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HIV/AIDS

A Cost-effectiveness Analysis of Preexposure Prophylaxis for the Prevention of HIV Among Los Angeles County Men Who Have Sex With Men

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(See the Editorial Commentary by Mayer and Krakower on pages 1505–7.)

Background. Substantial gaps remain in understanding the trade-offs between the costs and benefits of choosing alternative human immunodeficiency virus (HIV) prevention strategies, including test-and-treat (expanded HIV testing combined with immediate treatment) and PrEP (initiation of preexposure prophylaxis by high-risk uninfected individuals) strategies.

Methods. We develop a mathematical epidemiological model to simulate HIV incidence among men residing in Los Angeles County, California, aged 15–65 years, 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 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 ($27 863/QALY and $19 302/QALY, respectively) relative to status quo and at a US willingness-to-pay threshold of $150 000/QALY saved. Status quo and 12 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 antiretroviral therapy (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.

Keywords. cost-effectiveness; HIV; PrEP; preexposure prophylaxis; test-and-treat.

The human immunodeficiency virus (HIV) infects approximately 50 000 individuals each year in the United States [1]. Although the number of new infections has remained relatively stable for the past decade [2], 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 nonelderly adult population (30–64 years of age) being the most afflicted groups [3].

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 healthcare settings for patients aged 13–64 years [4]. In 2013, the US Preventive Services Task Force also recommended HIV screening for all adolescents and adults aged 15–65 years, regardless of risk [5]. Evidence from national and international studies suggests this approach may be cost-effective [6, 7].

Before 2010, treatment guidelines recommended ART initiation only in known HIV-infected individuals with a CD4 count ≤350 cells/μL, or those with certain HIV-related comorbidities [8]. 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 [9]. 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 [10].

Preexposure 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 with tenofovir disoproxil fumarate, the only PrEP regimen approved by the US Food and Drug Administration and currently endorsed by the World Health Organization (WHO) [11, 12].

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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 [13].

Despite strong evidence from randomized controlled trials on the preventive efficacy of PrEP, limited evidence supports its cost-effectiveness relative to other strategies [14, 15]. 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 (eg, test-and-treat, testing) [16–19]. Others did not capture secondary infections [20] or resistance to ART and PrEP [16, 17]. Finally, some did not capture the effect of ART-related adverse events [17, 18], behavioral changes induced by PrEP (eg, decreased condom use) [16], or incomplete adherence to PrEP, which could undermine the efficacy of PrEP [21].

This study assesses the potential trade-offs between choosing the status quo (SQ; testing with treatment initiation at CD4 $\leq$ 500 cells/μL), Testing (expanded HIV testing), test-and-treat (expanded HIV testing combined with immediate treatment), and PrEP (initiation of PrEP) strategies among 15- to 65-year-old MSM in LAC, using a societal perspective. Similar to Juusola et al [18], we use a compartmental HIV transmission model. Our modeling approach addresses the limitations of Juusola et al [18] 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 [10], 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 1-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 whereas 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, respectively.

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) [22] and we assume in our base case analysis that 10% of uninfected MSM and 25% of MSM adopt PrEP (Tables 1 and 2) [23, 24]. 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 [10] and in the Supplementary 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 (Supplementary Table 20).

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, quality-adjusted life-years (QALYs), and the incremental cost-effectiveness ratio (ICER) of the 623 alternative strategies simulated with the epidemic model. We adopt a US societal perspective [25].

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 [26] 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 [27].

INPUT DATA

We derive the initial population data from Sood et al [10], 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] (Supplementary Appendix, Section 2.2). Average age group life expectancy estimates for the uninfected and HIV-infected males are derived from CDC life tables (Supplementary Tables 3 and 4). We obtain epidemic parameters (eg, HIV transmission rates, parameters associated with HIV natural history, HIV testing rates, ART and PrEP initiation and discontinuation

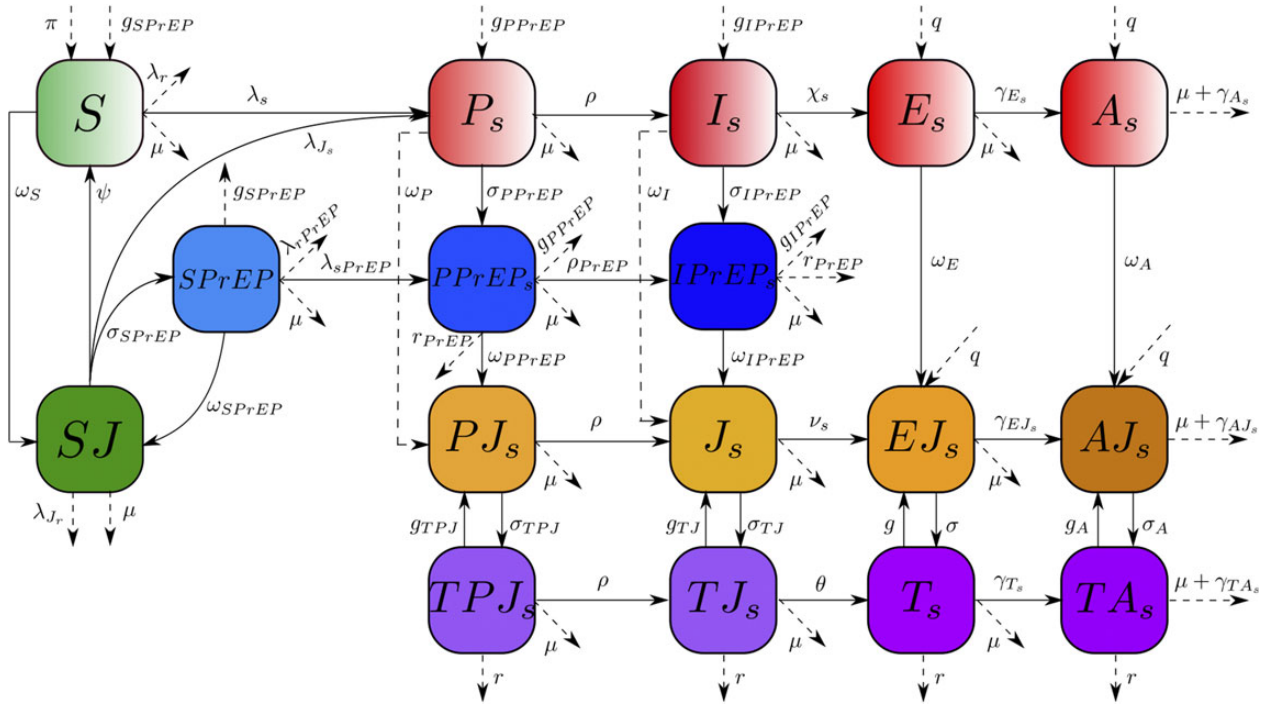

Figure 1. Schematics of the human immunodeficiency virus (HIV) model. Individuals enter the model through aging and discovery of sexual orientation at an annual rate π. Once in the model, they can transition between health states, which comprise the uninfected (*S*, *SJ*, *SPrEP*), primary (P_k, $PPrEP_k$, 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 antiretroviral therapy in the primary, asymptomatic, symptomatic and AIDS stages, respectively. Finally, *SPrEP*, *PPrEP*, and *IPrEP* denote individuals using preexposure prophylaxis (PrEP) in the uninfected, primary, and symptomatic stages, respectively. At any stage in the model, individuals can exit the model through death at a natural death rate μ, or from HIV/AIDS complications (γ_{A_k}, γ_{AJ_k} or γ_{TA_k}). Estimates of parameters and data sources entering the model are provided in Table 2 and in Supplementary Table 19 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 Supplementary Table 1 of the Appendix.

rates, ART and PrEP efficacy) from Sood et al [10] and from a systematic review of the evidence on HIV treatment and prevention (Supplementary 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 (Supplementary 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

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 count ≤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 in sexual infectivity owing to ART	0.900	0.900	0.900	0.900
Reduction in sexual infectivity owing to PrEP	. . .	. . .	. . .	0.920
Reduction in risk of infection owing to PrEP	. . .	. . .	. . .	0.440

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; PrEP, preexposure prophylaxis; STI, sexually transmitted infection.

infections; tests for HIV (eg, enzyme immunoassay, enzyme-linked immunosorbent assay, rapid HIV test, confirmatory testing using nucleic acid amplification testing), sexually transmitted infections, serum blood urea nitrogen level, and creatinine level; CD4 count and viral load monitoring; pretest and posttest counseling; and linkage to care. We convert all healthcare prices into 2013 US dollars assuming a 9% annual increase in healthcare prices [25]. We exclude direct nonmedical costs—that is, those incurred beyond the healthcare 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 healthcare costs [28], as well as estimates of AIDS patients' home care utilization [29], weighted by the national average hourly compensation rates of home health and personal care aides [30]. 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 [31].

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 (Supplementary Appendix, Section 3.2.4, Equation 81) [18]. The QALY and HRQOL score estimates are obtained from the published literature (Supplementary Appendix, Section 3.2; Supplementary Tables 17 and 18). All demographic, costs, and effectiveness parameters are summarized in Table 2 and described in Supplementary Table 19.

RESULTS

Efficient Strategies

Status quo 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 that 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 $19 302/QALY gained and is highly cost-effective at the current US willingness-to-pay threshold of $150 000/QALY gained [32]. Test-and-treat extendedly dominates strategies that combine SQ with less aggressive early treatment or HIV testing (eg, 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 $20 451/QALY gained. Similarly, the most aggressive enhanced test-and-treat strategy on the frontier (strategy 6) would cost $25 654/QALY relative to test-and-treat, and $38 492/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 $27 863, $29 492, and $63 269/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 $85 117, $104 788, $139 346, and $145 956/QALY, respectively (Table 3). The 2 remaining enhanced PrEP strategies (strategies 12–13) are cost-ineffective relative to the preceding rational enhanced PrEP strategy on the frontier ($188 714 and $234 726/QALY, respectively). All enhanced PrEP strategies are highly cost-effective relative to SQ ($28 529, $29 633, $31 045, $32 033, $33 429, and $37 181/QALY, respectively; Supplementary Table 20) and test-and-treat ($30 261, $31 538, $33 178, $34 321, $35 942, and $40 292/QALY, respectively). Relative to PrEP, all enhanced PrEP strategies (except for strategy 13, which costs $155 770/QALY) are also cost-effective ($85 117, $96 088, $110 557, $117 064, and $128 622/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 is likely owing to the preventive benefits of PrEP and the survival gains from early diagnosis and prompt ART initiation.

Table 2. Summary of Key Model Input Parameters

Parameter	Value	Range
Epidemic parameters		
Demographic parameters		
π: Annual inflow of susceptible individuals	3597	3143–3825
μ: Natural rate of death	0.0004	0.0003–0.0004
HIV transmission parameters		
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	. . .
Disease progression		
$\rho = \rho_{PrEP}$: 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-infected individuals)[a]	0.3200	0.2501–0.8302
$\nu_s = \nu_r$: Progression rate from asymptomatic to untreated symptomatic HIV (aware HIV-infected 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
HIV/AIDS-related mortality		
$\gamma_{AJ_s} = \gamma_{A_s}$: 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
Screening and counseling		
$1/\psi$: Average duration of identification for susceptible individuals	1.0000	0.5000–3.0000
ω_{S-SJ}: 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	. . .
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-infected 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-infected individuals in the primary stage of infection	Varies	. . .
σ_{IPrEP}: PrEP initiation rate by unaware HIV-infected individuals in the asymptomatic stage of infection	Varies	. . .
$\sigma_{TPJ} = \sigma_{TJ}$: ART initiation rate by identified (aware) HIV-infected 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-infected 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 healthcare costs ($)		
Acute HIV[b]	30	10–500
Asymptomatic HIV, untreated[b]	4130	3000–6000
Symptomatic HIV, untreated[b]	6934	5000–9000

Table 2 continued.

Parameter	Value	Range
Symptomatic HIV, treated with ART, excluding ART costs[b]	6181	5000–7000
AIDS, untreated[b,c]	21 863	15 000–25 000
AIDS, treated with ART, excludes ART costs[b,c]	9950	6000–17 000
Annual cost of ART[b]	15 000	13 520–17 109
Cost of PrEP (cost per test, refill, or visit; $)		
PrEP (tenofovir/emtricitabine): 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, 87 389) or rapid HIV test (CPT G0345)[d]	19	9–45
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; $)		
Pretest counseling[b]	13	0–100
Posttest counseling for HIV negative individuals[b]	7	0–50
Posttest linkage/counseling for HIV-positive individuals[b]	14	0–100
Other costs and cost-related parameters		
Cost of HIV diagnosis ($)[b]	500	125–1200
Annual cost discount rate	0.0300	0.0000–0.0500
2013 to 2010 inflation factor	1.0900	. . .
Effectiveness parameters		
Disease state QOL utility weights		
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
Other effectiveness parameters		
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

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 Supplementary Appendix, Section 1.4. References for the estimates and their ranges are provided in Supplementary Table 19.

Abbreviations: ART, antiretroviral therapy; CPT, Current Procedural Terminology; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; MDR, multidrug resistance; NAAT, nucleic acid amplification testing; PrEP, preexposure prophylaxis; QOL, quality of life; STI, sexually transmitted infection.

[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.

Epidemiological Outcomes

Our simulation indicates that the SQ approach would yield a cumulative HIV incidence of 99 874 cases. Relative to this figure, test-and-treat (strategy 2) and PrEP (strategy 7) would respectively avert 4332 (4.3%) and 58 881 (59.0%) new infections (Supplementary Table 19). The most aggressive enhanced

Table 3. Benefits and Costs of the Most Cost-effective Test-and-Treat and Preexposure Prophylaxis Strategies for 20 Years in the Los Angeles County Men Who Have Sex With Men Population

	Discounted[a]		Incremental Values Relative to Prior Rational Decision			
Rational Decision on the Efficient Frontier	Cost, 2013 $ (Billions)	QALYs (Millions)	Costs, 2013 $ (Billions)	QALYs	ICER, $/QALY	Extendedly Dominated Strategies[b]
SQ[c]	43.58	2.96	. . .	. . .	. . .	. . .
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	6111	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	7707	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	6945	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	4676	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	4892	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: ART, antiretroviral therapy; ICER, incremental cost-effectiveness ratio; PrEP, preexposure prophylaxis; QALY, quality-adjusted life-year; SQ, status quo; TT, test-and-treat.

[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 the Supplementary Appendix, Table 23.

[c] Test 4.4 years + ART 2.5 years at CD4 count ≤500 cells/μL.

[d] Early ART defined as ART start at CD4 count >500 cells/μL.

test-and-treat strategy (test-and-treat enhanced with annual HIV testing; strategy 6) would avert 47 759 (47.8%) infections relative to SQ. The most aggressive enhanced PrEP strategy (strategy 13) would avert 77 301 (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 distribution [33]. Cost parameters are sampled following a log-normal distribution to account for the skewed and fat-tail nature of cost data [34]. 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 (Supplementary Appendix, Sections 5.1–5.3; Supplementary Figures 4–7 and 9–18). 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 [35].

Third, we conduct a sensitivity analysis of the ICERs to changes in the initial HIV prevalence rates (Supplementary Figure 8 and Table 24) 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 $19 769 and $19 158 per QALY gained as the initial HIV prevalence rate varied from 5% to 40%; the corresponding range for the PrEP strategy (strategy 6) was $40 077–$27 029/QALY gained. Assuming a 12.3% initial HIV prevalence rate in 2013 as in

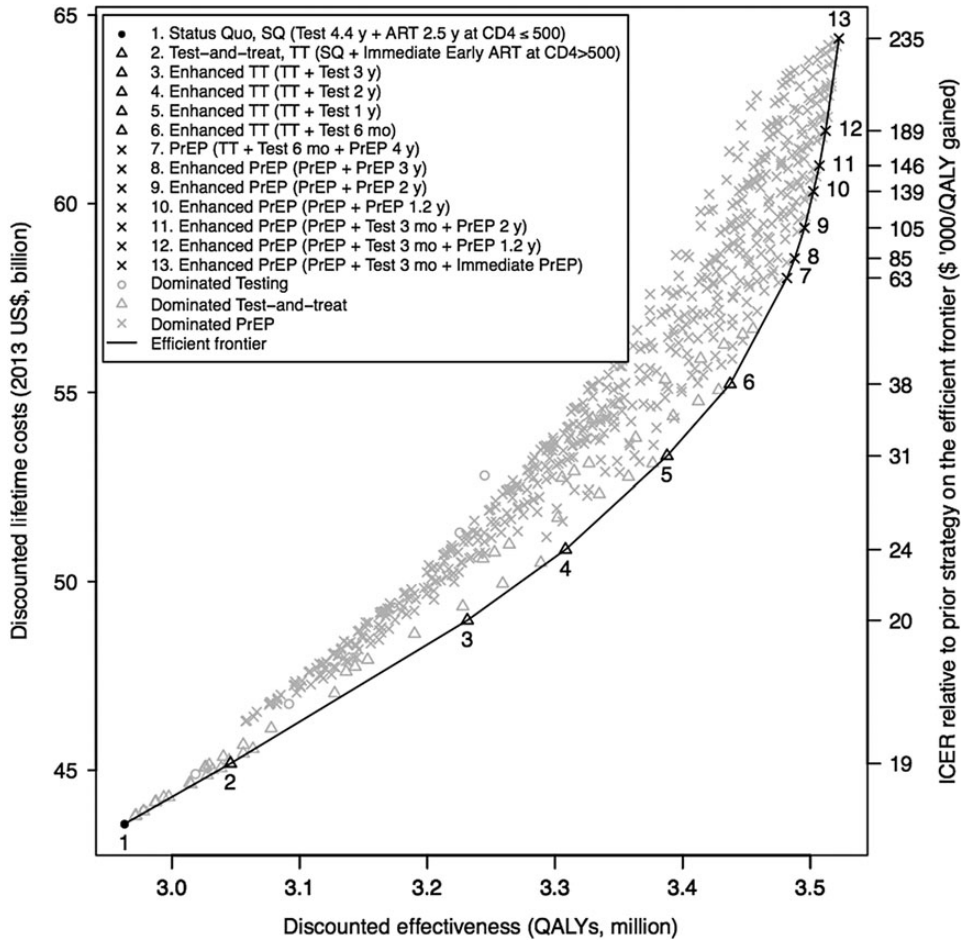

Figure 2. Efficient frontier for resource allocation. The efficient frontier, indicated by the solid black line, denotes strategies that yield the highest value (lowest cost per quality-adjusted life-years [QALYs] gained) for a defined level of societal willingness to pay. It can be used to determine 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 gray 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 (TT), and pre-exposure prophylaxis (PrEP) strategies, whereby the frequencies of testing, antiretroviral therapy (ART) coverage, and/or PrEP uptake are varied (these strategies are listed in Supplementary Appendix, Table 20). Positive gradients (eg, between points 3 and 4) reflect the incremental cost-effective ratios (ICERs) of each strategy on the frontier relative to the prior strategy on the frontier (ie, additional costs for increased health benefits), and are captured by the values on the right-hand side y-axis (eg, $24 394/QALY gained between points 3 and 4). Abbreviation: SQ, status quo.

Juusola et al [18], our ICERs estimates for the test-and-treat strategies (strategies 2–6) would range between $19 427 and $26 051 per QALY gained relative to SQ; the corresponding ICER range for the PrEP strategies (strategies 7–13) would be $30 812–$45 921/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 [36]. Our sensitivity analysis in this range of price reduction suggests that all cost-effectiveness profiles improve with generic entry (Supplementary Figures 19 and 20). 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 $18 162, $16 452, and $15 312 per QALY saved, while those for the PrEP strategy (strategy 7) improve to $26 671, $24 883, and $23 690/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 $62 333, $60 928, and $59 992 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 $27 863–$37 181/QALY gained, whereas the test-and-treat strategies could cost $19 302–$24 544/QALY gained. These results are consistent with the Desai et al [17] finding that PrEP for New York City high-risk MSM would cost $32 000/QALY.

They differ, however, from the Juusola et al [18] estimates of $50 000/QALY in high-risk MSM. They also differ from the Koppenhaver et al [16] estimates of $353 739 and $570 273 per QALY gained among highly adherent MSM (ie, 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 [18] (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 2 studies (Supplementary Figure 8 and Supplementary Table 24). 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's [16] report and our study.

This study has several limitations. First, our model assumes a proportional sexual mixing, but this assumption might be unrealistic [37]. 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 [38]. 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 is evaluated [39]. 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; 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 [40]. 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.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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