

Expanded HIV Screening in the United States: Effect on Clinical Outcomes, HIV Transmission, and Costs

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Background: An extensive literature supports expanded HIV screening in the United States. However, the question of whom to test and how frequently remains controversial.

Objective: To inform the design of HIV screening programs by identifying combinations of screening frequency and HIV prevalence and incidence at which screening is cost-effective.

Design: Cost-effectiveness analysis linking simulation models of HIV screening to published reports of HIV transmission risk, with and without antiretroviral therapy.

Data Sources: Published randomized trials, observational cohorts, national cost and service utilization surveys, the Red Book, and previous modeling results.

Target Population: U.S. communities with low to moderate HIV prevalence (0.05% to 1.0%) and annual incidence (0.0084% to 0.12%).

Time Horizon: Lifetime.

Perspective: Societal.

Interventions: One-time and increasingly frequent voluntary HIV screening of all adults using a same-day rapid test.

Outcome Measures: HIV infections detected, secondary transmissions averted, quality-adjusted survival, lifetime medical costs, and societal cost-effectiveness, reported in discounted 2004 dollars per quality-adjusted life-year (QALY) gained.

Results of Base-Case Analysis: Under moderately favorable assumptions regarding the effect of HIV patient care on secondary transmission, routine HIV screening in a population with HIV prevalence of 1.0% and annual incidence of 0.12% had incremental cost-effectiveness ratios of \$30 800/QALY (one-time screening), \$32 300/QALY (screening every 5 years), and \$55 500/QALY (screening every 3 years). In settings with HIV prevalence of 0.10% and annual incidence of 0.014%, one-time screening produced cost-effectiveness ratios of \$60 700/QALY.

Results of Sensitivity Analysis: The cost-effectiveness of screening policies varied within a narrow range as assumptions about the effect of screening on secondary transmission varied from favorable to unfavorable. Assuming moderately favorable effects of antiretroviral therapy on transmission, cost-effectiveness ratios remained below \$50 000/QALY in settings with HIV prevalence as low as 0.20% for routine HIV screening on a one-time basis and at prevalences as low as 0.45% and annual incidences as low as 0.0075% for screening every 5 years.

Limitations: This analysis does not address the difficulty of determining the prevalence and incidence of undetected HIV infection in a given patient population.

Conclusions: Routine, rapid HIV testing is recommended for all adults except in settings where there is evidence that the prevalence of undiagnosed HIV infection is below 0.2%.

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Early detection and timely access to medical care can substantially improve the course of HIV disease among infected persons (1, 2). Whether they also reduce the risk for transmitting the virus to others (3–7) is not clear because survival gains from antiretroviral therapy prolong infectious lifetimes and may lead to complacency toward HIV risk behavior (8). Recent studies report increases in HIV infections, other sexually transmitted diseases, and sexual risk behaviors in vulnerable populations (9–11); access to effective antiretroviral therapy may also be associated with sexual risk-taking (12–14).

As with any new method of screening for chronic disease (for example, hypercholesterolemia and breast, cervical, prostate, and colon cancer [15–19]), the challenge facing both physicians and public health experts is to determine whom to test for HIV infection and how frequently. We address the particular difficulties posed by HIV infection, an infectious disease whose detection and treatment have implications for both the individual being tested and the broader population.

METHODS

Study Design

We used a simulation model (20) to project the performance of increasingly frequent HIV screening of all adults using a rapid testing protocol (21–23) in communi

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Context

Two unsolved problems in HIV screening policy are the maximum cost-effective screening frequency and the minimum HIV prevalence for cost-effective screening.

Contribution

The authors used a decision model to estimate the cost-effectiveness of same-day rapid test HIV screening, considering outcomes experienced by the infected person and his or her sexual contacts. One-time screening was cost-effective when the prevalence of HIV was as low as 0.20%. Repeated screening every 5 years was cost-effective with an annual incidence of 0.0075% and an HIV prevalence of 0.45%.

Cautions

The authors did not count HIV transmission from infected contacts.

Implications

Screening for HIV is cost-effective when HIV prevalence is similar to that of average-risk populations.

—The Editors

ties with independently varying levels of prevalence of undetected HIV infection (0.05% to 1.0%) and annual HIV incidence (0.0084% to 0.12%). We considered medical

outcomes at the level of the individual HIV-infected patient and transmission at the population level (Appendix, available at www.annals.org). To evaluate transmission-related effects, we used published data on secondary HIV transmission and model-based estimates of lifetime costs and health-related quality-of-life losses attributable to new HIV infections. Following the recommendations of the U.S. Panel on Cost-Effectiveness in Health and Medicine (24), we evaluated outcomes from the societal perspective using a 3% annual discount rate. We expressed comparative value in 2004 U.S. dollars per quality-adjusted life-year (QALY) gained and used multiway sensitivity analysis to examine the effects of uncertainty about the data in the model.

Individual-Level Simulation

We used a widely published computer simulation, the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) Model, to characterize the progress of HIV disease in an infected individual (20, 25–27). The “health states” summarize the essential elements of patient status (CD4 cell count and HIV RNA level, history of opportunistic infections, quality of life, and resource use) (28). Effective antiretroviral therapy increases the probability of viral suppression and concomitant CD4 cell count increases, according to clinical trial results. Treated patients receive a sequence of up to 4 therapeutic regimens in which efficacy progressively diminishes. The model tracks

Table 1. Summary of Key Model Input Parameters and Sources for Efficacy of Antiretroviral Therapy and Rapid Test Protocol*

Variable	Value	Reference
Efficacy of antiretroviral therapy at the individual-patient level†		
Starting criterion	CD4 cell count < 0.2 × 10 ⁹ cells/L	
First-line regimen	80%	32
Second-line regimen	68%	33
Third-line regimen	56%	34
Fourth-line regimen	30%	35
Rapid test protocol‡		
Sensitivity, pre-seroconversion	2.5%	21–23, 36
Sensitivity, post-seroconversion	99.6%	21–23, 36
Specificity, pre-seroconversion	97.5%	21–23, 36
Specificity, post-seroconversion	97.5%	21–23, 36
Test acceptance rate	80% (67%–100%)	23
Rate of HIV-infected persons returning for test results and linkage to care	97% (50%–100%)	22, 23, 37
HIV-negative return rate	100% (50%–100%)	22, 23, 37
Rapid test cost	\$7 (\$1–\$100)	23, 36
Confirmatory test cost§	\$40	23, 36
Quality-of-life cost of initially false-positive results (quality-adjusted life-day)	14 (0–30)	See text
Pre-test counseling cost	\$25 (\$0–\$100)	23, 36
Post-test linkage/counseling costs for HIV-positive persons	\$24 (\$0–\$100)	23, 36
Post-test counseling costs for HIV-negative persons	\$13 (\$0–\$50)	23, 36
Probability of receiving HIV screening test (per month, current practice)	1/60 (0–1/36)	38

* Baseline estimates used in the analysis are reported with ranges used for sensitivity analysis, when applicable, in parentheses. Sources use reference numbers cited in the main body of the text.

† At the individual-patient level, antiretroviral efficacy is defined in terms of the rate of HIV RNA suppression below 400 copies/mL at 48 weeks. “Line” refers to the number of the regimen in sequence.

‡ Antibody test with results within 30 minutes.

§ All positive rapid test results were confirmed by using enzyme-linked immunosorbent assay repeated in duplicate, followed by a Western blot (36).

|| Defined as the monthly probability of receiving a background enzyme-linked immunosorbent assay HIV test. Thus, a value of (60 months)⁻¹ implies an average time to HIV detection of 5 years, even in the absence of expanded HIV screening.

Table 2. Summary of Key Model Input Parameters and Sources for Target Population Characteristics and Effect of Patient Care on HIV Transmission*

Variable	Undetected HIV Prevalence	Annual HIV Incidence	Lifetime HIV Risk	Reference
Target population characteristics				
Baseline population scenario	1.0%	0.12%	6.1%	39, 40
U.S. general population scenario	0.10%	0.014%	0.70%	37, 42
Low-risk population scenario	0.05%	0.0084%	0.42%	Hypothetical
Effect of HIV patient care on HIV transmission (reproductive number)				
Mechanism of HIV detection	No Effect of Screening and Treatment on Transmission	Favorable Transmission Impact	Adverse Transmission Impact	
Background detection	1.44	1.27 (0.9)†	1.61	43, 44
Opportunistic infection presentation	1.44	1.44 (1.27)†	1.44	43, 44
Screening	1.44	1.27 (0.9)†	1.61	43–46
Never detected	1.44	1.44	1.44	43

* Baseline estimates used in the analysis are reported with ranges used for sensitivity analysis, when applicable, in parentheses. Sources use reference numbers cited in the main body of the text.

† In sensitivity analysis, we also considered a more optimistic set of values that capture the combined benefits of both treatment-related, virologic reductions in infectivity and counseling-related attenuations in risk behavior (6, 36, 44). These values are presented in parentheses.

each patient's clinical course from entry until death. It then aggregates the simulated clinical courses of individuals to estimate the average quality-adjusted survival and costs for screening and treatment alternatives.

The model's screening simulation accounts for whether and when detection, follow-up, and linkage to HIV care occur (29–31). Detection of HIV takes place through 1 of 3 discrete mechanisms: a specific HIV screening program; nonroutine, “background” testing (for example, testing in medical settings, sexually transmitted disease clinics, or correctional institutions or for employment or immigration purposes); and clinical presentation with an AIDS-defining illness. While the model simulates the course of HIV illness for all infected individuals, only patients with detected HIV infection who are successfully linked to care are eligible for antiretroviral therapy and opportunistic infection prophylaxis.

Key input data are (21–23, 32–46) provided in Tables 1 and 2. We considered rapid testing because of its current policy relevance (47, 48). Rapid testing elicits higher levels of test acceptance, follow-up, and linkage to care (baseline overall likelihood of test acceptance, follow-up, and linkage is 77.6% vs. 32.6% for standard antibody testing [29, 30]). However, rapid testing may exacerbate the distress associated with false-positive results, since the patients learn the preliminary findings before Western blot confirmation. We conducted extensive sensitivity analysis on the morbidity penalty (base value, 14 quality-adjusted life-days) attributable to false-positive results, ranging from no penalty to 30 quality-adjusted life-days.

Target Populations

We considered all adults (mean age, 33 years) with unknown HIV status in U.S. health care settings. The baseline analysis uses a population (1.0% undetected HIV prevalence, 0.12% annual incidence, and 6.1% lifetime HIV infection risk) that reflects pre–September 2006 guidelines for HIV screening (39). We also simulated the

effects of screening the “U.S. general population” (0.1% prevalence, 0.014% annual incidence, and 0.7% lifetime HIV infection risk), using the widely cited estimate of 252 000 to 312 000 undetected, prevalent HIV infections and 40 000 annual infections in a population of 290 million (42). In sensitivity analysis, we considered additional target populations, varying both the prevalence (0.05% to 1.0%) and the annual incidence (0.0084% to 0.12%) as estimated by interpolating and extrapolating the specific values reported here.

Effect of Patient Care on HIV Transmission

To describe secondary HIV transmission, we used the basic reproductive number, R_0 , a central concept in infectious disease epidemiology. R_0 can be interpreted as the lifetime number of subsequent infections, regardless of method of transmission, attributable to a single infected individual in a susceptible population. R_0 captures the interaction of 3 factors—HIV transmission efficiency; number of risky contacts; and duration of infectiousness—in producing a summary measure of the power of an infection to emerge and to persist (49). When R_0 is greater than 1, the average infected person generates at least 1 subsequent case and an epidemic can ensue; when R_0 is less than or equal to 1, the epidemic cannot persist.

We applied a baseline R_0 of 1.44 to all cases of undetected HIV infection and to situations where we assume no effect of screening and treatment (Table 2) (43). We also applied this value to cases of HIV infection detected through presentation with an opportunistic infection, an assumption that adopts the conservative view that individuals who decline HIV testing will respond less favorably to behavioral counseling (50). The “favorable transmission impact” scenario reflects the potential virologic benefit of antiretroviral therapy to reduce ($R_0 < 1.44$) HIV transmission. The value R_0 of 1.27 applies to all individuals identified through HIV screening (43). The “adverse transmission impact” scenario assumes that patients with screening

Table 3. Mechanisms of Detection through Alternative Screening Practices, Baseline Population Scenario*

Mechanism of Detection	Proportion of HIV-Infected Persons Detected, %				
	No Specific Screening Program	One-Time Rapid Screening Test	Rapid Screening Test Every 5 Years	Rapid Screening Test Every 3 Years	Rapid Screening Test Annually
Background screening	59.2	54.9	36.0	28.0	13.7
Presentation with opportunistic infection	31.7	26.6	14.5	10.9	6.1
Screening	0.0	10.0	44.7	57.6	78.7
Never detected	9.1	8.5	4.8	3.6	1.5

* Prevalence = 1%; annual incidence = 0.12%; lifetime HIV risk = 6.1%. Values expressed as percentages; some may not add up to 100% due to rounding.

detected HIV infection are at higher risk for transmitting HIV, presumably because of treatment-related behavioral disinhibition (45, 46). Lacking scientific evidence, we arbitrarily chose an R_0 value of 1.61, which is as far above the baseline value ($R_0 = 1.44$) as the “favorable impact” value ($R_0 = 1.27$) is below it.

Recognizing the critical role played by the transmission impact assumption, we conducted extensive sensitivity analyses by considering values ranging from -1.00 to 1.00 for ΔR_0 , the difference between R_0 in the presence and absence of care. ΔR_0 can be interpreted as the lifetime number of secondary HIV infections averted when an HIV-infected person in a susceptible population is identified by screening, counseled, and linked to treatment. By using ΔR_0 to represent the effect of screening on transmission, we could estimate the incremental cost-effectiveness ratios without specifying a base value for R_0 .

Population-Level Analysis

The expected number of secondary infections under a given HIV screening program is a key outcome measure. To estimate it, we first obtained the proportions of HIV infections identified by each detection mechanism from the simulation model (Table 3) (29). We used these proportions to compute a weighted average of the reproductive numbers for each mechanism for HIV detection (Table 2). This weighted average represents our estimate of the number of secondary transmissions per infected individual. We calculated total transmissions by multiplying this value by the lifetime risk for HIV infection (Table 2) in the target population.

We assigned each secondary infection a survival loss and an economic cost (51). We obtained a survival loss of 30.49 discounted quality-adjusted life-months (QALMs) by comparing a model-based estimate of life expectancy for a secondary infection—assuming current standards of care (52) and HIV-specific quality-of-life weights (53)—with survival without HIV infection. We obtained non-HIV, quality-adjusted survival from U.S. life tables (54) and age-specific, SF-6D utility weights from the Medical Expenditure Panel Survey (55, 56). (The SF-6D is a health state classification system based on 6 dimensions [“6D”] of the SF-36 health survey.) To determine the \$210 100 cost per secondary infection, we reduced a model-based estimate of

discounted lifetime costs of HIV patient care (52) to reflect offsetting, non-HIV-related medical costs (57) during the additional life span lived by avoiding HIV infection. We reduced both survival losses and incremental medical care costs to account for a delay of 14 years from the time of HIV transmission until entry into HIV care: 6 years for the average passage of time between primary HIV infection and a secondary HIV transmission and 8 years for the average time between a secondary HIV transmission and eventual entry into HIV care (58). In sensitivity analysis, we eliminated additional discounting (that is, secondary infections were assigned a survival loss of 46.18 QALMs and an economic cost of \$318 200).

Role of the Funding Source

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RESULTS

Baseline Analysis

When we restricted attention to clinical outcomes affecting only the individual infected patient, current practices of HIV detection (including but not limited to screening) produced discounted quality-adjusted life expectancy of 279.91 QALMs or 23.32 QALYs (Table 4). Discounted lifetime HIV-related costs averaged \$7640/person. Adding a single, rapid HIV screening conferred an additional 0.32 QALM (about 10 days in good health) per program participant at an average additional cost of \$1000 (\$40 for testing and \$960 for care). Viewed strictly in terms of individual-level effects, therefore, the addition of a single rapid screening costs \$37 100 per QALY gained. Increasing the intensity of screening to every 5 and 3 years would cost \$60 100 and \$96 800, respectively, per QALY. Annual screening conferred no additional health benefit over screening every 3 years: False-positive results and their associated quality-of-life losses offset the survival gains.

When we broadened the analysis to take into account

secondary HIV transmission, current practices resulted in 87.4 cases of secondary HIV transmission per 1000 members of the HIV-uninfected susceptible population. Under current policy, secondary transmission imposes a per capita survival “penalty” of 2.66 QALMs and \$18 360 in additional treatment costs. We applied these same survival and cost penalties to all screening strategies under the “no effect of screening and treatment on transmission” scenario. In this scenario, we assumed that expanded HIV detection and treatment improve the course of disease in the individual patient but have no incremental impact—as compared with current practice—on secondary transmissions. The reproductive number was assumed to be constant across all mechanisms of HIV detection (Table 2). Hence, as a consequence of the model structure and these assumptions, secondary transmission effects in this scenario did not affect cost-effectiveness ratios for expanded screening versus current practice.

Favorable Transmission Impact Scenario

With no specific screening program and favorable transmission assumptions ($R_0 = 1.27$ for individuals identified through HIV screening), 81.3 secondary HIV transmissions per 1000 population members occurred. These imposed a per capita survival “penalty” of 2.48 QALMs and \$17 070 in additional treatment costs. Adding a single, rapid screening lowered secondary HIV transmission rates to 80.7 per 1000 population, reducing per capita survival and cost penalties to 2.46 QALMs and \$16 950. Combining these population-level effects of favorable assumptions about the benefits of screening on transmission with the individual-level outcomes described earlier improved the cost-effectiveness ratio of a single, rapid screening to \$30 800/QALY from \$37 100/QALY (when we assumed no effect of screening and treatment on transmission). Rapid screening every 5 and 3 years had incremental cost-effective-

Table 4. Survival, Cost, and Cost-Effectiveness Results for HIV Screening Strategies in the Baseline Population*

Variable	No Specific Screening Program	One-Time Rapid Screening Test	Rapid Screening Test Every 5 Years	Rapid Screening Test Every 3 Years	Rapid Screening Test Annually
Part I: individual-patient-level analysis					
Individual-patient-level survival, QALMs					
Base survival in target population	279.91	279.91	279.91	279.91	279.91
Individual quality-adjusted survival gain from testing and care	–	0.32	0.53	0.58	0.51
Total individual-patient-level survival	279.91	280.24	280.44	280.49	280.43
Individual-patient-level costs, \$					
Base HIV care cost in target population	7640	7640	7640	7640	7640
Additional screening costs	–	40	190	300	860
Additional individual HIV care costs induced by testing	–	960	1840	2140	2570
Total individual-patient-level costs	7640	8640	9670	10 080	11 080
Individual-patient-level cost-effectiveness, \$/QALY†	–	37 100	60 100	96 800	Dominated‡
Part II: Population-level analysis					
No effect of screening/treatment on transmission scenario					
Secondary HIV transmissions per 1000 persons	87.4	87.4	87.4	87.4	87.4
Secondary transmission survival penalty, QALMs	2.66	2.66	2.66	2.66	2.66
Secondary transmission care cost penalty, \$	18 360	18 360	18 360	18 360	18 360
Total survival, QALMs	277.25	277.57	277.78	277.83	277.76
Total costs, \$	26 000	27 000	28 020	28 440	29 440
Cost-effectiveness ratio, \$/QALY	–	37 100	60 100	96 800	Dominated‡
Favorable transmission impact scenario					
Secondary HIV transmissions per 1000 persons	81.3	80.7	79.1	78.6	77.9
Secondary transmission survival penalty, QALMs	2.48	2.46	2.41	2.40	2.37
Secondary transmission care cost penalty, \$	17 070	16 950	16 610	16 500	16 360
Total survival, QALMs	277.44	277.78	278.03	278.10	278.05
Total costs, \$	24 720	25 590	26 280	26 590	27 440
Cost-effectiveness ratio, \$/QALY	–	30 800	32 300	55 500	Dominated‡
Adverse transmission impact scenario					
Secondary HIV transmissions per 1000 population	93.5	94.1	95.7	96.2	96.9
Secondary transmission survival penalty, QALMs	2.85	2.87	2.92	2.93	2.95
Secondary transmission care cost penalty, \$	19 640	19 760	20 110	20 210	20 360
Total survival, QALMs	277.06	277.37	277.52	277.56	277.46
Total costs, \$	27 280	28 410	29 770	30 300	31 440
Cost-effectiveness ratio, \$/QALY	–	44 200	105 700	173 400	Dominated‡

* Prevalence = 1%, annual incidence = 0.12%, lifetime HIV risk = 6.1%. QALM = quality-adjusted life month; QALY = quality-adjusted life-year.

† Cost-effectiveness = the difference in cost divided by the difference in quality-adjusted life expectancy for each strategy compared with the next least costly strategy. All survival, cost, and cost-effectiveness outcomes are reported on a present-value basis using an annual discount rate of 3% (24). Because of rounding, reported totals may not sum precisely and ratios may not precisely equal the ratios of reported costs and effects.

‡ When compared with “rapid test every 3 years,” this strategy is costlier and less effective. By widely accepted convention, such strategies are labeled as “dominated” and cost-effectiveness ratios are not reported (24).

ness ratios of \$32 300/QALY and \$55 500/QALY, respectively. The additional benefits of annual rapid screening did not offset the effects of increased false-positive results from screening more often.

Adverse Transmission Impact Scenario

Under adverse antiretroviral therapy impact assumptions ($R_0 = 1.61$ for individuals identified through HIV screening), we observed 93.5 secondary HIV transmissions per 1000 population members, with no specific screening program. One-time rapid screening increased secondary HIV transmissions to 94.1 per 1000 population members, which increased the per capita survival penalty from 2.85 to 2.87 QALMs and increased per capita additional care costs from \$19 640 to \$19 760. Because there were still survival benefits for the individual patients detected by screening, a single screening nonetheless conferred a positive net health benefit; however, the cost per QALY gained increased from \$37 100 in the “no impact” scenario to \$44 200. Under the adverse effect scenario, the incremental cost-effectiveness of screening every 3 to 5 years ex-

ceeded \$100 000/QALY; annual screening produced higher costs and poorer quality-adjusted survival.

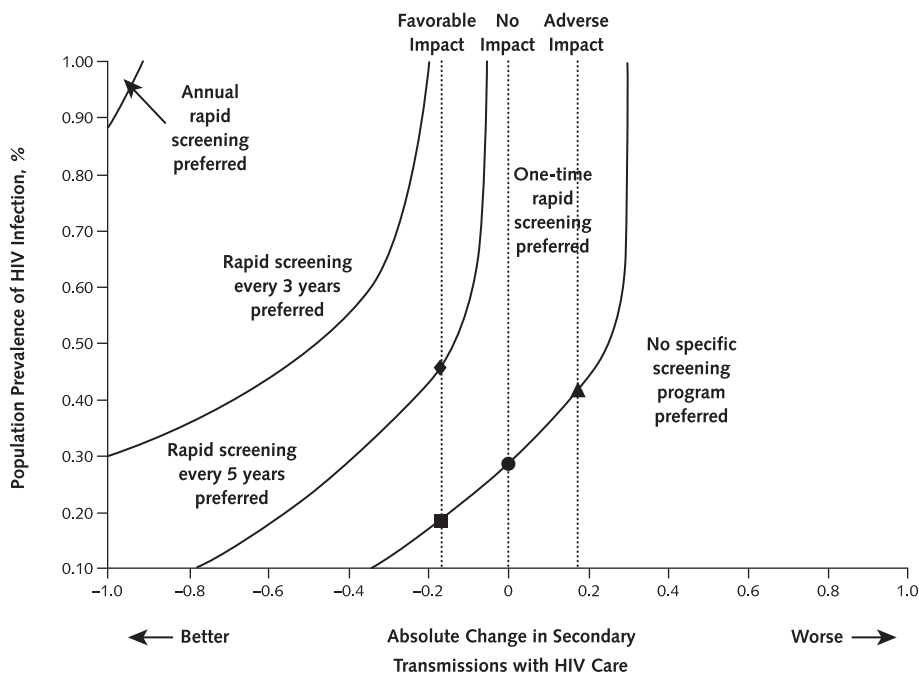
Alternative Target Population

When we applied the same screening interventions in a population with 0.1% prevalence and 0.014% annual incidence, a single rapid test had an incremental cost-effectiveness ratio of \$72 400/QALY when viewed only in terms of individual patient-level outcomes (“no impact” scenario). That ratio improved to \$60 700/QALY under the “favorable impact” scenario; it worsened to \$86 200/QALY under “adverse impact” assumptions. With repeated screening in this lower-incidence population, the negative impact of false-positive results on health-related quality of life more than offset any screening-related survival benefits.

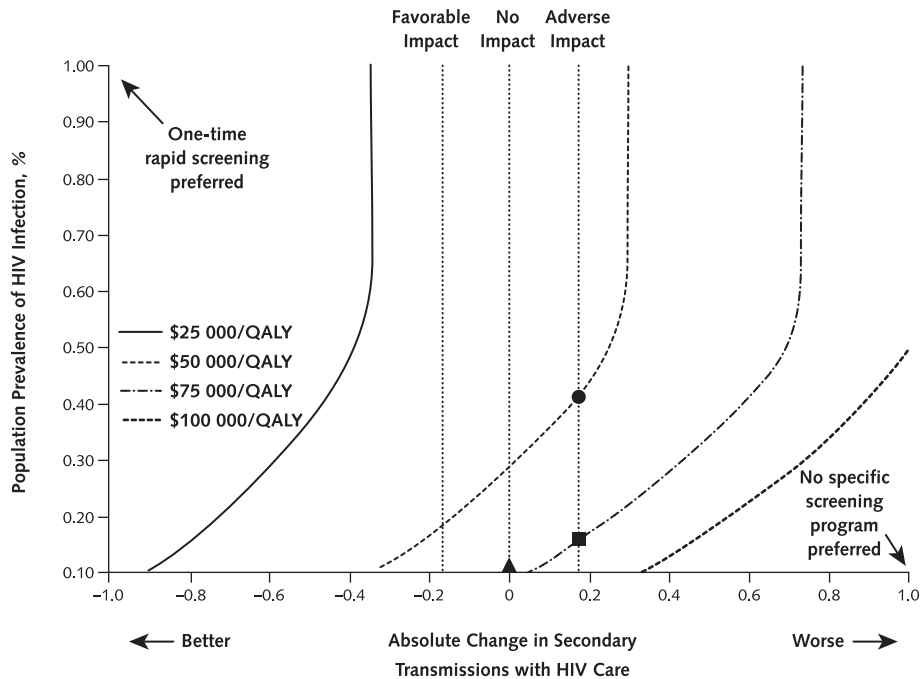
Guidance for Program Design

Our findings were not sensitive to plausible variation in testing program characteristics, cost structures, discount rates, or health-related quality-of-life valuations. However, we found more favorable cost-effectiveness ratios when we assumed less background testing, higher HIV prevalence

Figure 1. Recommended strategy regions: \$50 000 per quality-adjusted life-year threshold.



The figure recommends an HIV screening policy as a function of both the HIV prevalence in the target population (*vertical axis*) and the impact of HIV patient care on secondary transmission, ΔR_0 (*horizontal axis*). ΔR_0 can be interpreted as the lifetime number of secondary HIV infections averted when an HIV-infected person in a susceptible population is identified, counseled, and linked to treatment via HIV screening. Each prevalence value is associated with a specific incidence assumption (see Methods section for details). The figure recommends HIV screening policies, assuming that society is prepared to pay up to \$50 000 per additional quality-adjusted life-year of health for its citizens. The dotted lines represent the 3 transmission impact scenarios described in Table 2: “favorable impact,” “no effect of screening and treatment on transmission impact,” and “adverse impact.” The curves denote the circumstances under which a given HIV screening strategy is preferred. For example, assuming no impact on secondary transmission, a one-time screening is recommended for prevalences greater than 0.28% (*solid circle*). Assuming a favorable transmission impact, the one-time screening threshold falls to 0.20% (*solid square*); with an adverse transmission impact, it increases to 0.40% (*solid triangle*). The threshold population for screening every 5 years (assuming favorable transmission impact) is HIV prevalence of 0.45% and annual incidence of 0.0075% (*solid diamond*).

Figure 2. One-time screening versus no specific screening program: sensitivity to cost-effectiveness threshold.

The figure identifies the evolution of the boundary between current practice (that is, no specific screening program) and one-time HIV screening as a function of 3 factors: 1) the prevalence of HIV in the target population (*vertical axis*); 2) the impact of care on secondary transmission, ΔR_0 (*horizontal axis*); and 3) the value that society is prepared to pay to purchase an additional quality-adjusted life-year (QALY) of health for its citizens (as measured by the threshold cost-effectiveness ratio). Each prevalence value is associated with a specific incidence assumption (see Methods section for details). The figure reports results for threshold cost-effectiveness ratios ranging from \$25 000 to \$100 000 per QALY. The dotted lines represent the 3 transmission impact scenarios described in Table 2: “favorable impact,” “no effect of screening and treatment on transmission,” and “adverse impact.” The curves represent the borders of regions over which a given HIV screening strategy is preferred. For example, assuming that society is willing to pay up to \$50 000/QALY and an adverse transmission impact, one-time screening is recommended for prevalences above 0.40% (*solid circle*); if society is willing to pay even more (up to \$75 000/QALY), one-time screening is recommended for prevalences above 0.15% (*solid square*). Assuming no effect of screening and treatment on transmission and a societal willingness to pay \$75 000 per additional QALY, one-time screening is recommended for prevalences above 0.10% (*solid triangle*). At a societal willingness to pay of \$100 000/QALY, one-time screening is preferred under almost all plausible scenarios.

and incidence, and a greater impact of screening and treatment on secondary transmission, as measured by ΔR_0 (initial values = -0.17 , 0.00 , and 0.17 in the favorable impact, no impact, and adverse impact scenarios, respectively). **Figure 1** offers recommended HIV screening policies, assuming that society is prepared to pay up to \$50 000 to purchase an additional QALY of health for its citizens. Undetected HIV prevalence in the screened population is the principal consideration in choosing to initiate a first screening. If it is assumed that antiretroviral therapy has no impact on secondary transmission, one-time screening is recommended for prevalences greater than 0.28%. With a favorable transmission impact ($\Delta R_0 = -0.17$), the lowest prevalence for which one-time screening is recommended falls to 0.20%; with adverse transmission impact assumptions ($\Delta R_0 = 0.17$), it rises to 0.40%. In formulating a policy for repeated screening, both the prevalence and incidence of HIV infection are important. For testing every 5 years (assuming favorable transmission impact), the threshold population has a prevalence of 0.45% for HIV infection and an annual incidence of 0.0075%.

At prevalences of undetected HIV infection above 1.0%, the curves in **Figure 1** are vertical. This suggests that at a higher prevalence of undetected HIV infection in the population, the choice of screening policy no longer depends on the fraction of cases detected; rather, the principal driver of both costs and benefits is the treatment pathway triggered for the comparatively large number of HIV-positive patients identified. The test itself emerges as a critical cost component only at low prevalence (29). **Figure 2** illustrates how decision makers might choose between no specific screening program and one-time screening for a range of cost-effectiveness threshold values. If cost-effectiveness ratios up to \$75 000/QALY define good value for money, one-time screening is recommended for prevalences above 0.10%, even assuming no impact of screening and treatment on transmission. If society is prepared to pay up to \$100 000/QALY, one-time screening is preferred under virtually all plausible scenarios. More frequent screening at lower prevalences would become cost-effective if the 14-day quality-of-life penalty for false-positive reports was smaller (data not shown).

DISCUSSION

Our findings support routine, rapid HIV testing for all adults in the United States as long as the prevalence of undiagnosed HIV infection is above 0.20%. A single rapid HIV screening in such settings delivers value comparable to many commonly employed screening interventions for chronic disease (59). More generally, the prevalence of undetected HIV infection drives the decision to initiate a first screening while HIV incidence drives the choice of retest frequency. For example, repeated screening every 5 years achieves similar value in a population with a prevalence of 0.45% and an annual incidence of 0.0075%.

This analysis supports the new recommendations of the Centers for Disease Control and Prevention calling for routine HIV screening in all adults and adolescents in U.S. health settings (7). Our findings would lead to stronger recommendations than those of the U.S. Preventive Services Task Force (60), which limits its recommendation to individuals at “increased risk” for HIV infection. The Task Force considers the potential harms associated with screening those without risk factors to be greater than the potential benefits. Our analysis suggests that, from both the clinical and economic perspectives, the benefits of routine HIV testing in all adults in the United States outweigh the likely harms.

These results do not confirm the widely held belief that the preventive benefits of HIV screening for uninfected individuals at risk for acquiring HIV infection exceed the medical benefits to infected patients (61, 62). We find that transmission effects are less influential for decision making than suggested, for example, by Sanders and colleagues (63): \$41 700/QALY (excluding transmission) and \$15 100/QALY (including transmission) for one-time HIV screening in populations similar to our baseline. Our results are less optimistic for several reasons. First, we assumed a smaller impact of antiretroviral therapy on HIV infectivity. In our view, the evidence does not support the modeling assumption that high rates of antiretroviral therapy-induced suppression of serum HIV RNA reflect similar rates of eradication of semen or vaginal HIV RNA and, by extension, similar reductions in HIV infectivity. Recent studies report that semen and vaginal fluid contain HIV RNA during treatment and that concentrations of protease inhibitors are much lower in semen or vaginal fluids than in serum (64, 65), suggesting active viral replication within these compartments (66). Second, our analysis captures current uncertainty about the net effect of antiretroviral therapy on secondary HIV transmission (50); longer survival and therefore increased duration of infectiousness and behavioral disinhibition (plausible but unproven) could dampen—and possibly even reverse—any virologic benefits of therapy on transmission. Published assessments of secondary HIV transmission (51) and model-based estimates of R_0 in the presence of antiretroviral therapy (67) suggest point estimates of -0.17 to -0.10 for the param-

eter ΔR_0 . These are estimates; limited evidence suggests that people who learn their HIV status may reduce risky behaviors and that even larger negative values of ΔR_0 —perhaps representing instances where identification of index cases leads to earlier identification of partners (68)—might be achieved (4, 69). Finally, because of discounting, our assumption of a long delay between primary infection and the eventual clinical and economic benefits of averting a secondary transmission attenuates the comparative importance of transmission effects.

Our cost and survival findings differ from those we have previously reported (29). Here, we used updated cost and antiretroviral efficacy data (32–35) and focused entirely on rapid HIV tests (47). Our current assumption of a large quality-of-life penalty for preliminary false-positive reports highlights the tradeoff between increased rates of detection and increased false-positive penalties with greater retest frequencies.

This study has important limitations. First, we restricted attention to “first-generation” secondary transmissions, which understates the total infections attributable to each infected person. Second, we assigned a fixed survival and economic cost to each secondary infection, which does not fully capture variability in the time, mechanism, or likelihood of HIV detection or referral to care. Third, our model did not use recent evidence suggesting that the risk for HIV transmission varies widely over the course of infection (70). Fourth, we did not account for late antiretroviral-related toxicities that may result in cardiac disease or diabetes. Finally, we compared testing all adults, even in low HIV prevalence settings, with current practice, contrary to the previously recommended strategy of testing high-risk patients in high-risk settings (71).

The Centers for Disease Control and Prevention now recommends routine HIV testing for all patients 13 to 64 years of age in health care settings unless a formal survey documents the prevalence of undiagnosed HIV infection to be less than 0.1%. Our analysis arrived at a slightly higher point estimate for the prevalence threshold (0.2%) but entirely supports the shift from targeted screening based on patient risk factors to routine screening based on prevalence and incidence thresholds. Nevertheless, we recognize the difficulty practitioners face in determining whether the prevalence of undiagnosed HIV infection in their practice setting meets a given threshold. Providers may be able to obtain estimates of local prevalence from their state and local health departments. Ideally, public health departments would do formal seroprevalence surveys and cohort studies that could be analyzed to provide HIV prevalence for specific demographic and geographic target groups. Until then, we recommend that providers initiate routine, voluntary HIV screening for all adults in the United States, unless surveillance data in their particular setting, or in similar settings, show an HIV prevalence below 0.2%. We base this recommendation on the findings presented here and on evidence that the prevalence of

screening-detected HIV infection exceeds this threshold in most U.S. health care settings where voluntary HIV screening of all adults has been implemented (72).

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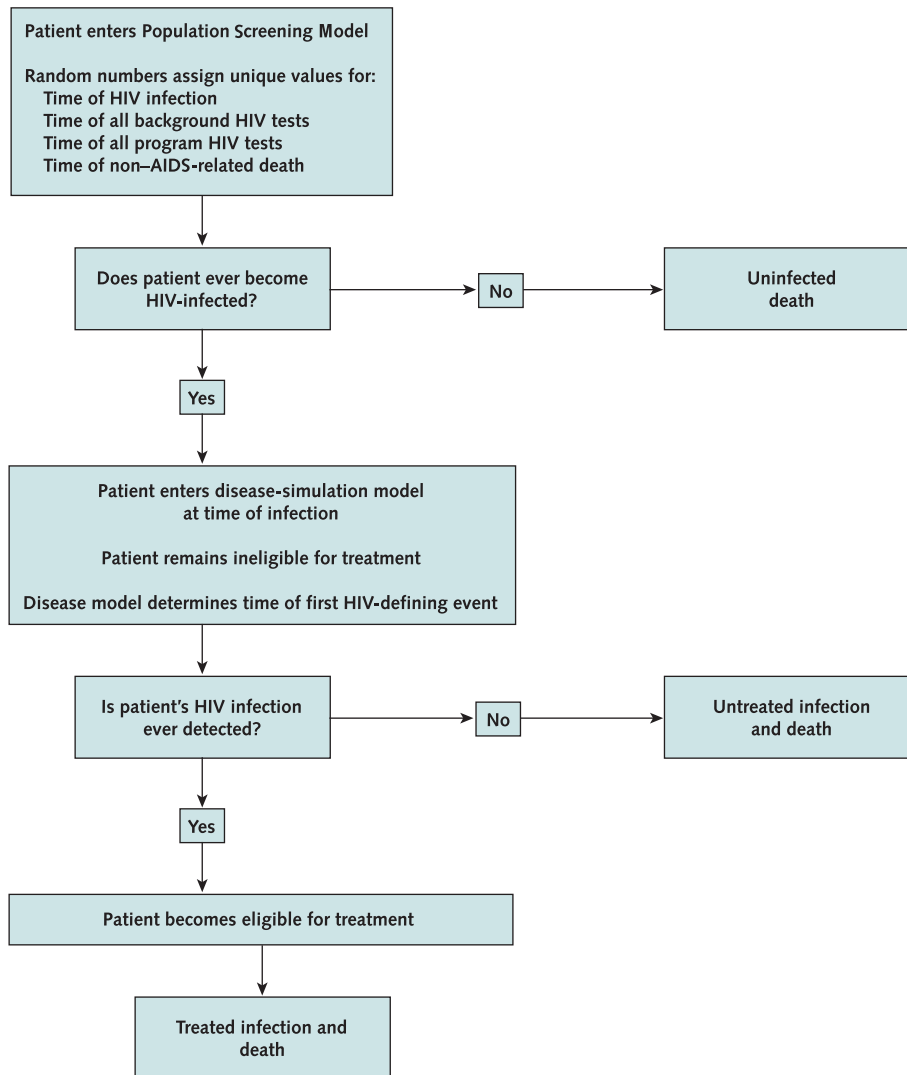
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Appendix Figure. Study flow diagram.



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APPENDIX

Analytic Overview

The Appendix Figure provides a conceptual overview of the analysis. Individuals drawn from the at-risk population enter the Population Screening Model one at a time. Based on the assumed

Appendix Table 1. Incremental Effects of Model Updates: Individual-Patient–Level Analysis*

Test Frequency	Individual Effects Only			Mechanism of Detection, %				Cost-Effectiveness Ratios \$/QALY
	Cost, \$	LMs	QALMs	Background	OI Present	Screening	Never Detected	
EIA								
No test	7642	280.74	279.91	59.20	31.71	0.00	9.09	–
1 time	8425	281.05	280.17	55.89	27.77	7.72	8.61	35 900
Every 60 mo	9282	281.32	280.38	40.95	18.02	35.31	5.73	50 500
Every 36 mo	9722	281.44	280.47	33.80	14.16	47.54	4.50	59 900
Every 12 mo	10 916	281.65	280.62	18.12	7.65	72.10	2.13	94 500
Rapid but no QOL penalty								
No test	7642	280.74	279.91	59.20	31.71	0.00	9.09	–
1 time	8641	281.14	280.25	54.93	26.62	9.98	8.47	36 000
Every 60 mo	9666	281.46	280.49	35.99	14.51	44.66	4.84	50 100
Every 36 mo	10 083	281.57	280.57	28.02	10.88	57.55	3.56	61 000
Every 12 mo	11 080	281.71	280.66	13.67	6.11	78.68	1.53	138 800
Rapid with QOL penalty								
No test	7642	280.74	279.91	59.20	31.71	0.00	9.09	–
1 time	8641	281.14	280.24	54.93	26.62	9.98	8.47	37 100
Every 60 mo	9666	281.46	280.44	35.99	14.51	44.66	4.84	60 100
Every 36 mo	10 083	281.57	280.49	28.02	10.88	57.55	3.56	96 800
Every 12 mo	11 080	281.71	280.43	13.67	6.11	78.68	1.53	Dominated†

* EIA = enzyme immunoassay; LM = life-month; OI = opportunistic infection; QALM = quality-adjusted life-month; QALY = quality-adjusted life-year; QOL = quality of life. † When compared with “rapid test every 36 months,” this strategy is costlier and less effective. By widely accepted convention, such strategies are labeled as “dominated” and cost-effectiveness ratios are not reported (24).

incidence/prevalence of HIV infection as well as life table–based estimates of life expectancy, a random-number generator immediately determines whether the individual will ever be infected with HIV. A simple “IF/THEN” statement makes this determination; uninfected cases never proceed to the Disease Simulation Model. The small fraction of individuals who do become HIV-infected during their lifetimes proceed to the Disease Simulation Model. However, they are ineligible to receive any kind of HIV clinical care or therapy until and unless their infection is identified. Instances where patients die before their infection is detected are represented by the lower NO branch; instances where patients are identified as infected and become eligible for therapy are represented by the lower YES branch. All patients who proceed to the disease simulation model remain there until death.

Incremental Effects of Model Updates

Our analysis contains several important modifications from previous models published by our group (notably, a 2005 paper [29]). These include focusing on rapid versus conventional testing; the inclusion of a large quality-of-life penalty for false-positive results; and taking into account the impact of HIV screening on secondary transmission. To assist readers in interpreting our findings in the context of previous models, we have replicated the baseline analysis reported in the current paper but with a few notable changes in the underlying assumptions. The new analyses, which are summarized in **Appendix Table 1** and **Appendix Table 2**, represent stepwise additions of the rapid testing and false-positive assumptions. The analyses are grouped into 3 sets: 1) baseline analysis using conventional enzyme immunoassay antibody testing rather than rapid testing; 2) rapid testing but assuming no quality-of-life penalty for false-positive results; and 3)

rapid testing under baseline assumptions (including the 14-day quality-of-life penalty for false-positive results).

Appendix Tables 1 and **2** report the effect on costs and QALYs of adding each feature, both with and without taking into account secondary transmission effects. We highlight the following findings from the analysis.

First, costs and survival benefits are uniformly lower for conventional testing than for rapid testing, reflecting the lower participation/detection/linkage rates achieved with conventional tests. Lower participation/detection via conventional testing also explains differences in the mechanism of detection: Under conventional testing, fewer cases are detected via the “screening” program and more cases are detected either via “background” testing or via presentation with an opportunistic infection.

Second, the quality-of-life penalty has no effect on the costs of rapid testing or on the mechanisms of detection under rapid testing. Its only impact is on quality-adjusted survival—and, by extension, on the costs/QALY cost-effectiveness ratios.

Third, compared with rapid testing without a 14-day penalty, quality-adjusted survival is lower under rapid testing with the 14-day penalty. Compared with conventional testing, the incremental benefit of rapid testing (assuming the 14-day penalty) first rises and then falls. This reflects the initial benefits of improved participation/detection/linkage as well as the increasingly harmful role played by false positives with increased test frequency.

Regardless of whether secondary transmission effects are taken into account, the cost-effectiveness differences among the 3 protocols are surprisingly small. This reflects the observation that costs and benefits typically move in lockstep with increased case

Appendix Table 2. Incremental Effects of Model Updates: Population-Level Analysis*

Test Frequency	Total Costs, \$			Total QALMs			Cost-Effectiveness Ratios, \$/QALY		
	Favorable Impact	No Impact	Adverse Impact	Favorable Impact	No Impact	Adverse Impact	Favorable Impact	No Impact	Adverse Impact
EIA									
No test	24 716	25 999	27 282	277.44	277.25	277.06	–	–	–
1 time	25 404	26 782	28 161	277.71	277.51	277.31	Dominated†	35 900	42 600
Every 60 mo	25 987	27 639	29 292	277.95	277.71	277.47	29 400	50 500	82 800
Every 36 mo	26 316	28 079	29 842	278.06	277.80	277.55	38 000	59 900	91 600
Every 12 mo	27 318	29 273	31 228	278.24	277.95	277.67	67 000	94 500	134 400
Rapid but no QOL penalty									
No test	24 716	25 999	27 282	277.44	277.25	277.06	–	–	–
1 time	25 591	26 998	28 405	277.79	277.58	277.38	Dominated†	36 000	42 800
Every 60 mo	26 275	28 023	29 771	278.08	277.83	277.57	29 000	50 100	83 600
Every 36 mo	26 586	28 440	30 295	278.18	277.91	277.64	38 200	61 000	94 300
Every 12 mo	27 436	29 437	31 439	278.29	278.00	277.71	94 800	138 800	211 700
Rapid with QOL penalty									
No test	24 716	25 599	27 282	277.44	277.25	277.06	–	–	–
1 time	25 591	26 998	28 405	277.78	277.57	277.37	31 000	37 100	44 200
Every 60 mo	26 275	28 023	29 771	278.03	277.78	277.52	32 300	60 100	105 700
Every 36 mo	26 586	28 440	32 095	278.10	277.83	277.56	55 500	96 800	173 400
Every 12 mo	27 436	29 437	31 439	278.05	277.76	277.47	Dominated‡	Dominated‡	Dominated‡

* EIA = enzyme immunoassay; QALM = quality-adjusted life-month; QALY = quality-adjusted life-year; QOL = quality of life.

† When compared with “no test,” this strategy is costlier and less effective. By widely accepted convention, such strategies are labeled as “dominated” and cost-effectiveness ratios are not reported (24).

‡ When compared with “rapid test every 36 months,” this strategy is costlier and less effective. By widely accepted convention, such strategies are labeled as “dominated” and cost-effectiveness ratios are not reported (24).

detection, whether the participation rate is 67% or 100% or anything in between.

Except at high retest frequencies, the principal driver of both costs and benefits is not the HIV test itself but the increased number of patients receiving expensive care as a result of improved case detection. The cost-effectiveness ratios associated with conventional testing are always more favorable than for rapid testing with no 14-day penalty. Adding the 14-day penalty further diminishes the attractiveness of rapid testing.

Briefly stated, then, the analysis highlights the tradeoff implicit in the switch from conventional to rapid tests: increased rates of detection and linkage versus increased false-positive penalties.

Incremental Effects of Data Updates

The present analysis uses newer data on cost and efficacy of antiretroviral therapy than those employed in our previous studies. To help readers to understand the impact of these new data, we have reproduced Table 1 from the current manuscript, using the cost and antiretroviral therapy efficacy data used in our 2005 paper (29) (Appendix 3). We highlight the following observations about the results.

Overall, there are no striking differences—either quantitatively or qualitatively—between the output obtained with the *New England Journal of Medicine* input values and the output obtained with updated cost and efficacy data. This is not terribly surprising since the absolute changes in the input data are small and all effects are averaged over large populations comprised pre-

dominantly of HIV-uninfected individuals in whom these input data changes have absolutely no effect.

In every instance, the older data produce marginally lower cost and life-expectancy estimates. This reflects the fact that the older data assumed slightly lower efficacy of antiretroviral therapy and slightly lower costs being incurred over slightly shorter lifespans.

Generally speaking, the older data produce less favorable cost-effectiveness ratios. Here again, however, the overall observation is that there is little difference—either in terms of quantitative magnitude or qualitative importance—between the results obtained with the *New England Journal of Medicine* input values and the results obtained with updated cost and efficacy data.

The Effects of HIV Screening Every 2 Years

Appendix Table 4 reproduces the baseline analysis with the addition of a “screen every 24 months” strategy. The performance of this strategy on every dimension—cost, survival, times to detection, CD4 cell counts at detection, percentage detected via screening, and cost-effectiveness—is intermediate to the strategies of screening every 12 months and every 36 months. Similarly, the curve in Figure 1 denoting settings over which screening every 2 years would be preferred is always intermediate to the curves for the “every 12 months” and “every 36 months” strategies. These observations hold for all target populations and all screening protocols, as well.

Appendix Table 3. Effects of Data Updates*

Variable	No Specific Screening Program	One-Time Rapid Screening Test	Rapid Screening Test Every 5 Years	Rapid Screening Test Every 3 Years	Rapid Screening Test Annually
Part I: individual-patient-level analysis					
Individual-patient-level survival, QALMs					
Base survival in target population	278.81	278.81	278.81	278.81	278.81
Individual quality-adjusted survival gain from testing and care	–	0.15	0.24	0.24	0.10
Total individual-patient-level survival	278.81	278.96	279.05	279.06	278.91
Individual-patient-level costs, \$					
Base HIV care cost in target population	4710	4710	4710	4710	4710
Additional screening costs	–	40	190	300	860
Additional individual HIV care costs induced by testing	–	460	980	1160	1430
Total individual-patient-level costs	4710	5200	5880	6170	7010
Individual-patient-level cost-effectiveness, \$/QALY†	–	40 200	90 400	513 500	Dominated‡
Part II: Population-level analysis					
No effect of screening/treatment on transmission scenario					
Secondary HIV transmissions per 1000 persons	87.4	87.4	87.4	87.4	87.4
Secondary transmission survival penalty, QALMs	2.66	2.66	2.66	2.66	2.66
Secondary transmission care cost penalty, \$	18 360	18 360	18 360	18 360	18 360
Total survival, QALMs	276.15	276.30	276.39	276.39	276.24
Total costs, \$	23 070	23 560	24 230	24 530	25 370
Cost-effectiveness ratio, \$/QALY	–	40 200	90 400	513 500	Dominated‡
Favorable transmission impact scenario					
Secondary HIV transmissions per 1000 persons	81.2	80.7	79.0	78.6	77.9
Secondary transmission survival penalty, QALMs	2.48	2.46	2.41	2.40	2.37
Secondary transmission care cost penalty, \$	17 080	16 950	16 610	16 500	16 360
Total survival, QALMs	276.33	276.50	276.64	276.66	276.54
Total costs, \$	21 790	22 160	22 490	22 670	23 360
Cost-effectiveness ratio, \$/QALY	–	26 800	28 500	100 400	Dominated‡
Adverse transmission impact scenario					
Secondary HIV transmissions per 1000 population	93.5	94.1	95.7	96.2	96.9
Secondary transmission survival penalty, QALMs	2.85	2.87	2.92	2.93	2.95
Secondary transmission care cost penalty, \$	19 640	19 760	20 110	20 210	20 360
Total survival, QALMs	275.96	276.09	276.13	276.12	275.95
Total costs, \$	24 350	24 970	25 980	26 380	27 370
Cost-effectiveness ratio, \$/QALY	–	57 300	307 800	Dominated§	Dominated‡

* Prevalence = 1%, annual incidence = 0.12%, lifetime HIV risk = 6.1%. QALM = quality-adjusted life month; QALY: quality-adjusted life-year.
 † Cost-effectiveness = the difference in cost divided by the difference in quality-adjusted life expectancy for each strategy compared with the next least costly strategy. All survival, cost, and cost-effectiveness outcomes are reported on a present-value basis using an annual discount rate of 3% (24). Because of rounding, reported totals may not sum precisely and ratios may not precisely equal the ratios of reported costs and effects.
 ‡ When compared with “rapid test every 3 years,” this strategy is costlier and less effective. By widely accepted convention, such strategies are labeled as “dominated” and cost-effectiveness ratios are not reported (24).
 § When compared with “rapid test every 5 years,” this strategy is costlier and less effective.

Appendix Table 4. Effects of Biennial HIV Screening*

CDC Threshold Population	Cost-Effectiveness, \$/QALY		
	Favorable Impact	No Impact	Adverse Impact
No test	–	–	–
1 time	30 801	37 115	44 172
Every 60 mo	32 296	60 117	105 699
Every 36 mo	55 462	96 789	173 398
Every 24 mo	237 849	1 102 703	Dominated†
Every 12 mo	Dominated‡	Dominated‡	Dominated‡

* CDC = Centers for Disease Control and Prevention; QALY = quality-adjusted life-year.
 † When compared with “rapid test every 36 months,” this strategy is costlier and less effective. By widely accepted convention, such strategies are labeled as “dominated” and cost-effectiveness ratios are not reported (24).
 ‡ When compared with “rapid test every 24 months,” this strategy is costlier and less effective. By widely accepted convention, such strategies are labeled as “dominated” and cost-effectiveness ratios are not reported (24).