

The Cost-Effectiveness of Treatment With Lamivudine and Zidovudine Compared With Zidovudine Alone: A Comparison of Markov Model and Trial Data Estimates

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Abstract

In this paper, we present a Markov model for estimating the cost-effectiveness of combination therapy with lamivudine (LMV) and zidovudine (ZDV) compared with ZDV alone. We also compare the predictions of the Markov model for the impact of combination therapy on trial period costs with the actual impact of combination therapy on selected trial period costs estimated from data collected during the clinical trials. In the Markov model, disease stages were defined by CD4 cell count. Based on clinical trial data for patients with CD4 counts higher than 100 cells/mm³, the model assumed that the CD4 cell count level could be maintained above the level at the initiation of therapy for 6.5 months with monotherapy and for 18 months with combination therapy. After this period, transition rates for natural disease progression were used. Incremental lifetime costs and quality-adjusted life years gained with LMV/ZDV compared with ZDV alone were estimated for cohorts of patients initiating antiretroviral therapy at four different CD4 cell count stages. Cost per life year gained varied from \$10,000 to \$18,000, and cost per quality-adjusted life year gained varied from \$14,000 to \$27,000. In both cases, the combination therapy was more cost-effective when started earlier in disease progression. These estimates were not sensitive to changes in key parameter values. In addition, the model was used to estimate the impact of combination therapy on healthcare costs during the trial period; these estimated costs were compared with data on the cost of resource use collected during the clin-

ical trial for hospital stays, unscheduled visits, medications, and outpatient procedures. Both the Markov model estimates and the trial data estimates for the trial period showed cost savings in other medical costs, though these were not large enough to completely offset the increased cost for antiretroviral therapy. The model estimates were more conservative than the estimates based on the trial data.

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Over the past few years, HIV infection has changed from being an acute and rapidly fatal illness requiring frequent hospitalizations to a chronic illness with a longer life expectancy, fewer hospital episodes, and long periods when only outpatient care is required.¹ The costs of treating HIV infection from seroconversion until death were estimated as \$119,000 in 1992.¹ With the recent introduction of new antiretrovirals (eg, lamivudine, stavudine) and protease inhibitors (indinavir, saquinavir, zidovudine), it is likely that life expectancy for HIV-infected patients will be further increased. What will happen to lifetime treatment costs is less certain.

As the number of HIV-infected individuals in the United States has increased, the cost of their care has become of increasing concern to healthcare payers, especially programs that receive public funding. These new patients in the healthcare system are coming at a time when healthcare budgets have been expanding rapidly for other reasons (increased number of elderly persons in the population, technological advances in medicine), thus, healthcare organizations are under increasing pressures to control costs. As treatment options for HIV-infected people expand, it becomes increasingly important to determine the relative cost-effectiveness of the different treatment options. Several recent publications have attempted to

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estimate the cost-effectiveness of new treatments for this disease.^{2,4}

When a decision maker wants to use the results of a cost-effectiveness analysis to make treatment decisions, the appropriate method is to rank the treatments according to increasing effectiveness and then calculate the incremental cost-effectiveness ratio for each successively effective treatment.⁵ For example, the appropriate comparator for a cost-effectiveness analysis of monotherapy with an antiretroviral agent in HIV-infected people is symptomatic treatment with no antiretroviral treatment. This comparator was used in the original cost-effectiveness analyses for zidovudine.^{6,7} For dual combination therapy, the most appropriate comparator would be monotherapy. To determine cost-effectiveness ratios for triple combination therapy, these regimens should be compared with dual combination therapy.⁸ In this way, the incremental costs associated with the incremental gains in health outcomes can be assessed, and the value of the more effective and expensive therapy can be determined.

Recent data have shown that the surrogate clinical markers typically measured in trials in HIV-infected patients, CD4 cell count and viral load, are predictive of long-term survival. People with higher CD4 cell counts and lower viral load have a longer life expectancy than those with lower CD4 cell counts or higher viral loads or both.^{9,10} In addition, several trials including DELTA, ACTG 175, and CAESAR have shown that reducing viral load or increasing CD4 cell counts with drug therapy slows disease progression and increases life expectancy.¹¹⁻¹⁴

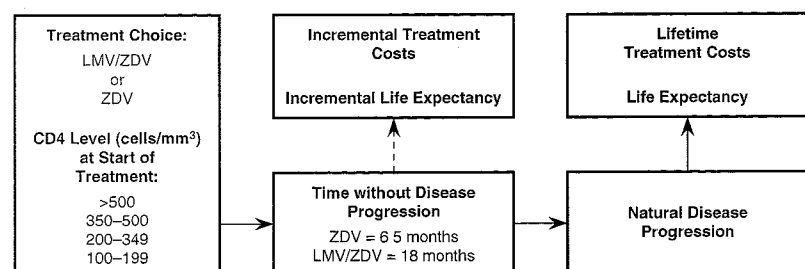
The typical surrogate-endpoint clinical trial has too few enrollees and is too brief to allow for definitive statements about the short- and long-term medical care cost impacts of a new treatment. Small trials allow for the possibility that cost outliers may obscure real treatment differences within the trial period. Very large sample sizes would be required to ensure that non-treatment related, high-cost events were randomly distributed among treatment arms.¹⁵ In addition, impacts of new treatments on lifetime costs can only be estimated by extrapolation beyond the trial time period.

Several researchers have attempted to estimate the lifetime cost-effectiveness of new drugs

using data from short-term trials by constructing Markov models and extrapolating from the trial data to the patient lifetime under different assumed scenarios.^{2,3,6,16} There may be some question, however, about the validity of the extrapolation estimates. One method that can be used for assessing the validity of an extrapolation model is to compare the model predictions with those from experimental data for a subset of patients¹⁷ or for part of the time period modeled. For example, model cost predictions for the trial time period could be compared with cost estimates based on resource use data collected during the trial.

In this paper, we present estimates of the lifetime cost-effectiveness of combination antiretroviral therapy with lamivudine (LMV) and zidovudine (ZDV) compared with ZDV alone using a Markov model populated with data from two surrogate-marker trials. These types of estimates are similar to those that have been done for other HIV treatments. To assess the validity of this model, we also used it to compute the impact of the combination therapy on medical treatment costs in the trial time period and compared these estimates with empirical estimates of the impact of combination therapy on trial period costs using resource use data collected during two clinical trials and US unit costs. The goals of this dual costing exercise were (1) to use a Markov model to estimate the lifetime cost-effectiveness of double combination therapy and (2) to compare the results when trial data were used to measure the impact of combination therapy on medical treatment costs in the trial period with the results when the Markov model was used.

Figure. Structure of the Cost-Effectiveness Model



LMV = lamivudine; ZDV = zidovudine.

... METHODS ...

Markov models frequently have been used to estimate the cost-effectiveness of new treatments for HIV infection.^{2,3} Markov models allow the researcher (1) to estimate the additional costs of disease treatment attributable to increased life expectancy and (2) to estimate the impact on lifetime costs and life expectancy of deferring the progression of disease under different assumptions about discount rates. Because one of the goals of this study was to assess the validity of Markov models for cost-effectiveness analysis, we used a Markov model in this study.

A Markov model, based on clinical decision analysis techniques,^{18,19} was constructed to simulate the clinical progression pathways for HIV infection, as well as to evaluate the lifetime health outcomes and economic impact of two treatment alternatives. The model was designed to compare combination therapy with LMV/ZDV with monotherapy with ZDV alone. The cost-effectiveness estimation model is illustrated in Figure 1. The Markov model was constructed assuming six possible disease states based on CD4 cell count ranges (cells/mm³): CD4 cell count of >500; CD4 of 350-500; CD4 of 200-349; CD4 of 100-199; CD4 of <100; and dead. The cycle time period for the model was 1 year, and the total time horizon modeled 40 years. Transitions through

the disease stages were assumed to occur only in the direction of worsening disease. In one year, a patient could only transition to the next worse disease stage. Thus, the minimum life time from a CD4 cell count of 500 until death is assumed to be 5 years.

Natural transition rates were estimated by using data in Hellinger.¹ The data were derived from multiple sources including the San Francisco Men's Health Study and the San Francisco and New York departments of public health. Based on the Hellinger data, we assumed the following mean times in each of the Markov states for our natural progression rates: 2 years at a cell count of >500 (time from the healthcare system) accessing; 1.8 years at 350-500; 1.8 years at 200-349; 1.5 years at 100-199; and 1.3 years from <100 to death (Table 1). These durations assume that an AIDS-defining diagnosis is not experienced until CD4 cell counts fall below 100. Using these mean duration times, we used the formula, $1/(\text{mean duration time})^{20}$, to compute the probabilities of leaving each Markov state during each year. This formula gives the transition rate (a probability between zero and one) that when used in the Markov model estimates a mean duration in each CD4 cell state that matches those presented in the Hellinger study. Transitions in the first year for monotherapy and the second year for combination therapy were computed as the weighted average of a

zero transition rate and the natural transition rate with the weights based on the proportion of the year associated with each transition rate. We assumed that transitions between states occur in the middle of each 1-year cycle, except for the first year for monotherapy and the second year for combination therapy. For these, we assumed that transitions between states occur in the midpoint of the time from the end of efficacy until the end of the year.

The efficacy of the two drug regimens was determined from data collected in two surrogate-marker trials that provided the evidence for the accelerated

Table 1. Input Parameter Values for Each Disease Stage

Parameter	CD4 Stage (cells/mm ³)				
	>500	350-500	200-349	100-199	<100
Mean number of years in each CD4 stage	2*	1.8	1.8	1.5	1.3
Annual costs while in each CD4 stage [†]	\$3,249	\$4,954	\$4,954	\$11,405	\$31,841
Utility weights—QWB [‡]	0.72	0.72	0.69	0.66	0.63

QWB = quality of well-being

* Once HIV-positive patients access the healthcare system.

[†]Adapted to 1995 dollar costs from 1992 dollar charge data in Hellinger¹ by using a 0.8 cost-to-charge ratio²¹ and a 1.2 inflation factor.²⁵ Assumptions are that costs for persons with a CD4 cell count range of 100-199 are equal to those for HIV-positive persons with a cell count of <200 without AIDS, and costs for persons with a CD4 cell count range of <100 are equal to those for persons with AIDS.

[‡]QWB is based on Tsevat et al.²⁶ Assumptions are that CD4 cell counts of >350 have a utility weight equal to people in Tsevat's HIV-positive/asymptomatic category; CD4 cell counts of 200-349 have a utility weight equal to 50% of people in the HIV+/symptomatic, but not AIDS, and 50% in the HIV+/asymptomatic categories; CD4 cell counts of 100-199 have a utility weight equal to people in the HIV+/symptomatic, but not AIDS, category; and CD4 cell counts of <100 have a utility weight equal to people in the AIDS category.

approval of LMV,^{21,22} as well as from studies with longer follow-up.²³ Patients in all active treatment arms experienced an initial rise in CD4 cell count levels. For patients in these trials who were treated with ZDV alone, the average time before CD4 cell counts returned to the baseline level was 6.5 months.²² For those patients who were treated with LMV/ZDV combination therapy and monitored beyond the end of the blinded trial, the mean CD4 cell count remained above baseline CD4 levels at 12 months^{21,22} and at 18 months.²³ Based on these data, we assumed in our model that the duration of treatment effect in the ZDV arm was 6.5 months and the duration of treatment effect in the LMV/ZDV arm was 18 months. To keep the model as simple as possible, we modeled the treatment effect as an average "freeze time" in disease progression. In other words, for 6.5 months or 18 months, while patients were on antiretroviral therapy, we assumed that there was no disease progression to lower CD4 cell count states. After that time, we assumed that patients reverted to the natural disease progression rates. Under these assumptions, extra disease costs because of increased life expectancy depend on the CD4 cell count when therapy is initiated. Extending the time that a patient spends in a lower CD4 cell stage will result in more costs being incurred than extending the time in a higher CD4 cell stage. The model assumes that the delay in disease progression attributable to treatment with antiretrovirals is independent of a patient's starting CD4 cell stage. This assumption is supported by studies showing similar reductions in progression rates in HIV patients with low CD4 cell levels¹⁴ and higher CD4 cell levels.^{21,22} These assumptions provide a conservative estimate of treatment effects because in the trial many patients experienced increases in CD4 cell counts of sufficient magnitude to elevate them to a higher CD4 cell count state.

Estimates of annual costs for each disease state were adapted from Hellinger¹ and are shown in Table 1. Hellinger presented charge estimates for all healthcare services used by the survey participants in 1992. These charges were converted to costs by using a 0.8 cost-to-charge ratio²⁴ and to 1995 costs by using the medical services consumer index.²⁵ The charges were estimated by Hellinger using data from the AIDS Cost and Service Utilization Survey, and they include drug charges as well as hospital, physician, laboratory, home health, and long term care charges. Because drug charges are not subdivided into antiretroviral drugs and other drugs in the Hellinger paper, in our model we assume that the annual drug charges do not include the cost of antiretroviral therapy for the patients. The costs of anti-

retroviral therapy are then added separately either for ZDV alone or LMV/ZDV. For the purposes of drug costing in the model, patients treated with either of the drug therapy regimens were assumed to continue therapy for 3 months past the efficacy time period for each drug regimen.

Utility weights in each stage (shown in Table 1) were estimated by using data presented by Tsevat et al,²⁶ who used the quality-of-well-being scale to measure utility in a population of HIV patients. In the base case, a discount rate of 3% was applied to both costs and life years gained.²⁷

The model was used to estimate the lifetime costs, expected life years, and quality-adjusted life years under each treatment regimen for population cohorts starting treatment at different CD4 cell counts. Incremental lifetime costs per life year gained and per quality-adjusted life year gained were computed. The model also was used to estimate the incremental lifetime cost per life year or quality-adjusted life year gained for a population cohort similar to that entered into the clinical trials. The CD4 cell count distribution in the trial population was as follows: CD4 cell count of >500, 8.0%; CD4 of 350-500, 28.9%; CD4 of 200-349, 47.5%; CD4 of 100-199, 14.6%; CD4 of <100, 1.0%. Although the lifetime estimates of costs and benefits implicitly assume that no further antiretroviral therapy was used, that would almost certainly not be the case. After failure with one regimen, a second regimen would be tried. This would increase the lifetime costs and lifetime benefits, but the incremental cost per life year gained and the incremental cost per quality-adjusted life year gained attributable to LMV/ZDV treatment would not be affected, assuming that patients would be switched to the same alternative regimen and it would have the same efficacy at the end of the initial treatment period with either LMV/ZDV or ZDV alone.

In the sensitivity analysis, discount rates, duration of efficacy, and postefficacy treatment duration were varied to determine the sensitivity of the model to these parameter values. Discount rates were varied from 0% to 5% for either costs or benefits, or both.²⁷ Duration of efficacy for LMV/ZDV therapy was varied from 12 months to 24 months. Postefficacy treatment duration was varied from 3 months to 1.5 months, reflecting the speed at which therapy would be changed once CD4 cell counts started to decline or viral load began to increase, or both. The speed of change depends partly on how frequently CD4 cell counts and viral load are monitored.

Selected resource use data were collected in two of the surrogate-marker clinical trials comparing ZDV

with LMV/ZDV, one lasting for 6 months (NUCB3002) and one for 12 months (NUCA3001). Included were data on hospital stays, unscheduled outpatient visits and procedures, and outpatient drugs. Data were not collected for nursing home, home healthcare, and routine monitoring. We also excluded protocol-required physician visits from the cost analysis because they were common to both treatment arms and so were unlikely to affect the differences in costs. When data on length of hospitalization were not available, the average length of stay for the same condition was taken from the 1994 Maryland Hospital Discharge Data Set.²⁸ As daily drug doses were not collected in the trial, the daily dose was imputed from the *Physician's Desk Reference*,²⁹ based on the reason for the drug use.

US unit costs were estimated for each of these service items. Drug costs were taken from the *1995 Red Book*³⁰ and represent average wholesale price for each medicine used in the trial at the recorded dose and frequency. Average charges per day for the hospital stays were determined by using data from the Maryland Hospital Discharge database for hospital stays for the HIV-related indications listed in the trial, as well as by using an average daily cost from the database for all non-HIV-related admissions.²⁸ The hospital charges were converted into costs with a 0.8 cost-to-charge ratio.²⁴ A cost for the unscheduled outpatient visits was estimated by inflating the ACSUS survey data estimate to 1995 dollars.²⁵

Differences between the dual and monotherapy treatment arms with respect to average trial period costs (not including the costs for antiretroviral therapy) were computed and were compared with the differences in trial period costs for the two treatment arms as estimated by using the Markov model for a comparable CD4 cell count cohort. The average trial period time was approximately 8.3 months because data were pooled from two trials, one that monitored patients for 6 months (61% of patients) and one that monitored patients for 12 months (39% of patients). We computed differences in aggregate costs and in-hospital costs between the two treatment groups. We computed differences in hospital costs separately because that is the only cost category that includes the same information in both the Hellinger study and our trial data. We did not attempt to model total costs for the trial data because our focus was on cost differences between the two treatment arms and not on the total costs.

... RESULTS ...

Discounted incremental lifetime costs and quality-adjusted life expectancy for patients presenting to the healthcare system and treated with LMV/ZDV rather than ZDV alone are presented in Table 2. The earlier in disease progression (ie, the higher the CD4 cell count range) that antiretroviral therapy was initiated, the lower the incremental lifetime costs were.

Although life expectancy gains in our model did not vary with the time at which therapy was initiated because of our modeling assumptions, discounted quality-adjusted life years gained were slightly lower the earlier therapy was initiated. However, the incremental costs per life year gained and per quality-adjusted life year gained were lower (more favorable) the earlier that antiretroviral therapy was initiated. Average cost-effectiveness ratios were computed for the trial cohort for

Table 2. Cost-Effectiveness of Combination Therapy Starting at Different CD4 Cell Count Ranges Assuming a 3% Discount Rate for Costs and Benefits

CD4 Stage (cells/mm ³) When Antiretroviral Therapy Is Initiated	Incremental Lifetime Costs for LMV/ZDV vs ZDV	Incremental QALYs for LMV/ZDV vs ZDV*	Cost Per Life Year Gained	Cost Per QALY Gained
>500	\$7320	0.53	\$10,063	\$13,821
350-500	\$8970	0.56	\$11,634	\$15,981
200-349	\$9130	0.56	\$11,235	\$16,195
100-199	\$15,315	0.57	\$17,879	\$27,045
Trial population [†]	\$10,095	0.56	\$12,603	\$18,006

LMV = lamivudine; ZDV = zidovudine; QALY = quality-adjusted life year

* For all populations, the incremental life years gained with no adjustment for quality and no discounting was 0.96.

[†]CD4 cell count distribution (cells/mm³) for trial population: >500, 8.0%; 350-500, 28.9%; 200-349, 47.5%; 100-199, 14.6%; CD4 of <100, 1.0%. Average cost per life year for the trial cohort for LMV/ZDV was \$12,226; for ZDV it was \$12,172; and for no antiretroviral therapy it was \$12,571.

no antiretroviral therapy, monotherapy, and dual combination therapy and are presented in the second footnote to Table 2. They are all within \$400 of each other with no antiretroviral therapy having the highest ratio.

The sensitivity of the incremental cost per life year gained or per quality-adjusted life year gained to changes in input parameter values is presented in Table 3. Changing discount rates, efficacy duration, and postefficacy treatment duration had some, but not a large, impact on the ratio estimates.

The Markov model and trial data estimates of trial period costs (not including the costs of antiretroviral therapy) with the different treatment regimens are shown in Table 4. These estimates show that the combination therapy arm had lower trial period treatment costs than the monotherapy arm because of the delayed disease progression. A population cohort similar to that included in the clinical trials would be predicted by the Markov model to have a decrease in trial period costs of \$144. The cost saving computed by using the actual trial data was higher: \$393. These cost savings would be more than offset by the estimated increase in antiretroviral costs for the trial period of \$1766. The table also shows the differences in the estimated and observed hospital costs for the two treatment arms. The difference is lower for the Markov model

Table 3. Sensitivity Analysis for Cost-Effectiveness of Treatment With LMV/ZDV vs ZDV

Parameters	CD4 Stage (cells/mm ³) at Start of Treatment	Incremental Cost Per Life Year Gained	Incremental Cost Per Quality-Adjusted Life Year Gained
Base Case			
3%/3%;QWB;18 mo; 3 mo*	>500	\$10,063	\$13,821
	100-199	\$17,879	\$27,045
Discount Rate			
0%/0%	>500	\$10,011	\$13,904
	100-199	\$18,155	\$27,507
5%/5%	>500	\$10,238	\$13,953
	100-199	\$17,704	\$26,749
3%/0%	>500	\$7,638	\$10,608
	100-199	\$15,981	\$24,213
Duration of LMV/ZDV Efficacy			
12 mo	>500	\$13,055	\$17,930
	100-199	\$24,080	\$36,743
24 mo	>500	\$9,256	\$12,713
	100-199	\$18,341	\$27,818
Postefficacy Treatment Duration			
1.5 mo	>500	\$9,675	\$13,289
	100-199	\$17,550	\$26,547

LMV = lamivudine; ZDV = zidovudine; QWB = quality of well-being.

*Base case assumes (1) a 3% discount rate for costs and benefits; (2) utility weights that were estimated by using the QWB scale⁶; (3) 18 months of efficacy for LMV/ZDV therapy and 6.5 months for monotherapy; and (4) 3 months of postefficacy treatment for each drug regimen.

Table 4. Model and Empirically Estimated Differences in Trial Period Costs for Trial Population Treated With LMV/ZDV vs ZDV*

Method of Analysis	Trial Period Costs		Difference in Trial Period Costs
	ZDV	LMV/ZDV	
Empirical Estimates			
Selected costs [†]	\$1752	\$1359	(\$393)
Hospital costs	\$1220	\$778	(\$442)
Markov Model Estimates			
Total costs	\$4333	\$4189	(\$144)
Hospital costs	\$1549	\$1446	(\$102)

LMV = lamivudine; ZDV = zidovudine.

*The mean length of the trial period was 8.33 months. Trial period costs do not include antiretroviral therapy. CD4 distribution in the trial population (cells/mm³) was as follows: >500, 8.0%; 350-500, 28.9%; 200-349, 47.5%; 100-199, 14.6%; <100, 1.0%.

[†]Selected trial period costs include only hospital, unscheduled visits, and medications.

estimates (a decrease of \$103 with combination therapy) than for the trial data estimates (a decrease of \$442 with combination therapy).

... DISCUSSION ...

The results of the modeling effort show that incremental costs per life year gained and per quality-adjusted life years gained are lower (and therefore more favorable) the earlier that combination therapy is started because patients are maintained for longer in lower-cost, higher-quality disease stages. The cost-effectiveness ratios are all in the range of what is considered to be good value for money in the United States,³¹ which accounts for the fact that combination therapy is considered standard therapy at this time.

The aggregate cost estimates for each treatment regimen during the trial period generated by using the Markov model are higher than those generated by using the trial data, but this difference is because the data collected in the trials only included a subset of total HIV treatment costs. The data collected include unscheduled visits and outpatient procedures, drug use, and hospital care. These items are the key items that would be expected to change if patient health status changed in a trial population that was asymptomatic or had minor symptoms only at trial entry. Routine office visits and disease monitoring do not depend on health status, and home healthcare or long term care services would not be expected to be used much in the typical non-AIDS patient. In addition, the Markov model costs may be overestimates of current costs (1) because of reductions in the use of hospital care since 1992, (2) because of the partial double counting of the costs of ZDV therapy, and (3) because those in the trial population with entering CD4 cell counts between 100 and 199 may have been less symptomatic than the typical patients in this cell count range because of trial in-clusion and exclusion criteria.

The Markov model's estimated decrease in disease costs other than costs for antiretroviral drugs for the trial period of therapy is lower than the decrease estimated with resource use data collected during two clinical trials. We did not include in our Markov model the possibility of a patient moving to a higher CD4 cell count with combination therapy. This may partly explain why the model estimates of cost savings during the trial time period due to delayed disease progression are lower than those estimated with the clinical trial data.

The extent to which the Markov model underestimates cost savings beyond the trial time period is

hard to determine. The results of recent clinical-endpoint trials for more advanced HIV patients, such as DELTA, ACTG 175, and CAESAR, have shown that reduction in viral load and increases in CD4 cell counts attributable to treatment with antiretroviral therapy are associated with slowed disease progression and allied cost savings as well as increased life expectancy.¹¹⁻¹⁴ Thus, the model assumption that delaying the decline in CD4 cell count will result in deferral of healthcare costs and an equivalent increase in life expectancy for the patient has some empirical foundation.

The incremental cost per life year gained was a little higher than that estimated by Chancellor et al for the United Kingdom.³² Using a four-stage Markov model and United Kingdom costs and assuming a 2-year effect, these authors predicted an incremental cost-effectiveness ratio for LMV/ZDV vs ZDV of £6726 (approximately \$10,762) per life year gained. Moore and Bartlett have demonstrated that when triple combination therapy is given to later-stage patients, the reductions in healthcare costs attributable to higher CD4 cell counts and fewer opportunistic infections may more than offset the increased costs of the triple therapy during the first few years of therapy.³ However, as in our model, the lifetime costs for the patient are projected to increase with triple combination therapy because of the increased life expectancy. Comparing triple combination therapy with ZDV monotherapy, Moore and Bartlett estimated an incremental cost per life year gained of between \$10,000 and \$18,000.³

The range of estimated costs per life year gained attributable to dual combination therapy with the Markov model (\$10,063 to \$17,879) is well below the incremental cost-effectiveness ratios for other commonly used therapies. For example, the cost-effectiveness ratio for hemodialysis is \$50,000 per life year gained and for coronary artery bypass surgery it is \$113,000.³ The very favorable cost-effectiveness ratios for dual and triple combination therapy are consistent with the observation that monotherapy is no longer considered the standard of care for HIV patients in the United States. These are favorable cost-effectiveness ratios in contrast to that for ganciclovir prophylaxis of cytomegalovirus disease in this same patient population. Recent analyses have shown cost-effectiveness ratios ranging between \$173,000 and \$1.7 million.^{4,33} The cost-effectiveness ratios are high because of the combination of high cost for this treatment option and very low increases in patient life expectancy attributable to prophylaxis. Gan-

ciclovir prophylaxis is not considered to be the standard of care at this time. Clearly, given the existence of healthcare budget limits, it is more efficient to spend available funds on antiretroviral therapy for these patients rather than on ganciclovir prophylaxis.

... CONCLUSION ...

This study has estimated the cost-effectiveness of dual combination therapy with LMV/ZDV compared with ZDV alone. Current clinical guidelines in the United States recommend the use of triple combination therapies that include a protease inhibitor. In addition, the results of the Moore and Bartlett study imply a favorable incremental cost-effectiveness ratio when comparing triple combination therapy to dual combinations.³ However, the difficulty of following such a regimen, which includes multiple pills and complex timing around meals, as well as the increased number of side effects has led to a high level of non-compliance with triple therapy and a resulting lack of efficacy.³⁴ LMV/ZDV is now available as a single pill, two of which are taken twice a day. It seems likely that a significant number of HIV-infected individuals and their physicians might seriously consider dual combination therapy as a valid treatment option.

In disease areas where surrogate-marker trials are necessary for ethical reasons, modeling may be the only way to estimate the full life expectancy and economic impacts associated with new therapies. This paper has shown that such models can be used to estimate the cost-effectiveness of new treatments. A comparison of the Markov model results with those generated by using trial data indicates that the model gave more conservative (lower) estimates of offsetting cost savings due to delayed disease progression during the trial period.

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