

## THE COST EFFECTIVENESS OF COMBINATION ANTIRETROVIRAL THERAPY FOR HIV DISEASE

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### ABSTRACT

**Background** Combination antiretroviral therapy with a combination of three or more drugs has become the standard of care for patients with human immunodeficiency virus (HIV) infection in the United States. We estimated the clinical benefits and cost effectiveness of three-drug antiretroviral regimens.

**Methods** We developed a mathematical simulation model of HIV disease, using the CD4 cell count and HIV RNA level as predictors of the progression of disease. Outcome measures included life expectancy, life expectancy adjusted for the quality of life, lifetime direct medical costs, and cost effectiveness in dollars per quality-adjusted year of life gained. Clinical data were derived from major clinical trials, including the AIDS Clinical Trials Group 320 Study. Data on costs were based on the national AIDS Cost and Services Utilization Survey, with drug costs obtained from the *Red Book*.

**Results** For patients similar to those in the AIDS Clinical Trials Group 320 Study (mean CD4 cell count, 87 per cubic millimeter), life expectancy adjusted for the quality of life increased from 1.53 to 2.91 years, and per-person lifetime costs increased from \$45,460 to \$77,300 with three-drug therapy as compared with no therapy. The incremental cost per quality-adjusted year of life gained, as compared with no therapy, was \$23,000. On the basis of additional data from other major studies, the cost-effectiveness ratio for three-drug therapy ranged from \$13,000 to \$23,000 per quality-adjusted year of life gained. The initial CD4 cell count and drug costs were the most important determinants of costs, clinical benefits, and cost effectiveness.

**Conclusions** Treatment of HIV infection with a combination of three antiretroviral drugs is a cost-effective use of resources. (N Engl J Med 2001;344:824-31.)

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IN the past decade, there have been dramatic changes in the treatment of human immunodeficiency virus (HIV) disease.<sup>1-3</sup> The use of combination antiretroviral therapy has led to decreased morbidity and mortality among patients with advanced HIV infection and the acquired immunodeficiency syndrome (AIDS).<sup>1-3</sup> Published guidelines currently recommend a three-drug antiretroviral regimen as the standard of care for the treatment of HIV-infected patients in the United States.<sup>4,5</sup> However, antiretroviral drugs are expensive, with wholesale prices

ranging from about \$2,500 per person per year for the nucleosides to \$8,000 per person per year for one of the protease inhibitors.<sup>6</sup> The high cost of combination antiretroviral therapy has resulted in widespread disparities in its availability in the United States and has prompted debate over the appropriate use and financing of these medications.<sup>7-9</sup>

Early observational studies suggested that combination antiretroviral therapy might be cost effective<sup>10-13</sup> or might even result in a cost savings.<sup>14-16</sup> However, these studies did not include the results of major clinical trials of HIV therapy, did not account for the effect of the level of HIV RNA on the progression of disease, and did not examine the implications of starting antiretroviral therapy at different stages of HIV disease. We developed a comprehensive model of HIV disease that included the CD4 cell count and HIV RNA level as predictors of disease progression. Using data from several clinical trials,<sup>1,2,17,18</sup> we evaluated the clinical effect, cost, and cost effectiveness of various strategies for the treatment of HIV disease.

### METHODS

#### Study Design

We used a computer-based simulation model of HIV disease to compare alternative antiretroviral treatment strategies. Monthly probabilities of clinical events, including changes in both the CD4 cell count and the HIV RNA level, the development of opportunistic infections, adverse reactions to medications, and death were used to simulate the course of disease in a hypothetical cohort of HIV-infected persons. The outcomes included primary and recurrent opportunistic infections, life expectancy, life expectancy adjusted for the quality of life, and lifetime costs. We adopted a societal perspective<sup>19</sup> — that is, we included in the model all costs and health effects. However, we did not include the cost of patients' time (e.g., lost wages due to time spent obtaining care), since it was considered to be negligible as compared with drug costs and the cost of hospitalization. Future costs and benefits were discounted at a rate of 3 percent per year.<sup>19</sup>

The benefits of alternative regimens were compared by calcu-

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lating the incremental cost-effectiveness ratio, defined as the additional cost of a specific regimen divided by its additional clinical benefit in terms of life saved or quality-adjusted years of life saved. Sensitivity analyses were conducted to determine the stability of the results in the presence of reasonable variations in the data and assumptions. We also evaluated the timing and duration of the benefit of antiretroviral therapy and compared a three-drug regimen with a two-drug regimen.

### Study Model

The model included three general categories of health and vital status (chronic illness, acute illness, and death), which were stratified according to important clinical characteristics (e.g., the CD4 cell count, the HIV RNA level, and the history of clinical events). The progression of HIV disease was considered to occur in a state of chronic illness. An opportunistic infection reflected a temporary state of acute illness, with associated costs and an effect on the quality of life. *Pneumocystis carinii* pneumonia, toxoplasmosis, *Mycobacterium avium* complex infection, disseminated fungal infections, and cytomegalovirus infection were specified as distinct opportunistic infections in the model.<sup>20</sup> Deaths were classified as due to an opportunistic infection, chronic AIDS, or a condition or event unrelated to HIV infection.

The progression of HIV disease, risks of clinical events, effects of treatment, and use of resources were linked to both the CD4 cell count and the HIV RNA level. We defined six categories for the CD4 cell count (>500, 301 to 500, 201 to 300, 101 to 200, 51 to 100, and 0 to 50 cells per cubic millimeter) and five categories for the HIV RNA level (>30,000, 10,001 to 30,000, 3001 to 10,000, 501 to 3000, and ≤500 copies per milliliter).<sup>21</sup> We used a cutoff point of 500 copies per milliliter because data on viral suppression with the use of lower cutoff points were not available from most of the clinical trials.<sup>1,17,18</sup> A more detailed description of the study model, as well as other information described below, is available from the National Auxiliary Publications Service (NAPS).\*

With the use of Monte Carlo simulation, the clinical courses of 1 million hypothetical patients were individually modeled. The characteristics of each patient (age, sex, CD4 cell count, and HIV RNA level) were randomly drawn from distributions derived from the AIDS Clinical Trials Group 320 Study<sup>1</sup> for the main analysis. A cohort of 1 million patients was required to obtain stable estimates of average life expectancy, quality-adjusted life expectancy, and cost. Because the patients in the AIDS Clinical Trials Group 320 Study had advanced disease, we also used data from the Johns Hopkins HIV Clinic cohort study<sup>17</sup>; the Italy, the Netherlands, Canada, and Australia (INCAS) trial<sup>2</sup>; and the Dupont 006 trial<sup>18</sup> in secondary analyses. Information on the characteristics of each study cohort is available from NAPS.\*

The efficacy of antiretroviral regimens was represented by a decrease in the HIV RNA level, leading to an increase in the CD4 cell count and a decreased probability of opportunistic infections and AIDS-related death.<sup>1,3</sup> We assumed that the immunologic efficacy of regenerated CD4 cells was similar to that of the cells that predated the HIV-associated decline in the CD4 cell count.<sup>22-24</sup> Virologic failure was represented by a 0.5 log increase in the HIV RNA level for two consecutive months. We conservatively assumed that antiretroviral therapy ceased to confer a benefit after two years, even among patients in whom therapy had not yet failed.<sup>25</sup> The efficacy of second-line therapy among patients in whom the initial regimen had failed was represented as a reduction in the efficacy of the first-line regimen.<sup>26</sup> The CD4 cell count and HIV RNA level were measured one month after a change in antiretroviral therapy and every three months in patients who were clinically stable. Prophylaxis against opportunistic infections was initiated on the basis of the CD4 cell count, and changes in antiretroviral therapy were based on the HIV RNA level.

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The data on outcomes from the intention-to-treat analyses reported for each clinical trial reflect the underlying levels of nonadherence to treatment and viral resistance in the study population. We evaluated alternative levels of nonadherence and viral resistance by applying a percent increase or decrease to the base-case estimates of efficacy in sensitivity analyses. Adverse effects of antiretroviral therapy, such as lipodystrophy, resulted in long-term decrements in the quality of life for all patients in whom such effects occurred.

### Decline in the CD4 Cell Count and the Risk of Opportunistic Infections

The monthly decline in the CD4 cell count in the absence of antiretroviral therapy and as a function of the HIV RNA level was estimated with the use of data from the Multicenter AIDS Cohort Study for the period from 1985 through 1994.<sup>21,27</sup> Although patients in this study included some who were treated with zidovudine alone, we have previously shown that there was no difference in the progression of HIV disease between these patients and those who received no therapy.<sup>20,27</sup> We estimated the monthly probabilities of opportunistic infections and death as a function of the CD4 cell count, using an incidence-density analysis (Table 1).<sup>31</sup> A random-effects model was used to estimate missing CD4 cell counts at the time of an opportunistic infection or death.<sup>20,32</sup>

### Efficacy of Antiretroviral Therapy

#### AIDS Clinical Trials Group 320 Study

To evaluate the efficacy of three-drug antiretroviral therapy (zidovudine, lamivudine, and indinavir), patients with responses to therapy were moved to successively lower HIV RNA categories until the lowest category (≤500 copies per milliliter) was reached. Patients without responses were moved to successively higher categories until the category to which they had initially been assigned was reached. Initial estimates of the likelihood of these changes were based on the change in the HIV RNA level from base line to four weeks in the group of patients assigned to the three-drug regimen in the AIDS Clinical Trials Group 320 Study.<sup>1</sup> We then adjusted the monthly probability of a decrease in the HIV RNA level to match the overall rate of viral suppression (defined as a level ≤500 copies per milliliter) in the three-drug group in the AIDS Clinical Trials Group 320 Study (60 percent at 24 weeks). We assumed that once therapy failed, the HIV RNA level would begin to rise and the CD4 cell counts would in turn begin to decline. We varied the amount of time it took after treatment failure for the HIV RNA level to return to the initial level and examined the possibility that HIV RNA remained partially suppressed — that is, at a lower level than the initial value. For the efficacy of the two-drug regimen in the AIDS Clinical Trials Group 320 Study and the other clinical trials described below, we multiplied the monthly probability of treatment failure by a fixed number and recalculated the probability of a move to another HIV RNA category (data are available from NAPS\*).

#### Other Trials

Data from the Johns Hopkins HIV Clinic cohort study, the INCAS trial, and the Dupont 006 trial were used to evaluate additional antiretroviral regimens in patients at various stages of disease and in various clinical settings (data are available from NAPS\*). The Johns Hopkins HIV Clinic cohort study was an observational study of a cohort of patients who had not previously been exposed to protease inhibitors.<sup>17</sup> The initial mean CD4 cell count was 217 per cubic millimeter, and the rate of HIV RNA suppression was 44 percent at 24 weeks.

The INCAS trial compared two-drug therapy with zidovudine and nevirapine, two-drug therapy with zidovudine and didanosine, and three-drug therapy with zidovudine, didanosine, and nevirapine in patients with CD4 cell counts of 200 to 600 per cubic millimeter who had never been treated with non-nucleoside reverse-transcriptase inhibitors.<sup>2</sup> The initial mean CD4 cell count was 377 per cubic millimeter, and the rate of viral suppression at 52 weeks was 53 percent in the three-drug group.

**TABLE 1. BASE-CASE VALUES FOR MODEL VARIABLES.\***

Mean monthly decline in the CD4 cell count according to the HIV RNA level†						
HIV RNA	DECLINE IN CD4 COUNT cells/mm <sup>3</sup>					
>30,000 copies/ml	6.375					
10,001–30,000 copies/ml	5.400					
3001–10,000 copies/ml	4.600					
501–3000 copies/ml	3.733					
≤500 copies/ml	3.025					

Monthly probability of opportunistic infection according to the CD4 cell count‡						
CD4 CELL COUNT	PROBABILITY OF INFECTION					
	PCP	MAC INFECTION	TOXO- PLASMOSIS	CMV INFECTION	FUNGAL INFECTION	OTHER
0–50/mm <sup>3</sup>	0.03700	0.01220	0.00270	0.01857	0.01123	0.03940
51–100/mm <sup>3</sup>	0.03100	0.00375	0.00140	0.00523	0.00591	0.02460
101–200/mm <sup>3</sup>	0.009600	0.001010	0.000670	0.002140	0.001350	0.007160
201–300/mm <sup>3</sup>	0.003730	0.000220	0.000420	0.000580	0.000290	0.002240
301–500/mm <sup>3</sup>	0.000850	0.000055	0.000092	0.000129	0.000276	0.000870
>500/mm <sup>3</sup>	0.000410	0.000059	0.000029	0.000059	0.000088	0.000470

Efficacy of prophylaxis§	
PROPHYLAXIS	DECREASE IN INCIDENCE OF INFECTION %
Against PCP (trimethoprim–sulfamethoxazole)	97.32
Against MAC infection (azithromycin)	63.35

Annual cost of antiretroviral regimens and tests¶	
REGIMEN OR TEST	COST \$
Zidovudine, lamivudine, and indinavir	11,610
Zidovudine and didanosine	5,880
Zidovudine, didanosine, and nevirapine	8,940
Zidovudine, lamivudine, and efavirenz	10,400
CD4 cell count (per test)	83
HIV RNA level (per test)	110

\*PCP denotes *Pneumocystis carinii* pneumonia, MAC *Mycobacterium avium* complex, and CMV cytomegalovirus.

†Data are from Mellors et al.<sup>21</sup> and the Multicenter AIDS Cohort Study.<sup>27</sup>

‡Other infections included bacterial infections, tuberculosis, and Kaposi's sarcoma. Data are from the Multicenter AIDS Cohort Study.<sup>27</sup>

§Data on prophylaxis against *Pneumocystis carinii* pneumonia are from El-Sadr et al.<sup>28</sup> Data on prophylaxis against *Mycobacterium avium* complex infection are from Havlir et al.<sup>29</sup> and Nightingale et al.<sup>30</sup>

¶In the base-case analysis, a CD4 cell count and an HIV RNA test were performed every three months. Data on the costs of antiretroviral regimens are from the *Red Book*.<sup>6</sup> Data on the costs of tests are from the Payment Office, Boston Medical Center, Boston.

The Dupont 006 trial compared a two-drug regimen consisting of efavirenz and indinavir with a three-drug regimen of zidovudine, lamivudine, and either indinavir or efavirenz. The initial mean CD4 cell count was 350 per cubic millimeter, and the rate of viral suppression at 48 weeks ranged from 48 to 70 percent.<sup>18</sup>

**Prophylaxis against Opportunistic Infections**

We assumed that prophylaxis against *P. carinii* pneumonia, beginning with a daily regimen of trimethoprim (80 mg) and sul-

famethoxazole (400 mg), was started when the CD4 cell count dropped below 200 per cubic millimeter<sup>28,33</sup> and that prophylaxis against *M. avium* complex infection, with a weekly regimen of azithromycin (1200 mg), was started when the CD4 cell count dropped below 50 per cubic millimeter (Table 1).<sup>29,30</sup> We evaluated the effect of stopping prophylaxis against *P. carinii* pneumonia and stopping prophylaxis against *M. avium* complex infection in patients whose CD4 cell count during antiretroviral therapy exceeded 200 per cubic millimeter and 100 per cubic millimeter, respectively.<sup>22–24</sup>

### Data on Costs

The direct costs of treatment for acute illnesses and of routine medical care were estimated on the basis of data from the AIDS Cost and Services Utilization Survey,<sup>34</sup> the costs for CD4 cell counts and HIV RNA tests were obtained from the Payment Office at Boston Medical Center, Boston, and drug costs were obtained from the 1998 *Red Book* (Table 1).<sup>6</sup> Charges reported in the AIDS Cost and Services Utilization Survey were converted to costs with the use of a national cost-to-charge ratio, as previously described.<sup>20,35</sup> Costs were converted to 1998 dollars with the use of the medical-care component of the Consumer Price Index.<sup>36</sup> We also conducted sensitivity analyses using other reported data on costs.<sup>37,38</sup>

### Data on Health-Related Quality of Life

For the base case, data on the quality of life were derived from a questionnaire item about overall health status used in several AIDS Clinical Trials Group studies. Patients' responses were converted to quality-of-life scores by the method of Torrance.<sup>20,39</sup> Although these values are not true measures of patients' preferences, we also conducted sensitivity analyses using preference weights reported by Holtgrave and Pinkerton.<sup>38</sup>

## RESULTS

### Reference-Case Analyses

The clinical trajectories of two randomly selected patients chosen from 1 million simulations of the three-drug group in the AIDS Clinical Trials Group 320 Study are shown in Figure 1A and 1B. On the basis of 1 million such simulations, the discounted life expectancy for a patient receiving no antiretroviral therapy was 1.97 years (1.53 years adjusted for the quality of life), and the total discounted lifetime cost was \$45,460 (Table 2). With three-drug therapy, as compared with no therapy, the life expectancy was 3.51 years (2.91 quality-adjusted years), the lifetime cost was \$77,300, and the incremental cost per quality-adjusted year of life was \$23,000.

Table 2 also shows the outcomes for the Johns Hopkins HIV Clinic cohort study, the INCAS trial, and the Dupont 006 trial. In all three cases, the life expectancies were higher, reflecting higher initial CD4 cell counts. Although the total lifetime medical costs increased with prolonged survival for all the studies, the cost-effectiveness ratios were stable, ranging from \$13,000 to \$23,000 per quality-adjusted year of life gained with combination antiretroviral therapy, as compared with no therapy.

### Outcome According to the CD4 Cell Count at Presentation

Using data from the AIDS Clinical Trials Group 320 Study, we considered cohorts of patients presenting with an initial CD4 cell count of 500, 200, or 50 per cubic millimeter for each of the HIV RNA categories. The results for patients with an HIV RNA level of 3001 to 10,000 copies per milliliter are shown in Table 3. Both discounted quality-adjusted life expectancy and discounted total costs increased as the initial CD4 cell count increased. However, incremental cost-effectiveness ratios for three-drug therapy, as compared with no therapy, stayed within a relatively narrow range (from \$14,000 to \$26,000 per quality-

adjusted year of life gained). In separate sensitivity analyses, we examined the efficacy and costs of two-drug therapy on the basis of data from the AIDS Clinical Trials Group 320 Study, the INCAS trial, and the Dupont 006 trial. In each case, two-drug therapy was superior to no therapy but was less effective and less cost-effective than three-drug therapy.

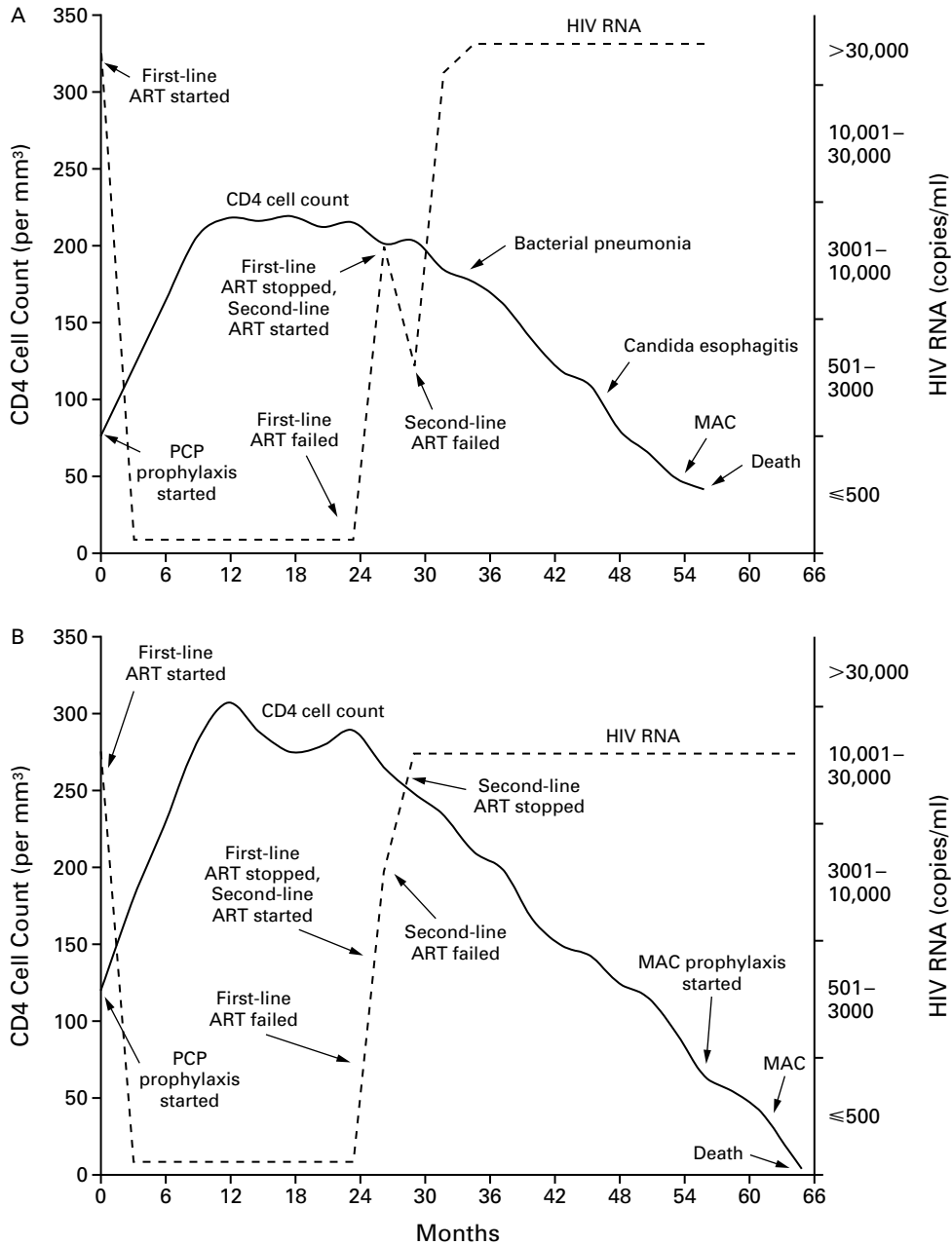
### Initiation of Therapy at Higher CD4 Cell Counts

Starting three-drug therapy when the patient presented with a CD4 cell count that was 500 per cubic millimeter (and an HIV RNA level that exceeded 30,000 copies per milliliter) increased total lifetime costs from \$64,210 to \$90,980 and increased quality-adjusted life expectancy from 5.10 to 6.94 years, with an incremental cost of \$15,000 per quality-adjusted year of life gained, as compared with no therapy. This approach was more effective and a more efficient use of resources than starting therapy when the CD4 cell count was 350 per cubic millimeter.<sup>4,5</sup> Waiting until the CD4 cell count was 200 per cubic millimeter resulted in higher total costs and a lower quality-adjusted life expectancy. With the improved efficacy reported in more recent trials,<sup>18</sup> the cost-effectiveness ratio for therapy initiated when the CD4 cell count was 500 per cubic millimeter was decreased to \$11,000 per quality-adjusted year of life gained.

### Additional Sensitivity Analyses

We also performed sensitivity analyses of the duration of efficacy and toxicity of first-line therapy and cost estimates used in the base-case analysis (data available from NAPS\*). Although both life expectancy and total medical costs were dependent on the efficacy of three-drug antiretroviral therapy, the cost-effectiveness ratios were not. The duration of viral suppression had the greatest effect on total lifetime costs. Although we assumed that there was no suppression after two years,<sup>25</sup> electing not to extrapolate beyond the period for which data are available, we allowed for the possibility of HIV RNA suppression for up to five years in patients who had continued responses to therapy.<sup>40</sup> In this case, the total cost with three-drug therapy increased to \$88,570, but the cost-effectiveness ratio for three-drug therapy, as compared with no therapy, remained about \$23,000 per quality-adjusted year of life gained. In contrast, the cost-effectiveness ratio associated with three-drug therapy was more sensitive to the cost of antiretroviral drugs. When the cost of antiretroviral drugs was reduced by 50 percent, the total projected medical cost decreased to \$67,620 per person with three-drug therapy, and the cost-effectiveness ratio decreased to \$16,000 per quality-adjusted year of life gained, as compared with no therapy.

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**Figure 1.** Two Hypothetical Patients Treated with a Three-Drug Antiretroviral Regimen.

These patients were randomly selected from 1 million simulations with the use of data from the AIDS Clinical Trials Group 320 Study. The patient in Panel A was a 42-year-old man with an initial CD4 cell count of 76 per cubic millimeter and an initial HIV RNA level of more than 30,000 copies per milliliter. After a complicated course, his discounted life expectancy was 56.30 months, his quality-adjusted life expectancy was 48.30 months, and the total discounted medical cost was \$89,400. The patient in Panel B was a 24-year-old man with an initial CD4 cell count of 119 per cubic millimeter and an initial HIV RNA level of 10,001 to 30,000 copies per milliliter. His discounted life expectancy was 64.80 months, his quality-adjusted life expectancy was 57.40 months, and the total medical cost was \$78,000. PCP denotes *Pneumocystis carinii* pneumonia, MAC *Mycobacterium avium* complex infection, and ART combination antiretroviral therapy.

**TABLE 2.** COSTS, CLINICAL BENEFITS, AND COST EFFECTIVENESS OF VARIOUS THREE-DRUG ANTIRETROVIRAL REGIMENS.

SOURCE OF DATA*	TOTAL LIFETIME COSTS	LIFE EXPECTANCY		INCREMENTAL COST PER YEAR OF LIFE GAINED†	
		UN-ADJUSTED	ADJUSTED FOR QUALITY OF LIFE	UN-ADJUSTED	ADJUSTED FOR QUALITY OF LIFE
			yr		\$
	\$				\$
ACTG 320 Study <sup>1</sup>					
No antiretroviral therapy	45,460	1.97	1.53	—	—
Zidovudine, lamivudine, and indinavir	77,300	3.51	2.91	21,000	23,000
Johns Hopkins HIV Clinic cohort study <sup>17</sup>					
No antiretroviral therapy	54,150	3.48	2.92	—	—
Zidovudine, lamivudine, and indinavir	80,460	5.11	4.43	16,000	17,000
INCAS trial <sup>2</sup>					
No antiretroviral therapy	61,180	4.65	3.99	—	—
Zidovudine, didanosine, and nevirapine	89,820	6.99	6.20	12,000	13,000
Dupont 006 trial <sup>18</sup>					
No antiretroviral therapy	59,790	4.61	3.96	—	—
Zidovudine, lamivudine, and efavirenz	94,290	7.45	6.63	12,000	13,000

\*ACTG denotes AIDS Clinical Trials Group and INCAS Italy, the Netherlands, Canada, and Australia trial.

†The cost-effectiveness ratios have been rounded to two significant digits.<sup>19</sup> The data on costs and life expectancy in the absence of antiretroviral therapy are from the Multicenter AIDS Cohort Study<sup>27</sup>; estimates of life expectancy and cost differ because of base-line differences in the stage of disease among the study cohorts.

**TABLE 3.** COSTS, CLINICAL BENEFITS, AND COST EFFECTIVENESS OF THREE-DRUG ANTIRETROVIRAL THERAPY ACCORDING TO THE INITIAL CD4 CELL COUNT.\*

INITIAL CD4 CELL COUNT	TOTAL LIFETIME COSTS	LIFE EXPECTANCY		INCREMENTAL COST PER YEAR OF LIFE GAINED†	
		UN-ADJUSTED	ADJUSTED FOR QUALITY OF LIFE	UN-ADJUSTED	ADJUSTED FOR QUALITY OF LIFE
			yr		\$
	\$				\$
50/mm <sup>3</sup>					
No antiretroviral therapy	41,850	1.39	1.05	—	—
Three-drug regimen	74,050	2.84	2.28	22,000	26,000
200/mm <sup>3</sup>					
No antiretroviral therapy	55,400	3.33	2.70	—	—
Three-drug regimen	88,250	5.32	4.60	16,000	17,000
500/mm <sup>3</sup>					
No antiretroviral therapy	70,100	7.05	6.25	—	—
Three-drug regimen	96,790	9.13	8.21	13,000	14,000

\*In all analyses, the HIV RNA level was 3001 to 10,000 copies per milliliter, and the three-drug regimen was zidovudine, lamivudine, and indinavir. Data on efficacy were derived from the AIDS Clinical Trials Group 320 Study.<sup>1</sup>

†The cost-effectiveness ratios have been rounded to two significant digits.<sup>19</sup>

In addition, we increased and decreased by 50 percent the base-line cost estimates for the treatment of opportunistic infections and for routine care to reflect uncertainty about the cost data from the AIDS Cost and Services Utilization Survey. The cost-effectiveness ratio for three-drug therapy remained between \$19,000 and \$27,000 per quality-adjusted year of life gained.

We also examined the influence of chronic toxic effects, such as lipodystrophy, on the cost effectiveness of three-drug therapy, particularly protease-containing regimens. Even when we assumed that the value for the health-related quality of life was reduced to 60 percent of the base-line value after one year of treatment with zidovudine, lamivudine, and indinavir, the quality-adjusted life expectancy decreased from 2.91 to 2.71 years, but the cost-effectiveness ratio increased to only \$27,000 per quality-adjusted year of life gained, as compared with no therapy.

### DISCUSSION

Using data from the AIDS Clinical Trials Group 320 Study, the Johns Hopkins HIV Clinic cohort study, the INCAS trial, and the Dupont 006 trial, we found that a three-drug regimen of combination antiretroviral therapy increased the projected quality-adjusted life expectancy by 1.38 to 2.67 years, with cost-effectiveness ratios ranging from \$13,000 to \$23,000 per quality-adjusted year of life gained, as compared with no therapy. These increases in life expectancy represent clinically meaningful improvements in survival and are similar to the benefit of thrombolytic therapy in patients with suspected acute myocardial infarction (gain in life expectancy, 1.25 years).<sup>41</sup>

Combination antiretroviral therapy is not as cost effective as prophylaxis against *P. carinii* pneumonia (cost-effectiveness ratio, \$2,300 per quality-adjusted year of life gained) but is more cost effective than prophylaxis against *M. avium* complex infection (\$31,000 per quality-adjusted year of life gained)<sup>20,33</sup> and compares favorably with the cost effectiveness of HIV-prevention efforts.<sup>42</sup> Although costly, antiretroviral therapy is more cost effective than many therapies for non-HIV diseases, such as radiation therapy for early-stage breast cancer (cost-effectiveness ratio, \$30,000 per quality-adjusted year of life gained), treatment of hypercholesterolemia (\$47,000 per year of life gained), and dialysis in patients expected to live for less than six months (\$150,000 per quality-adjusted year of life gained).<sup>43-45</sup>

Our analysis has several limitations. Our data on the efficacy of antiretroviral therapy were derived from large randomized trials, with one exception. In other populations of patients, the rate of adherence to the treatment regimen may be lower and the rates of viral resistance and drug toxicity may be higher, resulting in smaller clinical benefits. However, even the analysis of data from the Johns Hopkins HIV Clinic

cohort study, which found a lower rate of efficacy than the other trials, had similar results with respect to cost effectiveness.<sup>17</sup> Thus, although the life expectancy and total lifetime costs were highly dependent on the efficacy of antiretroviral therapy, cost effectiveness was not. We conservatively assumed that the benefit of three-drug therapy would persist for two years; with a larger period of benefit,<sup>40</sup> life expectancy and lifetime costs increased, but the cost effectiveness of therapy remained stable.

We made several assumptions about the complex relation between the CD4 cell count and the HIV RNA level. Although in the absence of therapy, an increase in the HIV RNA level causes a decline in the CD4 cell count, the main predictor of opportunistic infections and mortality is the CD4 cell count. Our model can, however, incorporate the joint predictive value of the CD4 cell count and the HIV RNA level on clinical outcomes when these data become available. Our results suggest that the initiation of antiretroviral therapy at higher CD4 cell counts may be reasonable. However, better data on the long-term effects and toxicity of combination antiretroviral therapy, the costs of routine care with current regimens, and the effects of interventions designed to improve adherence to the regimens and decrease the rate of treatment failure are needed to refine this analysis.

A three-drug regimen of combination antiretroviral therapy for HIV disease has been proved to be clinically effective.<sup>1-3</sup> The results of ongoing trials will help determine the optimal timing of treatment and the most effective ways to decrease the risk of treatment failure, but these data are not yet available. HIV-infected patients, clinicians, and policymakers face crucial decisions now.<sup>46</sup> Our results, based on the best available data from a wide range of studies, suggest that three-drug antiretroviral therapy is highly cost effective and should be made available to all the patients who can benefit from it.

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