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Economic savings versus health losses: The cost-effectiveness of generic antiretroviral therapy in the United States

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Abstract

Background—US HIV treatment guidelines recommend branded once-daily, one-pill efavirenz/emtricitabine/tenofovir as preferred first-line antiretroviral treatment (ART). With the anticipated approval of generic efavirenz in 2012 in the US, the cost of a once-daily, three-pill alternative (generic efavirenz, generic lamivudine, tenofovir) will decrease, but adherence and virologic suppression may be reduced.

Objectives—To assess the clinical impact, costs, and cost-effectiveness of the generic-based three-pill regimen compared to the branded, co-formulated regimen. To project the potential national savings in the first year of a switch to generic-based ART.

Design—Mathematical simulation of HIV disease.

Data Sources—Published data from US clinical trials and observational cohorts.

Target Population—HIV-infected patients eligible to start on or switch to an efavirenz-based generic ART regimen.

Time Horizon—Lifetime, One-year

Perspective—US health system

Interventions—No ART (for comparison), Three-pill Generic ART, and Branded ART

Outcome Measures—Quality-adjusted life expectancy, costs, and incremental cost-effectiveness ratios (ICER, \$/quality-adjusted life expectancy [QALY]).

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Results of Base-Case Analysis—Compared to No ART, Generic ART has an ICER of \$21,100/QALY. Compared to Generic 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 US patients start on or switch to Generic ART, are \$920 million.

Results of Sensitivity Analysis—Most plausible assumptions about Generic ART efficacy and costs lead to Branded ART ICERs >\$100,000/QALY.

Limitations—The efficacy and price reduction associated with generics are unknown; estimates are intended to be conservative.

Conclusions—Compared to a slightly less effective generic-based regimen, the cost-effectiveness of first-line Branded ART exceeds \$100,000/QALY. Generic-based ART in the US could yield substantial budgetary savings to HIV programs.

INTRODUCTION

For the first time since the 1996 US Food and Drug Administration (FDA) approval of combination antiretroviral therapy (ART), there is now potential for a potent, largely generic, first-line regimen. In January 2012, generic versions of lamivudine became available in the US, and later in 2012, generic versions of efavirenz are expected. The once-daily, three-pill regimen of generic efavirenz, generic lamivudine, and branded tenofovir could substantially reduce costs of first-line ART.

Even if the potency, tolerability, and safety of generic lamivudine and efavirenz meet the required FDA standards of their proprietary equivalents, there remain two potential disadvantages. The first is increased pill burden; the currently recommended branded tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) is co-formulated as a single, once-daily pill. If pill burden hinders adherence, thereby reducing viral suppression, a three-pill generic alternative may lead to worse outcomes (1, 2). Second, substituting lamivudine for emtricitabine may reduce potency and increase the frequency of M184V mutations upon first-line failure, thereby compromising the effectiveness of subsequent regimens (3, 4). A once-daily two-pill option (tenofovir/emtricitabine, efavirenz) offers a potential intermediate alternative, with some cost savings (by using generic efavirenz), lower pill burden, and avoidance of lamivudine. Given these trade-offs, we sought to assess the clinical impact, cost, and cost-effectiveness of the generic-based ART compared to branded co-formulated alternatives.

METHODS

Analytic Overview

We evaluate three strategies for HIV-infected persons eligible to initiate an efavirenz-based regimen: 1) *No ART* (for comparison); 2) *Three-pill Generic ART*, consisting of efavirenz (generic), lamivudine (generic), and tenofovir (patented Viread®, Gilead Sciences); or 3) *Branded ART*, consisting of the one-pill co-formulated efavirenz/emtricitabine/tenofovir (Atripla®, Gilead/Bristol-Myers Squibb). For ease of identification, we refer to the “Generic ART strategy”, even though it contains one branded component. In the base case, Generic ART differs from Branded ART in three ways. First-line viral suppression efficacy is lower owing to both increased pill burden (poorer adherence) and decreased potency (substitution of lamivudine for emtricitabine). Second, viral suppression efficacy in second-line therapy is lower due to reported increased frequency of M184V mutations associated with failure of first-line viral suppression on lamivudine (vs. emtricitabine). Finally, first-line drug costs are lower. We vary all of these parameters in sensitivity analyses.

We use the Cost-effectiveness of Preventing AIDS Complications (CEPAC) US Model – a previously published mathematical simulation of HIV (5–9) – to project clinical outcomes (quality-adjusted life years [QALYs]) and economic outcomes (per-person lifetime costs) for the three strategies. These projections are then used to evaluate incremental cost-effectiveness ratios, which we report from a US health system perspective, discounted at 3%/annum (10). We also project the undiscounted savings in the first year among all patients who are on or starting on an efavirenz-based treatment and eligible to switch from Branded to Generic ART.

The CEPAC-US Model

CEPAC-US characterizes HIV disease progression as a sequence of monthly transitions between “health states.” These health states summarize current status, relevant history, quality of life, and resource use; they also determine the risk of future clinical events. Health states are stratified by CD4 count (5 strata), HIV RNA level (6 strata), ART regimen, and disease acuity (e.g. treatment-related toxicity or opportunistic infection [OI]). In the model, the level of HIV RNA determines the rate of CD4 decline, and the CD4 count determines the frequency of OIs and AIDS-related death. Patients face a risk HIV-related mortality (OIs and otherwise), or age- and sex-adjusted background mortality (11, 12).

We capitalize on the model's capacity to consider early-regimen mutations and virologic failure in determining the efficacy of subsequent regimens. Per current US guidelines (13), we assume all newly-presenting patients initiate therapy immediately. Effective ART functions to suppress HIV RNA and increase CD4 count at rates reported (14–21). Quarterly clinic visits, CD4 and HIV RNA monitoring confirm the possibility of “early suppression” followed by “late failure,” two model-based parameters that define ART efficacy. Early suppression of a regimen is the fraction of patients virologically suppressed after 24 weeks. Suppressed patients 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 changes in clinical and cost outcomes.

Input Parameters

Cohort—The entering cohort is modeled as similar to those newly diagnosed HIV-infected patients in the US in 2009 (22), among whom 84% were male. Recent US data suggest a mean CD4 count at presentation of 317/ μ l (Table 1) (22, 23).

ART Efficacy—In the No ART strategy, patients follow the natural history of HIV disease without access to ART. Branded ART results in 24-week virologic suppression of 85% – from a clinical trial using co-formulated, one-pill tenofovir/emtricitabine/efavirenz -- with a 0.21% monthly probability of late failure after 24 weeks (14). For this strategy, we use a second-line, protease-inhibitor-based regimen with a 24-week suppression efficacy of 73% (17, 18). Three-pill Generic ART leads to 24-week virologic suppression of 78%, from a clinical trial of efavirenz, lamivudine, and tenofovir (15). Using trial data, we derive the monthly probability of failure after 24 weeks as 0.45%, substantially higher than that of Branded ART. We also decrease the suppression rate of second-line ART by 5%, from 73% with Branded to 68% with Generic ART, an assumption that captures the increased risk of M184V mutations resulting from first-line lamivudine use (3, 4). Efficacies for subsequent ART regimens (Appendix Table 1) are otherwise identical between treatment strategies.

An intermediate option to Three-pill Generic ART is a two-pill alternative, using co-formulated tenofovir/emtricitabine (Truvada®, Gilead Sciences) and generic efavirenz. Recognizing the uncertainty surrounding the comparative efficacy of once-daily one-versus two- versus three-pill regimens, we examine all options together in generalized sensitivity analyses designed to illuminate the trade-offs among early efficacy, late failure, and costs. We begin with a Two-pill Generic ART 24-week suppressive efficacy of 84% and a monthly probability of failure thereafter of 0.43% (19); we maintain the full potency of the second-line regimen because of the inclusion of emtricitabine in the first-line regimen (Table 1). Other efficacy/cost combinations are also examined.

Costs—The annual cost for Branded ART is \$15,300 (25), 77% of the published average wholesale price (AWP) for standard dosing (Table 1) (26). We assume a 75% price reduction from AWP for the generic components of the Three-pill Generic ART regimen (\$9,200/year) and the Two-pill Generic ART regimen (\$11,600/year) and explore reductions from 35% to 95%. Subsequent ART regimen, laboratory monitoring, and routine care costs are in Appendix Table 1. All costs are in 2009 USD.

Sensitivity Analyses—We use one-way and multi-way sensitivity analyses to understand the impact of uncertainty in early virologic suppression efficacies, probabilities of late failure, and the comparative cost-savings from Generic ART. We also examine alternative second-line ART efficacies associated with an increased presence of M184V mutations, and consider a cohort with higher/lower CD4 counts leading to varying durations on ART. Finally, we examine the impact of our results with risk-group adjustments to our estimates of non-HIV-related mortality.

Potential Savings in the First Year—To determine the potential savings in the US during the first year, we multiply the number of persons eligible to start or switch to Generic ART by the per-person savings. “Incident cases” likely to be prescribed efavirenz are calculated as the product of: the anticipated new diagnoses in the US per year (8,294 in 2009) (22); the estimated fraction of HIV-infected people on ART (36%) (27); and the likelihood that an efavirenz-based regimen is selected as first-line (85%) (28). “Prevalent cases” switching from an efavirenz-based branded regimen to its generic-based alternative are calculated as the product of: CDC-based projections of the number of persons living with HIV in the US (1,200,000) (22); the estimated proportion on ART (36%) (27); and the estimated proportion of those on ART who receive an efavirenz-based regimen (34%, Gebo K, Personal communication) (27). We multiply the number of persons eligible for a generic start or switch by the potential per-person savings associated with Generic ART in the first year. These savings are the difference between the undiscounted annual costs of Branded (\$15,300) and Generic (\$9,200) ART, or \$6,100 per person.

RESULTS

Base Case Results

In the base case, the discounted per-person quality-adjusted life expectancies from age 43 are 4.05 QALYs (undiscounted 4.58) for No ART, 12.08 QALYs (undiscounted 18.36) for Three-pill Generic ART, and 12.45 QALYs (undiscounted 19.32) for Branded ART (Table 2). Per-person discounted lifetime costs increase from \$131,200 (No ART) to \$300,300 for Generic ART to \$342,800 for Branded ART. Compared to No ART, Three-pill Generic ART results in an ICER of \$21,100/QALY. The ICER for Branded ART, compared to Generic ART, is \$114,800/QALY (Table 2, Figure 1a).

Two-pill Generic ART

Two-pill Generic ART results in greater survival than Three-pill Generic in the base case (12.25 vs. 12.08 QALYs). When Three- and Two-pill Generic ART, and Branded ART are compared incrementally, ICERs are \$21,100/QALY for Three-pill Generic ART vs. No ART, \$95,400/QALY for Two-pill Generic vs. Three-pill Generic ART, and \$130,600/QALY for Branded vs. Two-Pill Generic ART (Table 2, bottom, Figure 1b).

Sensitivity Analyses

Three-pill Generic ART—The ICER for Branded ART compared to Three-pill Generic ART is sensitive to the comparative cost and efficacy of Generic ART (Figure 2a). At the base case Generic ART efficacy (78% 24-week suppression, 0.45%/month probability of late failure), Branded ART has an ICER >\$100,000/QALY, provided that the discount from AWP for Generic ART is greater than 65% (⊙, Figure 2a). If the probability of 24-week suppression remains lower for Three-pill Generic compared to Branded ART, but the monthly probability of late failure is the same for both (0.21%), then the ICERs of Branded compared to Three-pill Generic ART are substantially higher at every combination of Generic ART 24-week efficacy and price reduction (Figure 2b). Under such conditions, even modest price reductions (>40% AWP) for the generic regimen components result in ICERs for Branded ART compared to Generic ART >\$100,000/QALY (⊙, Figure 2b).

Two-pill Generic ART—Results for Two-pill Generic ART are similarly sensitive to regimen efficacy – most importantly to the probability of late failure – as well as to costs. When Two-pill Generic, Three-pill Generic, and Branded ART all have the same probability of late failure (0.21% at 24 weeks), then Two-pill Generic ART has an ICER <\$100,000/QALY compared to Three-pill Generic ART at price reductions of 50% AWP (\$62,600/QALY Table 3, top). If Branded and Two-pill Generic ART have similar probabilities of late failure (0.21%) -- lower than that of the Three-pill Generic ART (0.45%) -- then Two-pill Generic ART becomes much more attractive. At all price reductions examined, Two-pill Generic ART becomes the best choice, because it dominates (more effective and less costly) Three-pill Generic ART and because of the very high ICERs for Branded ART (\$101,300–2,540,100/QALY, Table 3, middle).

Other Sensitivity Analyses—In other sensitivity analyses we observe variability in outcomes, but no material impact on the qualitative cost-effectiveness findings when we change the efficacy of second-line ART (to capture changes related to potential lamivudine-related resistance, Branded ART ICERs \$109,300–120,600/QALY); when we consider a healthier presenting cohort (mean CD4 count = 650/μl, Branded ART ICER \$143,200/QALY); or when we adjusted background mortality rates by risk group (Branded ART ICER \$117,400/QALY, (Appendix Tables 2–5).

Potential Savings in the First Year

The per-person undiscounted savings for Three-pill and Two-pill Generic ART compared to Branded ART are \$6,100/year and \$3,700/year. We estimate that there are 2,500 persons newly-diagnosed and initiating ART (“incident cases”) and 147,300 HIV-infected persons (“prevalent cases”) currently taking an efavirenz-based regimen who could switch to Generic ART in the US (27). Combining the benefits from both incident and prevalent cases, the potential estimated savings in the first year associated with use of Three-pill Generic ART in the base case are \$920 million; the anticipated savings are substantially less for Two-pill Generic ART (\$560 million). Anticipated savings in the first year from Three-pill Generic ART range from \$200 million to \$1.29 billion at price reductions from AWP from 35 to 95% (Appendix Figure 1).

DISCUSSION

We project that a population-wide switch from first-line Branded to Generic ART in the US will result in lifetime average savings of \$42,500 per eligible patient with only a modest survival loss of 0.37 QALYs. Viewed on a population-wide basis, the aggregate savings in the first year alone would amount to nearly \$1 billion. Accounting for potential decrements in the short- and long-term efficacy of generic-based regimens, we find that the incremental cost-effectiveness of a first-line branded regimen becomes unattractive by a standard ($> \$100,000/\text{QALY}$) recently used in the US (29–31).

The market for antiretrovirals in the US – largely financed with governmental support – was estimated at nearly \$9 billion in 2011 (32). Much is at stake as major components of effective HIV therapy become generically available this year. The significance 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 antiretrovirals – and the trade-off between drug efficacy and costs savings – may be evaluated.

Generics will save money but may reduce health benefits, a trade-off that may be emotionally unattractive. Fewer than 2% of published cost-effectiveness analyses report on this combination of both lower health benefits but also lower costs (33). 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, lifesaving alternatives. This is particularly true as an increasing number of proven effective, yet costly interventions further stretch the resources of the US health care system. For example, fewer than half the state AIDS Drug Assistance Programs (ADAPs) in the US include protease-inhibitor-based Hepatitis C virus (HCV) regimens (\$90,100/treatment course) in their formularies, despite these drugs having ICERs $< \$100,000/\text{QALY}$ (as reported in mono-infected patients)^{33,34}. (34, 35) For every fifteen people switched to a generic-based HIV regimen (potential annual savings ~\$6,100/person), one person with HIV/HCV co-infection could be treated for – and potentially cured of – chronic hepatitis C (34). With 300,000 people in the US eligible for these new HCV therapies, this would represent a major treatment opportunity (35). President Obama's 2010 National HIV/AIDS Strategy (NHAS) (36) is explicitly financed by “re-purposed” rather than new funds (37). In an era where dedication to the national HIV mission requires “re-directed” financing, the potential \$1 billion savings from generic-based regimens might be an efficient source available for national reinvestment (38).

Our assumptions with regard to generic drug efficacy and pricing are conservative. Despite the absence of clinical trial evidence suggesting any differential, we assumed that daily lamivudine would be less effective and promote more resistance, compared to emtricitabine, when used as either a first- or second-line regimen. We also assumed an adherence advantage for a daily single-pill regimen, despite mixed data on how pill burden affects virologic suppression (1, 39). Our 75% price reduction is justified by evidence that generic prices fall by as much as 80–85% of published branded prices when five or more manufacturers enter a market^{39,40}. (40, 41) More than seven suppliers currently provide FDA-approved generic efavirenz outside the US, under PEPFAR auspices (42).

We note several limitations in this analysis. First, the \$100,000/QALY threshold for cost-effectiveness, while frequently cited, may be debated (30, 43, 44). Higher willingness-to-pay thresholds could result in branded regimens falling within an acceptable range. While we conduct this analysis from the US health system perspective, we acknowledge that the savings realized from a policy switch to generic-based regimens will accrue differently from

one payer to the next (e.g. state ADAPs vs. state Medicaid programs vs. the US Veterans Administration); these savings may not be reinvested in HIV care, or even in health care. The savings may also be greater than we project. If efforts to improve HIV case identification, linkage to and retention in care are successful-- thus increasing the outlay for HIV medications -- the anticipated savings from generics could exceed our \$920 million estimate (45).

Compared to a slightly less effective regimen containing generics, we find that the incremental cost-effectiveness for the branded one-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

Appendix Table 1

Base case ART efficacy inputs and costs for later ART regimens in an analysis for first-line Generics vs. Branded ART in the US

Variable	Base case value	Range	Reference
Efficacy of ART (% patients with HIV RNA suppression at 24 weeks, CD4 increase at 48 weeks, monthly probability of late failure after 24-weeks)			
<i>All regimen efficacy of 3rd-6th line</i>			
Third-line	61%; 121 cells/ μ l, 1.71%		(17, 18)
Fourth-line	65%; 102 cells/ μ l, 1.71%		(16)
Fifth-line	40%; 119 cells/ μ l, 2.19%		(20, 21)
Sixth-line	15%; 45 cells/ μ l, 2.19%		(20)
Costs (2009 USD)			
Antiretroviral therapy, annual			(25)
Third-line	21,900		
Fourth-line	28,600		
Fifth-line	51,700		
Sixth-line	19,100		
CD4 test, annual	820		(46)
HIV RNA test, annual	1,500		(46)
Routine care by CD4 count, annual			(47-49)
>500/ul	2,900		
301-500/ul	5,700		
201-300/ul	5,800		
101-200/ul	6,700		

Variable	Base case value	Range	Reference
50–100/ul	13,000		
<50/ul	11,900		

Appendix Table 2Sensitivity analysis on the 2nd-line ART efficacy for the Three-pill Generic ART

	Per-person costs 2009 USD	Per-person life expectancy QALY	Incremental cost- effectiveness ratio \$/QALY
2nd Line ART Efficacy = 73%			
No ART	131,200	4.05	
Three-pill Generic ART	301,300	12.11	21,100
Branded ART	342,800	12.45	120,600
2nd Line ART Efficacy = 72%			
No ART	131,200	4.05	
Three-pill Generic ART	300,800	12.09	21,100
Branded ART	342,800	12.45	117,300
2nd Line ART Efficacy = 67%			
No ART	131,200	4.05	
Three-pill Generic ART	299,800	12.07	21,000
Branded ART	342,800	12.45	112,400
2nd Line ART Efficacy = 63%			
No ART	131,200	4.05	
Three-pill Generic ART	299,300	12.05	21,000
Branded ART	342,800	12.45	109,300

ART: Antiretroviral therapy; USD: United States dollar; QALY: Quality-adjusted life year

Appendix Table 3

Sensitivity analysis demonstrating the impact on clinical outcomes, cost, and cost-effectiveness for alternative mean CD4 cell counts of the presenting cohort

	Per-person costs 2009 USD	Per-person life expectancy QALY	Incremental cost- effectiveness ratio \$/QALY
Mean CD4 = 350/μl			
No ART	131,300	4.30	
Three-pill Generic ART	303,800	12.37	21,400
Branded ART	346,900	12.73	118,500
Mean CD4 = 400/μl			
No ART	131,400	4.70	
Three-pill Generic ART	308,600	12.77	22,000
Branded ART	352,800	13.13	121,700

	Per-person costs 2009 USD	Per-person life expectancy QALY	Incremental cost- effectiveness ratio \$/QALY
Mean CD4 = 450/μl			
No ART	131,300	5.11	
Three-pill Generic ART	312,900	13.13	22,600
Branded ART	358,000	13.49	125,200
Mean CD4 = 500/μl			
No ART	131,000	5.51	
Three-pill Generic ART	316,500	13.44	23,400
Branded ART	362,700	13.80	128,200
Mean CD4 = 550/μl			
No ART	130,700	5.92	
Three-pill Generic ART	319,700	13.71	24,300
Branded ART	366,400	14.06	133,700
Mean CD4 = 600/μl			
No ART	130,200	6.33	
Three-pill Generic ART	322,200	13.93	25,300
Branded ART	369,400	14.27	139,800
Mean CD4 = 650/μl			
No ART	129,600	6.73	
Three-pill Generic ART	324,200	14.12	26,400
Branded ART	371,900	14.45	143,200

ART: Antiretroviral therapy

Appendix Table 4

Sensitivity analysis demonstrating the impact on clinical outcomes, cost, and cost-effectiveness when background mortality is adjusted by risk-group*

	Per-person costs 2009 USD	Per-person life expectancy QALY (undiscounted)	Incremental cost- effectiveness ratio \$/QALY
No ART	130,700	4.02 (4.54)	
Three-pill Generic ART	294,700	11.79 (17.78)	21,100
Branded ART	336,200	12.14 (18.69)	117,400
No ART	130,700	4.02 (4.54)	
Three-pill Generic ART	294,700	11.79 (17.78)	21,100
Two-pill Generic ART	310,300	11.95 (18.13)	95,000
Branded ART	336,200	12.14 (18.69)	136,900

USD: United States Dollar; QALY: quality-adjusted life year; ART: antiretroviral therapy

* 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 five 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 of these groups, we applied a published risk-group specific standardized mortality ratio (SMR) to age- and sex-adjusted non-HIV related mortality rates. (50) We then weighted these risk-group-specific mortality rates according to the distribution of risk-groups among HIV-

infected individuals in the US,(51) 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 5

Three-way sensitivity analysis on Two-pill vs. Three-pill Generic ART, probability of virologic failure after 24 weeks and price reduction when background mortality is adjusted by risk group*

	Per-person costs 2009 USD	Per-person life expectancy QALY	Incremental cost- effectiveness ratio \$/QALY
Probability of late virologic failure (Branded=0.21%, Two-pill Generic=0.21%, Three-pill Generic=0.21%)			
<i>25% generic drug price reduction</i>			
No ART	130,700	4.02	
Three-pill Generic ART	334,600	11.97	dominated
Two-pill Generic ART	334,800	12.13	25,200
Branded ART	336,200	12.14	124,700
<i>50% generic drug price reduction</i>			
No ART	130,700	4.02	
Three-pill Generic ART	307,800	11.97	22,300
Two-pill Generic ART	317,800	12.13	63,100
Branded ART	336,200	12.14	1,680,400
<i>75% generic drug price reduction</i>			
No ART	130,700	4.02	
Three-pill Generic ART	281,000	11.97	18,900
Two-pill Generic ART	300,600	12.13	122,700
Branded ART	336,200	12.14	3,391,200
Probability of late virologic failure (Branded=0.21%, Two-pill Generic=0.21%, Three-pill Generic=0.45%)			
<i>25% generic drug price reduction</i>			
No ART	130,700	4.02	
Two-pill Generic ART	334,800	12.13	25,200
Branded ART	336,200	12.14	124,700
Three-pill Generic ART	337,000	11.79	DOMINATED
<i>50% generic drug price reduction</i>			
No ART	130,700	4.02	
Three-pill Generic ART	315,900	11.79	dominated
Two-pill Generic ART	317,800	12.13	23,100
Branded ART	336,200	12.14	1,608,400
<i>75% generic drug price reduction</i>			
No ART	130,700	4.02	
Three-pill Generic ART	295,000	11.79	dominated
Two-pill Generic ART	300,600	12.13	21,000
Branded ART	336,200	12.14	3,391,200
Probability of late virologic failure (Branded=0.21%, Two-pill Generic=0.45%, Three-pill Generic=0.45%)			

	Per-person costs 2009 USD	Per-person life expectancy QALY	Incremental cost- effectiveness ratio \$/QALY
25% generic drug price reduction			
No ART	130,700	4.02	
Branded ART	336,200	12.14	25,300
Three-pill Generic ART	337,000	11.79	DOMINATED
Two-pill Generic ART	337,600	11.94	DOMINATED
50% generic drug price reduction			
No ART	130,700	4.02	
Three-pill Generic ART	315,900	11.79	23,900
Two-pill Generic ART	324,200	11.94	54,800
Branded ART	336,200	12.14	60,300
75% generic drug price reduction			
No ART	130,700	4.02	
Three-pill Generic ART	295,000	11.79	21,200
Two-pill Generic ART	310,900	11.94	107,000
Branded ART	336,200	12.14	127,800

Dominated: A strategy that is more expensive but confers less clinical benefit than some combination of other strategies;
 DOMINATED: A strategy that is more expensive and confers less clinical benefit than the next least expensive strategy;
 Antiretroviral therapy; ART; ART: Antiretroviral therapy; USD: United States dollar; 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 five 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 of these groups, we applied a published risk-group specific standardized mortality ratio (SMR) to age- and sex-adjusted non-HIV related mortality rates (50). We then weighted these risk-group-specific mortality rates according to the distribution of risk-groups among HIV-infected individuals in the US (51), as well as to the predicted changes in the distribution over time to get age-, sex-, and risk-adjusted non-HIV mortality rates.

Appendix Figure 1.

Potential annual cost savings in the US with Three-pill or Two-pill Generic ART compared to Branded ART. The potential annual savings on a Two-pill (black bars) or Three-pill (gray bars) Generic ART are compared to Branded ART over a range of generic drug price reductions (%). The horizontal axis shows the range of price reductions, which span from 35% to 95% savings; the base case of 75% savings is indicated by the arrow. The vertical axis shows the amount of money projected to be saved (2009 USD in millions) over one-year horizon. Calculations in this analysis assume that all persons remain on 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 months. (ART: Antiretroviral therapy)

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Figure 1.

The clinical and economic outcomes of Branded and Generic ART. Per-person lifetime costs are on the horizontal axis and quality-adjusted life expectancy on the vertical axis. Gray solid lines indicate the anticipated incremental cost-effectiveness ratios of Branded ART compared to No ART in the absence of a generic alternative. Figure 1a shows Three-pill Generic ART; Figure 1b shows both Two-pill and Three-pill Generic ART.

Figure 2.

Two-way sensitivity analyses demonstrating the changes in the incremental cost-effectiveness ratio (ICER) of Branded ART, compared to the Three-pill Generic ART (vertical axis), as a function of the generic drug price reduction (horizontal axis) and the early efficacy of Three-pill Generic ART (alternative lines). In the base case, Branded ART has an ICER > \$100,000/QALY, as long as the generic drug discount from AWP is greater than 65% (⊙). Figure 2a represents results when the monthly probability of late failure (after 24 weeks) is 0.45% in the Three-pill Generic ART strategy (probability of late failure for Branded ART is 0.21%). Figure 2b represents results when the monthly probability of late failure is 0.21% in the Three-pill Generic ART strategy (probability of late failure after for Branded ART is also 0.21%). Even modest price reductions (>40%) for the generic regimen components result in ICERs for Branded ART > \$100,000/QALY (⊙). In both graphs, the arrow and vertical line indicate the base case Generic ART savings (75%).

Table 1

Base case inputs for a model of Generics vs. Branded ART in the US

Variable	Base case value	Range	Reference
Cohort Characteristics			
Age, mean years (SD)	43 (12)		(23)
Male sex, (%)	84		(23)
Initial CD4 cell count, mean cells/ μ l (SD)	317 (283)		(23)
HIV RNA distribution, (%)			(24)
> 100,000 copies/ml	12.9%		
30,001–100,000 copies/ml	12.9%		
10,001–30,000 copies/ml	25.0%		
3,001–10,000 copies/ml	25.2%		
501–3,000	16.3%		
<500 copies/ml	7.7%		
Efficacy of ART (% patients with HIV RNA suppression at 24 weeks, CD4 increase at 48 weeks, monthly probability of late failure after 24-weeks)			
<i>Branded efficacy of 1st- and 2nd-line</i>			
First-line (EFV/FTC/TDF)	85%; 206 cells/ μ l, 0.21%		(14)
Second-line (ATV/r+TDF/FTC)	73%; 110 cells/ μ l, 1.71%		(17, 18)
<i>Two-pill Generic efficacy of 1st- and 2nd-line</i>			
First-line (EFV+TDF/FTC)	84%; 206 cells/ μ l, 0.43%		(19)
Second-line (ATV/r+TDF/FTC)	73%; 110 cells/ μ l, 1.71%		(17, 18)
<i>Three-pill Generic efficacy of 1st- and 2nd-line</i>			
First-line (EFV+3TC+ TDF)	78%; 206 cells/ μ l, 0.45%		(15)
Second-line (ATV/r+TDF/FTC)	68%; 110 cells/ μ l, 1.71%		(17, 18)
Costs (2009 USD)			
Antiretroviral therapy, annual			(25)
First-line, brand name (EFV/TDF/FTC)	15,300		
First-line, generic two-pill (EFV+TDF/FTC)	11,600		
First-line, generic three-pill (EFV+3TC+TDF)	9,200		
Second-line (ATV/r+TDF/FTC)	22,100		

3TC: Lamivudine; ATV/r: Atazanavir/Ritonavir; EFV: Efavirenz; FTC: Emtricitabine; LPV/r: Lopinavir/Ritonavir; TDF: Tenofovir

Table 2

Clinical outcomes, cost, and cost-effectiveness of Generic vs. Branded ART in the US

	Per-person costs 2009 USD	Per-person life expectancy QALY (undiscounted)	Incremental cost-effectiveness ratio \$/QALY
No ART	131,200	4.05 (4.58)	---
Three-pill Generic ART	300,300	12.08 (18.36)	21,100
Branded ART *	342,800	12.45 (19.32)	114,800
No ART	131,200	4.05 (4.58)	---
Three-pill Generic ART	300,300	12.08 (18.36)	21,100
Two-pill Generic ART	316,100	12.25 (18.73)	95,400
Branded ART *	342,800	12.45 (19.32)	130,600

USD: United States Dollars; QALY: quality-adjusted life year; ART: antiretroviral therapy

* Note: Incremental cost-effectiveness ratio for Branded ART vs. No ART is \$25,200 QALY/year

Table 3

Three-way sensitivity analysis on Two-pill vs. Three-pill Generic ART, probability of late failure after 24 weeks, and price reduction.

	Per-person costs 2009 USD	Per-person life expectancy QALY	Incremental cost-effectiveness ratio \$/QALY
Probability of late virologic failure (Branded=0.21%, Two-pill Generic=0.21%, Three-pill Generic=0.21%)			
<i>25% generic drug price reduction</i>			
No ART	131,200	4.05	---
Three-pill Generic ART	341,000	12.27	Dominated
Two-pill Generic ART	341,300	12.43	25,100
Branded ART	342,800	12.45	101,300
<i>50% generic drug price reduction</i>			
No ART	131,200	4.05	---
Three-pill Generic ART	313,600	12.27	22,200
Two-pill Generic ART	323,800	12.43	62,600
Branded ART	342,800	12.45	1,162,000
<i>75% generic drug price reduction</i>			
No ART	131,200	4.05	---
Three-pill Generic ART	286,200	12.27	18,900
Two-pill Generic ART	306,400	12.43	121,600
Branded ART	342,800	12.45	2,540,100
Probability of late virologic failure (Branded=0.21%, Two-pill Generic=0.21%, Three-pill Generic=0.45%)			
<i>25% generic drug price reduction</i>			
No ART	131,200	4.05	---
Two-pill Generic ART	341,300	12.43	25,100
Branded ART	342,800	12.45	101,300
Three-pill Generic ART	343,000	12.08	DOMINATED
<i>50% generic drug price reduction</i>			
No ART	131,200	4.05	---
Three-pill Generic ART	321,700	12.08	Dominated
Two-pill Generic ART	323,800	12.43	23,000
Branded ART	342,800	12.45	1,162,000
<i>75% generic drug price reduction</i>			
No ART	131,200	4.05	---
Three-pill Generic ART	300,300	12.08	Dominated
Two-pill Generic ART	306,400	12.43	20,900
Branded ART	342,800	12.45	2,540,100
Probability of late virologic failure (Branded=0.21%, Two-pill Generic=0.45%, Three-pill Generic=0.45%)			
<i>25% generic drug price reduction</i>			
No ART	131,200	4.05	---
Branded ART	342,800	12.45	25,200
Three-pill Generic ART	343,000	12.08	DOMINATED
Two-pill Generic ART	343,900	12.24	DOMINATED

	Per-person costs 2009 USD	Per-person life expectancy QALY	Incremental cost-effectiveness ratio \$/QALY
50% generic drug price reduction			
No ART	131,200	4.05	---
Three-pill Generic ART	321,700	12.08	23,700
Two-pill Generic ART	330,300	12.24	55,600
Branded ART	342,800	12.45	57,100
75% generic drug price reduction			
No ART	131,200	4.05	---
Three-pill Generic ART	300,300	12.08	21,100
Two-pill Generic ART	316,700	12.24	105,600
Branded ART	342,800	12.45	121,100

Dominated: A strategy that is more expensive but confers less clinical benefit than some combination of other strategies; DOMINATED: A strategy that is more expensive and confers less clinical benefit than the next least expensive strategy; ART: Antiretroviral therapy; USD: United States dollar; QALY: Quality-adjusted life year