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Economic Savings Versus Health Losses: The Cost-Effectiveness of Generic Antiretroviral Therapy in the United States

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Background: U.S. HIV treatment guidelines recommend branded once-daily, 1-pill efavirenz–emtricitabine–tenofovir as first-line antiretroviral therapy (ART). With the anticipated approval of generic efavirenz in the United States, a once-daily, 3-pill alternative (generic efavirenz, generic lamivudine, and tenofovir) will decrease cost but may reduce adherence and virologic suppression.

Objective: To assess the clinical effect, costs, and cost-effectiveness of a 3-pill, generic-based regimen compared with a branded, coformulated regimen and to project the potential national savings in the first year of a switch to generic-based ART.

Design: Mathematical simulation of HIV disease.

Setting: United States.

Patients: HIV-infected persons.

Intervention: No ART (for comparison); 3-pill, generic-based ART; and branded ART.

Measurements: Quality-adjusted life expectancy, costs, and incremental cost-effectiveness ratios (ICERs) in dollars per quality-adjusted life-year (QALY).

Results: Compared with no ART, generic-based ART has an ICER of $21 100/QALY. Compared with generic-based ART, branded ART increases lifetime costs by $42 500 and per-person survival gains by 0.37 QALYs for an ICER of $114 800/QALY. Estimated first-year savings, if all eligible U.S. patients start or switch to generic-based ART, are $920 million. Most plausible assumptions about generic-based ART efficacy and costs lead to branded ART ICERs greater than $100 000/QALY.

Limitation: The efficacy and price reduction associated with generic drugs are unknown, and estimates are intended to be conservative.

Conclusion: Compared with a slightly less effective generic-based regimen, the cost-effectiveness of first-line branded ART exceeds $100 000/QALY. Generic-based ART in the United States could yield substantial budgetary savings to HIV programs.

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A convenient, frequently prescribed, and currently recommended first-line antiretroviral therapy (ART) regimen is branded tenofovir–emtricitabine–efavirenz, which is coformulated as a single once-daily pill (1). For the first time since the initial U.S. Food and Drug Administration (FDA) approval of combination ART in 1996, there is the potential for a potent and largely generic first-line ART regimen. In January 2012, generic versions of lamivudine became available in the United States (2), and generic versions of efavirenz are expected soon (3). A once-daily, 3-pill regimen of generic efavirenz, generic lamivudine, and branded tenofovir could substantially reduce the costs of first-line ART.

However, even if the suppressive efficacy, tolerability, and safety of generic lamivudine and efavirenz meet the required FDA standards of their proprietary equivalents, at least 2 potential disadvantages remain (**Appendix Table 1**, available at www.annals.org). First, the increased pill burden—3 pills versus 1 pill daily—could hinder adherence and reduce viral suppression, thus leading to worse outcomes (4, 5). Second, although lamivudine is generally considered to be a safe alternative to emtricitabine, lamivudine has been associated with slightly inferior antiretroviral efficacy and an increased frequency of drug resistance on treatment failure in laboratory and clinical studies (6–9). Given these tradeoffs, we sought to assess the clinical effect, cost, and cost-effectiveness of generic-based ART compared with branded coformulated alternatives.

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METHODS

Analytic Overview

We evaluated 3 strategies for HIV-infected persons eligible to initiate an efavirenz-based regimen: no ART (for comparison); 3-pill, generic-based ART consisting of efavirenz (generic), lamivudine (generic), and tenofovir (Viread; Gilead Sciences, Foster City, California); or branded ART, consisting of the 1-pill efavirenz–emtricitabine–tenofovir formulation (Atripla; Gilead Sciences and Bristol-Myers Squibb, Newark, New Jersey). For ease of identification, we refer to the "generic-based ART strategy" even though it contains 1 branded component. In the base case, generic-based ART differs from branded ART in 3 ways. First, viral suppression efficacy in first-line therapy is presumed to be lower because of increased pill burden (poorer adherence) and decreased potency (substitution of lamivudine for emtricitabine). Second, viral suppression efficacy in second-line

therapy is presumed to be lower because of reported increased frequency of M184V mutations associated with failure of first-line viral suppression from lamivudine versus emtricitabine. Finally, first-line drug costs are lower. We varied all of these parameters in sensitivity analyses.

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)–US Model, a previously published mathematical simulation of HIV (10–14), to project clinical outcomes (quality-adjusted life-years [QALYs]) and economic outcomes (per-person lifetime costs) for the 3 strategies. These projections were then used to evaluate incremental cost-effectiveness ratios (ICERs), which we report from a U.S. health system perspective, discounted at 3% per year (15). We also projected the undiscounted savings in the first year among all patients who are receiving or starting an efavirenz-based treatment and are eligible to switch from branded to generic-based ART.

The CEPAC-US Model

The CEPAC-US Model characterizes HIV disease progression as a sequence of monthly transitions between "health states." These states comprise current status, relevant history, quality of life, and resource use and determine the risk for future clinical events. Health states are stratified by CD4 cell count (5 strata), HIV RNA level (6 strata), ART regimen, and disease acuity (for example, treatment-related toxicity or opportunistic infection). In the model, the level of HIV RNA determines the rate of the decrease in CD4 cell count, and the CD4 cell count determines the frequency of opportunistic infections and AIDS-related deaths. Patients face a risk for HIV-related mortality (opportunistic infections and otherwise) or age- and sex-adjusted background mortality (16).

We capitalized on the model's capacity to consider early-regimen mutations and virologic failure in determining the efficacy of subsequent regimens. Per current U.S. guidelines (1), we assumed that all newly presenting patients initiate therapy immediately. Effective ART functions to suppress HIV RNA and increase CD4 cell count at rates reported (**Table 1** and **Appendix Table 2**, available at www.annals.org) (20–27). Quarterly clinic visits and monitoring of CD4 cell count and HIV RNA confirm the possibility of "early suppression" followed by "late failure," 2 model-based parameters that define ART efficacy (**Appendix Figure 1**, available at www.annals.org). Early suppression of a regimen is the fraction of patients virologically suppressed after 24 weeks. Patients with suppression subsequently have a probability of late failure, defined as a monthly probability of virologic rebound after initial suppression. Once detected, virologic failure results in a switch to a subsequent regimen and another—albeit diminishing—opportunity for suppression. The model translates input variation in adherence and regimen selection into changes in ART efficacy and thereby into changes in clinical and cost outcomes.

Context

In the United States, provision of HIV treatment relies heavily on government funding. A recommended option for first-line treatment of HIV infection is the daily administration of a single pill containing 3 branded drugs.

Contribution

In a mathematical simulation, daily administration of 3 pills (2 of which are generic drugs and 1 of which is a branded drug) taken simultaneously dramatically reduced cost and only slightly reduced survival gain compared with the use of a fully branded regimen.

Caution

Simulation models may not reflect real-world results.

Implication

The use of first-line, generic-based HIV treatment in the United States could save nearly $1 billion a year.

—The Editors

Input Parameters

Further details on the protocols we used for model validation and to assemble appropriate literature-derived estimates are available in the **Appendix** (available at www.annals.org) and elsewhere (14).

Cohort

The entering cohort was modeled similarly to newly diagnosed HIV-infected patients in the United States in 2009 (28), among whom 84% were male. Recent U.S. data suggest a mean CD4 count at presentation of 0.317×10^9 cells/L (**Table 1**) (17, 28).

ART Efficacy

In the no-ART strategy, patients follow the natural progression of HIV disease without access to ART. A clinical trial using coformulated 1-pill tenofovir–emtricitabine–efavirenz found that branded ART results in 24-week virologic suppression of 85%, with a 0.21% monthly probability of late failure after 24 weeks (20). For this strategy, we used a second-line, protease inhibitor–based regimen with a 24-week suppression efficacy of 73% (21, 22). A clinical trial of efavirenz, lamivudine, and tenofovir found that 3-pill, generic-based ART leads to 24-week virologic suppression of 78% (24). Using trial data, we derived the monthly probability of failure after 24 weeks as 0.45%, which is substantially higher than that of branded ART. To capture the laboratory-described increased risk for M184V mutations resulting from first-line lamivudine, we also decreased the suppression rate of second-line ART by 5%, from 73% with branded ART to 68% with generic-based ART (6, 7). Because there are currently no data suggesting that efavirenz-based toxicity will differ between the brand-name and generic drugs, we attribute this difference to first-line

Table 1. **Base-Case Inputs for Model of Generic-Based Versus Branded ART in the United States**

Variable	Value	Patients With HIV RNA Suppression After 24 Wk, %	CD4 Count Increase at 48 Wk, × 10^9 cells/L	Monthly Probability of Late Failure After 24 Wk, %	Reference
Cohort characteristics					
Mean age (SD), *y*	43 (12)	–	–	–	17
Male, %	84	–	–	–	17
Mean initial CD4 count (SD), × 10^9 cells/L	0.317 (0.283)	–	–	–	17
HIV RNA distribution, %					
>100 000 copies/mL	12.9	–	–	–	18
30 001–100 000 copies/mL	12.9	–	–	–	18
10 001–30 000 copies/mL	25.0	–	–	–	18
3001–10 000 copies/mL	25.2	–	–	–	18
501–3000 copies/mL	16.3	–	–	–	18
<500 copies/mL	7.7	–	–	–	18
Efficacy of ART					
Branded					
First-line (efavirenz–emtricitabine–tenofovir)	–	85	0.206	0.21	20
Second-line (atazanavir–ritonavir plus tenofovir–emtricitabine)	–	73	0.110	1.71	21, 22
2-pill, generic-based					
First-line (efavirenz plus tenofovir–emtricitabine)	–	84	0.206	0.43	23
Second-line (atazanavir–ritonavir plus tenofovir–emtricitabine)	–	73	0.110	1.71	21, 22
3-pill, generic-based					
First-line (efavirenz plus lamivudine plus tenofovir)	–	78	0.206	0.45	24
Second-line (atazanavir–ritonavir plus tenofovir–emtricitabine)	–	68	0.110	1.71	21, 22
Annual costs, *2009 U.S. $*					
First-line, branded ART (efavirenz–tenofovir–emtricitabine)	15 300	–	–	–	19
First-line, 2-pill, generic-based ART (efavirenz plus tenofovir–emtricitabine)	11 600	–	–	–	19
First-line, 3-pill, generic-based ART (efavirenz plus lamivudine plus tenofovir)	9200	–	–	–	19
Second-line ART (atazanavir–ritonavir plus tenofovir–emtricitabine)	22 100	–	–	–	19

ART = antiretroviral therapy.

lamivudine use only. Efficacies and costs for subsequent ART regimens (provided in **Appendix Table 2**) are otherwise identical between treatment strategies.

An intermediate alternative to 3-pill, generic-based ART is a 2-pill formulation that uses coformulated tenofovir–emtricitabine (Truvada; Gilead Sciences) and generic efavirenz. Recognizing the uncertainty surrounding the comparative efficacy of once-daily regimens consisting of 1, 2, or 3 pills, we examined all options together in generalized sensitivity analyses designed to illuminate the tradeoffs among early efficacy, late failure, and costs. We began with a 24-week suppressive efficacy of 84% and a monthly probability of failure thereafter of 0.43% with 2-pill, generic-based ART (23); we maintained the full potency of the second-line regimen because of the inclusion of emtricitabine in the first-line regimen (**Table 1**). Other efficacy and cost combinations were also examined.

Costs

The annual cost for branded ART is $15 300 (19), 77% of the published average wholesale price (AWP) for standard dosing (**Table 1**) (29). We assumed a 75% price reduction from AWP (including discounts) for the generic components of the 3-pill, generic-based ART regimen ($9200/year) and the 2-pill, generic-based ART regimen ($11 600/year) and explored reductions from 35% to 95%. Subsequent ART regimen, laboratory monitoring, and costs of routine care are shown in **Appendix Table 2**. All costs are in 2009 U.S. dollars.

Sensitivity Analyses

We used 1-way and multiway sensitivity analyses to understand the effect of uncertainty in efficacies of early virologic suppression, probabilities of late failure, and the comparative cost savings from generic-based ART. We also examined alternative second-line ART efficacies associated with an increased presence of M184V mutations and considered cohorts with higher or lower CD4 cell counts leading to varying durations of ART. Finally, we examined the effect on our results from risk-group adjustments to our estimates of non–HIV-related mortality.

Potential Savings in the First Year

To determine the potential savings in the United States during the first year, we multiplied the number of persons eligible to start or switch to generic-based ART by the per-person savings. "Incident cases" likely to be pre-

scribed efavirenz were calculated as the product of the anticipated new diagnoses in the United States per year (8294 in 2009) (28), the estimated fraction of HIV-infected persons receiving ART (36%) (30), and the likelihood that an efavirenz-based regimen is selected as first-line therapy (85%) (31). "Prevalent cases" who switched from an efavirenz-based branded regimen to the generic-based alternative were calculated as the product of Centers for Disease Control and Prevention–based projections of the number of persons living with HIV in the United States (1 200 000) (28), the estimated proportion receiving ART (36%) (30), and the estimated proportion receiving an efavirenz-based ART regimen (34%) (Gebo K. Personal communication.) (30). We multiplied the number of persons eligible for a generic start or switch by the potential per-person savings associated with generic-based ART in the first year. These savings are the difference between the undiscounted annual costs of branded ($15 300) and generic ($9200) ART ($6100 per person).

Role of the Funding Source

The National Institute of Allergy and Infectious Diseases supported the study. The funding source did not have any role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Base-Case Results

In the base case, the discounted per-person quality-adjusted life expectancies from age 43 years were 4.05 QALYs (undiscounted, 4.58 QALYs) for no ART; 12.08 QALYs (undiscounted, 18.36 QALYs) for 3-pill, generic-based ART; and 12.45 QALYs (undiscounted, 19.32 QALYs) for branded ART (**Table 2**). Mean duration of receipt of the first-line regimen decreased from 12.1 years for branded ART to 10.0 years for 3-pill, generic-based ART (both undiscounted). Per-person discounted lifetime costs increased from $131 200 (no ART) to $300 300 for generic-based ART and $342 800 for branded ART. Compared with no ART, 3-pill, generic-based ART resulted in an ICER of $21 100/QALY. The ICER for branded ART, compared with generic-based ART, was $114 800/QALY (**Table 2** and **Figure 1**).

Two-Pill, Generic-Based ART

Two-pill, generic-based ART resulted in greater survival than 3-pill, generic-based ART in the base case (12.25 vs. 12.08 QALYs). When 3- and 2-pill, generic-based ART and branded ART were compared incrementally, ICERs were $21 100/QALY for 3-pill, generic-based ART versus no ART; $95 400/QALY for 2-pill, generic-based ART versus 3-pill, generic-based ART; and $130 600/QALY for branded versus 2-pill, generic-based ART (**Table 2** and **Appendix Figure 2**, available at www.annals.org).

Sensitivity Analyses

Three-Pill, Generic-Based ART

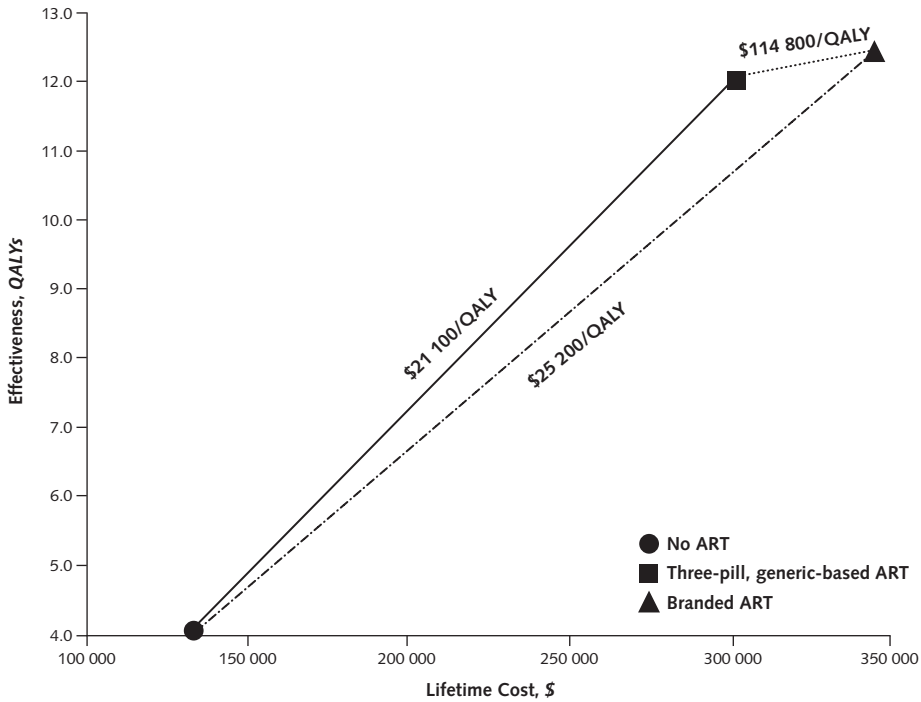
The ICER for branded ART compared with 3-pill, generic-based ART was sensitive to the comparative cost and efficacy of generic-based ART (**Figure 2**). At the base-case efficacy of generic-based ART (24-week suppression, 78%; probability of late failure, 0.45%/month), branded ART had an ICER greater than $100 000/QALY, provided that the discount from AWP for generic-based ART was greater than 69% (**Figure 2**). If the probability of 24-week suppression remained lower for 3-pill, generic-based ART than for branded ART but the monthly probability of late failure was the same (0.21%), the ICERs of branded compared with 3-pill, generic-based ART were substantially higher at every combination of 24-week efficacy and price reduction for generic-based ART (**Appendix Figure 3**, available at www.annals.org). Under such conditions, even modest price reductions (>40% AWP) for the generic regimen components resulted in ICERs greater than $100 000/QALY for branded ART compared with generic-based ART (**Appendix Figure 3**).

Table 2. **Clinical Outcomes, Cost, and Cost-Effectiveness of Generic-Based Versus Branded ART in the United States**

Variable	Per-Person Cost, *2009 U.S. $*	Per-Person Life Expectancy, *QALY*		ICER, *$/QALY*
		Discounted	Undiscounted	
Base case				
No ART	131 200	4.05	4.58	–
3-pill, generic-based ART	300 300	12.08	18.36	21 100
Branded ART*	342 800	12.45	19.32	114 800
Base case, including 2-pill, generic-based ART				
No ART	131 200	4.05	4.58	–
3-pill, generic-based ART	300 300	12.08	18.36	21 100
2-pill, generic-based ART	316 100	12.25	18.73	95 400
Branded ART*	342 800	12.45	19.32	130 600

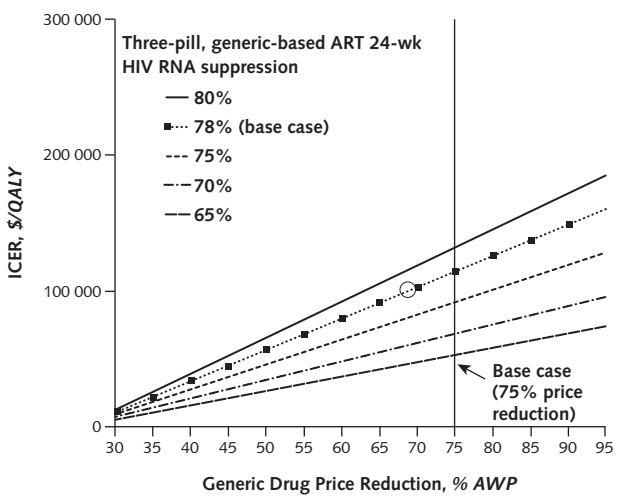
ART = antiretroviral therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
* ICER for branded ART vs. no ART is $25 200/QALY.

Figure 1. **Clinical and economic outcomes of branded and 3-pill, generic-based ART.**



Per-person lifetime costs are on the *x*-axis, and life expectancy in QALYs is on the *y*-axis. The dotted-and-dashed line indicates the anticipated incremental cost-effectiveness ratio of branded ART compared with no ART in the absence of a generic alternative. ART = antiretroviral therapy; QALY = quality-adjusted life-year.

Figure 2. **Two-way sensitivity analyses with base-case rates of late failure.**



The graph shows the changes in the ICER of branded ART compared with 3-pill, generic-based ART (*y*-axis) as a function of the generic drug price reduction (*x*-axis) and the early efficacy of 3-pill, generic-based ART in HIV RNA suppression. In the base case, branded ART has an ICER greater than $100 000/QALY as long as the generic drug discount from the AWP is greater than 69% (*circle*). This figure represents results when the monthly probability of late failure (after 24 wk) is 0.45% for both 3-pill, generic-based ART and 0.21% for branded ART. ART = antiretroviral therapy; AWP = average wholesale price; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Two-Pill, Generic-Based ART

Results for 2-pill, generic-based ART were similarly sensitive to regimen efficacy—most important, to the probability of late failure—and costs. When 2-pill, generic-based; 3-pill, generic-based; and branded ART all had the same probability of late failure (0.21% at 24 weeks), 2-pill, generic-based ART had an ICER less than $100 000/QALY compared with 3-pill, generic-based ART at price reductions of 50% AWP ($62 600/QALY) (**Table 3**). If branded and 2-pill, generic-based ART had similar probabilities of late failure (0.21%) (lower than that of 3-pill, generic-based ART [0.45%]), 2-pill, generic-based ART became much more attractive. At all price reductions examined, 2-pill, generic-based ART was the best choice because it dominated (was more effective and less costly than) 3-pill, generic-based ART and because of the very high ICERs for branded ART ($101 300 to $2 540 100/QALY) (**Table 3**).

Other Sensitivity Analyses

In other sensitivity analyses, we saw variability in outcomes but no material effect on the qualitative cost-effectiveness findings when we changed the efficacy of second-line ART to capture changes related to potential lamivudine-related resistance (branded ART ICERs, $109 300 to $120 600/QALY), when we considered a healthier presenting cohort (mean CD4 count, 0.650 ×

10^9 cells/L; branded ART ICER, $143 200/QALY), or when we adjusted background mortality rates by risk group (branded ART ICER, $117 400/QALY) (**Appendix Tables 3** to **6**, available at www.annals.org).

Potential Savings in the First Year

The per-person undiscounted savings for 3-pill and 2-pill, generic-based ART compared with branded ART were $6100/year and $3700/year. We estimate that there are 2500 persons newly diagnosed and initiating ART ("incident cases") and 147 300 HIV-infected persons ("prevalent cases") currently receiving an efavirenz-based regimen who could switch to generic-based ART in the United States (30). Combining the benefits from incident and prevalent cases, the potential estimated savings in the first year associated with the use of 3-pill, generic-based ART in the base case were $920 million; the anticipated savings were substantially less for 2-pill, generic-based ART ($560 million). Anticipated savings in the first year from 3-pill, generic-based ART ranged from $200 million to $1.29 billion at price reductions of 35% to 95% from AWP (**Appendix Figure 4**, available at www.annals.org).

DISCUSSION

We project that a population-wide switch from first-line branded ART to generic-based ART in the United States will result in lifetime average savings of $42 500 per eligible patient, with a modest loss of survival of only 0.37 QALY. On a population-wide basis, the aggregate savings in the first year alone would amount to nearly $1 billion. When potential decrements in the short- and long-term efficacy of generic-based regimens are accounted for, we find that the incremental cost-effectiveness of a first-line branded regimen becomes unattractive by a standard recently used in the United States (>$100 000/QALY) (32–34).

The market for antiretroviral drugs in the United States, largely financed with governmental support, was

Table 3. **Three-Way Sensitivity Analysis of 2-Pill Versus 3-Pill, Generic-Based ART; Probability of Late Failure After 24 Weeks; and Price Reduction**

Probability of Late Virologic Failure	Generic Drug Price Reduction, %	ART Strategy	Per-Person Cost, *2009 U.S. $*	Per-Person Life Expectancy, *QALY*	ICER, *$/QALY*
Branded ART: 0.21% 2-pill, generic-based ART: 0.21% 3-pill, generic-based ART: 0.21%	25	No ART 3-pill, generic-based 2-pill, generic-based Branded	131 200 341 000 341 300 342 800	4.05 12.27 12.43 12.45	– Weakly dominated* 25 100 101 300
Branded ART: 0.21% 2-pill, generic-based ART: 0.21% 3-pill, generic-based ART: 0.21%	50	No ART 3-pill, generic-based 2-pill, generic-based Branded	131 200 313 600 323 800 342 800	4.05 12.27 12.43 12.45	– 22 200 62 600 1 162 000
Branded ART: 0.21% 2-pill, generic-based ART: 0.21% 3-pill, generic-based ART: 0.21%	75	No ART 3-pill, generic-based 2-pill, generic-based Branded	131 200 286 200 306 400 342 800	4.05 12.27 12.43 12.45	– 18 900 121 600 2 540 100
Branded ART: 0.21% 2-pill, generic-based ART: 0.21% 3-pill, generic-based ART: 0.45%	25	No ART 2-pill, generic-based Branded 3-pill, generic-based	131 200 341 300 342 800 343 000	4.05 12.43 12.45 12.08	– 25 100 101 300 Strongly dominated†
Branded ART: 0.21% 2-pill, generic-based ART: 0.21% 3-pill, generic-based ART: 0.45%	50	No ART 3-pill, generic-based 2-pill, generic-based Branded	131 200 321 700 323 800 342 800	4.05 12.08 12.43 12.45	– Weakly dominated* 23 000 1 162 000
Branded ART: 0.21% 2-pill, generic-based ART: 0.21% 3-pill, generic-based ART: 0.45%	75	No ART 3-pill, generic-based 2-pill, generic-based Branded	131 200 300 300 306 400 342 800	4.05 12.08 12.43 12.45	– Weakly dominated* 20 900 2 540 100
Branded ART: 0.21% 2-pill, generic-based ART: 0.45% 3-pill, generic-based ART: 0.45%	25	No ART Branded 3-pill, generic-based 2-pill, generic-based	131 200 342 800 343 000 343 900	4.05 12.45 12.08 12.24	– 25 200 Strongly dominated† Strongly dominated†
Branded ART: 0.21% 2-pill, generic-based ART: 0.45% 3-pill, generic-based ART: 0.45%	50	No ART 3-pill, generic-based 2-pill, generic-based Branded	131 200 321 700 330 300 342 800	4.05 12.08 12.24 12.45	– 23 700 55 600 57 100
Branded ART: 0.21% 2-pill, generic-based ART: 0.45% 3-pill, generic-based ART: 0.45%	75	No ART 3-pill, generic-based 2-pill, generic-based Branded	131 200 300 300 316 700 342 800	4.05 12.08 12.24 12.45	– 21 100 105 600 121 100

ART = antiretroviral therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
* More expensive but confers less clinical benefit than some combination of other strategies.
† More expensive and confers less clinical benefit than the next least expensive strategy.

estimated at nearly $9 billion in 2011 (35). Much is at stake as major components of effective HIV therapy become generically available this year. The importance of this analysis lies not only in its relevance to the current discussion of generic efavirenz but also in the development of a framework by which future generations of generic antiretroviral drugs—and the tradeoff between drug efficacy and cost savings—may be evaluated. Our assessment may be updated on report of head-to-head comparisons of the 2- and 3-pill generic regimens or of other generic regimens, including those using abacavir. These studies would be most helpful if they described the relative efficacy (that is, immediate virologic suppression and durability over time) and resource utilization (for example, hospitalizations and drug costs) associated with these 2 alternatives.

Generic drugs will save money but may reduce health benefits, a tradeoff that may be controversial. Fewer than 0.4% of published cost-effectiveness analyses report on interventions that confer a combination of lower health benefits and lower costs. Some may reject such interventions as substandard and therefore eliminate their consideration on ethical grounds. However, economic evaluation of "decremental cost-effectiveness" can identify opportunities to improve efficiency in health care delivery by reallocating resources to higher-value, life-saving alternatives. This is particularly true as an increasing number of proven effective but costly interventions further stretch the resources of the U.S. health care system. The U.S. 2010 National HIV/AIDS Strategy (36) is explicitly financed by "repurposed" rather than new funds (37). In an era in which dedication to the national HIV mission requires "redirected" financing, the potential $1 billion savings from generic-based regimens might be an efficient source available for national reinvestment (38). For example, fewer than half of the state AIDS Drug Assistance Programs in the United States include protease inhibitor–based hepatitis C virus (HCV) regimens ($90 100 per treatment course) in their formularies, despite these drugs having ICERs less than $100 000/QALY (as reported in monoinfected patients) (39, 40). For every 15 persons who switch to a generic-based HIV regimen (potential annual savings of approximately $6100/person), 1 person co-infected with HIV and HCV could be treated for and potentially cured of chronic hepatitis C (39). With approximately 300 000 U.S. persons co-infected with HIV and HCV and eligible for these new HCV therapies, this would represent a major treatment opportunity, although it remains unclear whether such saved resources would be reallocated in this direction (40, 41).

Our assumptions about generic drug efficacy and pricing are conservative. We assumed, on the basis of in vitro clinical trials and observational data, that daily lamivudine would be less effective and would promote more resistance than emtricitabine when used as either a first- or second-line regimen. We also assumed an adherence advantage for a daily single-pill regimen because, with 1 exception, literature on observational studies indicates that there is a relationship between taking fewer pills and better HIV regimen adherence (4, 42–44). Taken as a whole, these assumptions suggest that the potential loss of life expectancy for generic-based ART could be as high as 0.37 QALY. To put this value in perspective, this is also the approximate survival benefit associated with intensive hypertension control in patients with type 2 diabetes (45). Our 75% price reduction is justified by evidence that generic prices decrease by as much as 80% to 85% of published branded prices when 5 or more manufacturers enter a market (46, 47). More than 7 suppliers currently provide FDA-approved generic efavirenz outside the United States under the auspices of the U.S. President's Emergency Plan for AIDS Relief (48).

We note several limitations in this analysis. The $100 000/QALY threshold for cost-effectiveness, although frequently cited, may be debated (33, 49, 50). Higher willingness-to-pay thresholds could result in branded regimens falling within a range considered acceptable. Although we conducted this analysis from the U.S. health system perspective, we acknowledge that the savings realized from a policy switch to generic-based regimens may be applied differently from one payer to the next (for example, state AIDS Drug Assistance Programs vs. state Medicaid programs or the U.S. Veterans Administration); these savings may not be reinvested in HIV care or even in health care. They may also be greater than we project. If efforts to improve HIV case identification and linkage to and retention in care are successful, this would increase the outlay for HIV medications and the anticipated savings from generic drugs could exceed our $920 million estimate (51).

Compared with a slightly less effective regimen containing generic drugs, we found that the incremental cost-effectiveness for the branded 1-pill, first-line ART regimen exceeds $100 000/QALY. Starting or switching to generic-based regimens would initially yield annual savings approaching $1 billion for programs that fund HIV treatment in the United States.

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Appendix: Approach to CEPAC Model Validation

Our approach to evaluating the validity of our models was premised on the view that their purpose is to inform decisions. In that spirit, we adhered, whenever possible, to the widely accepted recommendations of the U.S. Panel on Cost-Effectiveness in Health and Medicine (15) and the following evaluation criteria (52): transparency (whether the assumptions, input parameters, and logic are stated with complete clarity and are left open to peer review), verification (whether the outputs are consistent with observed data and whether the model has been debugged and tested for internal consistency), corroboration (whether other models have produced similar results contingent on similar assumptions and input parameters), face validity (whether the results of the model make sense in relation to theoretical considerations and can be explained in intuitive terms), and accreditation (whether the model has been subjected to peer review by a dispassionate reviewer and found to be true to its claims).

We ascertained internal consistency in several steps. First, we examined the face validity of randomly selected, individual patient "traces." These detailed views of a patient's month-to-month experience offered both a first check on the reasonableness of our output and a convenient means of debugging. Next, we checked "internal validity" by verifying that the output of the model accurately approximated the data used to derive input parameters. This is an area of growing interest in the field of disease policy modeling and one in which our team has taken a leadership role (52, 53). A recent illustration uses our work to assess the internal consistency of the Disease Module, reparameterized using data from the WIHS (Women's Interagency HIV Study) (54). Kaplan–Meier survival curves based on data from WIHS were visually compared with preliminary, model-estimated survival (**Appendix Figure 5**). When WIHS data were used, model-projected survival over 36 months in women with CD4 counts less than 0.050×10^9 cells/L and greater than 0.350×10^9 cells/L closely approximated empirical survival data. Model-projected survival in women with CD4 counts of 0.050 to 0.199×10^9 cells/L and 0.200 to 0.349×10^9 cells/L substantially underestimated survival between 12 and 36 months. A series of 1-way sensitivity analyses showed that the best visual fit to the WIHS empirical survival data required updating the model to assume a 50% reduction in either the incidence of opportunistic infections or rates of chronic AIDS deaths in patients with a prior opportunistic infection.

With regard to predictive validity, the Panel on Cost-Effectiveness in Health and Medicine has noted that, when models are used for purposes of informing decisions, tests of predictive validity are valuable but may not always be possible and should not be considered essential. We have used the CEPAC Model to simulate both natural history and the effect of ART on the incidence of AIDS-related opportunistic infections in the Swiss HIV Cohort Study (55). We have found that the CEPAC Model output very closely mirrors the Swiss Cohort data for most opportunistic infections.

Appendix Table 1. Tradeoffs Between Generic-Based and Branded ART

Branded ART (Tenofovir–Emtricitabine–Efavirenz)	Generic-Based ART (Tenofovir Plus Lamivudine Plus Efavirenz)
Coformulated, once-daily single pill	3 once-daily pills
No generic components	2 generic components (lamivudine and efavirenz)
More expensive	Less expensive
Lower pill burden may lead to better adherence and higher efficacy	Higher pill burden may lead to lower adherence and efficacy
–	Compared with emtricitabine, lamivudine may be less effective and has been associated with an increased frequency of drug resistance upon treatment failure

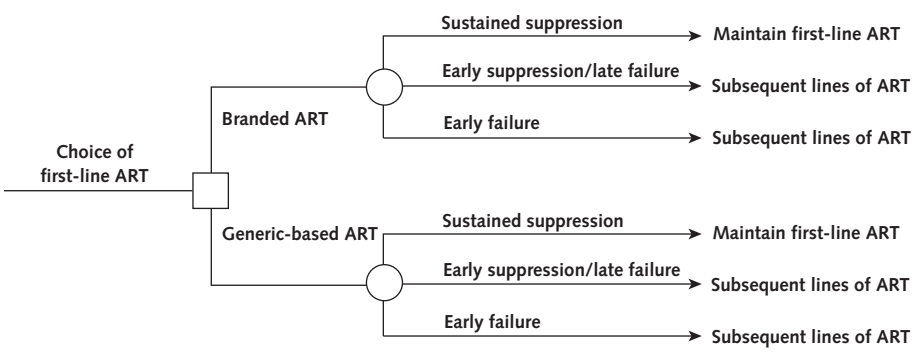
ART = antiretroviral therapy.

Appendix Table 2. Base-Case ART Efficacy Inputs and Costs for Later ART Regimens in Analysis of First-Line Generic-Based Versus Branded ART in the United States

Variable	Value, *2009 U.S. $*	Patients With HIV RNA Suppression After 24 Wk, %	Increase in CD4 Count at 48 Wk, $\times 10^9$ *cells/L*	Monthly Probability of Late Failure After 24 Wk, %	Reference
Efficacy of ART					
Third-line	–	61	0.121	1.71	21, 22
Fourth-line	–	65	0.102	1.71	25
Fifth-line	–	40	0.119	2.19	26, 27
Sixth-line	–	15	0.045	2.19	27
Annual costs					
Third-line ART	21 900	–	–	–	19
Fourth-line ART	28 600	–	–	–	19
Fifth-line ART	51 700	–	–	–	19
Sixth-line ART	19 100	–	–	–	19
CD4 cell test	820	–	–	–	56
HIV RNA test	1500	–	–	–	56
Routine care, by CD4 count					
$>0.500 \times 10^9$ cells/L	2900	–	–	–	57–59
$0.301–0.500 \times 10^9$ cells/L	5700	–	–	–	57–59
$0.201–0.300 \times 10^9$ cells/L	5800	–	–	–	57–59
$0.101–0.200 \times 10^9$ cells/L	6700	–	–	–	57–59
$0.050–0.100 \times 10^9$ cells/L	13 000	–	–	–	57–59
$<0.050 \times 10^9$ cells/L	11 900	–	–	–	57–59

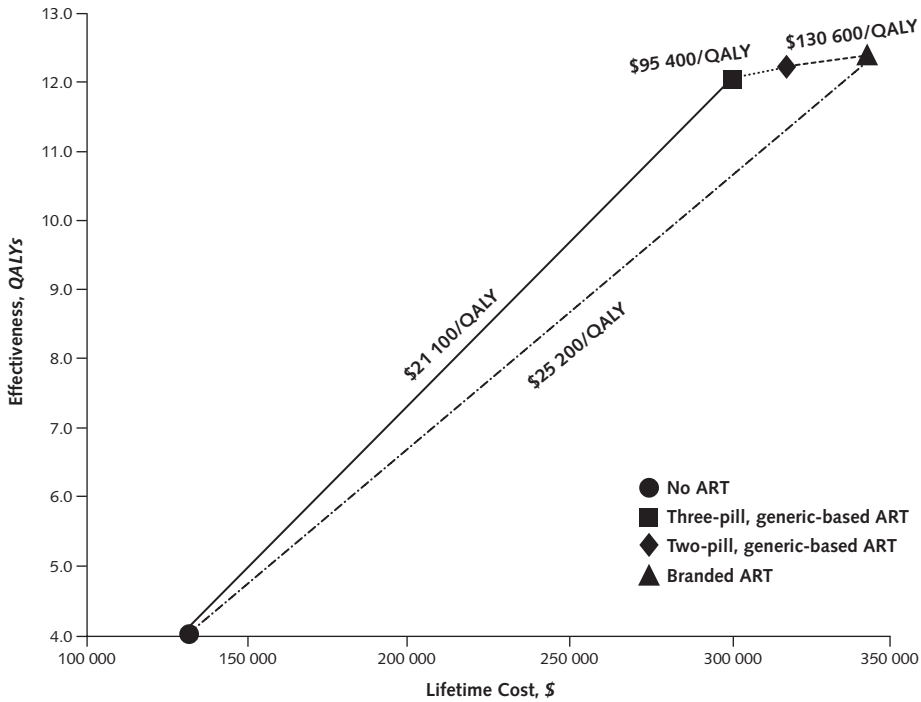
ART = antiretroviral therapy.

Appendix Figure 1. Simplified schema of modeled patients as they progress through first-line ART (branded or generic-based) in the CEPAC Model.



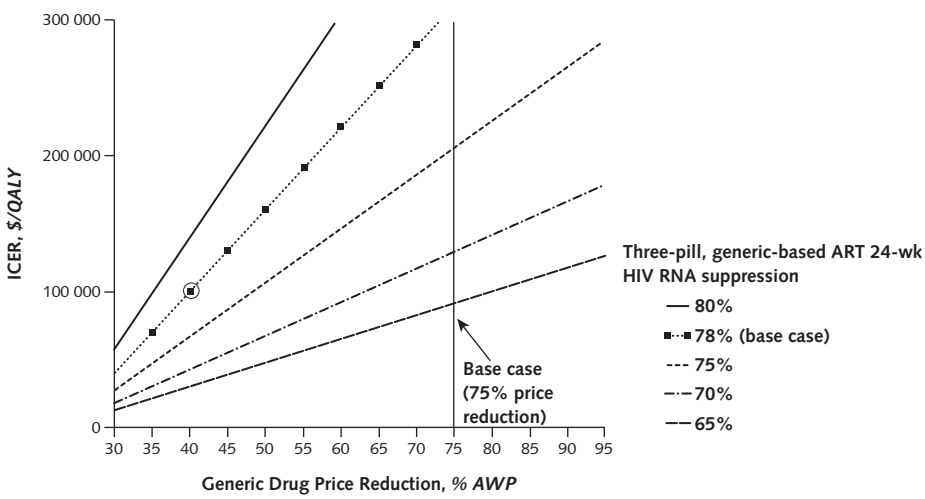
Squares indicate decision nodes, and circles indicate chance nodes. ART = antiretroviral therapy; CEPAC = Cost-Effectiveness of Preventing AIDS Complications.

Appendix Figure 2. **Clinical and economic outcomes of branded compared with 2-pill and 3-pill, generic-based ART.**



Per-person lifetime costs are on the *x*-axis, and life expectancy QALYs in on the *y*-axis. The dotted-and-dashed line indicates the anticipated incremental cost-effectiveness ratio of branded ART compared with no ART in the absence of a generic alternative. ART = antiretroviral therapy; QALY = quality-adjusted life-year.

Appendix Figure 3. **Two-way sensitivity analyses with equal rates of late failure for generic-based and branded ART.**



The graph shows the changes in the ICER of branded ART compared with 3-pill, generic-based ART (*y*-axis) as a function of the generic drug price reduction (*x*-axis) and the early efficacy of 3-pill, generic-based ART in HIV RNA suppression. This figure represents results when the monthly probability of late failure (after 24 wk) is 0.21% for both 3-pill, generic-based ART and branded ART. Even modest price reductions (>40%) for the generic regimen components result in ICERs for branded ART greater than $100 000/QALY (*circle*). ART = antiretroviral therapy; AWP = average wholesale price; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Appendix Table 3. **Sensitivity Analysis of Second-Line ART Efficacy for 3-Pill, Generic-Based ART**

Second-Line ART Efficacy	ART Strategy	Per-Person Cost, *2009 U.S. $*	Per-Person Life Expectancy, *QALY*	ICER, *$/QALY*
73%	No ART	131 200	4.05	–
	3-pill, generic-based	301 300	12.11	21 100
	Branded	342 800	12.45	120 600
72%	No ART	131 200	4.05	–
	3-pill, generic-based	300 800	12.09	21 100
	Branded	342 800	12.45	117 300
67%	No ART	131 200	4.05	–
	3-pill, generic-based	299 800	12.07	21 000
	Branded	342 800	12.45	112 400
63%	No ART	131 200	4.05	–
	3-pill, generic-based	299 300	12.05	21 000
	Branded	342 800	12.45	109 300

ART = antiretroviral therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Appendix Table 4. **Sensitivity Analysis Showing the Effect on Clinical Outcomes, Cost, and Cost-Effectiveness for Alternative Mean CD4 Cell Counts of Presenting Cohort**

Mean CD4 Count	ART Strategy	Per-Person Cost, *2009 U.S. $*	Per-Person Life Expectancy, *QALY*	ICER, *$/QALY*
0.350×10^9 cells/L	No ART	131 300	4.30	–
	3-pill, generic-based	303 800	12.37	21 400
	Branded	346 900	12.73	118 500
0.400×10^9 cells/L	No ART	131 400	4.70	–
	3-pill, generic-based	308 600	12.77	22 000
	Branded	352 800	13.13	121 700
0.450×10^9 cells/L	No ART	131 300	5.11	–
	3-pill, generic-based	312 900	13.13	22 600
	Branded	358 000	13.49	125 200
0.500×10^9 cells/L	No ART	131 000	5.51	–
	3-pill, generic-based	316 500	13.44	23 400
	Branded	362 700	13.80	128 200
0.550×10^9 cells/L	No ART	130 700	5.92	–
	3-pill, generic-based	319 700	13.71	24 300
	Branded	366 400	14.06	133 700
0.600×10^9 cells/L	No ART	130 200	6.33	–
	3-pill, generic-based	322 200	13.93	25 300
	Branded	369 400	14.27	139 800
0.650×10^9 cells/L	No ART	129 600	6.73	–
	3-pill, generic-based	324 200	14.12	26 400
	Branded	371 900	14.45	143 200

ART = antiretroviral therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Appendix Table 5. **Sensitivity Analysis Showing the Effect on Clinical Outcomes, Cost, and Cost-Effectiveness When Background Mortality Is Adjusted by Risk Group***

Variable	Per-Person Cost, *2009 U.S. $*	Per-Person Life Expectancy (Undiscounted), *QALY*	ICER, *$/QALY*
Base case, with risk-group adjustment			
No ART	130 700	4.02 (4.54)	–
3-pill, generic-based ART	294 700	11.79 (17.78)	21 100
Branded ART	336 200	12.14 (18.69)	117 400
Base case, including 2-pill, generic-based ART, with risk-group adjustment			
No ART	130 700	4.02 (4.54)	–
3-pill, generic-based ART	294 700	11.79 (17.78)	21 100
2-pill, generic-based ART	310 300	11.95 (18.13)	95 000
Branded ART	336 200	12.14 (18.69)	136 900

ART = antiretroviral therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

* Risk-group adjustments account for differences in non–HIV-related (background) mortality between those at highest risk for HIV and the general population. We considered 5 sex/risk groups in our adjustment: men who have sex with men, male and female injection drug users, and male and female high-risk heterosexuals. For each group, we applied a published risk group–specific standardized mortality ratio to age- and sex-adjusted non–HIV-related mortality rates (60). We then weighted these risk group–specific mortality rates according to the distribution of risk groups among HIV-infected persons in the United States (61), as well as to the predicted changes in the distribution over time to get age-, sex-, and risk-adjusted non-HIV mortality rates.

Appendix Table 6. **Three-Way Sensitivity Analysis of 2-Pill Versus 3-Pill, Generic-Based ART; Probability of Virologic Failure After 24 Weeks; and Price Reduction When Background Mortality Is Adjusted by Risk Group***

Probability of Late Virologic Failure	Generic Drug Price Reduction, %	ART Strategy	Per-Person Cost, *2009 U.S. $*	Per-Person Life Expectancy, *QALY*	ICER, *$/QALY*
Branded ART: 0.21%	25	No ART	130 700	4.02	–
2-pill, generic-based ART: 0.21%		3-pill, generic-based	334 600	11.97	Weakly dominated†
3-pill, generic-based ART: 0.21%		2-pill, generic-based	334 800	12.13	25 200
		Branded	336 200	12.14	124 700
Branded ART: 0.21%	50	No ART	130 700	4.02	–
2-pill, generic-based ART: 0.21%		3-pill, generic-based	307 800	11.97	22 300
3-pill, generic-based ART: 0.21%		2-pill, generic-based	317 800	12.13	63 100
		Branded	336 200	12.14	1 680 400
Branded ART: 0.21%	75	No ART	130 700	4.02	–
2-pill, generic-based ART: 0.21%		3-pill, generic-based	281 000	11.97	18 900
3-pill, generic-based ART: 0.21%		2-pill, generic-based	300 600	12.13	122 700
		Branded	336 200	12.14	3 391 200
Branded ART: 0.21%	25	No ART	130 700	4.02	–
2-pill, generic-based ART: 0.21%		2-pill, generic-based	334 800	12.13	25 200
3-pill, generic-based ART: 0.45%		Branded	336 200	12.14	124 700
		3-pill, generic-based	337 000	11.79	Strongly dominated‡
Branded ART: 0.21%	50	No ART	130 700	4.02	–
2-pill, generic-based ART: 0.21%		3-pill, generic-based	315 900	11.79	Weakly dominated†
3-pill, generic-based ART: 0.45%		2-pill, generic-based	317 800	12.13	23 100
		Branded	336 200	12.14	1 608 400
Branded ART: 0.21%	75	No ART	130 700	4.02	–
2-pill, generic-based ART: 0.21%		3-pill, generic-based	295 000	11.79	Weakly dominated†
3-pill, generic-based ART: 0.45%		2-pill, generic-based	300 600	12.13	21 000
		Branded	336 200	12.14	3 391 200
Branded ART: 0.21%	25	No ART	130 700	4.02	–
2-pill, generic-based ART: 0.45%		Branded	336 200	12.14	25 300
3-pill, generic-based ART: 0.45%		3-pill, generic-based	337 000	11.79	Strongly dominated‡
		2-pill, generic-based	337 600	11.94	Strongly dominated‡
Branded ART: 0.21%	50	No ART	130 700	4.02	–
2-pill, generic-based ART: 0.45%		3-pill, generic-based	315 900	11.79	23 900
3-pill, generic-based ART: 0.45%		2-pill, generic-based	324 200	11.94	54 800
		Branded	336 200	12.14	60 300
Branded ART: 0.21%	75	No ART	130 700	4.02	–
2-pill, generic-based ART: 0.45%		3-pill, generic-based	295 000	11.79	21 200
3-pill, generic-based ART: 0.45%		2-pill, generic-based	310 900	11.94	107 000
		Branded	336 200	12.14	127 800

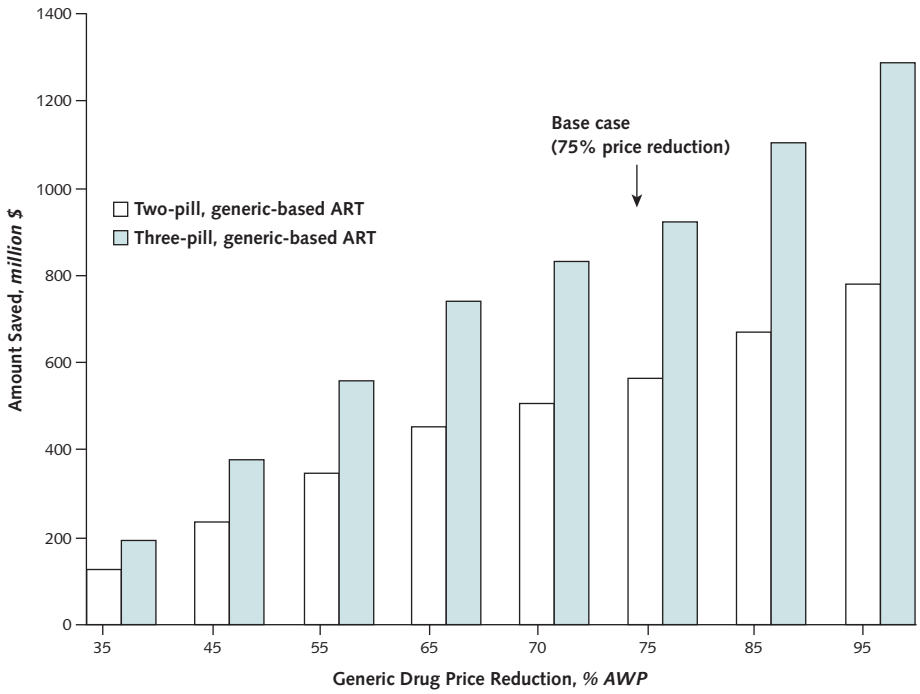
ART = antiretroviral therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

* Risk-group adjustments account for differences in non–HIV-related (background) mortality between those at highest risk for HIV and the general population. We considered 5 sex/risk groups in our adjustment: men who have sex with men, male and female injection drug users, and male and female high-risk heterosexuals. For each group, we applied a published risk group–specific standardized mortality ratio to age- and sex-adjusted non–HIV-related mortality rates (58). We then weighted these risk group–specific mortality rates according to the distribution of risk groups among HIV-infected persons in the United States (59), as well as to the predicted changes in the distribution over time to get age-, sex-, and risk-adjusted non-HIV mortality rates.

† More expensive but confers less clinical benefit than some combination of other strategies.

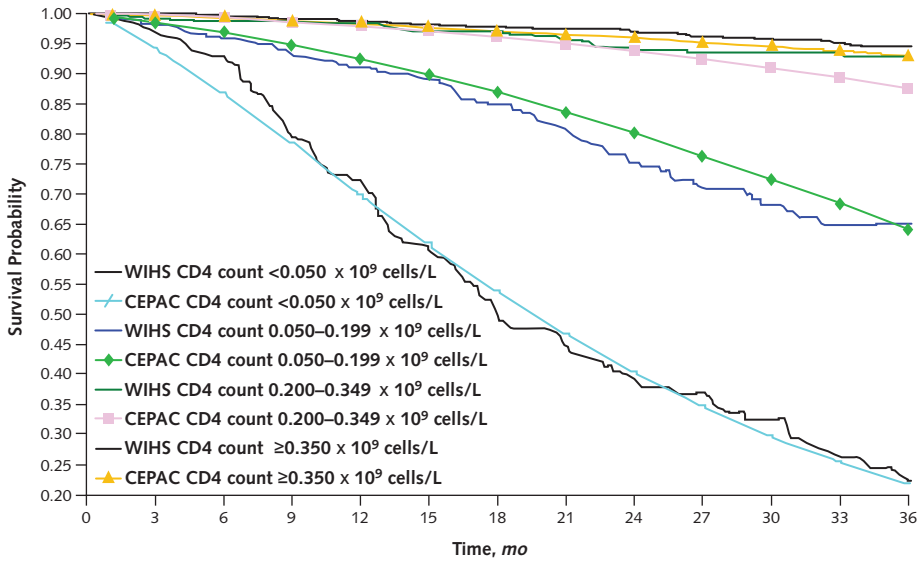
‡ More expensive and confers less clinical benefit than the next least expensive strategy.

Appendix Figure 4. **Potential annual cost savings in the United States with 3-pill or 2-pill, generic-based ART compared with branded ART.**



The potential annual savings for 2-pill or 3-pill, generic-based ART are compared with branded ART over a range of generic drug price reductions. The *x*-axis shows the price reductions, which range from 35% to 95%; the base case of 75% savings is indicated by the arrow. The *y*-axis shows the amount of money projected to be saved (million 2009 U.S. dollars) over a 1-y horizon. Calculations in this analysis assume that all persons maintain their designated generic or branded ART regimen for the first year and do not switch to a subsequent line of therapy before the end of 12 mo. ART = antiretroviral therapy; AWP = average wholesale price.

Appendix Figure 5. **Comparison of CEPAC Model outcomes and data reported from WIHS.**



Kaplan–Meier survival curves based on data from WIHS were compared with preliminary, model-estimated survival over 36 mo in women with CD4 counts $<0.050 \times 10^9$ cells/L and $>0.350 \times 10^9$ cells/L. Lines with symbols represent model-based projections, whereas those without symbols represent WIHS data. CEPAC = Cost-Effectiveness of Preventing AIDS Complications; WIHS = Women's Interagency HIV Study.