

A Cost-Effectiveness Analysis Of Pre-Exposure Prophylaxis For The Prevention Of HIV Among Los Angeles County Men Who Have Sex With Men

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SUMMARY OF THE ARTICLE'S MAIN POINT

This article highlights the portfolio of the most cost-effective HIV prevention strategies for different levels of spending on HIV prevention. Our findings suggest that relative to the status quo, PrEP and Test-and-Treat are highly cost-effective.

ABSTRACT

BACKGROUND

Substantial gaps remain in understanding the trade-offs between the costs and benefits of choosing alternative HIV prevention strategies, including Test-and-Treat (expanded HIV testing combined with immediate treatment), and PrEP (initiation of pre-exposure prophylaxis [PrEP] by high risk uninfected individuals) strategies.

METHODS

We develop a mathematical epidemiological model to simulate HIV incidence among men residing in Los Angeles County, CA, aged 15-65 year, who have sex with men.

We combine these incidence data with an economic model to estimate the discounted cost, effectiveness (quality-adjusted life years [QALYS]) and incremental cost-effectiveness ratios (ICERs) of various HIV prevention strategies using a societal perspective and a lifetime horizon.

RESULTS

PrEP and Test-and-Treat yield the largest reductions in HIV incidence, and are highly cost-effective (\$27863/QALY and \$19302/QALY, respectively) relative to Status Quo and at a US willingness-to-pay threshold of \$150000/QALY saved. Status Quo and twelve Test-and-Treat and PrEP strategies determine the frontier for efficient decisions.

More aggressive strategies are costlier, but more effective, albeit with diminishing returns. The relative effectiveness of PrEP is sensitive to the initial HIV prevalence rate, PrEP and ART adherence and initiation rates, the probabilities of HIV transmission, and the rates of sexual partner mixing.

CONCLUSIONS

PrEP and Test-and-Treat offer cost-effective alternatives to the Status Quo. The success of these strategies depends on ART and PrEP adherence and initiation rates. The lack of evidence on adherence behaviors toward PrEP, therefore, warrants further studies.

INTRODUCTION

The human immunodeficiency virus (HIV) infects approximately 50000 individuals each year in the United States. Although the number of new infections has remained relatively stable for the past decade [1], HIV prevalence has increased, in part owing to the longevity afforded by antiretroviral therapy (ART). However, disparities remain in the disease burden, with men who have sex with men (MSM), African Americans and the non-elderly adult population (30-64 years old) being the most afflicted groups [2].

Early detection of HIV infection followed by prompt treatment initiation and counseling, may avert secondary HIV infections. Thus, the Centers for Disease Control and Prevention (CDC) revised its guidelines in 2006 by calling for routine HIV screening in all health care settings for patients aged 13 to 64 years [3]. In 2013, the US Preventive Services Task Force also recommended HIV screening for all adolescents and adults aged 15-65 years, regardless of risk [4]. Evidence from national and international studies suggests this approach may be cost-effective [5].

Before 2010, treatment guidelines recommended ART initiation only in known HIV-positive individuals with $CD4 \leq 350$ cells/ μ L, or those with certain HIV-related

comorbidities [6, 7]. However, in 2010, the more aggressive test-and-treat policy was recommended and became widely adopted. Test-and-Treat calls for routine testing and prompt treatment start for all diagnosed cases, regardless of stage of illness [8]. Although this approach could help identify more cases and avert new infections, it may result in increased resistance to ART and could be financially burdensome [9].

Pre-exposure prophylaxis (PrEP) offers another viable strategy for preventing HIV infections in high-risk subgroups. With this strategy, high-risk uninfected individuals receive daily doses of a combination cocktail of emtricitabine (FTC) with tenofovir disoproxil fumarate (TDF), the only PrEP regimen approved by the Food and Drug Administration and currently endorsed by the World Health Organization (WHO) [10]. Recently, Los Angeles County (LAC) officials also voted to roll out PrEP to its residents with high HIV-exposure risk, following similar programs in San Francisco and New York State [11, 12].

Despite strong evidence from randomized controlled trials on the preventive efficacy of PrEP, limited evidence supports its cost-effectiveness relative to other strategies [13]. Cost-effectiveness studies of PrEP for the US MSM population offer mixed results and have limitations: Most only compared scenarios implementing PrEP with scenarios without PrEP, rather than comparing competing strategies (e.g. Test-and-Treat, Testing) [14, 15]. Others did not capture secondary infections [16-19] or resistance to ART and PrEP [20]. Finally, some did not capture the effect of ART-related adverse events [16, 17], behavioral changes induced by PrEP (e.g. decreased condom use) [17, 18] or incomplete adherence to PrEP, which could undermine the efficacy of PrEP [16].

This study assesses the potential trade-offs between choosing the Status Quo (SQ; testing with treatment initiation at $CD4 \leq 500$ cells/ μ L), Testing (expanded HIV testing),

Test-and-Treat (expanded HIV testing combined with immediate treatment), and PrEP (initiation of PrEP) strategies among the 15- to 65-year-old MSM in LAC, using a societal perspective. Similar to Juusola et al [21], we use a compartmental HIV transmission model. Our modeling approach addresses the limitations of Juusola et al and other prior work by comparing PrEP to competing prevention strategies, and by accounting for secondary infections, changes in drug resistance, and incomplete adherence.

METHODS

Epidemiological model structure

We extend the model in Sood et al [18], which reproduced the dynamics of the LAC HIV epidemic from 2000 to 2010, and simulated the effect of Testing and Test-and-Treat in the LAC MSM population beyond 2010. We use a one-year time step for each iteration of the model. Each year, new susceptible men enter the model through aging and discovery of sexual orientation, and exit the model through death. Once in the model, they can transition between health states, which comprise the uninfected ($S, SJ, SPrEP$), primary ($P_k, PPrEP_k, PJ_k, TPJ_k$), asymptomatic ($I_k, IPrEP_k, J_k, TJ_k$), symptomatic (E_k, EJ_k, T_k) and AIDS (A_k, AJ_k, TA_k) stages of HIV infection, where the subscript k denotes the drug-sensitive (s) or drug-resistant (r) strata (Figure 1). In these specifications, S, P, I, E and A denote individuals unaware of their serostatus while SJ, PJ, J, EJ and AJ denote MSM aware of their serostatus. TPJ, TJ, T and TA denote individuals treated with ART in the primary, asymptomatic, symptomatic and AIDS stages, respectively. Finally, $SPrEP, PPrEP$ and $IPrEP$ denote PrEP adopters in the uninfected, primary and asymptomatic stages.

In the model, individuals are offered HIV testing at specified rates, based on current programs or more aggressive strategies. Starting in 2013, uninfected MSM can initiate PrEP at specified rates of uptake, adherence, and efficacy in preventing HIV infection. We estimate that 12% of susceptible MSM are eligible for PrEP (as determined by high-risk behaviors) [10] and we assume in our base case analysis that 10% of uninfected MSM and 25% of MSM adopt PrEP (Tables 1-2) [22]. Newly diagnosed men are offered ART at specified rates of uptake and adherence.

A detailed description of this model and its calibration to the LAC HIV epidemic is provided in Sood et al [23, 24] and in the Appendix (Section 2). This population-level model can capture secondary infections and predict the population-level effects of various HIV interventions. We use the model to simulate the HIV epidemic in the LAC MSM population under 623 alternative strategies consisting of variants and combinations of the Testing, Test-and-Treat, and PrEP strategies, whereby the intensity of testing, ART coverage and PrEP uptake are changed (Table S20).

Economic model structure

We use the estimates of new infections and the annual populations in each compartment as inputs for our economic model which estimates the total discounted costs, QALYs, and the incremental cost-effectiveness ratio (ICER) of the 623 alternative strategies simulated with the epidemic model. We adopt a US societal perspective [10].

Starting in 2013, and for each policy scenario, we simulate the annual number of MSM in each health state over a lifetime horizon. Next, we multiply the estimated population in each health state and each year by their associated annual costs and QALYs to obtain the total lifetime costs and QALYs and use a 3% annual discount rate to calculate discounted costs and QALYs [25]. Finally, for each pair of strategies compared,

we compute the incremental discounted costs and QALYs to calculate the corresponding ICER. We also calculate sequential ICERs [25] and trace the cost-effectiveness frontier, which represents strategies that achieve the maximum effectiveness for a given value of societal costs.

We implement both epidemiological and economic models in the R programming package [26].

INPUT DATA

We derive the initial population data from Sood et al [27], the LAC annual HIV surveillance reports and the RAND California Population and Demographics database. Our methodology for estimating the compartment-specific populations follows Sood et al [10] (Appendix Section 2.2). Average age group life expectancy estimates for the uninfected and HIV-positive males are derived from CDC life tables (Tables S3-S4). We obtain epidemic parameters (e.g. HIV transmission rates, parameters associated with HIV natural history, HIV testing rates, ART and PrEP initiation and discontinuation rates, ART and PrEP efficacy) from Sood et al [10] and from a systematic review of the evidence on HIV treatment and prevention (Appendix: Sections 2.4 and 6).

We derive health state specific costs and effectiveness parameters for the economic model from the published literature and from government fee schedules (Appendix: Sections 3 and 6). Using these estimates, we calculate the annual costs for the health states to include goods and services involved in the delivery of medical care, such as physician visits, drugs (ART and PrEP regimens), management of opportunistic infections, tests for HIV (eg, enzyme immunoassay [EIA]; enzyme-linked immunosorbent assay [ELISA]; rapid HIV test; confirmatory testing using nucleic acid

amplification testing [NAAT]), STIs, serum BUN and creatinine levels; CD4 count and viral load monitoring; and pretest and posttest counseling, and linkage to care. We convert all health care prices into 2013 US dollars assuming 9% annual increase in health care prices [10]. We exclude direct nonmedical costs, i.e., those incurred beyond the health care setting (eg, transportation costs, other out-of-pocket expenses, resources from other agencies) because they are small and likely similar across the assessed alternatives [25]. Indirect costs associated with informal caregiver support and unpaid help by family and friends are calculated using estimated average home health care costs [25], as well as estimates of AIDS patients' home care utilization [28], weighted by the national average hourly compensation rates of home health and personal care aides [29]. Other indirect costs related to the value of the individual's forgone (or gained) productivity attributable to the illness-related morbidity and mortality, are measured in utility and captured by the QALY estimates [30].

We calculate the health state QALYs by multiplying the health-state-adjusted average health-related quality of life score (HRQOL) with the number of MSM in that health state (Appendix: Section 3.2.4, Equation 81) [31]. The QALY and HRQOL score estimates are obtained from the published literature (Appendix: Section 3.2, Tables S17-S18). All demographic, costs and effectiveness parameters are summarized in Table 2 and described in the Appendix (Table S19).

RESULTS

Efficient strategies

SQ and 12 of the 623 strategies assessed determine the cost-effectiveness frontier and consist of variants of the Test-and-Treat and PrEP strategies (Table 3 and Figure 2),

but exclude all Testing strategies which are extendedly dominated (have a higher ICER than the next more effective alternative strategy) or strongly dominated (have higher costs and lower effectiveness than the alternative strategy).

The cost-effectiveness frontier represents the range of strategies yielding the maximum value (lowest cost per health benefit) relative to SQ for a defined resource allocation to HIV treatment and prevention. For example, with a \$46 billion budget constraint, Test-and-Treat (Figure 2: strategy 2; hereafter, the reader should refer to Figure 2 for any mention of strategy 2-13 in parentheses) is optimal. However, with \$55 billion, strategies 2-6 are all optimal interventions, meaning that implementing strategies 2-6 in that order until the budget is exhausted would yield the maximum societal value.

Table 3 and Figure 2 indicate that the least costly efficient strategy relative to SQ is the Test-and-Treat strategy (strategy 2) which costs \$19302/QALY gained, and is highly cost-effective at the current US willingness-to-pay threshold of \$150000/QALY gained [18]. Test-and-Treat extendedly dominates strategies that combine SQ with less aggressive early treatment or HIV testing (e.g. early ART start every month, HIV testing every 4 years combined with early ART start every 6 months; Table 3). Test-and-Treat is followed by 4 Test-and-Treat strategies enhanced with HIV testing every 3 years, 2 years, 1 year, and 6 months (strategies 3-6). Relative to the preceding rational strategy on the frontier and to SQ, all 4 Enhanced Test-and-Treat strategies are highly cost-effective. For example, relative to Test-and-Treat, Test-and-Treat enhanced with HIV testing every 3 years (strategy 3) would cost \$20451/QALY gained. Similarly, the most aggressive enhanced Test-and-Treat strategy on the frontier (strategy 6) would cost \$25654/QALY relative to Test-and-Treat, and \$38492/QALY relative to Test-and-Treat enhanced with annual testing (strategy 5).

The most aggressive and optimal Enhanced Test-and-Treat strategy (strategy 6) is followed by the PrEP strategy, which combines Test-and-Treat with HIV testing every 6 months and PrEP start every 4 years (strategy 7). PrEP would cost \$27863, \$29492 and \$63269/QALY relative to SQ, Test-and-Treat, and Test-and-Treat enhanced with HIV testing every 6 months, respectively. PrEP is followed by 3 PrEP strategies enhanced with PrEP start every 3, 2 and 1.2 years (strategies 8-10), as well as 3 PrEP strategies enhanced with HIV testing every 3 months, and PrEP start every 2 years, 1.2 years, and immediately (strategies 11-13). Relative to the prior rational PrEP strategies on the frontier, 4 enhanced PrEP strategies (strategies 8-11) are cost effective and would cost \$85117, \$104788, \$139346 and \$145956/QALY, respectively (Table 3). The two remaining enhanced PrEP strategies (strategies 12-13) are cost-ineffective relative to the preceding rational enhanced PrEP strategy on the frontier (\$188714 and \$234726/QALY, respectively). All enhanced PrEP strategies are highly cost effective relative to SQ (\$28529, \$29633, \$31045, \$32033, \$33429 and \$37181/QALY, respectively; Table S20) and Test-and-Treat (\$30261, \$31538, \$33178, \$34321, \$35942 and \$40292/QALY, respectively). Relative to PrEP, all enhanced PrEP strategies (except for strategy 13 which costs \$155770/QALY) are also cost effective (\$85117, \$96088, \$110557, \$117064, \$128622/QALY, respectively).

Collectively, these results suggest that the most aggressive strategies are more expensive and more effective, albeit with diminishing returns, as indicated by the curvature of the frontier (Figure 2). However, relative to SQ, even the most aggressive intervention (strategy 13) remains highly cost-effective. The results also support the hypothesis that PrEP and Test-and-Treat are cost-effective alternatives to SQ. This likely

owes to the preventive benefits of PrEP and the survival gains from early diagnosis and prompt ART initiation.

Epidemiological outcomes

Our simulation indicates that the SQ approach would yield a cumulative HIV incidence of 99874 cases. Relative to this figure, Test-and-Treat (strategy 2) and PrEP (strategy 7) would respectively avert 4332 (4.3%) and 58881 (59.0%) new infections (Table S19). The most aggressive Enhanced Test-and-Treat strategy (Test-and-Treat enhanced with annual HIV testing; strategy 6) would avert 47759 (47.8%) infections relative to SQ. The most aggressive Enhanced PrEP strategy (strategy 13) would avert 77301 (77.4%) infections relative to SQ.

Sensitivity analyses

We conduct several sensitivity analyses to assess the effect of uncertainty in our model parameter values on the ICERs. First, we conduct a series of 1-way sensitivity analyses by varying each parameter value one at a time within the uncertainty ranges of the parameters. Second, we conduct a probabilistic sensitivity analysis by simultaneously varying all parameter values within their uncertainty ranges. We sample policy and effectiveness (QOL) parameters according to a program evaluation and review technique (PERT) distribution [32]. Cost parameters are sampled following a lognormal distribution to account for the skewed and fat-tail nature of cost data [33]. Other parameters are sampled following a normal or uniform distribution. We independently sampled all parameters throughout the analysis. All ICERs remain robust to perturbations of the epidemic, cost, and effectiveness parameter values (Appendix: Sections 5.1-5.3, Figures

S4-S7 and S9-S18). Sexual mixing and transmission parameters, intensity of testing, rates of adherence to the treatment regimen, and initiation of PrEP and ART are significant modulators of the ICERs. These findings agree with prior studies on the benefits of adherence to ART in reducing viral load and the risk of resistance to ART [34].

Third, we conduct a sensitivity analysis of the ICERs to changes in the initial HIV prevalence rates (Figure S8 and Table S24) and find that the ICERs are highly sensitive to assumptions about the initial HIV prevalence rate: ICERs for Test-and-Treat (strategy 2) ranged between \$19769 and \$19158 per QALY gained as the initial HIV prevalence rate varied from 5% to 40%; the corresponding range for the PrEP strategy (strategy 6) was \$40077–\$27029/QALY gained. Assuming a 12.3% initial HIV prevalence rate in 2013 as in Juusola et al, our ICERs estimates for the Test-and-Treat strategies (strategies 2-6) would range between \$19427 and \$26051 per QALY gained relative to SQ; the corresponding ICER range for the PrEP strategies (strategies 7-13) would be \$30812–\$45921/QALY gained.

Finally, we assess the effect of ART and PrEP price reductions on the ICERs. Several studies showed that the expiration of a brand-name drug patent leads to price reductions between 20% and 70% of the brand-name product price [35]. Our sensitivity analysis in this range of price reduction suggests that all cost-effectiveness profiles improve with generic entry (Figures S19-S20). The 95% simulation intervals are relatively narrow, suggesting robustness of the ICERs. For example, relative to SQ, the ICERs for Test-and-Treat (strategy 2) improve to \$18162, \$16452 and \$15312 per QALY saved, while those for the PrEP strategy (strategy 7) improve to \$26671, \$24883 and \$23690/QALY gained, as the annual price of PrEP declines by 20%, 50% and 70%, respectively. Relative to the prior efficient strategy and for a similar decline in the cost of

PrEP, the ICERs for the PrEP strategy (strategy 7) improve to \$62333, \$60928 and \$59992 per QALY gained.

DISCUSSION

Our study suggests that PrEP and Test-and-Treat constitute cost-effective HIV prevention alternatives to SQ, and that relative to SQ, the most efficient PrEP strategies could cost \$27863-\$37181/QALY gained, whereas the Test-and-Treat strategies could cost \$19302-\$24544/QALY gained. These results are consistent with the Desai et al [36] finding that PrEP for the New York City high-risk MSM would cost \$32000/QALY. They differ, however, from the Juusola et al [17] estimates of \$50000/QALY in high-risk MSM. They also differ from the Koppenhaver et al [18] estimates of \$353739 and \$570273 per QALY gained among highly adherent MSM (i.e. taking >90% of PrEP doses [pill counts]) and in the overall population, respectively, at universal PrEP coverage. These discrepancies likely owe to differences in modeling assumptions and epidemic trends in the study settings. For example, initial HIV prevalence in our study (LAC MSM; 24.1% in 2010 and 24.6% in 2013) is nearly double that in Juusola et al (US MSM; 12.3% in 2010). Indeed, in sensitivity analysis, these differences account for a significant portion of the discrepancy between the ICERs of the two studies (Figure S8 and Table S24). Likewise, differences in initial HIV prevalence (17.5% vs 24.6%) and the assumptions about PrEP coverage (universal vs 10% coverage) likely explain the discrepancy between the ICERs in Koppenhaver et al and our study.

This study has several limitations. First, our model assumes a proportional sexual mixing, but this assumption might be unrealistic [16]. Our robustness analysis mitigates this limitation by accounting for the effects of variations in the mixing rates on the

ICERs. Second, our model accounts for neither MSM injection-drug users nor those with female partners. An explicit accounting for these individuals might affect the sexual mixing rates and transmission parameters, although with marginal effect on our ICERs. Third, the HRQOL estimates in the study were developed using the widely used EQ-5D instrument. Because QOL estimates are sensitive to the instrument used, our ICERs may be affected [37]. However, the sensitivity analysis mitigates this threat because the estimates remained robust to variations in QOL weights.

Our results support prior findings that PrEP can be cost-effective in highly concentrated epidemic settings even when a richer set of alternate HIV policies are evaluated [38]. However, the optimal strategy depends on the costs society is willing to incur for HIV prevention. With constrained budgets Test-and-Treat is the optimal policy and with less constrained budgets Test-and-Treat combined with PrEP is the optimal policy. Overall these results help policymakers and public health officials choose the optimal HIV prevention strategy given their budget constraints. The results also support the recent LAC, WHO and US officials' endorsement of PrEP, as well as New York Governor Cuomo's call for a statewide adoption of the strategy [39]. However, our results also suggest that even the most aggressive cost-effective HIV prevention strategy is unlikely to eliminate the HIV epidemic. The success of these strategies depends on the uptake of and adherence to treatment. The lack of evidence on behavioral responses to PrEP, therefore, warrants further studies.

NOTES:**AUTHOR'S CONTRIBUTIONS**

Drabo, Hay, Sood, Wagner, and Vardavas had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Drabo, Hay, Sood, Wagner, Vardavas.

Acquisition of data: Drabo, Wagner.

Analysis and interpretation of data: Drabo, Hay, Sood, Vardavas.

Drafting of the manuscript: Drabo, Sood.

Critical revision of the manuscript for important intellectual content: Hay, Sood, Drabo.

Statistical analysis: Drabo, Hay, Sood.

Administrative, technical, or material support: Drabo, Hay, Sood, Wagner, Vardavas.

Study supervision: Hay, Sood.

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CONFLICT OF INTEREST DISCLOSURES

None

DISCLAIMER

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FIGURE LEGENDS

Figure 1. Schematics of the HIV model.

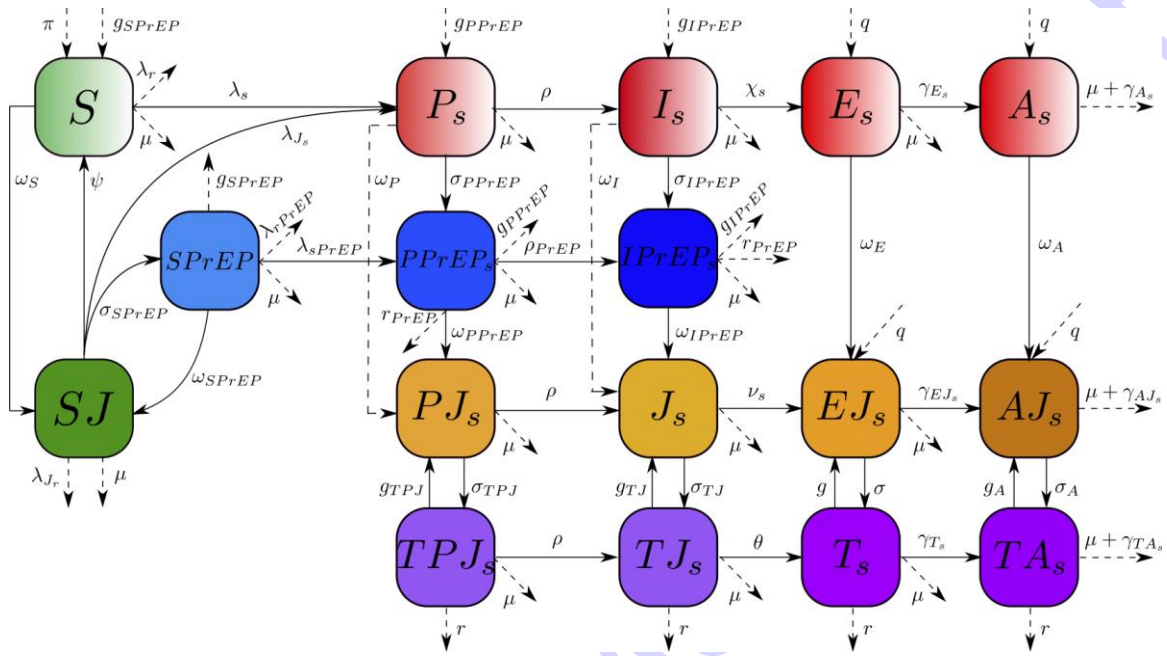
Individuals enter the model through aging and discovery of sexual orientation at an annual rate π . Once in the model, they can transition between health states, which comprise the uninfected ($S, SJ, SPrEP$), primary ($P_k, PPrEP_k, PJ_k, TPJ_k$), asymptomatic ($I_k, IPrEP_k, J_k, TJ_k$), symptomatic (E_k, EJ_k, T_k), and AIDS (A_k, AJ_k, TA_k) stages of HIV infection, where the subscript k denotes the drug-sensitive (s) or drug-resistant (r) strata. S, P, I, E and A denote the populations of individuals unaware of their serostatus; SJ, PJ, J, EJ and AJ denote individuals aware of their serostatus through testing. TPJ, TJ, T and TA denote individuals treated with ART in the primary, asymptomatic, symptomatic and AIDS stages, respectively. Finally, $SPrEP, PPrEP$ and $IPrEP$ denote individuals using PrEP in the uninfected, primary and symptomatic stages. At any stage in the model, individuals can exit the model through death at a natural death rate μ , or from HIV/AIDS complications ($\gamma_{A_k}, \gamma_{AJ_k}$ or γ_{TA_k}). Estimates of parameters and data sources entering the model are provided in Table 2 and in Table S19 of the Appendix, and are discussed in the Methods section. The directed arrows denote the transition of men between health states; the associated transition rates are denoted by the adjacent symbols to the arrows, and are defined in Table 2 and in Table S1 of the Appendix.

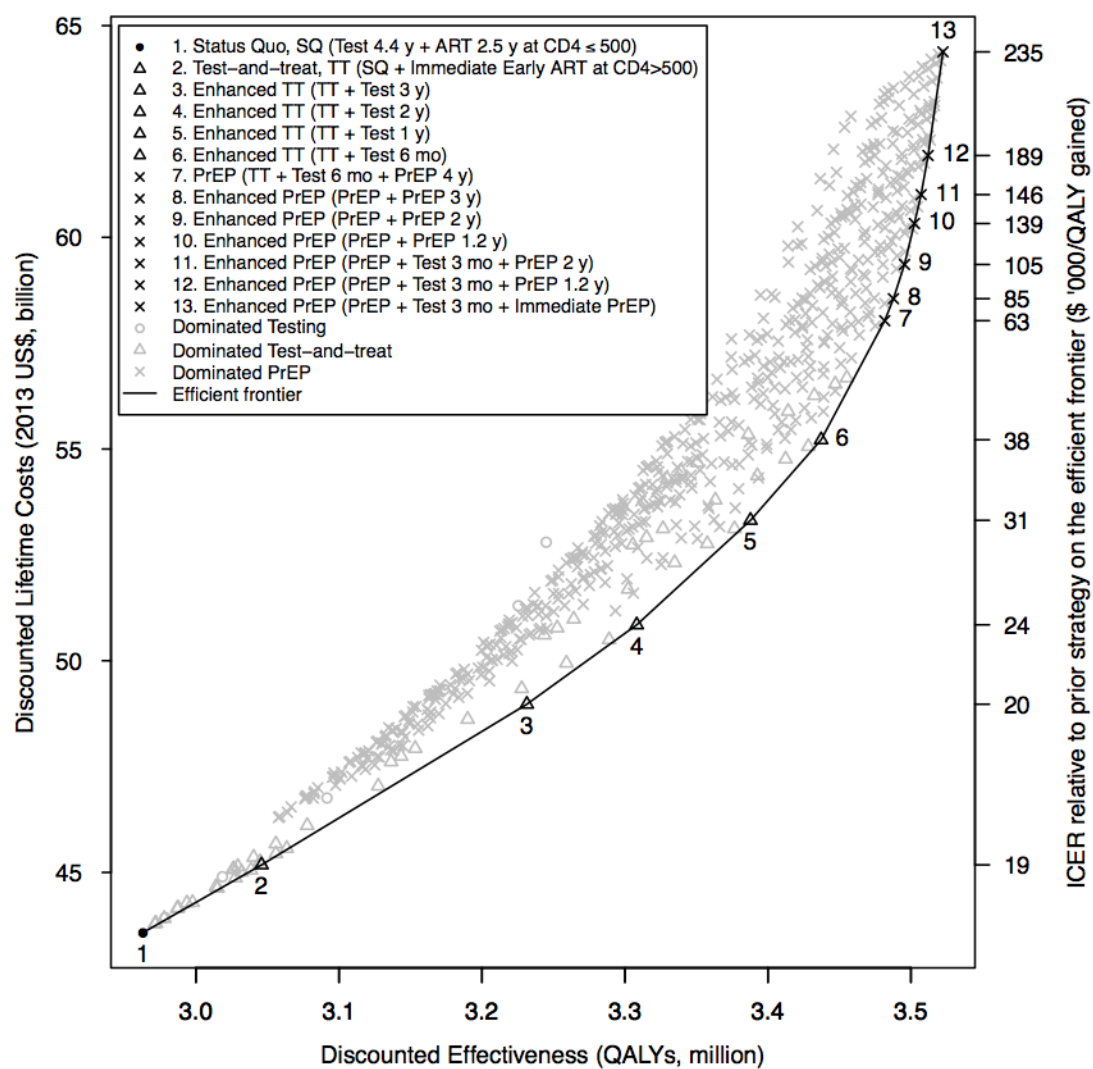
Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; PrEP, pre-exposure prophylaxis; ART, antiretroviral therapy.

Figure 2. Efficient frontier for resource allocation.

The efficient frontier, indicated by the solid black line, denotes strategies that yield the highest value (lowest cost per QALYs gained) for a defined level of societal willingness to pay. It can be used to determine how much health benefits are obtainable from the resources used by a specific clinical intervention and under a given budget constraint.

Points on the efficient frontier (strategies 1-13) are cost-effective; the grey points to the left of the efficient frontier indicate strongly and extendedly dominated alternative strategies, which are variants or combinations of the testing, test-and-treat, and PrEP strategies, whereby the frequencies of testing, ART coverage and/or PrEP uptake are varied (these strategies are listed in Table S20 in the Appendix). Positive gradients (e.g. between points 3 and 4) reflect the ICERs of each strategy on the frontier relative the prior strategy on the frontier (i.e. additional costs for increased health benefits), and are captured by the values on the right-hand side y-axis (e.g. \$24394/QALY gained between points 3 and 4). Abbreviations: y, year; mo, month; SQ, Status Quo; ART, antiretroviral therapy; TT, test-and-treat; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.





TABLES

Table 1. Base Case Model Assumptions

| Parameter | Status Quo | Testing | Test-and-Treat | PrEP |
|---|------------------------|------------------------|------------------------|------------------------|
| HIV testing rate (Frequency) | 0.227 (Every 4.4 y) | 1.000 (Annually) | 0.500 (Every 2 y) | 0.500 (Every 2 y) |
| Blood urea nitrogen concentration, serum creatinine levels, and STI testing frequency | - | - | - | Every 3 mo |
| ART initiation rate at CD4≤500 cells/μL (frequency) | 0.404 (Every 2.5 y) | 0.404 (Every 2.5 y) | 0.404 (Every 2.5 y) | 0.404 (Every 2.5 y) |
| Early ART initiation rate | - | - | Immediate | Immediate |
| PrEP initiation rate | - | - | - | 0.250 (Every 4 y) |
| ART and PrEP adherence rates | 0.282 | 0.282 | 0.282 | 0.282 |
| ART and PrEP discontinuation rates | 0.116 | 0.116 | 0.116 | 0.116 |
| Reduction in risky sexual behavior owing to testing and counseling | - | - | - | 0.200 |
| Reduction sexual infectivity owing to ART | 0.900 | 0.900 | 0.900 | 0.900 |
| Reduction sexual infectivity owing to PrEP | - | - | - | 0.920 |
| Reduction in risk of infection owing to PrEP | - | - | - | 0.440 |

Table 2. Summary of Key Model Input Parameters

| Parameters | Value | Range |
|---|---------|----------------|
| Epidemic Parameters | | |
| <i>Demographic Parameters</i> | | |
| π : Annual inflow of susceptible individuals | 3 597 | 3 143–3 825 |
| μ : Natural rate of death | 0.0004 | 0.0003–0.0004 |
| <i>HIV Transmission Parameters</i> | | |
| C_{mix} : Sexual mixing rate | 4.5046 | 2.2798–8.4753 |
| $\lambda_s = \lambda_{J_s}$: Transmission rate for the aware and unaware susceptible populations not receiving PrEP (drug sensitive) | Varies | - |
| $\lambda_r = \lambda_{J_r}$: Transmission rate for the aware and unaware susceptible populations not receiving PrEP (drug resistant) | Varies | - |
| λ_{PrEP_s} : Transmission rate for the susceptible populations treated with PrEP (drug sensitive) | Varies | - |
| λ_{PrEP_r} : Transmission rate for the susceptible populations treated with PrEP (drug resistant) | Varies | - |
| <i>Disease Progression</i> | | |
| $\rho = \rho_{PrEP}$: Progression rate from the primary to the asymptomatic HIV stage | 11.0136 | 6.7713–22.1852 |
| $\chi_s = \chi_r$: Progression rate from asymptomatic to untreated symptomatic HIV (unaware HIV+ individuals) ^a | 0.3200 | 0.2501–0.8302 |
| $\nu_s = \nu_r$: Progression rate from asymptomatic to untreated symptomatic HIV (aware HIV+ individuals) | 0.3200 | 0.000–0.8302 |
| θ : Rate of disease progression from the treated asymptomatic HIV stage to the treated symptomatic HIV stage | 0.1949 | 0.1158–1.7500 |
| $\gamma_{EJ_s} = \gamma_{E_s}$: Progression rate to AIDS in treatment-eligible individuals (drug-sensitive strata) | 0.6658 | 0.2674–0.6693 |
| $\gamma_{EJ_r} = \gamma_{E_r}$: Progression rate to AIDS in treatment-eligible individuals (drug-resistant strata) | 1.3080 | 0.5314–1.3386 |
| γ_{T_s} : Progression rate to AIDS in ART-treated individuals | 0.0777 | 0.0468–0.0875 |
| γ_{T_r} : Progression rate to AIDS in ART-treated individuals | 0.1947 | 0.1045–0.5370 |
| <i>HIV/AIDS-related Mortality</i> | | |
| $\gamma_{AJs} = \gamma_{A_s}$: Untreated individuals with AIDS (drug sensitive) | 0.5427 | 0.5093–7.8389 |
| $\gamma_{AJ_r} = \gamma_{A_r}$: Untreated individuals with AIDS (drug resistant) | 1.7016 | 1.1098–19.8800 |
| γ_{TA_s} : ART-treated individuals with AIDS (drug sensitive) | 0.1187 | 0.0795–0.4120 |
| γ_{TA_r} : ART-treated individuals with AIDS (drug resistant) | 0.4891 | 0.1643–0.8296 |
| <i>Screening and Counseling</i> | | |
| $1/\psi$: Average duration of identification for susceptible individuals | 1.0000 | 0.5000–3.0000 |
| ω_{S-J} : Rate of identification for susceptible individuals | Varies | - |
| $\omega_{SPrEP-SJ}$: Rate of HIV testing in susceptible individuals discontinuing PrEP | Varies | - |
| ω_{P-PJ} : Rate of serostatus identification for non-PrEP users in the primary disease stage | Varies | - |
| $\omega_{PPrEP-PJ}$: Rate of serostatus identification for PrEP users in the primary disease stage | Varies | - |
| ω_{I-J} : Rate of serostatus identification for non-PrEP users in the asymptomatic disease stage | Varies | - |
| $\omega_{IPrEP-J}$: Rate of serostatus identification for PrEP users in the asymptomatic disease stage | Varies | - |
| Parameters | Value | Range |

| | | |
|--|--------------|----------------|
| ω_{E-EJ} : Rate of serostatus identification for individuals in the symptomatic disease stage | Varies | - |
| ω_{A-AJ} : Rate of serostatus identification for individuals in the AIDS stage | Varies | - |
| τ_C : Reduction in risky sexual behavior owing to testing and counseling | 0.2000 | 0.0000–0.5000 |
| ART and PrEP | | |
| σ : ART initiation rate in HIV+ individuals without AIDS | 0.4040 | 0.3353–6.8907 |
| σ_{SPrEP} : PrEP initiation rate in the susceptible population | 0.0987 | 0.0888–0.1098 |
| σ_{PPrEP} : PrEP initiation rate by unaware HIV+ individuals in the primary stage of infection | Varies | - |
| σ_{IPrEP} : PrEP initiation rate by unaware HIV+ individuals in the asymptomatic stage of infection | Varies | - |
| $\sigma_{TPJ} = \sigma_{TJ}$: ART initiation rate by identified (aware) HIV+ individuals in the asymptomatic stage of infection | 365 | 0.0000–365 |
| σ_A : ART initiation rate in individuals with AIDS | 10.8637 | 0.6766–20.6688 |
| $g = g_{SPrEP} = g_{PPrEP} = g_{IPrEP} = g_{TPJ} = g_{TJ}$: ART discontinuation rate in HIV+ individuals without AIDS | 0.1160 | 0.0234–0.1576 |
| g_A : ART discontinuation rate in individuals with AIDS | 0.0314 | 0.0024–0.0774 |
| τ_{ART} : Reduction in sexual infectivity owing to ART | 0.9000 | 0.5000–0.9900 |
| τ_{PrEP} : Reduction in sexual infectivity owing to PrEP | 0.9200 | 0.5000–0.9900 |
| Resistance | | |
| $r = r_{TJ}$: Rate of acquired MDR | 0.0278 | 0.0061–0.0535 |
| r_{PrEP} : Rate of acquired MDR in PrEP users | 0.0000 | 0.0000–0.0161 |
| h_r : MDR transmissibility multiplicative factor | 0.1232 | 0.1000–0.1756 |
| q : Rate of mutation from acquired resistant to the drug sensitive strain | 0.0043 | 0.0006–0.0307 |
| Cost Parameters | | |
| Annual HIV-related Health Care Costs (\$) | | |
| Acute HIV ^b | 30 | 10–500 |
| Asymptomatic HIV-untreated ^b | 4 130 | 3 000–6 000 |
| Symptomatic HIV-untreated ^b | 6 934 | 5 000–9 000 |
| Symptomatic HIV-treated with ART, excluding ART costs ^b | 6 181 | 5 000–7 000 |
| AIDS untreated ^{b,c} | 21 863 | 15 000–25 000 |
| AIDS-treated with ART, excludes ART costs ^{b,c} | 9 950 | 6 000–17 000 |
| Annual cost of antiretroviral therapy (ART) ^b | 15 000 | 13 520–17 109 |
| Cost of PrEP (cost per test, refill, or visit; \$) | | |
| PrEP (tenofovir, TDF/emtricitabine, FTC): 30-d supply ^b | 776 | 672–925 |
| STI testing: cost per test ^b | 54 | 25–75 |
| Blood urea nitrogen concentration and serum creatinine level testing: cost per test ^b | 23 | 10–40 |
| Physician visit: cost per visit ^b | 100 | 10–200 |
| Cost of HIV Testing (cost per test; \$) | | |
| Cost of initial test: 3rd/4th generation test (EIA/ELISA; CPT 86703, G0432, G0433, 87389) or rapid HIV test (CPT G0345) ^d | 19 | 9–45 |
| Parameters | Value | Range |
| Cost of confirmatory testing or HIV RNA test (NAAT test for HIV RNA; CPT 87535) ^d | 48 | 16–158 |
| Cost of CD4 cell count monitoring (CPT 86359, 86360, 86361) ^d | 52 | 10–87 |
| Cost of HIV genotype test (CPT 87901, 87906) ^d | 177 | 54–239 |
| Cost of Counseling (cost per visit; \$) | | |

| | | |
|---|--------|---------------|
| Pretest counseling ^b | 13 | 0–100 |
| Posttest counseling for HIV negative individuals ^b | 7 | 0–50 |
| Posttest linkage/counseling for HIV-positive individuals ^b | 14 | 0–100 |
| <i>Other Costs and Cost-related Parameters</i> | | |
| Cost of HIV diagnosis (\$) ^b | 500 | 125–1200 |
| Annual cost discount rate | 0.0300 | 0.0000–0.0500 |
| 2013 to 2010 inflation factor | 1.0900 | - |
| <i>Effectiveness Parameters</i> | | |
| <i>Disease State QOL Utility Weights</i> | | |
| Uninfected (no PrEP) | 1.0000 | - |
| Uninfected (PrEP) | 1.0000 | 0.9000–1.0000 |
| Acute HIV, unidentified | 0.9200 | 0.7300–0.9700 |
| Acute HIV, identified | 0.8600 | 0.6800–0.9100 |
| Acute HIV, treated with ART | 0.8800 | 0.6800–0.9400 |
| Asymptomatic HIV, unidentified | 0.9100 | 0.8500–0.9500 |
| Asymptomatic HIV, identified (Year 1) | 0.8400 | 0.8400–0.9500 |
| Asymptomatic HIV, identified (Year 2+) | 0.8900 | 0.8500–0.9500 |
| Asymptomatic HIV, treated with ART | 0.9100 | 0.8500–0.9500 |
| Symptomatic HIV, unidentified | 0.8000 | 0.7000–0.8000 |
| Symptomatic HIV, identified | 0.7200 | 0.7000–0.8000 |
| Symptomatic HIV, treated with ART | 0.8300 | 0.7800–1.0000 |
| AIDS, unidentified | 0.7200 | 0.2400–0.8000 |
| AIDS, identified | 0.7200 | 0.6000–0.7500 |
| AIDS-treated with ART | 0.8200 | 0.8200–0.8700 |
| <i>Other Effectiveness Parameters</i> | | |
| QOL decrement factor for false-positive result | 0.1200 | 0.0000–0.4800 |
| QOL decrement factor owing to resistance to ART or PrEP | 0.0000 | 0.0000–0.0100 |
| Annual QOL discount rate | 0.0300 | 0.0000–0.0500 |

Note: Disease state QOL utility weights are age-unadjusted. Values are indicated by the mention “varies” whenever the parameter estimate varies with time or the scenario; details on parameter calculations are provided in the Supplemental Appendix (Section 1.4). References for the estimates and their ranges are provided in Appendix (Table S19).

^a Estimate based on the 2011 treatment guidelines. Prior to 2011, the estimate used is 0.1700 (range, 0.1450–0.1956).

^b Year 2013 US dollars.

^c Inclusive of informal support costs.

^d Year 2010 US dollars.

Table 3. Benefits and Costs of the Most Cost-effective Test-and-treat and PrEP Strategies for 20 Years in the LAC MSM Population

| Rational Decision on the Efficient Frontier | Discounted ^a | | Incremental Values Relative to Prior Rational Decision | | | Extendedly Dominated Strategies ^b |
|---|--------------------------|------------------|--|---------|---------------|---|
| | Cost, 2013 \$ (billions) | QALYs (millions) | Costs, 2013 \$ (billions) | QALYs | ICER, \$/QALY | |
| Status Quo (SQ) ^c | 43.58 | 2.96 | - | - | - | - |
| Test-and-treat, TT (SQ + Immediate Early ART ^d) | 45.18 | 3.05 | 1.60 | 82 915 | 19 302 | SQ + Test 4 y SQ + Early ART 1 mo SQ + Test 4 y + Early ART 6 mo |
| Enhanced TT (TT + Test 3 y) | 48.97 | 3.23 | 3.79 | 185 522 | 20 451 | Enhanced TT (TT + Test 4 y) Enhanced TT (TT + Test 2 y) TT + Test 4 y + PrEP 3 y |
| Enhanced TT (TT + Test 2 y) | 50.85 | 3.31 | 1.88 | 76 882 | 24 394 | SQ + Test 2 y + Early ART 3 mo SQ + Test 2 y + Early ART 1 mo |
| Enhanced TT (TT + Test 1 y) | 53.32 | 3.39 | 2.47 | 79 527 | 31 036 | SQ + Test 1 y + Early ART 3 mo SQ + Test 1 mo + Early ART 3 mo TT + Test 3 y + PrEP 2 y |
| Enhanced TT (TT + Test 6 mo) | 55.22 | 3.44 | 1.90 | 49 415 | 38 492 | SQ + Test 6 mo + Early ART 1 mo TT + Test 2 y + PrEP 2 y |
| PrEP (TT + Test 6 mo + PrEP 4 y) | 58.03 | 3.48 | 2.81 | 44 457 | 63 269 | SQ + Test 1 y + Early ART 1 mo + PrEP 3 y TT + Test 1 y + PrEP 2 y |
| Enhanced PrEP (PrEP + PrEP 3 y) | 58.55 | 3.49 | 0.52 | 6 111 | 85 117 | SQ + Test 3 mo + Early ART 1 mo + PrEP 3 y |
| Enhanced PrEP (PrEP + PrEP 2 y) | 59.36 | 3.50 | 0.81 | 7 707 | 104 788 | SQ + Test 6 mo + Early ART 1 mo + PrEP 2 y |
| Enhanced PrEP (PrEP + PrEP 1.2 y) | 60.33 | 3.50 | 0.97 | 6 945 | 139 346 | Enhanced PrEP (PrEP + Test 3 mo + PrEP 4 y) Enhanced PrEP (PrEP + Test 3 mo + PrEP 3 y) |
| Enhanced PrEP (PrEP + Test 3 mo + PrEP 2 y) | 61.01 | 3.51 | 0.68 | 4 676 | 145 956 | Enhanced PrEP (PrEP + PrEP 1.2 y) |
| Enhanced PrEP (PrEP + Test 3 mo + PrEP 1.2 y) | 61.93 | 3.51 | 0.92 | 4 892 | 188 714 | Enhanced PrEP (PrEP + PrEP 6 mo) |
| Enhanced PrEP (PrEP + Test 3 mo + Immediate PrEP) | 64.38 | 3.52 | 2.45 | 10 429 | 234 726 | Enhanced PrEP (PrEP + Immediate PrEP) |

Abbreviations: y, year; mo, month; SQ, status quo; ART, antiretroviral therapy; TT, test-and-treat; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year.

^a Discounted at 3% annual discount rate

^b Only includes selected extendedly dominated strategies due to spacing. The complete list of the extendedly dominated strategies is provided in Table S23 of the Appendix

^c Test 4.4 y + ART 2.5 y at CD4≤500

^d Early ART defined as ART start at CD4>500