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Cost-Effectiveness of HIV Preexposure Prophylaxis for People Who Inject Drugs in the United States

Cora L. Bernard, MS; Margaret L. Brandeau, PhD; Keith Humphreys, PhD; Eran Bendavid, MD, MS; Mark Holodniy, MD; Christopher Weyant, MS; Douglas K. Owens, MD, MS; and Jeremy D. Goldhaber-Fiebert, PhD

Background: The total population health benefits and costs of HIV preexposure prophylaxis (PrEP) for people who inject drugs (PWID) in the United States are unclear.

Objective: To evaluate the cost-effectiveness and optimal delivery conditions of PrEP for PWID.

Design: Empirically calibrated dynamic compartmental model.

Data Sources: Published literature and expert opinion.

Target Population: Adult U.S. PWID.

Time Horizon: 20 years and lifetime.

Intervention: PrEP alone, PrEP with frequent screening (PrEP+screen), and PrEP+screen with enhanced provision of antiretroviral therapy (ART) for individuals who become infected (PrEP+screen+ART). All scenarios are considered at 25% coverage.

Outcome Measures: Infections averted, deaths averted, change in HIV prevalence, discounted costs (in 2015 U.S. dollars), discounted quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios.

Results of Base-Case Analysis: PrEP+screen+ART dominates other strategies, averting 26 700 infections and reducing HIV prevalence among PWID by 14% compared with the status quo. Achieving these benefits costs $253 000/QALY gained. At current drug prices, total expenditures for PrEP+screen+ART could be as high as $44 billion over 20 years.

Results of Sensitivity Analysis: Cost-effectiveness of the intervention is linear in the annual cost of PrEP and is dependent on PrEP drug adherence, individual transmission risks, and community HIV prevalence.

Limitations: Data on risk stratification and achievable PrEP efficacy levels for U.S. PWID are limited.

Conclusion: PrEP with frequent screening and prompt treatment for those who become infected can reduce HIV burden among PWID and provide health benefits for the entire U.S. population, but, at current drug prices, it remains an expensive intervention both in absolute terms and in cost per QALY gained.

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For author affiliations, see end of text.
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People who inject drugs (PWID) account for a disproportionate share of the U.S. HIV burden (1). Although PWID make up less than 1% of the U.S. adult population, approximately 10% of new HIV infections are attributable to injection drug use alone or in combination with male-to-male sexual contact (2–4). Focusing HIV interventions on PWID may thus have an outsized public health benefit.

Many trials have shown that daily oral preexposure prophylaxis (PrEP) can prevent heterosexual and same-sex transmission of HIV (5–7). The Bangkok Tenofovir Study, a randomized trial of PrEP, reported a 49% reduction in HIV infection among PWID in Thailand (8). The Centers for Disease Control and Prevention (CDC) revised their clinical practice guidelines in 2014 to recommend that PrEP be considered for any adult who injected drugs within the past 6 months and, additionally, shared injection equipment, enrolled in drug-dependence treatment, or was at increased risk for sexual transmission (9).

However, the population health benefits and costs of implementing a national program remain unclear. Currently, PrEP, a daily antiretroviral oral pill, is expensive. The U.S. Food and Drug Administration approved the combination of 300 mg of tenofovir disoproxil fumarate (TDF) and 200 mg of emtricitabine (FTC) (Truvada, Gilead Sciences), which alone costs approximately $10 000 annually (10–12). The CDC's recommended package of preventive care around PrEP, including HIV screening and assessment for adverse effects every 3 months and monitoring for toxicities every 6 months, adds to the cost. Although prior studies have explored the cost-effectiveness of PrEP for men who have sex with men (MSM) (10, 11), PWID differ in risk behaviors and HIV incidence. Therefore, we performed a model-based evaluation of the cost-effectiveness of expanding PrEP for PWID in the United States. We incorporated new clinical trial results with epidemiologic and economic data to determine the optimal conditions under which PrEP can be delivered to this high-risk population.

METHODS

Overview

We developed an empirically calibrated dynamic compartmental model of the U.S. HIV epidemic (**Figure**

See also:

Editorial comment 1

Web-Only
Supplement

1 of the Supplement, available at www.annals.org) to evaluate the benefits and costs of a national PrEP program for PWID. Our model captured sexual and injection transmission between PWID with and without PrEP, MSM, and all other U.S. adult heterosexuals (a generally low-risk group) between 2015 and 2035. Sexual mixing patterns between groups captured risk behavior overlaps, such as the PWID–MSM population (Supplement, section 4.1.2). The model included opioid agonist therapy (for example, methadone maintenance), HIV screening and awareness, and antiretroviral treatment (ART) both at current and enhanced levels. Table 1 and Table 1 of the Supplement show model inputs and their sources. We calibrated the model to CDC estimates of HIV prevalence (4, 13–17), incidence (1, 17), and infection awareness (4, 13–15, 18) by risk group (Supplement, section 5). We adopted a societal perspective and computed total lifetime quality-adjusted life-years (QALYs) and health care costs, discounted at 3% annually (19, 20). We evaluated each scenario in terms of HIV infections averted and incremental cost-effectiveness ratios (ICERs).

Population

To capture the actively injecting population, the model follows U.S. adults aged 18 to 64 years stratified by risk group (21, 22) with underlying age mixing. We subdivided PWID by enrollment in opioid agonist therapy and subdivided all groups by HIV status and awareness of this status. To capture differences in infectivity, mortality, costs, and quality of life, we further stratified infected individuals by HIV stage and ART status (Supplement, section 1.1). Initial 2015 HIV prevalence in each risk group is consistent with CDC estimates (16, 17) and independent of age. Most individuals in the model are low-risk heterosexuals (1, 23): People who inject drugs make up 0.56% of the U.S. adult population (2, 3, 21), and MSM, 1.5% (11, 18). Consistent with national estimates, starting HIV prevalence is 9.8% in PWID (4), 11.4% in MSM (14), and 0.18% in the low-risk group (16, 23). We used calibration to determine the distribution of subgroups within each risk group (for example, the distribution of CD4 counts among PWID unaware of their HIV status) (Supplement, sections 1.2, 5).

Models

Reflecting the subpopulations described above, our dynamic compartmental model has 62 active compartments (Supplement, section 1). During a 20-year time horizon, a system of differential equations updates each compartment's population at monthly time steps (Supplement, section 4). Additional Markov models capture the life trajectories and health care costs of individuals maturing out of the model at age 65 years and those still active in the model at the end of the time horizon (Supplement, section 6). All models are programmed in Matlab R2013a (MathWorks).

Mortality

All individuals face background mortality rates plus additional rates reflecting risk status (11, 24, 25), HIV status, and treatments (Supplement, section 3.1.3) (18, 26–29).

Injecting Behavior and Treatment

Injecting behaviors increase health risks and HIV transmission. Opioid agonist therapy includes methadone and buprenorphine maintenance therapies, which reduce injections by 55% (30) and decrease mortality but do not affect risky sexual behavior (31, 32). We assumed that 25% of PWID receive opioid agonist therapy and assessed varying levels of enrollment in sensitivity analysis (Supplement, section 4.1.1) (4, 13, 31, 33, 34). The model is calibrated to U.S. HIV dynamics and hence reflects current levels of injection, including the effect of needle–syringe exchange programs.

Awareness of HIV Status and Subsequent Behavior

Infected individuals discover their status through HIV testing, with uptake of testing depending on risk group and, for PWID, on enrollment in opioid agonist therapy (35, 36). We assumed that detection is more likely in later, more symptomatic HIV stages (29). Recent U.S. guidelines recommend ART for all HIV-infected patients, regardless of CD4 count (37). There is no estimate for how this will affect future viral suppression rates for high-risk populations; consequently, we calibrated the model to reflect current ART enrollment levels (18, 28, 33). To match current ART uptake data, after a positive HIV diagnosis, individuals initiate treatment and become virally suppressed with a probability dependent on their risk characteristics (28, 38). We also incorporated risk behavior change (for example, condom use) after an HIV diagnosis (11, 15, 33, 34).

HIV Transmission

Transmission occurs via sexual contact and via sharing injection equipment. Infection depends on 2 factors: frequency of risky contact based on mixing patterns and probability of infection given a serodiscordant contact (Supplement, section 2).

We assumed preferential sexual mixing (for example, PWID are more likely to have high-risk sexual partners) (Supplement, section 2.2.1) (4, 33, 34, 36, 39–42). After accounting for preferential mixing, we assumed proportional mixing (for example, no preference is given to choosing a partner of similar HIV status) (11, 33, 43, 44). We assumed that PWID aware of their HIV infection and PWID in opioid agonist therapy are less likely to share equipment (30, 32) but that, when they do, injection equipment sharing follows proportional mixing (13, 31, 33, 42, 43).

Sexual transmission between serodiscordant partners depends on male condom use (4, 14, 15, 33, 34, 42, 45), condom effectiveness (46), the infected partner's HIV stage (43, 47–49, 74) and ART status (48, 50), along with the uninfected partner's use of PrEP (8). We assumed a higher transmission risk for unprotected sexual acts that occur between MSM (47). Transmission through shared injection equipment depends on the infected partner's HIV stage (47, 48) and ART status (8,

Table 1. Estimates for Key Model Parameters

Parameter*	Value	Range†	Reference
Demographics, *n*			
Population (age 18–64 y)			
Total	200 million	198–203 million	1, 23
PWID	1.1 million	0.8–1.4 million	2, 3, 21
MSM	3.0 million	2.0–4.5 million	11, 18
Initial HIV conditions, %			
HIV prevalence			
PWID	9.8	8.0–12.1	4
MSM	11.4	8.8–14.7	11, 14, 17
Low-risk	0.18	0.14–0.23	Calculated (16, 17, 23)
Aware of HIV status			
PWID	69.9	59.1–78.6	4, 13
MSM	75.3	64.3–84.4	14, 15, 18
Low-risk	84.7	76.3–89.9	18
ART enrollment given aware			
PWID	40.9	29.3–51.7	18, 28
MSM	53.1	41.5–64.5	18
Low-risk	73.7	58.4–82.6	18, 33
Annual mortality rate			
PWID	0.015	0.011–0.021	24, 25
Hazard ratio for opioid agonist therapy	0.39	0.12–0.96	24, 33
MSM	0.0044	0.0034–0.0053	11, 25
Low-risk	0.0015	0.0011–0.0021	25
HIV natural history (average disease duration)			
Acute HIV, *mo*	2.2	1.2–4.6	48, 49
Asymptomatic HIV, *y*	5.3	3.1–9.8	21, 29, 48
Symptomatic HIV, *y*	7.1	4.5–14.4	21, 29, 48
Symptomatic HIV receiving ART, *y*	20.0	12.6–37.4	26, 27, 48
AIDS, *y*	1.7	0.9–3.8	48
AIDS receiving ART, *y*	5.3	3.1–9.8	26, 27, 48
ART (transmission reduction if partner is receiving ART), %			
Injecting partner	59	14–82	8, 43
Sexual partner	90	68–99	43, 48, 50
PrEP			
Infection reduction (injection and sexual routes), %	48.9	10.0–89.1	8
Screening frequency‡, *mo*	3	1.2–4.9	9
Injecting behavior			
Risky injections annually, *n*	48	17–89	4, 13, 31, 42
Probability of transmission per injection, asymptomatic HIV, %	0.05	0.03–0.07	47, 48
Relative risk for transmission per injection			
Symptomatic relative to asymptomatic	2.85	2.85–3.28	47, 48
AIDS relative to symptomatic	2.49	1.99–3.17	47, 48
Acute relative to AIDS	3.45	2.33–5.10	47–49
Decrease in risky injections due to awareness of HIV status	23.2	0.0–55.0	33, 34
Opioid agonist therapy, %			
Initial PWID enrollment	24.8	13.2–34.4	4, 13, 31, 33, 34
PWID who quit annually	32.1	18.1–43.6	31, 70
PWID who transition to lower-risk groups annually	3.6	1.9–5.4	31, 70
Decrease in risky injections	54.7	0.004–82.2	30
Sexual behavior			
Annual partners, *n*			
PWID	3.1	1.2–5.4	4, 34, 42, 44
MSM	4.1	2.4–6.3	11, 34, 39, 69
Low-risk	1.5	0.8–2.5	33, 43–45
Partnerships, %			
PWID with other PWID	45.6	27.0–65.8	33, 42
PWID with MSM	8.0	4.9–11.2	4, 34, 39
MSM with other MSM	92.9	73.6–99.9	36, 39–41
Monthly probability of transmission in heterosexual partnership, asymptomatic HIV	0.87	0.49–1.29	43, 47, 48, 74

Continued on following page

Table 1–Continued

Parameter*	Value	Range†	Reference
Relative risk for transmission per sexual partnership			
Symptomatic relative to asymptomatic	2.85	2.85–3.28	47, 48
AIDS relative to symptomatic	2.49	1.99–3.17	47, 48
Acute relative to AIDS	3.45	2.33–5.10	47–49
MSM partnership relative to heterosexual asymptomatic	4.46	2.45–7.27	43, 47
Annual costs, *2015 U.S. $*			
Uninfected PWID	3000	630–7200	31, 33
Uninfected non-PWID	5000	3060–7440	33
Opioid agonist therapy	7000	4320–10 430	31, 33
PrEP drug	10 000	7150–13 320	10–12, 53
PrEP screening services	800	100–2240	11, 54
ART	15 000	9170–22 300	29, 43, 54, 72
Asymptomatic HIV, not receiving ART	4000	2460–5950	29, 31, 43, 54, 72
Symptomatic HIV, not receiving ART	7000	4270–10 330	29, 31, 43, 54, 72
Symptomatic HIV, receiving ART§	6500	4190–9280	29, 31, 43, 54, 72
AIDS, not receiving ART	20 040	10 380–33 240	29, 31, 43, 54, 72
AIDS, receiving ART§	10 000	4870–17 160	29, 31, 43, 54, 72
Annual discount rate, %	3		19, 20
Quality-of-life multipliers‖			
Uninfected (non-PWID)	1.00		11, 43, 67
PWID	0.90	0.67–1.00	43, 67
PWID receiving opioid agonist therapy	0.95	0.82–1.00	31, 33, 67
Asymptomatic HIV	0.94	0.76–1.00	43, 73
Symptomatic HIV	0.81	0.68–0.95	43, 73
AIDS	0.70	0.57–0.86	43, 73
ART multiplier	1.15	1.00–1.35	11, 29, 43, 67

ART = antiretroviral therapy; MSM = men who have sex with men; PrEP = preexposure prophylaxis; PWID = people who inject drugs.
* Additional model parameters in **Table 1** of the **Supplement** (available at www.annals.org).
† Range refers to the 95% CI used in probabilistic sensitivity analysis.
‡ Denotes a control variable characterizing a specified intervention and is not considered uncertain. The associated range was used in 1-way sensitivity analysis only.
§ Disease costs during ART exclude cost of ART.
‖ The quality weight for any given compartment is capped at the underlying risk-group baseline quality weight (that is, cannot exceed 1).

50), along with the uninfected partner's use of PrEP (8). PrEP provides partial protection: a 49% reduction for both sexual and injection-based risk for HIV (8). We varied the efficacy of PrEP from 10% to 90% in sensitivity analysis to account for uncertainty in effectiveness and differential adherence patterns (5–9, 51).

HIV Infection and Treatment

An HIV-infected individual enters an acute phase and then progresses through asymptomatic (CD4 count, 0.50 to 1.20 × 10^9 cells/L) and symptomatic (0.20 to 0.50 × 10^9 cells/L) stages before developing AIDS (≤0.20 × 10^9 cells/L). Without ART, the duration in each HIV stage is consistent with the literature (21, 29, 48, 49). ART suppresses HIV-1 viral load, which improves quality of life, decreases infectivity, and extends life expectancy (26–28). We assumed that ART reduces the chance of sexual transmission by 90% (43, 48, 50) and transmission from shared injection equipment by 60% (8, 43).

PrEP Scenarios

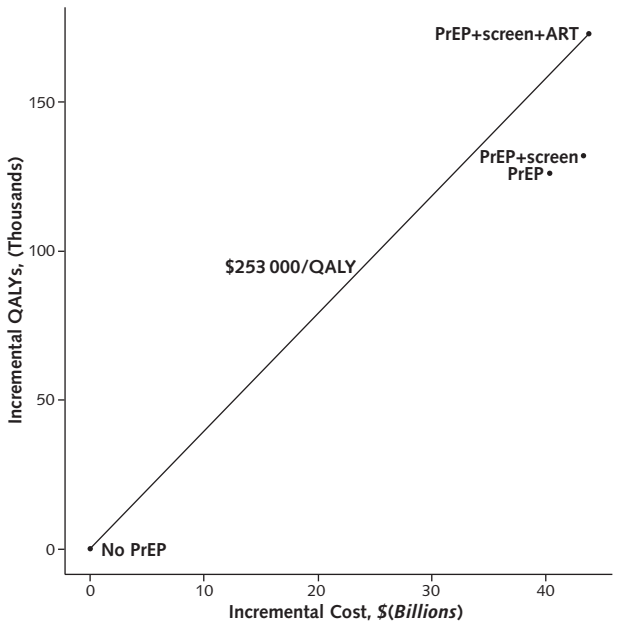
Per the CDC's guidelines, PrEP includes both a daily oral pill and an accompanying package of clinical care (for example, HIV screening every 3 months, toxicity monitoring every 6 months) (9). To assess how much of the benefit from a PrEP program accrues from each component, we evaluated 3 delivery scenarios: 1) PrEP in isolation with screening at the same rate as in the general PWID population; 2) PrEP with increased HIV screening and toxicity monitoring (PrEP+screen), which decreases the time between infection and diagnosis; and 3) PrEP+screen in which 50% of newly diagnosed PWID in the early stages of HIV receive prompt, sustained ART (PrEP+screen+ART). (In contrast, only 10% of PWID not enrolled in PrEP+screen+ART receive ART in the early stages.) Enhanced ART delivery also yields indirect benefits because shortened time to diagnosis and treatment for a patient reduces HIV transmission.

Because of PWID's generally lower access to health care and retention in treatment (4, 38), all delivery scenarios assume that 25% of uninfected PWID would enroll in a PrEP program (9). PrEP is discontinued at the time of a positive HIV diagnosis. A PrEP program moderately increases HIV awareness for all PWID because uninfected and infected-but-unaware individuals are equally likely to be screened before enrollment in PrEP (9).

Economic Model

Depending on risk group and health status, different costs and QALYs accrue to individuals (**Supplement**, section 7.1). We derived costs, adjusted for inflation by using the Consumer Price Index (52) and expressed in 2015 U.S. dollars, from previous HIV models (11, 33, 43). PrEP program costs reflect the cost of

Figure 1. Main analysis: incremental costs incurred and QALYs gained.



To assess delivery scenarios, we evaluated 1) PrEP alone with status quo population-level screening rates for people who inject drugs; 2) PrEP with HIV screening every 3 mo (PrEP+screen); and 3) PrEP+screen with prompt and sustained linkage to ART for individuals who do become infected (PrEP+screen+ART). All cases assume 25% coverage, 49% PrEP efficacy, and $10 000 annual PrEP drug cost. The x-axis shows incremental cost in billions of U.S. dollars compared with the status quo of no PrEP; the y-axis shows incremental QALYs in thousands. The point labeled PrEP+screen shows that at current levels of ART initiation and adherence, screening provides a small QALY increase for a large cost increase. When screening is combined with increased ART, however, screening delivers synergistic benefit, resulting in an ICER of $253 000/QALY gained. This scenario, PrEP+screen+ART, dominates the other 2 scenarios (i.e., is more effective and has a lower ICER). ART = antiretroviral therapy; ICER = incremental cost-effectiveness ratio; PrEP = preexposure prophylaxis; QALY = quality-adjusted life-year.

TDF–FTC (Truvada) (12, 53) as well as of monitoring for PrEP+screen and PrEP+screen+ART (10, 11, 54). We assessed value by comparing the incremental discounted costs and QALYs of each PrEP delivery scenario to the next-best alternative (20).

Model Calibration

We obtained initial estimates and distributions for each model input from the published literature and then empirically calibrated the model to U.S. epidemiologic data, resulting in 182 best-fitting parameter sets (**Supplement**, section 5) (55, 56). We accounted for parameter uncertainty by repeating our analyses across these calibrated sets (57).

Role of the Funding Source

No funder had a role in the design, conduct, and analysis of the study or in the decision to submit the manuscript for publication.

RESULTS

Figure 1 and Table 2 show that PrEP+screen+ART is more effective and less expensive per QALY gained than both PrEP alone and PrEP+screen, illustrating that prompt and sustained ART provision is crucial to delivering PrEP with maximal value. PrEP+screen+ART for 25% of uninfected PWID (approximately 280 000 individuals) averts 21 500 new HIV infections (−20.0%) and 5300 deaths from AIDS (−7.4%) within the PWID population over 20 years. For all risk groups, 26 700 HIV infections (−8.2%) and 6300 deaths from AIDS (−1.4%) are averted. We projected that PrEP+screen+ART could reduce HIV prevalence by 14% in the PWID population by 2035 (from 6.5% to 5.6%). These health effects translate to an increase of 173 000 QALYs. However, PrEP+screen+ART increases costs by $44 billion over the period despite the averted costs from prevented HIV infections; this is approximately $2.2 billion per year or 9% of the 2015 federal budget for domestic HIV/AIDS (58). Compared with the status quo, PrEP+screen+ART costs $253 000/QALY gained.

Sensitivity Analysis

For the PrEP+screen+ART delivery scenario, we performed multiple one-way sensitivity analyses on all model parameters (**Supplement**, section 8.1), with key results presented below. Our findings are robust to parameter uncertainty, with 98% of instances in a probabilistic sensitivity analysis costing more than $100 000

Table 2. Results of Main Cost-Effectiveness Analysis

Scenario*	PWID HIV Infections Averted, *n*†	Total Population HIV Infections Averted, *n*†	Change in PWID HIV Prevalence at 20 y, %†	Total Costs, *U.S. $ (Trillions)*	Total QALYs (Billions)	Incremental Costs, *U.S. $ (Billions)*†	Incremental QALYs (Thousands)†	ICER, $†
No PrEP	–	–	–	32.528	6.4340	–	–	–
PrEP	18 600	21 800	−12.9	32.568	6.4341	39.9	126	Dominated
PrEP+screen	19 800	23 700	−14.1	32.571	6.4341	42.8	132	Dominated
PrEP+screen+ART	21 500	26 700	−14.0	32.572	6.4342	43.8	173	253 000

ART = antiretroviral therapy; ICER = incremental cost-effectiveness ratio; PrEP = preexposure prophylaxis; PWID = people who inject drugs; QALY = quality-adjusted life-year.
* Every PrEP scenario assumes 25% coverage, or approximately 280 000 PWID enrolled, and 49% reduction in HIV acquisition from PrEP. In PrEP+screen, PrEP is delivered with HIV screening every 3 months. PrEP+screen+ART includes enhanced linkage to ART for individuals who do become infected. (**Supplement**, section 7.2, available at www.annals.org, provides details and intuition on prevalence changes for each intervention.) PrEP+screen+ART (weakly) dominates the other 2 scenarios because it is more effective and less expensive per QALY gained. Therefore, PrEP+screen+ART is compared directly to no PrEP, which is the next-best alternative on the cost-effectiveness frontier.
† Relative to no-PrEP scenario.

Table 3. Sensitivity Analysis: Preexposure Prophylaxis Value as a Function of Drug Cost

Scenario*	Total Costs of PrEP, *U.S. $ (Trillions)*	Total QALYs (Billions)	Incremental Costs, *U.S. $ (Billions)*†	Incremental QALYs (Thousands)†	ICER, $†
No PrEP	32.528	6.4340	–	–	–
PrEP at $2000 (80% price reduction)	32.539	6.4342	11.2	173	65 000
PrEP at $3500 (65% price reduction)	32.545	6.4342	17.3	173	100 000
PrEP at $6000 (40% price reduction)	32.555	6.4342	27.5	173	159 000
PrEP at $10 000 (current price)	32.572	6.4342	43.8	173	253 000
PrEP at $14 000 (40% price increase)	32.588	6.4342	60.0	173	347 000

ICER = incremental cost-effectiveness ratio; PrEP = preexposure prophylaxis; QALY = quality-adjusted life-year.
* Every PrEP scenario assumes 25% coverage in a PrEP program with HIV screening every 3 months and enhanced linkage to antiretroviral treatment (ART) for individuals who do become infected (PrEP+screen+ART), where PrEP is 49% effective. Costs are annual drug costs.
† Relative to no-PrEP scenario.

per QALY gained (**Figure 12** of the **Supplement**; **Supplement**, section 8.2).

Cost of PrEP

The drug costs of PrEP are based on the U.S. Food and Drug Administration–approved combination of TDF–FTC (Truvada) (10–12). **Figure 1** illustrates that drug costs drive most of the costs accruing over the next 20 years in all PrEP scenarios and thus critically determine cost-effectiveness. (Section 3.5.2 of the **Supplement** discusses sensitivity around screening costs.) Truvada is available at substantially reduced cost abroad and even within the United States for qualifying uninsured patients (59); moreover, patents for Truvada will expire within 5 years, when a generic drug might become available (**Supplement**, section 3.5.1) (60). We evaluated the cost-effectiveness of PrEP+screen+ART over a range of drug costs (**Table 3**). At a 65% price reduction, the intervention costs approximately $100 000 per QALY gained; nonetheless, it would cost $17 billion to deliver over 20 years (60).

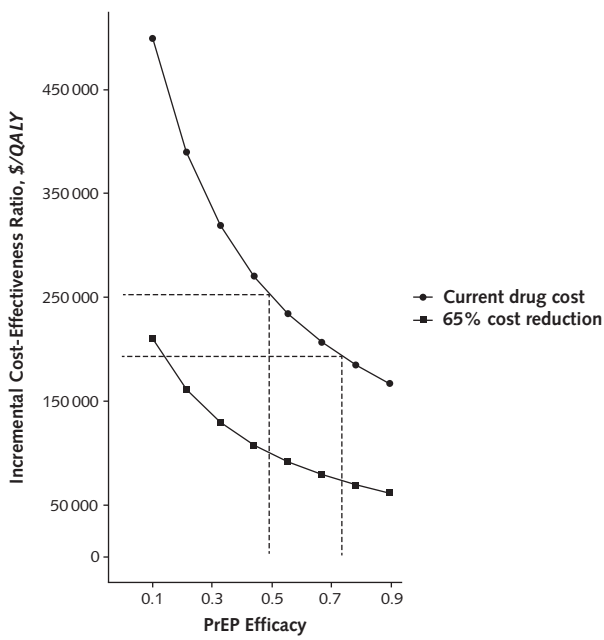
PrEP Efficacy

PrEP's efficacy in reducing HIV acquisition critically determines cost-effectiveness. Consistent with trial data, we assume a 49% (10% to 70%) reduction in sexual and injection transmission (8). PrEP trials in other populations estimate reductions in HIV acquisition via sexual transmission ranging from negligible to 92%, with efficacy depending strongly on adherence, which may be lower outside of study settings (5–9, 51). We evaluated PrEP with efficacy ranging from 10% to 90%, finding that the cost per QALY gained remains greater than $150 000 (**Figure 2** and **Table 2** of the **Supplement**). Nonetheless, cost-effectiveness improves substantially, especially at the lower end of the efficacy range, as adherence increases. This suggests an adherence threshold below which PrEP provides very little value. An important consideration is whether those who are less adherent may fill PrEP prescriptions less frequently, implying a correlation between lower efficacy and lower cost. In a 2-way sensitivity analysis, we find that low adherence levels, even if they result in low drug costs, provide low value, thus underscoring the conclusion that high value necessitates sufficient adherence (**Figure 2** of the **Supplement**).

Transmission

The magnitude of PrEP's health benefits is largely driven by an individual's risk for HIV infection without PrEP (**Figure 3** of the **Supplement**). A good proxy for an individual's HIV risk is community prevalence; given

Figure 2. Sensitivity analysis: PrEP value as a function of drug efficacy and drug cost.



We evaluate a program of PrEP with frequent HIV screening and enhanced ART provision (PrEP+screen+ART) with 25% coverage and $10 000 annual PrEP drug cost varying PrEP efficacy from 10% to 90%. The *y*-axis shows the ICER corresponding to efficacy levels specified on the *x*-axis. At current drug costs, the cost per QALY gained remains greater than $150 000 for all efficacy levels but substantially decreases as efficacy improves, with the largest jumps in cost-effectiveness coming at lower levels of efficacy. At 49% efficacy (leftmost vertical line), we see our base-case analysis with an ICER of $253 000/QALY gained. The Bangkok Tenofovir Study estimates a 74% reduction (rightmost vertical line) in HIV acquisition for high adherers. This results in a more favorable ICER of $193 000/QALY gained. At a 65% cost reduction PrEP delivers higher value and crosses the $100 000/QALY gained threshold at reported efficacy levels, although low levels of efficacy still result in high ICERs. PrEP = preexposure prophylaxis; ICER = incremental cost-effectiveness ratio; ART = antiretroviral therapy; QALY = quality-adjusted life-year.

similar ART coverage levels, populations with higher concentrations of infection will have higher transmission rates. Although average HIV prevalence among U.S. PWID is around 10%, prevalence varies from 2% to 19% among Metropolitan Statistical Areas (4, 13), suggesting a similarly wide range of incidence and risk levels. Targeting PrEP to highest-prevalence (and therefore highest-incidence) communities where other intervention resources are scarce will thus deliver greatest value, potentially costing less than $100 000/QALY gained.

Coverage

The main analysis assumes 25% coverage as complete population coverage is unlikely in the near term (4, 38). **Figure 4** of the **Supplement** and **Table 3** of the **Supplement** show the results of alternate coverage scenarios. Though PrEP would be maximally beneficial in a scenario in which herd immunity could be achieved, within feasible levels of coverage and efficacy in the PWID population, PrEP+screen+ART delivers slightly less incremental benefit as coverage increases (8).

Discussion

The value of PrEP is maximal when PrEP is delivered with frequent HIV screening and enhanced ART provision for those who become infected. Over 20 years, enrolling 25% of uninfected PWID in PrEP+screen+ART would reduce HIV burden among PWID and provide health benefits for the entire U.S. population, averting 26 700 new HIV infections and thereby gaining 173 000 QALYs. Nonetheless, PrEP+screen+ART is an expensive intervention at current prices of TDF–FTC (Truvada), costing $253 000 per QALY gained, well above generally accepted thresholds for cost-effectiveness. In comparison, needle–syringe exchange programs cost in the range of $4500 to $34 000 per QALY gained (61, 62). Our analysis also indicates that a PrEP program creates affordability challenges. At current drug costs, PrEP for 25% of PWID would cost an additional $44 billion over 20 years. This is equivalent to annually spending 9% of the current federal budget for domestic HIV/AIDS on PrEP for PWID (58). We found cost-effectiveness and total budget outlays to be approximately linear in the cost of PrEP: Thus, if the release of a generic medication reduced the drug cost by 65%, then PrEP+screen+ART would cost approximately $100 000 per QALY gained. Additionally, in settings with high HIV transmission risk, a PrEP program could cost less than $100 000 per QALY gained, although budget impact in both cases would still be substantial. These large expenditures will create challenges for both public and private payers that cover PrEP.

Cost-effectiveness is only one of many considerations for policymakers, who must also evaluate the ethical dimensions of an HIV prevention program for a population with generally low access to health services (4). PrEP for PWID can deliver individual-level protection and population-level health benefits, both of which provide substantial value in an underserved and high-risk group. In fact, the benefit of all PrEP programs is highest for individuals at greatest risk for HIV. Although it may be difficult for a clinician to distinguish between a lower- and higher-risk PWID, our analysis suggests that transmission rates within a population are a good proxy for individual risk, and thus PrEP delivers greater value in PWID communities with high HIV prevalence (and thus high HIV incidence) (13). Because high-prevalence populations are often the most marginalized, targeting PrEP to localized epidemics can serve the dual purpose of maximizing its value while addressing pressing social inequities (63).

The Bangkok Tenofovir Study participants were in drug-dependence treatment programs and received modest reimbursement for their time, which raises the question of whether their reductions in HIV transmission would generalize to PWID who are not in treatment. As is now evident from prior PrEP trials, efficacy depends on adherence (51). Whether adherence in the United States would reach (or exceed) levels achieved in the trial has not yet been demonstrated. If adherence were lower, then PrEP would be less cost-effective than we have estimated. These questions highlight the importance of ongoing evaluation of PrEP programs for PWID as they are initiated.

Our study has several limitations. First, PrEP+screen+ART could be more cost-effective than estimated if delivered to individuals centrally located in injecting or sexual networks. It could be substantially less cost-effective if considered within a portfolio of cheaper interventions (**Supplement**, section 9). **Figure 14** of the **Supplement** illustrates the substantially higher ICER of PrEP relative to a needle–syringe exchange program.

Second, because we are evaluating the effect of a national program, our input parameters as well as our results reflect population-level averages. Where possible, we accounted for this in sensitivity analyses: For instance, we assessed the value of PrEP+screen+ART over a range of HIV-risk scenarios. The model examines PWID as one risk group, although PWID have differing levels of risk (**Supplement**, section 4.1). Two important dimensions along which PWID could be stratified are substance injected, which affects frequency of injecting and effectiveness of opioid agonist therapy, and sexual behavior (for example, PWID who are also MSM). Despite a lack of data to properly stratify the model in these ways, our findings do suggest that PrEP would deliver greater value for both of these higher-risk subpopulations. The potential value for PrEP in high-risk/high-prevalence communities underscores the importance of localized epidemiologic surveillance to inform both future models and policy.

Third, new ART initiation guidelines will likely increase the number of virally suppressed individuals in coming years (37). Without data on future changes, we calibrated the model to reflect current practice patterns. More individuals on ART, while increasing HIV prevalence because of the longer lifespan of treated individuals, would decrease the risk for HIV transmis-

sion, making other prevention programs seem less favorable. Thus, if anything, our estimate of a high cost per QALY gained for PrEP+screen+ART is biased favorably toward the intervention.

Fourth, a concern about PrEP is the facilitation of drug-resistant HIV. However, resistance did not occur in the Bangkok Tenofovir Study (8). Moreover, the CDC's frequent screening guidelines decrease the likelihood of drug-resistant mutations in practice (5, 8, 9, 64, 65).

Finally, although we address parameter uncertainty within the model, we cannot address structural uncertainties, such as the choice of risk categories or transmission pathways (66). This is a limitation of disease modeling and should be considered when our conclusions are being evaluated.

Our study assesses the total population health benefits and costs of PrEP for U.S. PWID within a dynamic transmission framework. Other studies have explored the cost-effectiveness of a national PrEP program for MSM and heterosexuals, where efficacy estimates are higher than in the PWID population (5–8), and have found that the intervention is both expensive in absolute cost and most valuable in highest-risk subpopulations (10, 11). Similarly, we find that greater adherence and higher transmission risk increase the value of the intervention, but at current costs a substantial budgetary increase of $44 billion would be required to deliver PrEP+screen+ART to 25% of PWID over 20 years. For similar cost, greater benefit can be delivered by combining PrEP and screening services with enhanced ART provision for those who do become infected, highlighting the importance of the CDC's recommendations regarding services to be administered with PrEP (9).

In conclusion, we find that PrEP programs provide optimal value when combined with frequent HIV screening and enhanced ART provision for those who become infected. PrEP+screen+ART for PWID in the United States can reduce HIV incidence and have health benefits for the entire U.S. population, but it is currently expensive both in absolute terms and in cost per QALY gained. The cost-effectiveness of PrEP+screen+ART depends greatly on the efficacy and cost of PrEP, as well as transmission rates in the covered population. Thus, PrEP+screen+ART has increased value for PWID with high levels of adherence or for PWID most at risk for HIV.

From Stanford University, Stanford, California, and Veterans Affairs Palo Alto Health Care System, Palo Alto, California.

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Requests for Single Reprints: Cora L. Bernard, MS, Department of Management Science and Engineering, Huang Engineering Center, 475 Via Ortega, Stanford University, Stanford, CA 94305-4026; e-mail, clb210@stanford.edu.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Ms. Bernard: Department of Management Science and Engineering, Huang Engineering Center, 475 Via Ortega, Stanford University, Stanford, CA 94305-4026.
Dr. Brandeau: Department of Management Science and Engineering, Huang Engineering Center, 475 Via Ortega, Stanford University, Stanford, CA 94305-4026.
Dr. Humphreys: Stanford School of Medicine, Department of Psychiatry, 401 N. Quarry Road, Room C-305, Stanford, CA 94305-5717.
Dr. Bendavid: Center for Primary Care and Outcomes Research/Center for Health Policy, Stanford University, 117 Encina Commons, Room 204, Stanford, CA 94305-6019.
Dr. Holodniy: AIDS Research Center, VA Palo Alto Health Care System, 3801 Miranda Ave. (132), Palo Alto, California 94304-5107.
Mr. Weyant: Department of Management Science and Engineering, Huang Engineering Center, 475 Via Ortega, Stanford University, Stanford, CA 94305-4026.
Dr. Owens: Center for Primary Care and Outcomes Research/Center for Health Policy , Stanford University, 117 Encina Commons, Stanford, CA 94305-6019.
Dr. Goldhaber-Fiebert: Center for Primary Care and Outcomes Research/Center for Health Policy, Stanford University, 117 Encina Commons, Room 217, Stanford, CA 94305-6019.

Author Contributions: Conception and design: E. Bendavid, C.L. Bernard, M.L. Brandeau, J.D. Goldhaber-Fiebert, K. Humphreys, D.K. Owens, C. Weyant.
Analysis and interpretation of the data: C.L. Bernard, M.L. Brandeau, J.D. Goldhaber-Fiebert, M. Holodniy, K. Humphreys, D.K. Owens, C. Weyant.
Drafting of the article: C.L. Bernard, J.D. Goldhaber-Fiebert, D.K. Owens.
Critical revision for important intellectual content: E. Bendavid, C.L. Bernard, M.L. Brandeau, J.D. Goldhaber-Fiebert, M. Holodniy, K. Humphreys, D.K. Owens.
Final approval of the article: E. Bendavid, C.L. Bernard, M.L. Brandeau, J.D. Goldhaber-Fiebert, M. Holodniy, K. Humphreys, D.K. Owens, C. Weyant.
Statistical expertise: C.L. Bernard, J.D. Goldhaber-Fiebert, D.K. Owens.
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