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Cost effectiveness analysis of early zidovudine treatment of HIV infected patients

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Abstract

Objective—To compare cost effectiveness of early and later treatment with zidovudine for patients infected with HIV.

Design—Markov chain analysis of cost effectiveness based on results of use of health care and efficacy from a trial of zidovudine treatment.

Setting—Seven Veterans Affairs medical centres in the United States.

Subjects—338 patients with symptomatic HIV infection and a lymphocyte count of 200×10^6 to 500×10^6 CD4 cells/l.

Interventions—Zidovudine 1500 mg/day started either at recruitment to the trial or when CD4 cell count fell below 200×10^6 /l.

Main outcome measures—Health care costs and rates of disease progression between six clinical states of HIV infection.

Results—Patients given early treatment with zidovudine remained without AIDS for an extra two months at a cost of \$10 750 for each extra month without AIDS (at 1991 costs). Cost effectiveness ratio was most sensitive to the cost of zidovudine and to the quality of life of patients receiving early treatment. At treatment of 500 mg/day the cost effectiveness ratio for early treatment was \$5432 for each extra month without AIDS. Patients given early treatment experienced more side effects, and if their quality of life was devalued by 8% compared with patients treated later the two treatments were equivalent in terms of quality adjusted months of life without AIDS.

Conclusions—Early treatment with zidovudine is expensive and is very sensitive to the cost of zidovudine and to potential reductions in quality of life of patients who experience side effects. Doctors should reconsider early treatment with zidovudine for patients who experience side effects that substantially compromise their quality of life.

Introduction

Treatment with zidovudine has been shown to prolong survival in patients with newly diagnosed AIDS or advanced AIDS related complex.¹ At this stage of HIV infection zidovudine is so effective that a doctor need only treat eight patients to prevent one death after six months of treatment. There is, however, much controversy over the efficacy of zidovudine when it is prescribed earlier in the course of HIV infection. Three randomised trials have documented delayed progression to AIDS for patients receiving zidovudine early compared with placebo^{2,3} or with zidovudine

given later but still before development of AIDS.⁴ The Concorde trial, the largest and most recent, reported no delay in progression to AIDS for patients treated early in their infection.⁵ None of the published controlled trials have documented additional survival benefit when zidovudine is given before diagnosis of AIDS.

In spite of this, the current recommended medical practice is to prescribe zidovudine for patients with symptomatic HIV whose lymphocyte counts are below 500×10^6 CD4 cells/l.⁶ However, the cost implications of giving zidovudine early in HIV infection have not been fully explored. We examined the cost effectiveness of early treatment with zidovudine using data recorded in a Veterans Affairs cooperative study.

Methods

Data sources—The Veterans Affairs cooperative study (number 298) was a four year, multicentre, randomised, double blind trial that compared early and later treatments with zidovudine for patients with symptomatic HIV infection and lymphocyte counts of 200×10^6 to 500×10^6 CD4 cells/l.⁴ Patients were randomised to receive zidovudine (1500 mg/day) either at enrolment into the study (early treatment) or when their CD4 cell count fell below 200×10^6 /l (later treatment). Patients were enrolled from January 1987 to January 1990 and were followed up until January 1991. The trial showed that patients given zidovudine early in their infection experienced a delay in the development of AIDS but no improvement in overall survival. This trial was the only one of its kind to keep detailed records of the use of health care by all patients.

Markov decision model—In order to accurately model risk of progression of HIV infection and associated health care costs over an extended period and to perform sensitivity analyses for important cost variables we employed a Markov chain analysis.⁷ We defined six clinically relevant and mutually exclusive states of HIV infection; mildly symptomatic with a CD4 cell count of 200×10^6 to 500×10^6 /l (state 1); mildly symptomatic with a CD4 count under 200×10^6 /l (state 2); *Pneumocystis carinii* pneumonia being the first AIDS defining diagnosis (state 3); a different first AIDS defining diagnosis (state 4); two or more AIDS defining diagnoses (state 5); and death (state 6). The patients' progression through the clinical states was divided into cycles of 60 days. All the patients began in state 1, and during each subsequent cycle they could either remain in their current state or progress to another state. Patients changed from their current state to any state of greater severity except that

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patients in state 3 could not move to state 4 and patients in state 2 could move back to state 1. Transition probabilities between clinical states, calculated separately for each treatment group, were determined from the actual rates of disease progression for the patients in the study. The time independent assumption of this Markov chain accurately represented the observed survival and progression to AIDS recorded in the four year study.

Resource use and cost calculations—We separated resource use into four components: inpatient care, outpatient care (including laboratory and diagnostic tests), outpatient drugs except zidovudine, and zidovudine. Rates of resource use were calculated for each treatment group and each disease state based on a patient's state at the end of a cycle. To maximise cost homogeneity for each clinical state, rates were stratified according to whether or not hospitalisation occurred during each cycle. All costs were calculated from the perspective of the health care system. Indirect costs such as lost earnings due to poor health were not estimated. These costs were likely to be correlated with direct health care costs, and indirect costs not related to health (for example, lost earnings due to job market inequities) were likely to be similar for the two treatment groups. Thus, the overall bias due to exclusion of indirect costs is conservative (that is, to overestimate the cost effectiveness of zidovudine). Cost of inpatient care was based on the days spent in a hospital department (medicine, medical intensive care, surgery, surgical intensive care, or psychiatry) multiplied by the average total cost of staying in that department.⁸

Cost of outpatient services was based on the number of visits in each of five categories (medical or surgical clinic visits, psychiatric clinic visits, ancillary clinic visits, diagnostic tests, and procedures) and the average cost of visits in each category. Laboratory tests reported in the study were included in the cost analysis except for tests predetermined by the study protocol (for example, levels of p24 antigens and HIV cultures). Costs of outpatient drugs were based on the average cost of drugs per patient per cycle. Costs of zidovudine per patient per cycle were based on the prescribed dose in the protocol and the average prescription cost (\$1.20 for 100 mg). Costs were linked to the disease states based on the cycle during which the service was provided and the disease state of the patient at the end of the cycle. All cost calculations were based on 1991 prices.

Cost effectiveness ratio—All data on efficacy and cost were analysed on an intention to treat basis. Since patients given early zidovudine treatment had no additional survival benefit the unit of effectiveness was months without AIDS. The marginal cost effectiveness of early zidovudine treatment was calculated as the difference between the total costs (costs of drugs and health care) of early and late treatments divided by the difference between the months without AIDS associated with early and later treatments. All health care costs and efficacy data were discounted at an annual rate of 5%.⁹

Results

TRANSITIONS TO AIDS

The Markov model was run for four years (24 cycles) to correspond to the time of follow up in the study. After four years most of the patients were still without AIDS (in states 1 or 2 of HIV infection) (table I). Patients were more likely to remain in these states if they were given early zidovudine treatment: 64% of patients given early treatment were alive and without AIDS compared with 56% of patients given later treatment. Combination of the times spent in states 1

and 2 gave the length of time without AIDS (not discounted) as 39.9 months for the group given early treatment and 38.0 months for the group given later treatment (table I). The results generated by the Markov model were similar to the observed results generated by a life table analysis of trial data (fig 1). This shows that the assumptions of the Markov model used to calculate efficacy were generally satisfied during follow up.

TABLE I—Markov generated model of survival experience after four years (years not discounted) of patients infected with HIV who were given early or late treatment with zidovudine

State of HIV infection*	Expected time in each disease state (months)		Probability of being in each disease state (%)	
	Early treatment	Late treatment	Early treatment	Late treatment
1	34.3	28.5	50	38
2	6.6	9.5	14	18
3	0.8	1.6	2	5
4	2.3	3.7	7	11
5	0.8	1.3	3	5
6	NA	NA	24	23

NA—not applicable.

*See text for details.

FIG 1—Survival curves for HIV infected patients' progression to AIDS after early or late treatments with zidovudine. Curves generated by Markov model or by life table analysis of trial data

COSTS

Table II summarises the distribution of costs for hospital inpatient health care. For states 2, 3, and 5 of HIV infection inpatient costs were higher for patients given early treatment, while for states 4 and 6 inpatient costs were slightly higher for patients given later treatment. While outpatient costs accounted for a smaller proportion of total health care costs, they were consistently higher for the patients given early treatment. Average outpatient costs per cycle were \$65–\$1128 depending on disease state.

Total expected health care costs over four years for the group given early treatment were \$55 193, compared with \$36 918 for the group given later treatment (table III). All recorded health care costs were higher for patients given early treatment. Inpatient costs were 15% higher with a difference of \$3191 and outpatient costs were 19% higher with a difference of \$1523. Costs of zidovudine were almost threefold higher. The marginal cost effectiveness ratio of early zidovudine treatment was \$10750 per extra month of life without AIDS. While the patients given early treatment did not on average survive an extra year without AIDS the annual equivalent was about \$129 000 per year of life without AIDS.

TABLE II—Use of resources and costs for hospital inpatient care for patients infected with HIV who were given early or late treatment with zidovudine

State of HIV infection at end of cycle*	No (%) of patients in hospital	Probability of hospitalisation in a cycle (%)	Mean (interquartile range) length of stay (days)	Mean % of length of stay in each ward				Weighted cost per day (\$)	Hospital cost per cycle (\$)†
				Medical	Surgical	Intensive care	Psychiatric		
Early zidovudine treatment									
1	92 (56)	13	8.9 (2-11)	74	8	0	18	567	656
2	28 (48)	19	14.6 (3-13)	86	9	0	5	607	1639
3	9 (100)	62	19.2 (9-22)	92	7	1	0	632	7523
4	11 (69)	27	10.9 (3-14)	74	9	0	17	570	1676
5	9 (100)	70	18.6 (5-21)	99	0	1	0	633	8242
6	11 (48)	48	13.5 (5-18)	79	9	12	0	697	4517
Late zidovudine treatment									
1	83 (54)	10	10.6 (2-13)	71	7	0	22	555	588
2	37 (42)	16	7.2 (2-9)	85	10	1	4	616	710
3	9 (82)	24	18.4 (15-22)	85	0	3	12	608	2685
4	14 (52)	24	14.6 (5-21)	78	14	1	7	604	2116
5	10 (71)	41	26.2 (15-31)	100	0	0	0	627	6735
6	13 (65)	65	12.5 (6-21)	100	0	0	0	627	5094

*See text for details.

[†]Calculated as probability of hospitalisation × mean length of stay × weighted cost per day.

TABLE III—Costs and effects (discounted at annual rate of 5%) of early or late treatment with zidovudine for patients infected with HIV after four years

	Early treatment	Late treatment
Costs (\$):	55 193	36 918
Hospital inpatient (%)	24 162 (44)	20 971 (57)
Outpatient (%)	9 603 (17)	8 080 (22)
Zidovudine (%)	21 428 (39)	7 867 (21)
Effect (months without AIDS)	36.8	35.1
Cost/extra month without AIDS (\$)	10 750	

SENSITIVITY ANALYSES

The first sensitivity analysis varied the cost of zidovudine. This analysis was particularly important because the current recommended dose of 500 mg/day⁶ is one third that used in the trial (1500 mg/day). At a dose of 500 mg/day the cost effectiveness ratio for early treatment was \$5432 per month or about \$65 000 per year of life without AIDS.

In the trial the patients given early zidovudine treatment reported more nausea, vomiting, and diarrhoea while patients given later treatment reported more rashes.⁴ Because the impact of these symptoms on health care costs and the patients' quality of life was unclear and because some of the symptoms in the group given early treatment might have resulted from the higher dose of zidovudine used in the trial we performed two additional sensitivity analyses. Firstly, we reduced the use of health care associated with state 1 of HIV infection in the group given early treatment to the same level observed in the group given later treatment, thereby assuming that all additional costs in the early treatment were attributable to side effects of zidovudine. At a dose of zidovudine 500 mg/day the cost per additional year of life without AIDS was still \$48 000. Secondly, we calculated what decrease in quality of life caused by side effects of early zidovudine treatment would render the two treatments equal in quality adjusted time without AIDS (fig 2). Since the overall difference in efficacy between the two treatments was small only a minor decrease in quality of life (about 8%) was necessary to make the two treatments equal in quality adjusted time without AIDS.

Discussion

The debate over zidovudine treatment for patients with HIV centres on when it should be prescribed. The first randomised controlled trial established the efficacy of zidovudine given to patients with recently diagnosed AIDS.¹ The next step was to test its efficacy for patients earlier in the course of their infection. Two subsequent trials were stopped because patients given early zidovudine treatment progressed to AIDS later than those who received placebo.^{2,3} At that time a delay in progression to AIDS was deemed an important

clinical endpoint for improving quality of life. It was also assumed that a delay in progression to AIDS would prolong the lives of these patients. This assumption was supported by results from three large observational studies.¹⁰⁻¹³ The two most recent randomised controlled trials compared zidovudine given early with zidovudine given later but still before AIDS. One of the trials reported a small absolute delay in progression to AIDS⁴ while the other did not.⁵ We attempted to extend this investigation by considering not only the efficacy of zidovudine but also the costs associated with early and later treatments.

One strength of our study is that the analysis was based on data collected prospectively rather than on estimates of cost based on usual practice patterns. Also, the trial which generated our data was conducted at six medical centres so that the observed rates of use of health care were unlikely to be overly affected by the patterns of practice at any one hospital and are thus more suitable for generalisation than results from a single site. Similarly, cost calculations based on our data are likely to be representative of costs in other large managed health care systems: the doctors in the six medical centres were salaried and the hospitals operated under global budgeting, thereby minimising incentives for overuse of facilities.

We also varied the value assigned to life without AIDS for patients receiving early treatment. Our analysis indicated that only a small (8%) decrease in quality of life due to side effects of zidovudine treatment made the quality adjusted time without AIDS similar to that of patients not taking zidovudine. While the absolute number of side effects did not differ between the treatment groups in the trial, other studies have shown that patients given zidovudine early in the course of HIV infection experience significantly more anaemia needing transfusion, nausea, vomiting, and malaise.¹⁴ In addition, there is increasing evidence of a substantial decrease in the quality of life of patients as they progress from asymptomatic HIV infection to AIDS.^{15,16} Some studies have shown a drop of more than 30% in general health and wellbeing for patients who progress to AIDS.¹⁵ These findings and our analysis suggest that, in addition to higher economic costs of early zidovudine treatment, there is very little margin for side effects caused by early treatment before the additional quality adjusted time without AIDS conferred by the treatment disappears.

In this trial and two previously published trials^{2,3} the difference between treatment strategies in delaying progression to AIDS was small in absolute terms. If there is no delay in progression to AIDS, as was found in the Concorde trial, then the cost effectiveness ratio would be infinite. This study shows that even if early zidovudine treatment is moderately effective it is not cost effective. The cost effectiveness of early

FIG 2—Cost of early treatment with zidovudine for each extra quality adjusted month of life without AIDS against reduction in quality of life (from a maximum of 1.0). Threshold value is decrease in quality of life at which early and late zidovudine treatments equal in terms of quality adjusted time without AIDS

Clinical implications

- Zidovudine significantly improves survival for patients with newly diagnosed AIDS
- For patients earlier in their course of HIV infection, zidovudine confers no survival advantage and only a small advantage in delayed progression to AIDS
- At the currently recommended dose of zidovudine, early treatment costs an extra \$5432 per additional month of life without AIDS relative to treatment later in the course of infection
- This study shows that such early zidovudine treatment is very costly relative to the benefit conferred

zidovudine treatment for patients with HIV infection cannot be compared directly with other medical interventions because the unit of effectiveness in most other cost effectiveness analyses is years of life saved. However, we estimated that early zidovudine treatment (500 mg/day) cost \$65 000 for each year of life without AIDS. Schulman *et al* reported a cost of \$70 526 per year of life saved for early treatment with zidovudine (500 mg/day).¹⁷ Their analysis differed from ours because they assumed prolonged survival for patients with delayed progression to AIDS although there is no evidence from clinical trials to support this assumption. We could not calculate years of life saved as we did not observe any additional survival benefit conferred to patients given early treatment in this four year trial. Other cost effectiveness ratios of treatments for diseases with high mortalities include \$59 922 per year of life saved for haemodialysis in a renal centre¹⁸; \$67 057 per year of life saved for liver transplantation for patients with chronic hepatitis¹⁹; \$70 302 per year of life saved for bone marrow transplantation for acute non-lymphocytic leukaemia²⁰; and \$7m per quality adjusted life year gained for use of prophylactic intravenous immunoglobulin for chronic lymphocytic leukaemia.²¹ (All cost effectiveness ratios have been adjusted to 1991 costs.²²)

This study has several potential limitations. Firstly, the analysis was limited to benefits accrued over four years. We addressed this by reporting months of life without AIDS as the observed unit of effectiveness for the cost effectiveness ratios. We did not assume that prolonging the time to development of AIDS would prolong overall survival because no empirical evidence supports such an assumption. Secondly, we did not adjust the cost of zidovudine downward in either treatment group for patients whose dose had to be reduced because of zidovudine toxicity. We did, however, perform sensitivity analyses both on the cost of zidovudine and the differential cost of health care in the late treatment group before the patients were given zidovudine. Even with the assumption that all patients in the early treatment group received zidovudine 500 mg/day and that patients in both groups had equal health care costs before their CD4 cell counts fell below $200 \times 10^6/L$, the cost effectiveness ratio of early treatment was still high: \$48 000 per year of life without AIDS. Lastly, our results are applicable only to early single treatment with zidovudine. Recent combination strategies of zidovudine with didanosine and zalcitabine were not considered, but since these strategies may increase cost of treatment without necessarily improving efficacy the resulting cost effectiveness

ratios may well be less favourable than those reported here.

The high cost of zidovudine and the relatively short delay in progression to AIDS mean that early treatment with zidovudine is expensive and does not necessarily confer a survival benefit on treated patients. We conclude that at the current cost of zidovudine early treatment for patients infected with HIV is not cost effective. Furthermore, if patients experience even a small decrease in their quality of life the potential efficacy of early zidovudine treatment is negated.

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