	46 777
50% of high-risk start PrEP	95 185 (29)	27	817 655	32 743	35 236
20% of high-risk start PrEP	41 061 (13)	10	352 840	29 458	29 458
100% of ARV cost; PrEP efficacy, 73%					
100% of high-risk start PrEP	247 689 (77)	75	2 130 202	35 080	48 463
50% of high-risk start PrEP	154 639 (48)	35	1 313 908	26 766	30 448
20% of high-risk start PrEP	70 895 (22)	13	599 145	22 374	22 374
PrEP causes moderate resistance					
100% of high-risk start PrEP	157 743 (49)	79	1 368 643	57 861	59 388
50% of high-risk start PrEP	82 564 (26)	41	721 900	56 492	56 492‖
20% of high-risk start PrEP	26 446 (8)	19	241 079	78 884	Dominated

ARV = antiretroviral drug; ICER = incremental cost-effectiveness ratio; MSM = men who have sex with men; PrEP = preexposure prophylaxis; QALY = quality-adjusted life-year.

* In the base-case scenario, the daily cost of ARVs is $26, PrEP does not reduce quality of life, PrEP efficacy is 44%, the total annual cost of PrEP is $10 083, and PrEP does not cause any resistance. In the resistance scenario, average efficacy of antiretroviral therapy in reducing HIV infectivity is 85% vs. 90% in the base case, and annual cost of antiretroviral therapy is $19 000 vs. $15 589 in the base case. These strategies do not include any benefits to low-risk MSM because we did not model mixing between high-risk and low-risk MSM in the high-risk analysis.

† Undiscounted totals.

‡ Costs and QALYs are net present values (3% annual discount rate) over 20 y. Incremental costs and QALYs are relative to the status quo.

§ Relative to the next lower level of PrEP use that is not dominated by another strategy. A dominated strategy is not an efficient use of resources; thus, the next level of PrEP use would be implemented.

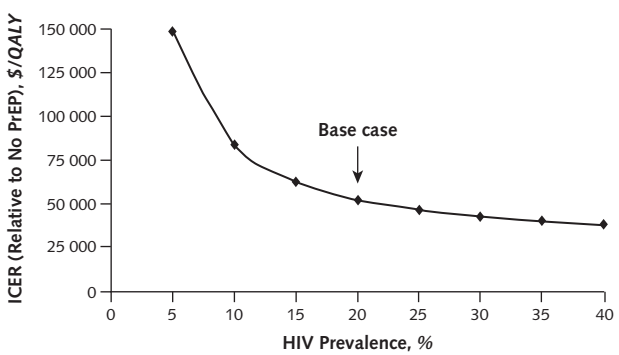
‖ The ICER of 50% PrEP is calculated relative to the status quo of no PrEP because 20% PrEP is dominated.

Appendix Table 5. Results of Sensitivity Analysis in Medium-Risk MSM*

Strategy	HIV Infections Prevented, *n (%)*†	Incremental Cost, *billion $*‡	Incremental QALYs‡	ICER, *$/QALY*	
				Relative to No PrEP	Relative to the Next Lower Level of PrEP
100% of medium-risk start PrEP	99 556 (53)	88	859 176	102 643	123 651
50% of medium-risk start PrEP	57 948 (31)	43	495 954	87 257	94 063
20% of medium-risk start PrEP	25 523 (14)	17	217 391	78 535	78 535

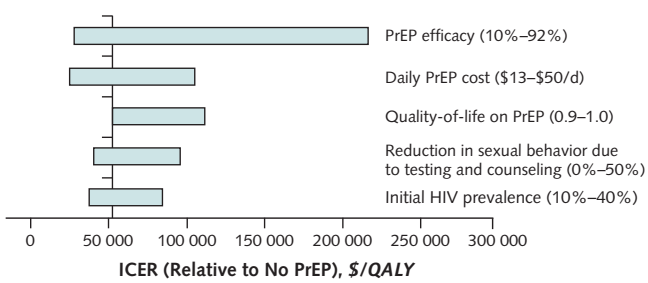
ICER = incremental cost-effectiveness ratio; MSM = men who have sex with men; PrEP = preexposure prophylaxis; QALY = quality-adjusted life-year.
* In the medium-risk scenario, initial prevalence is 15% and MSM have an average of 4 partners per year, leading to initial annual incidence of 1.3%. These strategies assume 20% of MSM are medium-risk, and they do not include any benefits to low-risk or high-risk MSM because we did not model mixing between risk groups in the risk level–specific analysis.
† Undiscounted totals.
‡ Costs and QALYs are net present values (3% annual discount rate) over 20 y. Incremental costs and QALYs are relative to the status quo.

Appendix Figure 4. ICER of PrEP for HIV prevention in all high-risk MSM as a function of HIV prevalence.



In the PrEP scenario, all high-risk MSM initiate PrEP immediately and continue PrEP for the 20-y time horizon or until they reach age 65 years. Incremental costs and QALYs used to calculate the ICER are calculated over a 20-y time horizon and are discounted to the present at 3% annually. ICER = incremental cost-effectiveness ratio; MSM = men who have sex with men; PrEP = preexposure chemoprophylaxis; QALY = quality-adjusted life-year.

Appendix Figure 5. Tornado diagram of the factors that affect the cost-effectiveness of PrEP for HIV prevention in all high-risk MSM.



The bars show the range of the ICER as each variable is varied by the range listed. The ICER in the base case, $52 443, is shown by the vertical line. In each scenario, all high-risk MSM initiate PrEP immediately and continue PrEP for the 20-y time horizon or until they reach age 65 y. Incremental costs and QALYs used to calculate the ICER are calculated over a 20-y time horizon and are discounted to the present at 3% annually. ICER = incremental cost-effectiveness ratio; MSM = men who have sex with men; PrEP = preexposure chemoprophylaxis; QALY = quality-adjusted life-year.