Supplementary Material for manuscript "Cost-effectiveness of Newer Antiretroviral Drugs in Treatment-Experienced Patients with Multi-drug Resistant HIV Disease": Additional Methods and Results

Model Structure

Strategies

Our model simulated a cohort of individuals. As such, we modeled average effects at a population level rather than individual treatment effects but did not model resistance directly, which would require modeling at an individual level. While such modeling approaches are of interest when the goal is examining heterogeneity of responses across individuals, our goal was to assess aggregate costs and effects in a population and to make inferences about cost-effectiveness. Accordingly, we modeled the proportion of people in a cohort who would experience virologic suppression.

We included enfuvirtide in the "conventional" therapy strategy; although it is the only entry inhibitor currently available, it was rarely used after alternative agents became available. Furthermore, many newer antiretroviral drugs were evaluated against background regimens that could include enfuvirtide. Hence, we selected 2005 as a cut-off date and classified enfuvirtide with conventional therapies.

We assumed that the number of antiretroviral drugs used in this group was 3 (ritonavir used in "boosting" doses was not considered an active antiretroviral) because the OPTIMA trial demonstrated no improvement when more than 3 or 4 drugs were used in combination.[1] This assumption minimizes the cost associated with conventional therapy and will result in a conservative estimate of the cost-effectiveness of newer antiretroviral drugs.

We made several modeling assumptions, as described below. Wherever possible, we modeled structural assumptions (such as the duration of an AIDS illness) using model parameters and conducted sensitivity analysis over a wide range.

Efficacy of Newer Antiretroviral Drugs

We estimated the odds of increased virologic suppression compared to an optimized background regimen (which could contain enfuvirtide). For the base case, we focused on analyses of subgroups that reported a phenotypic susceptibility score of 1. We include only Phase III randomized controlled trials of etravirine, maraviroc, raltegravir, tipranavir, or darunavir in treatment-experienced patients and searched Medline, SCOPUS, the Cochrane Library, and abstract archives from the Conference on Retroviruses and Opportunistic Infections (CROI) and International AIDS Society (IAS) through May 2011. We focused on week 24 data except for a study of maraviroc, where only week 48 was available.[2-7] We used the pooled odds ratio from a random effects meta-analysis to estimate the ability of regimens to suppress viral load to undetectable levels soon after initiating therapy (Figure S1, Supplementary Digital Content 2). Our review found that the odds ratio for virologic suppression with newer as compared to older antiretroviral drugs was 3.80 (95% confidence interval 2.76 to 5.23). We assumed homogeneity across studies and type of regimen (I^2 = 4.4%, p=0.38); hence, a pooled estimate accounting for the frequency with which different regimens would be used in

practice would yield similar results. Details of the review are available from the authors on request.

We assumed that there was no effect of drugs on the risk of new AIDS events or death beyond the effects on viral load and adverse events. We assumed that CD4 counts increased as a function of viral load only (that is, not as a function of specific antiretroviral drugs). In sensitivity analyses, we also examined possible effects of newer antiretroviral drugs on the duration of virologic control, viral load levels at rebound, and CD4 increases with therapy.

OPTIMA Trial

Our primary source of data to model the clinical course of advanced multi-drug resistant HIV was the OPTIMA trial.[1] OPTIMA evaluated two treatment approaches – structured treatment interruption compared to no interruption and standard antiretroviral therapy with 4 or fewer drugs compared to "mega"-antiretroviral therapy with 5 or more drugs. We used data from the entire study cohort when estimating natural history parameters because neither management approach in OPTIMA resulted in mortality or morbidity benefits. The patients in OPTIMA were HIV-infected adults who had experienced virologic and immunologic (CD4 count ≤ 300 cells/μL) failure while taking at least two conventional antiretroviral regimens or with laboratory evidence of resistance to antiretroviral drugs in each of three classes.

Patients enrolled in the OPTIMA trial were enrolled from 2001 to 2007 and followed until 2008; over 90% of the follow-up time was between 2003 and 2007. We calculated cumulative patient-days of antiretroviral exposure for each antiretroviral. The most commonly used antiretroviral drugs were tenofovir (17.8% of patient-days), lamivudine (11.9%), lopinavir/ritonavir (10.1%), abacavir (9.6%), atazanavir (5.5%), and stavudine (5.3%). All other antiretroviral drugs were used for <5% of patient-days.

Model States

We developed a Markov cohort simulation model of the clinical course of patients with advanced, multi-drug resistant HIV infection, adapted from a previous HIV model.[8, 9] The model has multiple health states defined by the following: the type of antiretroviral therapy; the cumulative number of treatment limiting serious adverse events; whether the individual had a current AIDS-defining condition; HIV viral load level; and CD4 count. A final (absorbing) state is death (Figure S2, Supplementary Digital Content 3). Transitions between states occur when there is one of the following events:

1. Failure to decrease a high viral load to a suppressed level (lack of virologic response). We defined suppression as 50 copies/mL or less.

2. Rebound from a suppressed to a "high" viral load (loss of virologic response). We modeled the level of the "high" viral load from OPTIMA data.

3. Treatment discontinuation due to a treatment limiting serious adverse event (intolerance).

4. Successful virologic suppression.

5. Changes in CD4 levels.
6. Development of a new AIDS-defining condition.
7. Resolution of an AIDS-defining condition.
8. Death.

Antiretroviral Therapy

Antiretroviral response is primarily modeled through viral load response and subsequent CD4 count rise. The goal of "active" antiretroviral treatment is to achieve virologic response. We assumed that patients would use two active regimens before progressing to non-suppressive therapy, as our base case represents patients with multi-drug resistant HIV. Changes of drugs within regimens for minor adverse events or patient preferences were not considered a change in therapy. The goal of non-suppressive therapy is to reduce viral load, but we assumed that full virologic suppression is not achievable. We further assumed that this response lasts for a limited duration. Patients in the model may experience either initial lack of suppression with a new antiretroviral regimen, initial suppression and subsequent virologic rebound, or continued suppression.

Viral Load

We modeled viral load levels at six points in the model: at baseline, during virologic suppression (<50 copies/mL), during virologic rebound (loss of response), during non-suppressive therapy when partial response is possible, during non-suppressive therapy after partial virologic response is lost, and during non-suppressive therapy with an AIDS-defining illness. We assumed that viral load level declined to undetectable over 3 months in all active strategies and was independent of CD4 count or AIDS status. We further assumed that viral load rebound rates were equal with each active regimen.

CD4 counts

We classified CD4 count into strata in increments of 50 cells/mm^3. In the model, the rate of CD4 increase or decrease was dependent on the viral load level. Based on our secondary analysis of OPTIMA data, we modeled CD4 increases as having an initial rapid phase followed by a slower persistent increase during virologic suppression. We modeled a maximum CD4 increase after successful virologic control of 750 cells/mm^3.

AIDS illnesses

Patients in our hypothetical cohort were also at risk of developing new AIDS illnesses. No patient had an active AIDS illness at the start of the model. We modeled the risk of a new AIDS illness as a function of log CD4 count and log viral load level, based on empirical observations in the OPTIMA trial. We assumed that AIDS events resolved if subsequent virologic suppression was achieved and, as a simplifying assumption, ignored the relatively few AIDS events that do not resolve despite virologic suppression (such as lymphoma). We assumed that AIDS events lasted at least six months or longer if virologic suppression was not attained. Among patients in the model with AIDS

who had persistent detectable viremia, we assumed that some AIDS illnesses did not resolve before death.

Death

We modeled the risk of death, based on OPTIMA data, as a function of log CD4 count, viral load level, the cumulative number of serious adverse events, and the presence of an AIDS illness. We modeled all-cause mortality for the cohort and did not separately consider HIV-specific and other causes of death. In our secondary analysis of OPTIMA data, the cumulative number of adverse events was an independent predictor of death. Accordingly, we tracked the number of events (to a maximum of two) and modified the probability of death by this parameter.

Serious Adverse Events

Health states are also characterized by the cumulative number of prior treatment-limiting serious adverse events, that is, those that resulted in a change in treatment regimen since the start of the model (serious adverse events prior to the time course of the model are not considered). Adverse events that do not lead to changes in regimens are assumed to be part of the health state. Cost and quality of life effects are components of the health states. We also incorporated the effects of adverse events as transient costs and quality of life effects that were assumed to last less than one month.

We assumed that the risk of virologic rebound with each regimen switch was equivalent and that the risk of discontinuing therapy due to a serious adverse event for each active regimen was equivalent. We further assumed that the maximum time within which discontinuations occur was 6 months.

Quality of Life

Regression analysis demonstrated that the following were associated with changes in quality of life: viral load level, pre-terminal health states, cumulative numbers of serious adverse events, and CD4 count.[10] We used random effects repeated measures models to estimate the regression coefficients.

Costs

We estimated non-antiretroviral drug costs and non-drug related health care costs as a function of CD4 strata (0 to 50, 51 to 100, 101 to 150, and greater than 150 cells/mm^3) and AIDS illness. Our analyses of the OPTIMA trial data indicated that there were increased health care costs in the pre-terminal phase, which was incorporated into the model as an additional cost prior to death. All cost regression equations used a log-link function with a gamma distribution.

We determined the average annual cost of a conventional antiretroviral by dividing the total antiretroviral drug cost in OPTIMA by the number of drug-years of observation. We estimated the cost of drugs, including antiretroviral drugs, as 64% of the average wholesale price, the average cost to the U.S. Medicaid program of brand name drugs.

We modeled the costs associated with a serious adverse event as a transient expenditure during the duration of the event. We estimated antiretroviral drug costs

separately for suppressive and non-suppressive antiretroviral regimens. Other costs were estimated as a function of CD4 count and AIDS illness.

When determining which drugs were used in combination, we assumed universal sensitivity to raltegravir, that tipranavir and etravirine would not be co-prescribed due to a drug-drug interaction, and that darunavir and tipranavir would not be co-prescribed due to similar resistance patterns. We used the prevalence of resistant virus (for etravirine [41%], darunavir [6.7%], and tipranavir [26%]) or the prevalence of CXCR4 tropism (for maraviroc [41%]) to estimate the frequency with which individual antiretroviral drugs would be prescribed in regimens containing newer antiretroviral drugs. [11-14] The final combinations reflect these assumptions (Table 2).

Analysis

For the probabilistic sensitivity analysis, we randomly sampled model parameters from distributions to estimate overall model uncertainty and to calculate the expected value of perfect information (Table 1). We report the mean values from the simulations as well as the 95% credible interval, the range that contains 95% of the values from the simulations. We used the probabilistic sensitivity analyses results to calculate individual and population-level expected value of information for the United States, assuming that the time horizon of the intervention was 10 years, a discount rate of 3% and that the population for this intervention consisted of about 11,500 people every year (an estimated 426,590 people receiving antiretroviral care, of whom 2.7% each year develop multi-drug resistant HIV). [15, 16]

For the analysis in which we assumed that efficacy varied with the number of newer antiretroviral drugs, we used the systematic review to estimate this effect size, focusing on the subgroup analysis of newer antiretroviral drugs in which the phenotypic sensitivity score was 2 or greater (Figure S3, Supplementary Digital Content 4). The pooled effect was 2.13, which was similar to the effect observed when enfuvirtide was used in a similar population (1.93), and that observed in an analysis of the relationship between HIV drug resistance and the response to antiretroviral therapy.[17] To perform this analysis, we assumed that a three-drug regimen in which one drug was a newer antiretroviral would be half as effective in achieving virologic suppression as a three-drug regimen in which two drugs were newer (the base case); similarly, we assumed that if all three drugs were newer, the regimen would be twice as effective in achieving initial virologic suppression as the base case.

We explored uncertainty related to heterogeneity by examining the cost-effectiveness of newer antiretroviral drugs among patient subgroups defined by baseline CD4 count, viral load level, baseline probability of achieving virologic suppression, and the efficacy of newer antiretroviral drugs.

Supplemental Results

Model Predictions and Calibration

The model estimated a mean survival of 8.6 years and a median survival of 6.5 years with conventional antiretroviral therapy. An average of 3.7 years was spent using suppressive antiretroviral therapy and 5.0 years using non-suppressive therapy.

Survival at two years in the OPTIMA trial and in the model was 82.9% and 83.5%, respectively; at three years survival estimates were 76.4% and 75.4%. Progression to first AIDS event in the OPTIMA trial and in the model at two years was 15.3% and 15.0%, respectively; at three years progression to AIDS estimates were 19.0% and 19.6%. The average time spent living with an AIDS illness was 6.8 months. The ratios of observed to predicted total costs at 12, 18, 24, and 36 months were 1.11, 1.04, 0.98 and 0.95. The ratios of observed to predicted cumulative QALYs at 12, 18, 24, and 36 months were 1.02, 1.00, 1.00 and 0.99.

Effectiveness of Conventional Antiretroviral Drugs

Newer antiretroviral drugs were less economically attractive, with an incremental cost-effectiveness ratio exceeding $100,000 / QALY, when patients were relatively well off with conventional antiretroviral therapies, such as when the probability of achieving virologic suppression with conventional antiretroviral therapy was high (>55 %). The analysis was not sensitive to other possible effects of newer antiretroviral therapy, including prolonged duration of virologic control, decreased viral load levels at rebound, or increased CD4 counts compared to conventional therapy.

Costs

Newer antiretroviral drugs were associated with lifetime costs of $346,877, of which $162,099 (47%) were attributable to antiretroviral drugs and $184,778 (53%) to other health care costs associated with longer survival. Using newer antiretroviral drugs cost $132,450 more than using regimens containing only conventional drugs. This increased cost consisted of an increase of $184,778 due to the use of newer drugs, a savings of $59,009 due to reduced use of conventional drugs, and an increase of $6,681 in other health care costs.

Expected Value of Information

The expected value of perfect information per person was $2,054 at a threshold of $75,000 / QALY and $54 at a threshold of $100,000 / QALY; the corresponding population-level values were $208 million and $5.5million (Figure S4, Supplementary Digital Content 5). The expected value of information analysis indicates that there is considerable residual uncertainty about the cost-effectiveness of newer antiretroviral medications in patients with multi-drug resistant virus and further research in this area is likely to be worthwhile.

References

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Table 1 Input Parameters

Variable	Baseline value (Standard Error)	Distribution
Baseline values		
Transition to AIDS		
Constant	-7.54 (0.83)	Normal
Log relative risk per 1 log increase in CD4 count	-0.536 (0.088)	Normal
Log relative risk per 1 $\log_{10}$ increase in viral load	0.388 (0.13)	Normal
Transition to Death		
Constant	-7.57 (0.69)	Normal
Log relative risk per 1 log increase in CD4 count	-0.464 (0.078)	Normal
Log relative risk per 1 $\log_{10}$ increase in viral load	0.179 (0.10)	Normal
Log relative risk after first serious adverse event	0.237 (0.30)	Normal
Log relative risk after second serious adverse event	1.01 (0.24)	Normal
Log relative risk with AIDS illness	0.666 (0.27)	Normal
Suppressive antiretroviral therapy		
Probability of achieving initial virologic suppression	0.35 (0.025)	Beta
Viral load when suppressed – $\log_{10}$ copies/mL	1.70 (0.3)	Beta
Difference from baseline when starting second-line therapy – $\log_{10}$ copies/mL	0.39 (0.11)	Normal
Viral load rebound rate coefficient (α)	1.117 (0.124)	Normal
Slope of CD4 count increase during virologic suppression (cells/mm^3/month)		
Initial rapid phase	5 (0.58)	Normal
Second slower phase	3 (0.61)	Normal
Probability of experiencing a serious adverse event resulting in drug discontinuation	0.49 (0.026)	Beta
Non-suppressive antiretroviral therapy		
Probability of recovering from an AIDS illness	0.75 (0.023)	Beta
Decrease in viral load with non-suppressive therapy – $\log_{10}$ copies/mL	1.20 (0.3)	Beta
Viral load increase after suppressive therapy exhausted	0.01 (0.008)	Gamma
Additional viral load increase with AIDS when using non-suppressive therapy	0.01 (0.008)	Gamma
Annual rate of experiencing a serious adverse event when using non-suppressive therapy	0.40 (0.026)	Gamma
Newer Antiretroviral Therapy		
Relative log odds of suppression	1.231 (0.1343)	Normal
Annual rate of experiencing a serious adverse event resulting in drug discontinuation	0.49 (0.026)	Beta
Utility		
Intercept	0.685 (0.0181)	Normal
Utility change with CD4 count 50-100 cells/mm^3	-0.023 (0.0105)	Normal
Utility change for CD4 count <50 cells/mm^3	-0.0426 (0.0121)	Normal
Utility change per 1 $\log_{10}$ increase in viral load	-0.0123 (0.003)	Normal
Utility change with one prior SAE	-0.0300 (0.0108)	Normal
Utility change with two prior SAEs	-0.0491 (0.0147)	Normal
Utility change with a severe AIDS event	-0.0505 (0.0362)	Normal
Utility change in pre-terminal health	-0.1125 (0.0226)	Normal
One-time utility loss associated with an adverse event	0.072 (0.0163)	Normal
Costs (gamma coefficients for cost models)		
Quarterly HIV-related treatment costs excluding drugs		
CD4 >150 cells/mm3	6.301 (0.095)	Normal
CD4 101 to 150 cells/mm3	0.351 (0.174)	Normal
CD4 51 to 100 cells/mm3	0.816 (0.185)	Normal
CD4 <50 cells/mm3	0.501 (0.161)	Normal
AIDS event	1.436 (0.267)	Normal
Quarterly drug costs, excluding antiretrovirals		
CD4 >150 cells/mm3	5.438 (0.086)	Normal
CD4 101 to 150 cells/mm3	0.358 (0.092)	Normal
CD4 51 to 100 cells/mm3	0.344 (0.104)	Normal
CD4 <50 cells/mm3	0.707 (0.104)	Normal

Variable	Baseline value (Standard Error)	Distribution
AIDS event	1.436 (0.267)	Normal
Quarterly antiretroviral costs		
Suppressive antiretroviral therapy	8.211 (0.026)	Normal
Incremental cost of suppressive therapy	0.026 (0.016)	Normal
Serious adverse event (per event)		
Cost of a first serious adverse event ($)	10467 (500)	Gamma
Cost of a second serious adverse event (%)	13434 (754)	Gamma

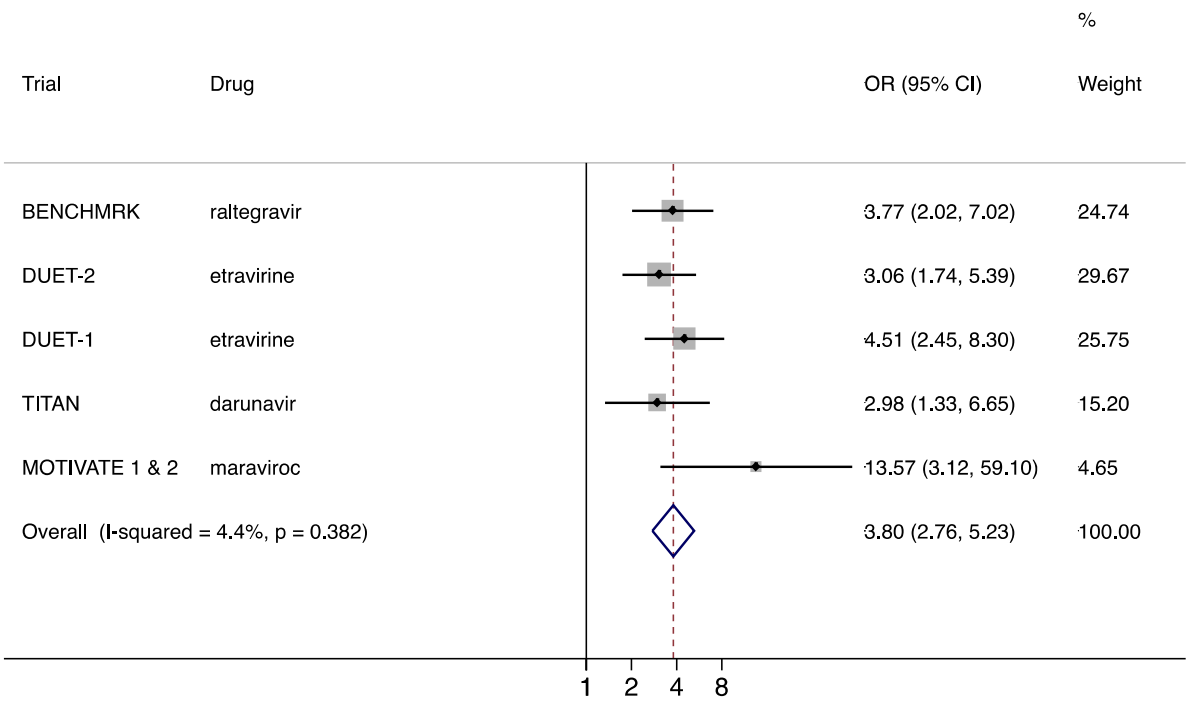
Table 2 Drug Combinations Used in "Newer" Antiretroviral Based Regimens

Drug Combination	Estimated Proportion
2 Drug Combinations	
Etravirine + Darunavir	11.6
Etravirine +Tipranavir	0.0
Etravirine +Raltegravir	12.5
Etravirine +Maraviroc	7.3
Darunavir+Raltegravir	19.7
Darunavir+Maraviroc	11.6
Tipranavir+Raltegravir	15.6
Tipranavir+Maraviroc	9.2
Raltegravir+Maraviroc	12.5
3 Drug Combinations	
Darunavir + Raltegravir + Etravirine	24.9
Darunavir +Maraviroc + Etravirine	14.6
Raltegravir + Maraviroc + Etravirine	15.7
Raltegravir + Maraviroc + Darunavir	24.9
Raltegravir + Maraviroc + Tipranavir	19.8

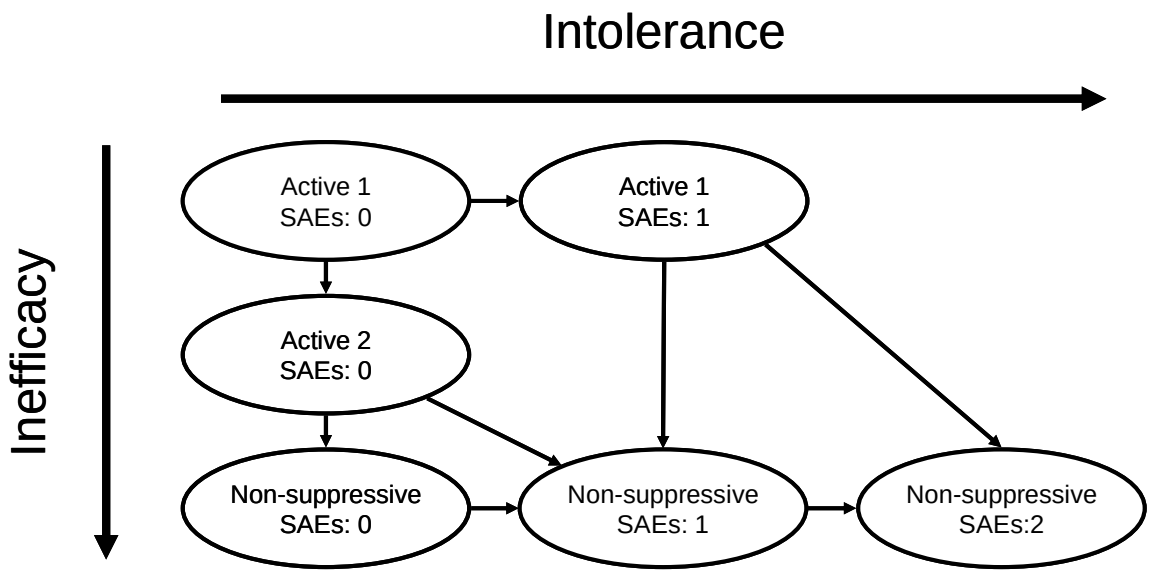
Table 3 Trials Included in the Systematic Review of Newer Drugs

Drug	Study	Publication Year	Newer drugs allowed in optimized background regimen	Resistance-related Inclusion Criteria	Median CD4 in Treatment / Control Group at baseline (cells/mm^3)	Median Viral load in Treatment / Control Group at baseline (log_{10} copies/ml)
Raltegravir	BENCHMRK [2, 18]	2008	Darunavir, Tipranavir	Phenotypic or genotypic resistance to at least one drug in each of three classes (NRTI, NNRTI, PI)	119 / 123	4.8 / 4.7
Etravirine	DUET-2 [3]	2007	Darunavir with ritonavir boosting (all patients received)	At least one NNRTI mutation and at least 3 primary PI mutations	100 / 108	4.8 / 4.8
Etravirine	DUET-1 [5]	2007	Darunavir with ritonavir boosting (all patients received)	At least one NNRTI mutation and at least 3 primary PI mutations	99 / 109	4.8 / 4.9
Darunavir	TITAN	2007	None	None	235 / 230	4.4 / 4.3
Maraviroc	MOTIVATE 1 and 2 [6, 19]	2008	Tipranavir	Documented resistance to at least 3 classes of NRTI, NNRTI, PI (at least 2 drugs), and FI or >6 months experience	171 / 167	4.9 / 4.9 (mean)

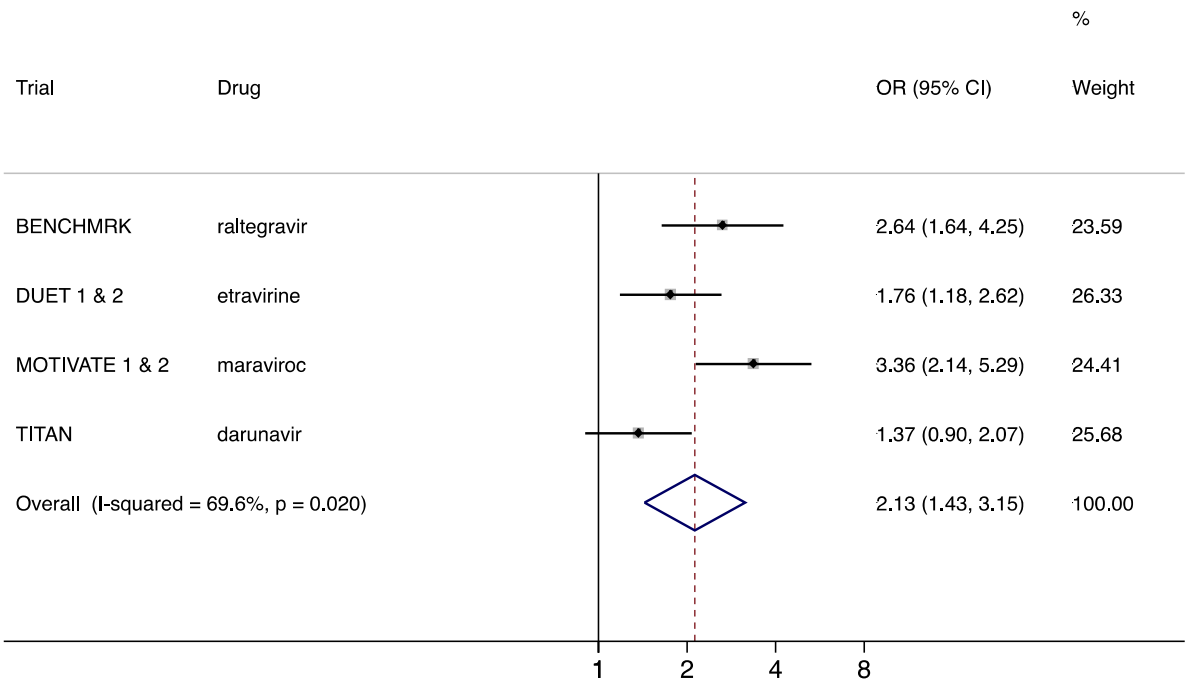
NRTI denotes nucleoside reverse transcriptase inhibitor; NNRTI denotes non-nucleoside reverse transcriptase inhibitor; PI denotes protease inhibitor; FI denotes fusion inhibitor.



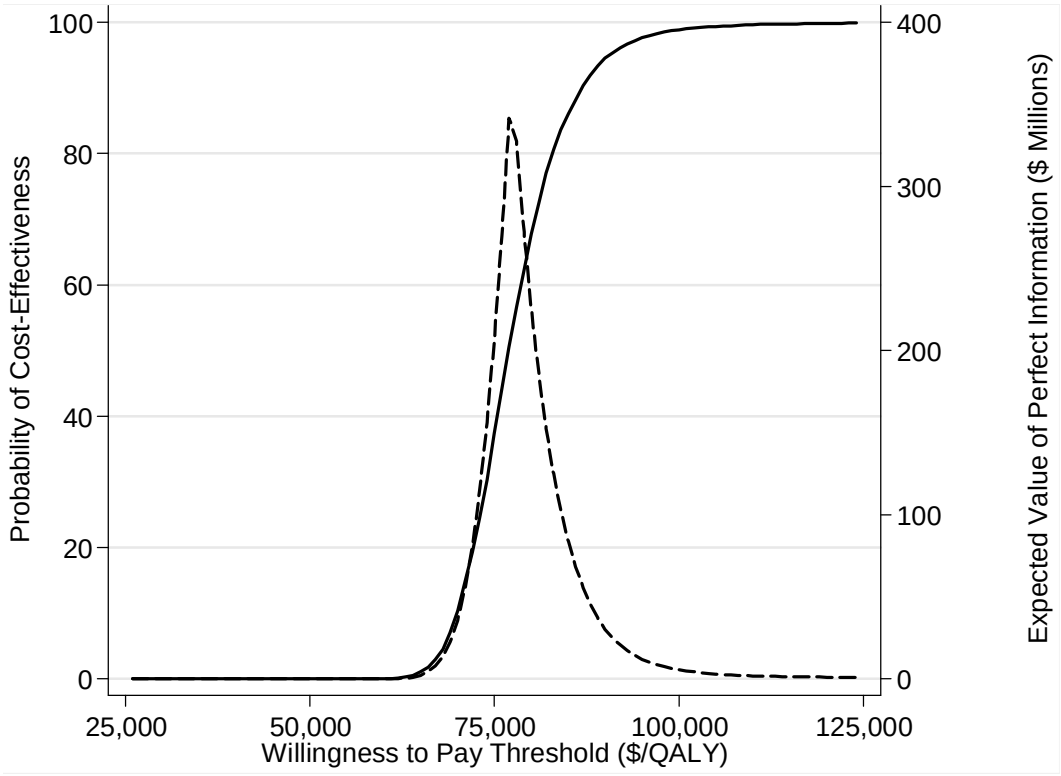
Supplementary Figure S1 Systematic Review of Newer Antiretroviral Drugs, Phase III Randomized Controlled Trials, Subgroup of patients with Phenotypic Susceptibility Score = 1



Supplementary Figure S2 Simplified Model Schematic.
Health states in the model are defined in part by antiretroviral drug regimen and history of serious adverse event. Health states are also defined by CD4 stratum, viral load level, AIDS-related illness, and death (not shown). Patients in the model change regimens due to intolerance (experiencing a serious adverse event resulting in change in regimen) or inefficacy (lack of initial virologic suppression or virologic rebound after initial suppression). Patients have a chance of attaining a viral load below the limit of quantification (suppression) during suppressive therapy. During non-suppressive therapy, viral load is decreased from baseline but not suppressed. SAE denotes serious adverse event.



Supplementary Figure S3 Systematic Review of Newer Antiretroviral Drugs, Phase III Randomized Controlled Trials, Subgroup of patients with Phenotypic Susceptibility Score = 2



Supplementary Figure S4 Cost-Effectiveness Acceptability Curve and Expected Value of Perfect Information

The solid line (left axis) represents the probability that newer antiretroviral drugs are cost-effective compared to conventional drugs across a range of societal willingness-to-pay thresholds for an additional quality-adjusted life year (left axis). The dashed line (right axis) represents the expected population level value of perfect information, in millions of dollars.