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Cost-effectiveness of Newer Antiretroviral Drugs in Treatment-Experienced Patients with Multi-drug Resistant HIV Disease

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Abstract

Objective—Newer antiretroviral drugs provide substantial benefits but are expensive. We determined the cost-effectiveness of using antiretroviral drugs in combination for patients with multi-drug resistant HIV disease.

Design—We built a cohort state-transition model representing treatment-experienced patients with low CD4 counts, high viral load levels, and multi-drug resistant virus. We estimated the effectiveness of newer drugs (those approved in 2005 or later) from published randomized trials. We estimated other parameters from a randomized trial and from the literature. The model had a lifetime time horizon and used the perspective of an ideal insurer in the United States. The interventions were combination antiretroviral therapy, consisting of two newer drugs and one conventional drug, compared to three conventional drugs. Outcome measures were life-years, quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness.

Results—Substituting newer antiretroviral drugs increased expected survival by 3.9 years in advanced HIV disease. The incremental cost-effectiveness ratio of newer, compared to conventional, antiretroviral drugs was \$75,556/QALY gained. Sensitivity analyses showed that substituting only one newer antiretroviral drug cost \$54,559 to \$68,732/QALY, depending on assumptions about efficacy. Substituting three newer drugs cost \$105,956 to \$117,477/QALY. Cost-effectiveness ratios were higher if conventional drugs were not discontinued.

Conclusions—In treatment-experienced patients with advanced HIV disease, use of newer antiretroviral agents can be cost effective, given a cost-effectiveness threshold in the range of \$50,000 to \$75,000 per QALY gained. Newer antiretroviral agents should be used in carefully selected patients for whom less expensive options are clearly inferior.

Keywords

Novel antiretroviral drugs; multi-drug resistant HIV infection; cost-effectiveness analysis; quality of life; health economics

Introduction

Until recently, extensively treatment-experienced patients with advanced human immunodeficiency virus (HIV) infection had limited treatment options and poor outcomes.¹ Prolonged treatment with antiretroviral drugs without full virologic suppression can lead to selective drug pressure and the emergence of resistant virus.² Furthermore, many mutations confer cross-resistance to other HIV antiretroviral drugs in the same class.³ In a recent trial of treatment options for patients with advanced multi-drug resistant HIV, 35% of patients died over 4 years and 27% experienced at least one AIDS-defining event.^{4, 5}

Several antiretroviral drugs approved since 2005 have offered patients with advanced HIV additional treatment options, including new drugs within conventional classes, such as the non-nucleoside reverse transcriptase inhibitors (NNRTI) etravirine and rilpivirine and the second-generation protease inhibitors darunavir and tipranavir as well as novel drug classes, such as maraviroc, an entry inhibitor, and raltegravir, an integrase inhibitor. In randomized controlled trials comparing regimens containing newer drugs (approved since 2005) to background regimens consisting of conventional drugs optimized through the use of resistance tests, the newer drug regimens more effectively suppressed viral load and increased CD4 counts.^{6–21} Newer drugs are particularly useful when used in combination. Epidemiological data from Western Europe in 2000 indicate that 32% of patients had

exhausted all available drug options; in 2008 this proportion had decreased to 1%, in large part due to the availability of newer antiretroviral drugs.²²

However, these newer antiretroviral drugs are also expensive. Because more than one newer drug is typically used when constructing a new regimen, the incremental costs of newer antiretroviral drug combinations are substantial. Furthermore, the health effects might be marginal in patients with multi-drug resistant virus. We used cost-effectiveness analysis to assess whether this increased cost was associated with a commensurate gain in health. We focused on evaluating strategies (composed of many different regimens) rather than individual drugs or specific regimens because treatment for patients with advanced HIV disease must be person-specific to account for resistance patterns and individual experiences with adverse events.

Methods

We evaluated the use of regimens that included both newer antiretroviral drugs in combination with conventional antiretroviral drugs compared to regimens that used only conventional antiretroviral drugs. We modified a previously published state-transition model of HIV infection to simulate the clinical course of individuals with advanced HIV infection who are heavily treatment-experienced.^{23, 24} We used the perspective of the ideal insurer and thus included all direct health-care costs. We used U.S. costs. We discounted costs and outcomes at 3% per annum, in accord with guidelines on the conduct of cost-effectiveness analyses.²⁵ We present a brief description of the model with further details available in the Supplementary Material (Supplementary Digital Content 1).

Strategies

We evaluated two treatment strategies. In the first strategy, which we labeled “conventional” therapy, patients were treated with three antiretroviral agents, including enfuvirtide, that were released prior to 2005. In the second strategy, “newer” antiretroviral drugs (etravirine, darunavir, tipranavir, maraviroc, and raltegravir) were used. In our base case, we assumed that two newer antiretroviral drugs were used in combination with one conventional antiretroviral, in accordance with the treatment principle that more than one active antiretroviral should be used when changing regimens.²⁶ We estimated the efficacy of newer antiretroviral drugs from a review of the literature and a pooled analysis of relevant studies (Figure, Supplementary Digital Content 2). To be conservative, we included only the effect of newer antiretroviral drugs on initial virologic suppression (and adverse event rates) in the base case analysis. We assumed that this benefit was obtained by using two newer drugs with at least one conventional drug. We assumed that discontinuation of older drugs was not associated with worse virologic outcomes, since randomized trials have demonstrated no benefit from continuing multiple conventional antiretroviral drugs.^{4, 27} We assumed that new regimens might contain some older drugs for two reasons. First, they might have residual antiretroviral activity. Second, they might select for mutations that increase susceptibility to other drugs in the regimen. We assumed that antiretroviral selection is optimal within the constraints of available drugs and is guided by the results of resistance testing.

Model Parameters

Most parameters describing the clinical course, costs, and utility of treatment-experienced patients treated with conventional (but not newer) antiretroviral drugs were estimated from the Options in Management with Antiretrovirals (OPTIMA) trial, the largest randomized controlled trial in patients with multi-drug resistant HIV infection (Table 1).⁴ We estimated

parameters that were not available within OPTIMA from the literature (Supplementary Digital Content 1).

Patient Population

The analysis represented patients who had extensive past experience with antiretroviral therapy and harbored multi-drug resistant virus. Our base-case analysis was for a 48 year old man with a CD4 count of 127 cells/mm³, a viral load of 89,000 (4.95 log₁₀) copies/mL, and no active AIDS illnesses at baseline, which was similar to the typical patient included in our secondary analysis of trial data. We did not consider patients co-infected with hepatitis B or C.

Model Structure

We constructed a Markov cohort simulation model, which characterizes the health of HIV-positive individuals by defining distinct health states, transitions between these states, and transient events that occur during a model cycle (Figure 2, Supplementary Digital Content 3). The model tracks the proportion of a hypothetical cohort in each health state at one-month time intervals over the entire lifetime of the cohort. Health states were defined according to regimen, viral load, CD4 count, adverse event history, and intercurrent AIDS illness. Transitions between states occurred due to failure to decrease viral load to undetectable levels from baseline levels (lack of virologic response), rebound from a suppressed to a detectable viral load level (loss of virologic response), treatment discontinuation due to a treatment-limiting serious adverse event, successful virologic control, changes in CD4 count, development of a new AIDS-defining condition, resolution of an AIDS-defining condition, or death.

We defined regimens by distinguishing between active and non-suppressive antiretroviral therapy. Active therapy was defined as treatment that was able to achieve virologic response (defined as virologic suppression below 50 copies/mL) in some proportion of the cohort, whereas non-suppressive therapy was defined as treatment that reduced, but never suppressed, viral load. We assumed that if patients did not experience a treatment-limiting adverse event, active therapies were continued as long as viral load was suppressed. Thus, treatment changes could result from either inefficacy (lack of initial viral suppression or initial suppression with subsequent rebound) or intolerance (experiencing a serious adverse event). We assumed that, from the time of entry into the model, patients in both newer and conventional treatment strategies used two active regimens before starting non-suppressive therapy. We further assumed that the first and second active regimens in each strategy were equally effective at suppressing viral load, associated with similar risks of rebound, and had the same rate of discontinuation due to adverse events, based on observations in the randomized controlled trial. We assumed that non-suppressive therapy was continued until death.

Costs

We estimated the cost associated with each health state and with transient adverse events based on data from the Department of Veterans Affairs, where 78% of trial participants were enrolled.^{28, 29} We used the prevalence of resistant virus (for efavirenz, darunavir, and tipranavir) or the prevalence of CXCR4 tropism (for maraviroc) to estimate the frequency with which individual antiretroviral drugs would be prescribed in regimens containing newer antiretroviral drugs.^{30–33} This analysis indicated that drugs associated with less frequent resistance on a population level also tended to be less expensive. Accordingly, the average incremental cost of each newer antiretroviral drug in a new regimen is slightly more than the last one. We varied the costs of newer antiretroviral drugs widely in sensitivity analyses,

recognizing that factors other than genetic susceptibility - including dosing, adverse effects, and patient preference - influence this choice.

Quality of Life

We estimated quality-of-life weights for the model from trial participants' responses to the Health Utilities Index (Mark 3).^{34, 35} We modeled a further transient decrease in quality of life for patients who experienced a serious adverse event at the time of the event.⁵

Model Calibration

We calibrated the conventional therapy strategy in the model to empirically observed data in the OPTIMA trial, including overall survival, time to development of a first AIDS-defining illness, cumulative costs, and cumulative quality-adjusted life years (QALYs). We manually adjusted input parameters that were uncertain (examples include the proportion of individuals using non-suppressive therapy who experience side effects and the proportion who recover from an AIDS illness) to yield survival curves and summary estimates that corresponded to observed values. Adequate fit of model outputs to observed data was assessed subjectively for survival curves and was judged acceptable if values were within 10% of observed values for cumulative costs and QALYs.

Analysis

We calculated incremental cost-effectiveness ratios (ICERs) based on the comparison of the two treatment strategies. We conducted extensive sensitivity analyses to assess the robustness of our model to underlying assumptions and to identify priorities for further research. To assess parameter uncertainty, we conducted both deterministic sensitivity analysis on each model parameter as well as probabilistic sensitivity analyses with 10,000 simulations. Detailed results of the probabilistic sensitivity analyses are in Supplementary Digital Content 1.

We assessed structural uncertainty by examining assumptions about the number of antiretroviral drugs used in conventional and newer regimens. In our base case we assumed that two newer antiretroviral drugs were used in a new combination regimen. In sensitivity analyses, we assessed how our results would change if the number of newer drugs were one or three. We assumed that one to two conventional antiretroviral drugs would be continued, with the constraint that a regimen always consisted of at least three antiretroviral drugs.

We initially assumed that efficacy was equivalent for all combinations incorporating newer antiretroviral drugs; this is effectively a sensitivity analysis on the cost of newer antiretroviral drug combinations. Next, we relaxed the assumption that efficacy was not related to the number of newer drugs and instead assumed that three newer antiretroviral drugs were more effective than two newer antiretroviral drugs. Based on our systematic review and other data^{36, 37}, we assumed that the odds ratio for suppression was further increased 2-fold with the addition of a third newer antiretroviral drug (Figure, Supplementary Digital Content 4). Further, we assumed that if only one newer antiretroviral drug was used, the odds ratio for suppression was decreased by half.

Finally, we conducted analyses in which we evaluated the cost-effectiveness of newer antiretroviral drugs for patient subgroups. We evaluated patients with worse than average expected outcomes based on CD4 count (75 cells/mm³), viral load level (500,000 copies/mL), and low likelihood of success with conventional therapy (20%), an indicator of drug experience. We also evaluated patients with a better than average expected outcome with a higher than baseline CD4 count (250 cells/mm³), a lower viral load level (30,000 copies/mL), and a higher probability of suppression (60%).

We used Decision Maker version 2011.01.30b and Stata version 11.2.

Role of the Funding Source

The US Department of Veterans Affairs, the UK Medical Research Council, and the Canadian Institutes for Health Research approved the design and conduct of the OPTIMA clinical trial but had no role in the writing of this report.

Results

Model Calibration

The conventional therapy outcomes were well calibrated to OPTIMA data. At one year of follow-up, the observed survival was 93.1% and the predicted survival by the model was 92.2% (Figure 1). The model was well calibrated to the time to first AIDS illness. At one year of follow-up, the observed proportion having experienced an AIDS illness was 8.9% and that predicted by the model was 9.5%. Further calibration results are reported in the Supplementary Material (Supplementary Digital Content 1).

Effectiveness and Cost Effectiveness of Newer Antiretroviral Drugs

We estimated a pooled odds ratio of 3.80 (95% confidence interval 2.76 to 5.23, Figure, Supplementary Digital Content 2) for suppression with a regimen containing newer drugs relative to a regimen containing only conventional drugs. This corresponds to an increase in the probability of initial suppression from 35% with conventional therapy to 67% with newer therapy. Similar rates have been seen in a recent trial of treatment-experienced patients treated with multiple newer drugs.²⁷ The model yielded an estimated survival gain of 3.9 years (2.6 QALYs), and 2.3 discounted life years (1.6 discounted QALYs). After discounting, the ICER was \$52,781/life year gained. With quality-of-life adjustment, the ICER was \$75,556/QALY gained (Table 2).

Effect of Treatment Strategy

The cost-effectiveness of newer antiretroviral drugs depends on the number of antiretrovirals started and the number discontinued. In the base case, we assumed that two newer antiretroviral drugs were started and two conventional antiretroviral drugs discontinued for patients changing to a new regimen. The odds ratio for initial suppression in our model is based on trials that used one or two newer drugs; thus our base-case may overestimate the cost by assuming that two newer drugs were always started. Alternatively, if we assumed that the same virologic suppression could be obtained by starting just one newer antiretroviral and discontinuing one conventional antiretroviral, the ICER was \$54,559/QALY. Conversely, assuming that this level of virologic suppression was obtained when two newer antiretroviral drugs were added to the pre-existing regimen with no discontinuation of antiretroviral drugs yielded an ICER of \$122,804/QALY. Finally, assuming this level of suppression from a regimen consisting solely of three newer antiretroviral drugs and discontinuing all conventional antiretroviral drugs yielded an ICER of \$105,956/QALY.

The preceding analysis assumed that the number of newer antiretroviral drugs changed the cost of antiretroviral therapy but not the efficacy. We tested this assumption by repeating the analyses, but now assuming that each newer drug was associated with a doubling of the odds ratio of suppression. We compared the incremental cost-effectiveness of substituting successive numbers of conventional drugs in a three-drug regimen under these assumptions. Substituting one, two, or three newer antiretroviral drugs was associated with ICERs of \$68,732, \$80,775, and \$117,477 per QALY, respectively (Figure 2).

The model was also sensitive to assumptions about the efficacy and tolerability of newer antiretroviral drugs. Some newer antiretroviral drugs, such as raltegravir, have demonstrated favorable toxicity profiles. If we changed the base-case estimate regarding the tolerability of newer antiretroviral drugs to assume that they were half as likely to cause serious adverse events resulting in discontinuation of drugs, the ICER was consistently below \$70,000/QALY throughout the 95% confidence interval estimate of the odds ratio for newer antiretroviral drug efficacy (Figure 3).

Cost of Newer Antiretroviral Drugs

The model was also sensitive to several other parameter assumptions, most notably the cost of newer antiretroviral drugs. If the annual cost of each newer antiretroviral drug was less than \$6206, the ICER was less than \$50,000/QALY. In the U.S, the annual cost to Medicare of most newer antiretroviral drugs ranges from approximately \$6,000 to \$7500, with maraviroc costing \$16,270 annually.

Subgroups

Patient heterogeneity is an important determinant of cost-effectiveness, particularly with respect to the starting CD4 count and viral load. To simulate very advanced patients with extensive multi-drug resistance, we analyzed the cost-effectiveness when there was a low probability of suppression with conventional drugs (20%), a low CD4 count (75 cells/mm³), and a high viral load level (500,000 copies/mL). For such patients, newer antiretroviral drugs cost \$69,028/QALY. In contrast, in a comparatively healthier cohort with a higher probability of suppression (60%), a higher CD4 count (250 cells/mm³), and a viral load level of 30,000 copies/mL, use of newer drugs cost \$121,492/QALY.

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis indicated that the mean discounted incremental cost was \$111,750 (95% credible interval [95%CrI] \$27,183 to \$196,675) and the mean discounted QALY gain was 1.46 (95% CrI 0.33 to 2.50). The mean ICER was \$76,910/QALY. The probability that the ICER was less than \$50,000, \$75,000, and \$100,000/QALY was 0%, 37%, and 99%, respectively (Figure, Supplementary Digital Content 5).

Discussion

We evaluated the cost-effectiveness of newer antiretroviral drugs (those approved for marketing since 2005) for the treatment of patients with advanced HIV infection who were extensively treatment-experienced. Treatment options based on newer drugs, when used in combination, are projected to yield significant health gains of about 3.9 additional years of life or 2.6 quality adjusted life years, reflecting the poor health of this population. These health gains require expenditures in the range of \$54,559/QALY to \$75,556/QALY gained, depending on whether we assumed that one or two newer drugs were required to achieve the rates of initial viral suppression seen in clinical trials of newer drugs.

The cost effectiveness of newer drugs depends on the number of drugs that are included and the number that are withdrawn to construct newer antiretroviral regimens. Some clinicians might advocate reusing or recycling drugs that have been well tolerated in the past since some virus strains might harbor residual sensitivity. However, we note that the OPTIMA trial demonstrated that a strategy of using multiple (five or more) conventional antiretroviral drugs with minimal efficacy is not more beneficial than using three or four antiretroviral drugs.⁴ Thus, continuation of ineffective drugs is likely to represent poor value for money. Use of three newer drugs, even with an assumption of considerably improved efficacy, is relatively expensive, with a cost effectiveness ratio of \$117,477/QALY. Thus, newer

antiretroviral drugs are most likely to be cost-effective when two newer drugs are added and two older drugs are withdrawn. Use of three newer antiretroviral drugs should be reserved for patients who have no other effective options.

The definition of advanced HIV disease is inconsistent throughout the medical literature. Classifications include low CD4 counts, uncontrolled high viral loads, experience with multiple antiretroviral drugs or classes of drugs, or harboring multi-drug resistant virus. Our scenario analyses suggest that such distinctions are important and careful selection of patients with advanced disease who are most likely to benefit is needed to maximize the efficient use of these drugs. Nevertheless, the complicated interactions between these factors, and the imprecision of predicting responses from the results of resistance tests, preclude the development of simple guidelines for limiting the use of these drugs. Patients with a history of intolerance or non-adherence to previous antiretroviral regimens might be at higher risk of such events with newer regimens and factors such as dosing and absorption might be important selection factors. Clinicians might continue antiretroviral drugs with activity against hepatitis B virus in co-infected patients despite the emergence of HIV resistance.

The cost of newer antiretroviral drugs varies considerably. In particular, the estimated annual cost to Medicare of maraviroc was \$16,270, which is considerably more expensive than other newer antiretroviral drugs (\$6,115 to \$7,573). We focused on strategies and combinations that included any newer antiretroviral drugs (rather than specific agents) because individualization of therapy is required for patients with complex histories. Accordingly, it is not feasible to consider all possible therapeutic combinations for all subsets of resistance patterns. Nevertheless, our assumptions about the frequency with which individual drugs are used are uncertain. We addressed these uncertainties through examining a wide range of assumptions regarding which combinations of drugs are used together and the corresponding costs in sensitivity analyses.

Although previous studies have analyzed the cost-effectiveness of individual drugs, we are unaware of a previous analysis that has evaluated newer drugs used in combination - as they are likely to be prescribed in clinical practice.³⁸⁻⁴⁹ Another strength of our study is the estimation of model parameters for patients treated with conventional antiretroviral drugs from the clinical and health economic data collected in the largest study of advanced multi-drug resistant HIV disease to date.

Our analysis also has some limitations. Our results were based on the cohort of patients recruited to participate in OPTIMA and might thus not be generalizable to all patients with advanced disease. OPTIMA patients were cared for in the Veterans Health Administration in the US and under public health care programs in Canada and the UK. Costs might differ for patients with private insurance. Similarly, the effectiveness of drugs in practice might differ from that observed in the trials we used to estimate effectiveness due to selection biases. Although women were eligible for inclusion in OPTIMA, 98% of the cohort was male and there might be important differences related to discontinuation of antiretroviral drugs.⁵⁰ Our model was well calibrated to known data, but was not externally validated against another data source. Furthermore, the time horizon of the decision is considerably longer than that of the clinical trial. As such, we extrapolated effects over time. We also assumed that different strategies had similar effects as direct comparisons between individual strategies for patients with multiple options are lacking. Finally, we did not separately model non-AIDS events, which might be important if patients with experienced disease are at increased risk for such complications with newer antiretroviral drugs. However, we modeled all-cause mortality, including both AIDS-related and non-AIDS related events, and our estimates of quality of life and costs appropriately capture the overall health and economic outcomes of the cohort.

In conclusion, our analysis indicates that newer drugs for the treatment of HIV infection yield very important health gains, and compare favorably to interventions considered cost effective in the U.S. The most important way to ensure that newer antiretroviral drugs provide good value are to carefully select patients with advanced disease for whom less expensive options are clearly inferior and to encourage discontinuation of older drugs whose benefits are minimal.

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Figure 1. Calibration of Model Outputs to OPTIMA data

Comparison of outcomes observed in the OPTIMA model (dark solid line) and those predicted by the simulation model using conventional antiretroviral drugs approved before 2005 (light dotted line). Observed curves are Kaplan-Meier plots. The top panel illustrates the time to death and the bottom panel the time to first AIDS-defining illness or death.

Figure 2. Costs and Quality-adjusted Survival Associated with Substituting Newer for Conventional Antiretroviral Drugs

Each point in the curve represents a distinct strategy, either treatment with conventional antiretroviral drugs or addition of newer antiretroviral drugs combined with withdrawal of an equal number of conventional drugs. Each additional drug is assumed to increase the odds of suppression 2-fold. The baseline estimate is assumed to apply to the situation in which 2 drugs are substituted. The slope of each line yields the incremental cost-effectiveness of each strategy relative to the next least expensive (boxes).

Figure 3. Sensitivity to Virologic Efficacy and Intolerance of Newer Antiretroviral Therapy

Sensitivity analysis of the odds ratio of achieving virologic suppression under assumptions of high discontinuation (49%, equal to conventional therapy, solid line) or low discontinuation (24.5%, dashed line) of newer antiretroviral drug therapies. The vertical line represents the base case estimate of the odds ratio and the shaded box represents the range of the 95% confidence interval (Supplementary Digital Content).

Table 1**Model Inputs and Sources***

Variable	Baseline value	Range for Sensitivity Analysis	Comment
Baseline values			
CD4 count – cells/mm ³	127	75 to 250	
Viral load – log ₁₀ copies/mL	4.95	3.10 to 6.80	
<u>Transition to AIDS</u>			
Rate of new AIDS events per 100 person-months	0.81	0.09 to 7.00	For patients with baseline CD4 count and viral load values
Relative risk per 1 log increase in CD4 count	0.59	0.50 to 0.67	
Relative risk per 1 log ₁₀ increase in viral load	1.47	1.00 to 2.23	
Duration of a resolvable AIDS event, in months	6	1 to 12	Modeling assumption, used in calibration
<u>Transition to Death</u>			
Death rate (events per 100 person-months)	0.40	0.07 to 2.40	For patients with starting CD4 count and viral load level
Relative risk per 1 log increase in CD4 count	0.63	0.55 to 0.74	
Relative risk per 1 log ₁₀ increase in viral load	1.20	1.00 to 1.65	
Relative risk after first serious adverse event	1.27	0.61 to 3.00	
Relative risk after second and subsequent serious adverse events	2.75	1.35 to 5.47	
Relative risk with an AIDS-defining illness	1.95	1.00 to 4.06	
Suppressive antiretroviral therapy			
Probability of achieving initial virologic suppression	0.35	0.20 to 0.50	
Viral load when suppressed – log ₁₀ copies/mL	1.70	0.90 to 2.50	
Time period over which viral load declines to undetectable levels - months	3	2 to 6	Modeling assumption, used in calibration
Difference from baseline level when starting second-line therapy – log ₁₀ copies/mL	0.39	0.10 to 0.70	
Viral load rebound rate events per 100 person-months	2.33	1.76 to 3.03	
Relative risk of virologic rebound with each progression through active regimen switches	1	1 to 3	
Slope of CD4 count increase during virologic suppression (cells/mm ³ /month)			
Initial rapid phase	5.0	3.4 to 6.6	Estimated from OPTIMA and adjusted for calibration
Second slower phase	3.0	1.4 to 4.6	
Maximum CD4 increase after successful virologic control	750	500 to 1000	Modeling assumption
Probability of experiencing a serious adverse event resulting in drug discontinuation	0.49	0.40 to 0.60	
Relative risk of experiencing a serious adverse event resulting in drug discontinuation with subsequent regimens	1	1 to 3	Modeling assumption, used in calibration
Maximum time within which discontinuation occurs – months	6	3 to 12	Modeling assumption, used in calibration
Non-suppressive antiretroviral therapy			

Variable	Baseline value	Range for Sensitivity Analysis	Comment
Probability of recovering from an AIDS illness	0.75	0.60 to 0.90	Estimated from model calibration
Decrease in viral load with non- suppressive therapy – log ₁₀ copies/mL	1.20	0.40 to 2.00	Estimated from model calibration; the range for sensitivity analysis reflects the test characteristic (26)
Viral load increase after suppressive therapy exhausted	0	0 to 0.04	
Additional viral load increase with AIDS when using non-suppressive therapy	0	0 to 0.04	
Rate of experiencing a serious adverse event when using non-suppressive therapy (per person- year)	0.40	0.30 to 0.50	Estimated from model calibration
New Antiretroviral Therapy			
Odds ratio of achieving virologic suppression	3.80	2.76 to 5.23	Pooled analysis of 13, 14, 17, 18, 21. See Supplementary Digital Content for details.
Annual rate of experiencing a serious adverse event resulting in drug discontinuation	0.49	0.20 to 0.80	Assumed equal in conventional and new therapies in base case
Utility			
Utility for patients with CD4 count >100 cells/mm ³ , viral load at baseline, and no prior SAE	0.62	0.54 to 0.74	(34)
Absolute utility difference with CD4 count 50–100 cells/mm ³	–0.02	–0.05 to 0.01	
Absolute utility difference for CD4 count <50 cells/mm ³	–0.04	–0.07 to –0.02	
Absolute utility difference per 1 log ₁₀ increase in viral load	–0.01	–0.02 to –0.01	
Absolute utility difference with one prior SAE	–0.03	–0.05 to –0.01	
Absolute utility difference with two prior SAEs	–0.05	–0.08 to –0.02	
Absolute utility difference with a severe AIDS event	–0.05	–0.14 to 0.05	
Absolute utility difference in pre-terminal health	–0.11	–0.17 to –0.06	
One-time utility loss associated with an adverse event	0.07	0.00 to 0.20	(5)
Costs			
<u>Monthly HIV-related treatment costs excluding drugs</u>			
CD4 >150 cells/mm ³ (\$)	182	134 to 245	
Multiplier for CD4 101 to 150 cells/mm ³	1.42	0.90 to 2.46	
Multiplier for CD4 51 to 100 cells/mm ³	2.26	1.35 to 3.67	
Multiplier for CD4 <50 cells/mm ³	1.65	1.00 to 2.72	
Multiplier for AIDS event	4.20	2.01 to 9.03	
<u>Monthly drug costs, excluding antiretroviral drugs</u>			
CD4 >150 cells/mm ³ (\$)	77	60 to 100	
Multiplier for CD4 101 to 150 cells/mm ³	1.43	1.11 to 1.82	
Multiplier for CD4 51 to 100 cells/mm ³	1.41	1.00 to 2.01	
Multiplier for CD4 <50 cells/mm ³	2.03	1.49 to 2.72	
Multiplier for AIDS event	1.06	0.74 to 1.65	
<u>Monthly antiretroviral therapy costs</u>			
Conventional suppressive therapy (\$)	1,227	1,098 to 1,341	

Variable	Baseline value	Range for Sensitivity Analysis	Comment
Multiplier for cost of non- suppressive therapy	1.04	1.00 to 1.11	
Cost per new antiretroviral drug (\$)	725	509 to 1356	(29) and Veterans Health Administration data
Multiplier for additional new antiretroviral drugs (times number of new drugs)	1.064	1 to 1.5	
<u>Serious adverse event (per event)</u>			
First event (\$)	10,467	9,000 to 12,000	
Second event (\$)	13,434	11,000 to 16,000	

* Parameters are derived from analysis of OPTIMA data except where indicated. SAE denotes serious adverse event.

Table 2

Costs, Survival, and Quality-adjusted Survival with Antiretroviral Drug Strategies

	Cost	Survival (Years)	Quality-adjusted Life Years
<u>No discounting</u>			
Conventional antiretroviral therapy *	\$214,427	8.62	5.03
New antiretroviral therapy	\$346,877	12.47	7.61
Incremental	\$132,450	3.85	2.58
Incremental Cost-effectiveness Ratio		\$34,383	\$51,282
<u>3% Discount rate</u>			
Conventional antiretroviral therapy	\$175,690	7.04	4.12
New antiretroviral therapy	\$298,475	9.37	5.75
Incremental	\$122,785	2.33	1.63
Incremental Cost-effectiveness Ratio		\$52,781	\$75,556

* Conventional combination antiretroviral therapy consists of three conventional drugs. New antiretroviral therapy consists of two new drugs and one conventional drug.