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Modelling the Cost Effectiveness of Lamivudine/Zidovudine Combination Therapy in HIV Infection

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Summary

The use of combination antiretroviral therapy is supported by clinical evidence for its superiority over monotherapy. Lamivudine (3TC) has been studied in combination with zidovudine (ZDV) and is recommended for use specifically in combination therapy. With the associated increase in drug acquisition cost, the economics of combination therapy versus monotherapy warrant study. An economic evaluation was undertaken to compare 3TC/ZDV combination therapy with ZDV monotherapy, taking a UK public finance perspective.

The cost effectiveness of each of the 2 treatments was estimated using a Markov model of progression through 3 HIV-positive disease states: (i) CD4 cells >200 and <500 cells/mm^3; (ii) CD4 <200 cells/mm^3, non-AIDS; and (iii) AIDS to eventual death. Progression probabilities and life expectancy were derived from a cohort treated at Chelsea and Westminster Hospital in London, using data for 1987 to 1995, along with cost data for a ZDV intent-to-treat population for 1994 and 1995. The relative risk of progression for 3TC/ZDV compared with ZDV monotherapy was estimated from meta-analysis of 4 completed comparative trials. To predict the effect of 3TC/ZDV on life expectancy and lifetime costs, progression probabilities were adjusted by the relative risk statistic for the duration of treatment with 3TC/ZDV.

On the basis of an estimated relative risk of progression of 0.509 (95% CI 0.365 to 0.710), treatment with 3TC/ZDV is predicted to yield an incremental cost-effectiveness ratio of £6276 (95% CI £5337 to £9075) per life year saved (discounted at 6% per year). Extensive sensitivity analyses were performed to test the effects of varying values of input parameters on the model results. Under reasonable assumptions, the predicted cost effectiveness of 3TC/ZDV combination therapy compares favourably with previously reported economic analyses of various HIV treatments.

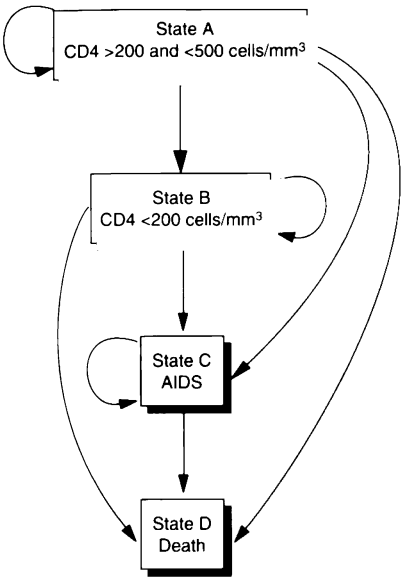

Fig. 1. State transition diagram for Markov model.

Recent clinical studies of antiretroviral therapy in HIV infection have demonstrated[1-4] that combination therapy is associated with greater clinical benefit than zidovudine (ZDV) monotherapy. These findings have stimulated increasing use of combination regimens, thus increasing drug acquisition costs. With the introduction of lamivudine (3TC), which is indicated for use in combination with ZDV,[5] this trend is continuing. Triple combination therapy incorporating protease inhibitors would further increase drug acquisition costs.

Hence, the cost of combination therapy raises budgetary issues for purchasing authorities. If decision makers are to accept increased antiviral drug acquisition costs, they need information about the predicted effects of combination therapy on outcomes, both in terms of health gain and financial impact. If disease progression can be slowed, a consequential decrease in annual costs of care could be expected as an offset against the increased initial antiviral drug cost. The question for the purchaser concerns the likely balance of these costs and consequences, as a basis for assessing the value for money of combination therapy.

The present study reports on the cost-effectiveness analysis of combination therapy with 3TC/ZDV compared with ZDV monotherapy. The selected measure of health outcome was life expectancy. The costs included in the study were those direct costs appropriate to a public finance perspective. We have estimated the additional cost per life year saved with 3TC/ZDV compared with ZDV.

There were 2 main reasons for the selection of ZDV monotherapy as the comparator. First, this was the most widely prescribed antiretroviral regimen before the advent of combination therapy. Second, the majority of the available clinical efficacy data for 3TC/ZDV compare this regimen with ZDV.

Life expectancy is an outcome which has been applied previously to antiretroviral therapy.[6,7] Unless longitudinal data are available to measure survival directly, estimates of life expectancy can only be made by extrapolation from intermediate outcomes. Such a modelling approach requires the use of assumptions for many input variables. In the interests of transparency, we have identified these variables as explicitly as possible and tested the effect of changing their values. It is particularly important to note that the estimates of life expectancy derived through modelling are predicted values.

Methods

Epidemiological Estimation

The estimation of life expectancy was carried out by Markov modelling.[8] This dynamic decision analytic technique allows medical prognosis to be modelled over time, so is particularly useful where uncertain events and outcomes may occur in chronic diseases.

Four Markov states were defined to represent the progression through disease states to eventual death, as follows:

Table I. Transition probability matrix for the Chelsea and Westminster Hospital cohort

One-year probability of transition	To state			
	A CD4 >200 and <500 cells/mm^3	B CD4 <200 cells/mm^3	C AIDS	D Death
From state:				
A	0.721	0.202	0.067	0.010
B	0	0.581	0.407	0.012
C	0	0	0.750	0.250

- State A: HIV positive, non-AIDS, CD4 >200 and <500 cells/mm^3
- State B: HIV positive, non-AIDS, CD4 <200 cells/mm^3
- State C: HIV positive, AIDS diagnosed
- State D: death.

The state transition diagram in figure 1 illustrates the observed transitions in the model.

Markov models require estimates of probability values for each of the possible state transitions during a specific time interval, called a Markov cycle. A 1-year Markov cycle period was selected for this study. The assumption was made that state transition probabilities are time independent. Others have concluded[9,10] that this 'Markov chain' assumption provides a good approximation of observed disease progression in HIV infection at the population level.

The model was based on a cohort of 1000 hypothetical individuals. The number of individuals in each state was calculated over 20 cycles, i.e. 20 years, reflecting what was felt to be the maximum realistic time horizon for decision making. From the resulting survival table, the expected number of years to be spent in each state was calculated by dividing the total person years in each state over the 20 cycles by the size of the cohort. Summing the expected years for each state gave the total life expectancy in years.[1]

1 Note that the use of a hypothetical cohort of 1000 is simply a device which allows the survival analysis to be considered in terms of numbers of patients. It would be equally possible to deal with probabilities of survival for a single patient. The result would be unaltered because the summed life years and costs are divided by 1000 later in the calculations.

Survival Analysis

The survival analysis was performed by populating the Markov chain model with estimates of the 1-year transition probabilities. These probabilities were estimated using Kaplan-Meier methods for a cohort of 4665 patients treated at Chelsea and Westminster Hospital in London. The analysis was performed on a subset of 4603 patients who had been treated at the centre between 1st January 1987 and 30th June 1995 in whom CD4 measurements were available. The starting year coincided with the introduction of ZDV and the final date was chosen to avoid any effect of combination therapies being studied in clinical trials at the centre.

The transitions included in the model reflected clinical experience with this cohort. For example, it was possible for patients to develop AIDS with a CD4 count above 200 cells/mm^3 without having to pass through the lower CD4 stage first. Likewise, although no transitions from less healthy to more healthy states were seen in this cohort, the model is designed such that 'reverse' transitions are allowed. Patients were assumed to have progressed into the next immunological stage only if they had had 2 consecutive CD4 counts measured below that level. The estimates of 1-year transition probabilities for each of the allowed disease progressions is shown as a matrix in table I.

The cohort of patients studied included 3857 (83.8%) patients infected through homosexual sex, 59 (1.3%) through heterosexual sex, 254 (5.5%) infected through intravenous drug use and 433 (9.4%) either infected through other transmission routes, including blood transfusion recipients, or in whom the route of transmission was unknown.

1735 (37.7%) patients passed through state A, 1259 (27.4%) patients passed through state B and 2240 (48.7%) patients passed through state C. At entry to stages A, B and C the median age (range) of patients included in the analysis was 32.05 years (17.7 to 70.7), 34.8 years (19.0 to 71.6) and 35.8 years (2.1 to 72.2), respectively.

Cost Estimation

On the basis of the changing pattern of costs reported by another London centre,[11] it was felt important to use the most recent information possible. Cost data for the years 1994 and 1995 were obtained from a ZDV intent-to-treat population from the Chelsea and Westminster Hospital cohort. Hence, both medical costs and transition probabilities were derived from a single source. Costs were calculated based on the number of hospital days, clinic visit, laboratory testing, day care and drug use for 389 HIV-infected patients who were treated with ZDV monotherapy at the Chelsea and Westminster Hospital during 1995. The cost per hospital day assigned to this patient cohort was developed through a 'bottom-up' cost finding study performed for over 100 admissions for HIV-infected patients. Visit costs were identified by sampling over 100 visits and recording treatment encounter data. Laboratory costs were priced at the Chelsea and Westminster Hospital internal charge rates. Drug costs were calculated using the hospital's bulk purchase price or, for free drugs given to patients on study protocols, using the unit cost reported in the *British National Formulary* for 1995. All component costs were weighted by the proportion of administrative overhead that was allocable to the clinical production function (excluding teaching and research costs). All component costs were aggregated first at the level of the individual patient. Annualised costs (similar to an incidence density function) were calculated for each patient from the date of a patient's first CD4 count in 1995 and forward for 12 months or until death. Patients who died before the end of 12 months were only contributing costs for the fraction of the year that they survived. Cost and survival years were summed for patients for each Markov state. Annual costs for a state were calculated by dividing the total cost for the patients in the state by the survival years generated by these patients.

An estimate of community care costs was also required to complete the public finance perspective of this study. This estimate was derived from a previously reported study[12] of patients treated at 2 other London centres: St Mary's Hospital and the Central Middlesex Hospital. Costing data in this study had been obtained from providers of community services throughout Greater London. Since these results were reported by a different staging system (asymptomatic, symptomatic non-AIDS and AIDS), it was necessary to transform the community care data to fit the staging system used for the Chelsea and Westminster cohort. The assumptions in table II were used for this transformation, based on the differences in risk of events observed in other data.[13]

All cost data are expressed as average annual cost per patient, as shown in table III. A pattern of increasing costs with disease severity and progression was clearly evident, consistent with data reported at other centres.[11,14]

The total expected cost of care per person year was found for each of the 3 disease states. For each Markov cycle, the expected cost of care for the cohort in each cycle was found by multiplying the number of surviving patients in each Markov state by the appropriate summary cost and summing across the 3 live Markov states. Summing these costs per cycle over the 20 cycles, the total cost of care for the whole cohort was derived. Dividing by 1000 gave the expected total cost per person over 20 cycles. The cost per life year was then

Table II. Assumed symptom status according to CD4 cell count

	Asymptomatic (%)	Symptomatic (%)
CD4 >200 and <500 cells/mm^3	86	14
CD4 <200 cells/mm^3	46	54

Table III. Mean annual costs (1995 values) per patient year from the Chelsea and Westminster Hospital cohort

Patient numbers and costs (pounds sterling; £)	Health state		
	A	B	C
	CD4 >200 and <500 cells/mm^3	CD4 <200 cells/mm^3	AIDS
Patient numbers from cohort of 389 patients	87	53	249
Costs (mean cost per patient per year)			
C&W direct medical (£)	1 701	1 774	6 948
ZDV (£)	2 278	2 278	2 278
Community care (£)	1 055	1 278	2 059
Total (£)	5 034	5 330	11 285
3TC @ daily NHS cost of £5.71 (£)	2 086	2 086	2 086
Total including 3TC (£)	**7 119**[a]	7 415[a]	**13 370**[a]

a Costs of each component have been rounded to the nearest whole number.

Abbreviations: C&W = Chelsea and Westminster Hospital; NHS = National Health Service; 3TC = lamivudine; ZDV = zidovudine.

calculated by dividing the total cost per person by the life expectancy.

As a base case, costs were discounted to present values at a rate of 6% per annum, reflecting current UK Treasury guidelines. Hence the total cost is actually the net present value of the cost stream over 20 cycles.

Estimating Treatment Effect

The above analysis was first performed for the ZDV control group, to provide baseline outcome statistics for life expectancy, costs and a resulting figure for cost per expected life year. A similar analysis was conducted for the 3TC/ZDV group as follows. An estimate was made of the relative risk of progression for the 3TC/ZDV group compared with ZDV, using clinical trial data as described below. The relevant baseline transition probabilities were multiplied by this relative risk (RR) statistic to reflect the reduced probability of progression for patients on 3TC/ZDV. This relative risk of clinical progression was taken as a proxy for the relative risk of transition between each of the Markov states, 2 of which are defined in immunological terms and two (AIDS and death) in clinical terms. This is appropriate since CD4 cell distributions are good predictors of clinical progression in the short term.[15]

At this time, the extent of the duration of effect of 3TC/ZDV is not known, although surrogate marker data from trials NUCA 3001,[16] NUCB 3001[17] and NUCA 3002[18] indicate that an effect persists for at least 1 year, and blinded follow up data to week 76 suggest that effects may persist for closer to 2 years.[19] The model therefore includes 3 different scenarios: a 1-year effect, a 2-year effect and a continuous effect. In the 1-year effect scenario, the RR-modified probabilities take effect on the first Markov cycle only, with subsequent cycles reverting to the baseline probabilities. In the 2-year scenario, the modified probabilities apply for the first 2 cycles, while in the continuous scenario they apply for the full 20 cycles. A similar procedure was used to modify the drug acquisition costs. The incremental annual cost to the UK National Health Service (NHS) of providing 3TC was added to total costs for the same number of cycles as its assumed duration of effect, as would be revealed by routine surrogate marker monitoring.

Clinical Efficacy

Data for the relative risk of progression of 3TC/ZDV combination therapy compared with control groups were obtained from a published meta-analysis[20] of the first 4 Phase III clinical trials[16-18,21] to be completed and the one further clinical trial (CAESAR)[3] completed subsequently. Hence, all the available randomised clinical trial information for 3TC/ZDV combination therapy

Table IV. Summary results of randomised clinical trials of 3TC and a meta-analysis of 4 trials

Trial	Treatment period (wk)	Relative risk	95% CI	p-Value	Active group(s) and daily dose in mg	Control group(s) and daily dose in mg
NUCA 3001[16]	52	0.389	0.206-0.733	0.004	3TC 300 or 600 + ZDV 600	3TC 600 or ZDV 600
NUCA 3002[18]	52	0.674	0.393-1.156	0.151	3TC 300 or 600 + ZDV 600	ZDV 600 + ddC
NUCB 3001[17]	24	0.492	0.183-1.328	0.162	3TC 600 + ZDV 600	ZDV 600
NUCB 3002[21]	24	0.452	0.226-0.902	0.024	3TC 300 or 600 + ZDV 600	ZDV 600
Meta-analysis of all 4 trials (taken as treatment effect in present study)[20]	NA	0.509	0.365-0.710	<0.001		
NUCB 3007[3] (CAESAR)	52	0.457 (risk of AIDS or death)	0.335 - 0.625	<0.0001	Add to current treatment: 3TC 300 or 3TC 300 + loviride 300	Add to current treatment: placebo
NUCB 3007[3] (CAESAR)	52	0.472 (risk of death)	0.260-0.856	0.012	As above	As above

Abbreviations: CAESAR = Canada, Australia, Europe and South Africa; CI = confidence interval; ddC = zalcitabine; NA = not applicable; 3TC = lamivudine; ZDV = zidovudine.

was used. The results of the individual trials and the meta-analysis are summarised in table IV.

In the first 4 studies, disease progression was defined as progression to new CDC B (non–AIDS-defining) or C (AIDS-defining) events. 3TC/ZDV combination therapy reduced progression to new events by 49% ($p < 0.0001$). The reduction was also significant in subgroups of patients (naive vs pre-treated, asymptomatic vs symptomatic, CD4 cell count <200 vs >200 cells/mm^3). Although 1 study, NUCA 3002,[18] used combination therapy with ZDV plus zalcitabine (ddC) as the control group rather than simple ZDV monotherapy, this was included to preserve consistency with the meta-analysis reported elsewhere. The RR statistic for this study was higher than those for the other 3 studies,[16,17,21] which made the cost effectiveness of 3TC/ZDV appear less favourable than it would with a strict comparison against ZDV monotherapy. The majority (64%) of patients entering the 4 early trials[16-18,21] were asymptomatic and most of the progressions involved pre-AIDS events.

Trial NUCB 3007 (CAESAR)[3] enrolled mainly symptomatic patients and was designed to measure the clinical endpoints of AIDS and death as the primary outcomes. The relative risk for a new AIDS event or death was 0.457 and for death alone was 0.472. Most (62%) of the individuals in the control group entered the trial on ZDV monotherapy. Subgroup analysis of the risk of a new AIDS event or death for these individuals gave an RR value of 0.432 (95% CI 0.268 to 0.697). The similarity of the results from CAESAR to the meta-analysis of the studies in less advanced patients[20] justified the assumption of a uniform treatment effect of 3TC/ZDV on all disease state transitions. The RR statistic of 0.509 from the meta-analysis was selected as a conservative estimate of this treatment effect and was applied as the baseline assumption for treatment effect in this study.

Table V. Values used in sensitivity analysis of costs

Disease stage	Annual average cost per patient [pounds sterling (£); 1995 values]		
	Chelsea & Westminster Hospital	alternative scenario[22]	community[12]
CD4 >200 and <500 cells/mm^3	1701	2 938	1055
CD4 <200 cells/mm^3	1774	4 398	1278
AIDS	6948	11 223	2059

Economic Analyses

The economic analysis performed brought together the epidemiological, cost and treatment estimates described above. Cost-effectiveness ratios were calculated for the ZDV control group and the 3TC/ZDV group and expressed as costs per life year. Both average and incremental cost-effectiveness ratios were calculated. The latter shows the additional cost per life year saved for combination therapy when compared with monotherapy.

The effects of changing values of input variables on the outcomes of lifetime cost, life expectancy and cost-effectiveness ratios were calculated. The following sensitivity analyses were conducted:

- The relative risk of progression. The upper and lower bounds of the 95% confidence interval around the point estimate were used, but our method permits reporting of the cost per life year saved as a function of any RR value between 0 and 1.
- The duration of effect of 3TC/ZDV therapy. Three scenarios were used: 1-year, 2-year and continuous effect.
- The case mix of the starting cohort of 1000 hypothetical individuals. The composition can reflect any desired mix of the 3 disease states. This allows inferences to be drawn about the relative cost effectiveness of starting therapy earlier versus later, all other things being equal.
- The base case cost structure. The parameters are described below and in table V.
- The discount rate applied to costs and benefits. The base case uses a 6% annual rate applied to costs (in line with UK Treasury recommendations) and 0% to benefits, but other combinations are reported.

The base case cost structure was based on the Chelsea and Westminster Hospital cohort for 1994/95. However, since substantial differences in costs have been observed between centres and over time, an alternative scenario was tested based on a set of costs reported by others[22] for 1992/93. It was necessary to adjust these reported data in order for them to fit the disease definitions of our model. We used the same method of adjustment as described earlier for deriving community costs (table II). The same set of community care costs was used in both cost scenarios, as shown in table V.

Table VI. Base case assumptions prior to sensitivity analyses

Variable	Assumed value
RR for progression	0.509
Duration of effect of 3TC/ZDV	2 years
Timing of treatment initiation	All 1000 patients in state A (fig. 1)
Cost structure	As per C&W database (table V)
Discount rate	Costs: 6% per annum Outcomes (life years): 0% per annum

Abbreviations: C&W = Chelsea and Westminster Hospital; RR = relative risk; 3TC = lamivudine; ZDV = zidovudine.

Results

Results for the control group (ZDV monotherapy) are reported first. The effects of 3TC/ZDV combination therapy are then reported for a 'base case' set of values for the input variables. The effects of the sensitivity analyses on the results are then explored.

ZDV Monotherapy

Applying the progression probability matrix in table I to a cohort of 1000 hypothetical patients in disease state A (CD4 >200 and <500 cells/mm^3), expected waiting times in each of the 3 states were calculated, i.e. the number of years that an individual would expect to remain in a given disease state. The waiting times were 3.6 years, 1.7 years and 3.7 years for states A, B and C, respectively, giving a total of 9.0 years of life expectancy from the point of entry into state A. This analysis used a 20-year time horizon, at the end of which period 968 patients of the 1000-patient cohort would be expected to have died; i.e. the probability of death over 20 years is 0.968. The expected cost (in constant monetary units) per patient over this 20-year time horizon was 63 653 pounds sterling (£), which when discounted at the 'base case' rate of 6% per

annum equated to a net value of £44 612 (1995 costs). Dividing this figure by the life expectancy of 9.0 years, an average annual cost of £4968 per life year was obtained. This is the average cost effectiveness for usual care that incorporates ZDV monotherapy. It is important to note that this is not the incremental cost-effectiveness ratio of ZDV monotherapy, since it is not based on the incremental cost or incremental survival for ZDV compared with no antiretroviral therapy at all.

Effect of 3TC/ZDV: Base Case

The base case assumptions for the effect of 3TC/ZDV therapy are given in table VI.

These assumptions yielded a life expectancy of 9.9 years, representing an average gain of 0.9 years compared with usual care with ZDV monotherapy (rounded values). Expected 20-year costs were £50 551, an incremental £5939 versus ZDV monotherapy. Hence, the incremental cost per life year saved (£5939/0.9) was estimated at £6276.

Figures 1, 2 and 3 depict the projected survival curves and cost trajectory for 3TC/ZDV compared with ZDV. The reduced risk of disease progression over the 2 years of assumed effect has the effect of shifting the survival curve to the right, as a greater number of patients remain alive for any year in the combination therapy group (fig. 2). The median

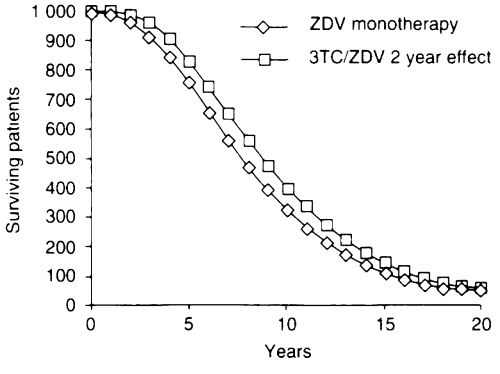

Fig. 2. Projected survival curves for lamivudine/zidovudine (3TC/ZDV) combination therapy and ZDV monotherapy.

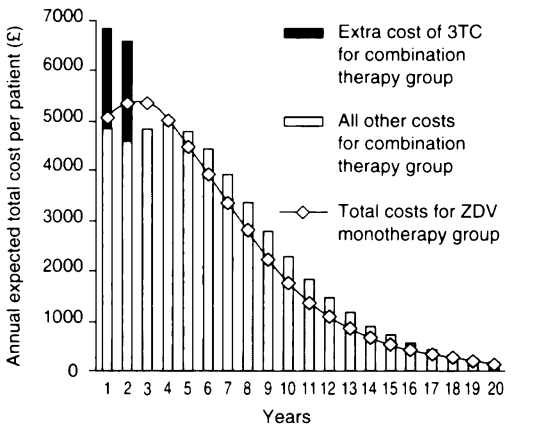

Fig. 3. Comparison of annual cost trajectories for lamivudine/zidovudine (3TC/ZDV) combination therapy and ZDV monotherapy. Costs are per patient and have been discounted at an annual rate of 6%.

survival, i.e. the time at which half of the cohort would be expected to have died, improves from 7.6 to 8.6 years. This also means that a greater number of patients are consuming resources. Figure 3 indicates that costs per patient are higher in the combination therapy group in the early years, but that some of these costs are recovered in later years. In years 1 and 2, the incremental cost of purchasing 3TC is readily apparent. In year 3, however, even after discontinuation of combination therapy, the effect over the preceding 2 years in delaying progression to more severe and more expensive health states results in annual cost savings. In year 4 onwards, as more patients progress to AIDS, costs in the group which were treated with combination therapy in years 1 and 2 once again track higher than the monotherapy group, because this cohort has a greater number of patients surviving

When costs are considered on a per surviving patient basis, the pattern is different, as demonstrated in figure 4. Although costs are substantially higher in years 1 and 2, owing to the cost of 3TC, in subsequent years the combination therapy group is associated with lower costs. This is because patients receiving combination therapy are likely to

be in less expensive health states at any given point in time.

Sensitivity to Relative Risk

The incremental cost-effectiveness ratio (ICER), i.e. cost per life year saved, was calculated for the lower and upper bounds of the confidence interval around the point estimate of the relative risk of progression. Compared with the base case of £6276 per life year saved, the ICER improved to £5337 using an RR value of 0.365 and deteriorated to £9075 with an RR value of 0.710. As expected, the relationship between relative risk and the ICER is nonlinear, as shown in figure 5, such that the ICER tends to infinity as the RR value approaches unity. Said simply, as the benefit of therapy is assumed to decline towards zero, the costs of achieving this minor benefit become higher. The shaded area of the graph shows the sensitivity of the ICER to the confidence interval around the RR estimate.

Sensitivity to Duration of Effect of 3TC/ZDV

Three scenarios of duration of effect were modelled: a 1-year 'pessimistic' effect size, a 2-year 'realistic' effect (the base case) and a continuous 'optimistic' effect. The results are summarised in table VII.

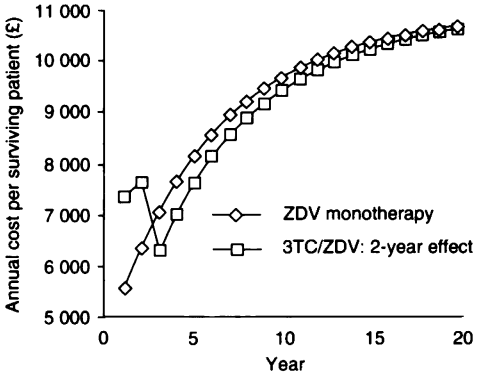

Fig. 4. Comparison of projected annual costs per surviving patient. Costs have been discounted at an annual rate of 6%.

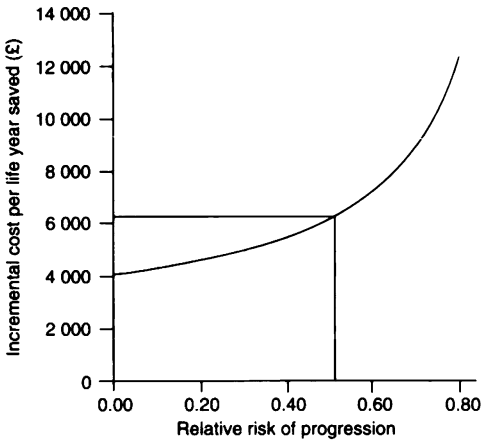

Fig. 5. Sensitivity of incremental cost-effectiveness ratio to relative risk of progression.

The different assumptions of the effect had, as expected, a marked impact on life expectancy and incremental costs. The continuous effect model would result in a life expectancy increase of 6.0 years. The longer survival and the 20-year drug cost account for the higher lifetime cost per patient. The incremental cost-effectiveness ratio decreases (i.e. improves) as survival increases, because the longer surviving cohort has more 'low-cost' years than the comparator group.

Sensitivity to Timing of Treatment Initiation

This sensitivity analysis was performed by allocating the 1000 hypothetical patients to start in states B and C and comparing the effects with the base case, in which the cohort is started in state A.

As table VIII shows, the more advanced the disease state for the control cohort, the smaller was the resulting life expectancy. By the same token, this was true also for the 3TC/ZDV group, although similar increases in absolute life expectancy were seen for both active and control groups regardless of case severity. The later therapy is started, the greater the incremental cost of 3TC/ZDV compared with ZDV monotherapy. This is because life years gained for patients who already have

AIDS are more expensive than life years gained for patients who are still relatively healthy and are consuming less healthcare resources. As a result, the ICER became more favourable the earlier treatment was assumed to be initiated. Such a prediction based on mathematical modelling required the assumption that the magnitude and duration of clinical effect of 3TC/ZDV is independent of the disease state at which it is initiated. Support for this assumption is provided by the similar progression risks seen across the 5 clinical trials[3,16-18,21] in which entry criteria spanned a wide range of severity. Nonetheless, the results in table VIII should be interpreted with caution, since these trials were not designed to study the question of early versus late initiation of therapy.

Sensitivity to Cost Structure

The effect of changes in the annual cost of care on total 20-year discounted costs was substantial. The control group costs rose from £44 612 to £60 885 per patient when the alternative set of cost data was used. However, the effect on the ICER was very small. The cost per life year saved was £6604 using the alternative scenario, compared with £6276 using the base case Chelsea and Westminster data.

Sensitivity to Discount Rates

Decision makers vary in how they value current over future costs. A discount rate which reflects societal preferences is difficult to determine, so common practice in the UK is to adopt the Treasury recommended rate, currently 6%. In the base case, costs were discounted at 6% per annum. In the present low inflation environment, assuming a discount rate higher than 6% is not reasonable, decision makers may prefer a lower rate, e.g. 3%, or even no discounting at all. A 0% discount rate assumes that decision makers are indifferent as to whether they incur a given cost now or at some time in the future, which is not normally true. The use of discount rates lower than 6% had the effect of increasing the 20-year cost of care per patient: from £50 551 at 6% to £59 908 at 3% and £72 482 at 0%. The ICER showed accompanying increases from £6276 per life year saved at an annual discount rate of 6% (for costs) to £7539 at a rate of 3% and £9330 at a rate of 0%.

The desirability of discounting both outcomes and costs remains controversial. Applying a 6% discount rate both to life expectancy and costs increased the cost per life year gained from £6276 to £10 201, while the use of a 3% rate (the currently recommended US rate) on both costs and outcomes results in an increase from £6276 to £7539.

Discussion

With the availability of new medicines, treatment strategies against HIV infection are evolving extraordinarily rapidly compared with other diseases. Monotherapy is being replaced by combination therapy with 2 or 3 agents. These therapeutic decisions are being made on the basis of incomplete information about long term outcomes. The need for economic information is acute, given the impact of drug innovation on annual budgets. However, the present shortage of prospective

Table VII. Sensitivity of results to alternative scenarios for duration of effect of combination drug therapy

	Life expectancy (years)		Lifetime costs per patient (£; 1995 values)	Cost per life year saved (£; 1995 values)	
	total	incremental	total	average	incremental
ZDV monotherapy	9.0		44 612	4968	
3TC/ZDV 1-year effect	9.5	0.5	47 613	5036	6311
3TC/ZDV 2-year effect	9.9	0.9	50 551	5093	6276
3TC/ZDV continuous effect	14.9	5.9	79 782	5367	5976

Abbreviations: 3TC = lamivudine; ZDV = zidovudine.

survival data means that modelling approaches must be employed if we are to gain early insights into the economics of combination antiretroviral therapy. Use of modelling may be expected to continue because ethical considerations may require stopping clinical trials as soon as differences in surrogate markers such as viral load are observed between treatment groups. Moreover, clinical trials in HIV infection are likely to remain too small to yield useful resource utilisation data for economic analysis.

All modelling studies have limitations imposed by data and knowledge constraints. However, we sought out the best available sources of experimental and observational data for the model inputs. Clinical evidence for the efficacy of 3TC/ZDV was taken from all randomised controlled trials that studied this combination. Not all the necessary data could be inferred from these clinical trials, but we used a large, external cohort which provided a robust source for baseline survival and cost patterns. It is recognised that the intensity of care may be higher for those patients enrolled in trials than in routine therapy, which may inflate reported costs.

Although the present study has focused on a specific antiretroviral regimen, 3TC/ZDV, the model could be used to estimate the cost effectiveness of other drug combinations, if good RR data for the treatment and comparator in question were available. It is clear that the cost-effectiveness ratio is very sensitive to relative risk. Above an RR value of about 0.7, the ICER rapidly becomes unfavourable; as the RR statistic approaches 1 the ICER tends to infinity. The second requirement is cost and progression data from a patient cohort, stratified according to use of the study comparator. The latter requirement may prove increasingly difficult, as the proliferation of different drug combinations could hamper efforts to isolate sufficiently large and well-matched samples. The fact that ZDV was the only licensed antiretroviral agent in the UK between 1987 and 1994 made it straightforward to extract a ZDV-treated cohort from the Chelsea and Westminster database.

Modelling approaches are by their nature an abstraction of reality. Judgement is required in selecting a degree of simplification which will give an approximation of reality without making the calculations intractable. For example, in selecting the Markov disease states, a 4-state model was chosen for analytical simplicity. However, various potential improvements became apparent during the course of model development. Alternative methods of disease staging may be preferable, for example a scheme incorporating viral load categories, particularly if the prognostic value of the scheme allows more reliable estimates of transition probabilities. It may be better to divide the AIDS state into subclasses according to severity or types of opportunistic infections encountered, because costs are not homogeneous within the AIDS state but increase with severity. Data on the high cost of the final weeks of life are emerging, which could be included in the model. Early indications with triple therapy are that reverse transitions out of less advanced AIDS may be possible.[23] If this is confirmed, reversals must be reflected in the transition probability matrix. All such refinements do of

Table VIII. Effect of timing of initiation of treatment on results

Case mix	Life expectancy (years)		Incremental expected costs for 3TC/ZDV *vs* ZDV (£; 1995 values)	ICER [cost per life year saved (£; 1995 values)]
	ZDV	3TC/ZDV		
All in state A[a]	9.0	9.9	5 939	6 276
All in state B[a]	6.2	7.2	6 994	7 203
All in state C[a]	4.0	4.9	11 269	12 300

a As defined in figure 1.

Abbreviations: ICER = incremental cost-effectiveness ratio; 3TC = lamivudine; ZDV = zidovudine; state A = CD4 >200 and <500 cells/mm^3; state B = CD4 <200 cells/mm^3; state C = AIDS.

course depend on the availability of such data from the patient cohort used to estimate progressions.

Economic Implications

Cost effectiveness is a relative term, which requires a benchmark of some kind against which to assess the intervention in question. Cost per life year saved statistics have been published for a wide range of interventions, both in the management of HIV infection/AIDS and other diseases. Assessing early ZDV therapy, Schulman and co-workers[6] reported in 1991 a cost per life year saved ranging from $US6553 to $US70 526 depending on assumptions used. In 1994, Moore et al.[24] reported a cost per life year saved of $US34 600 for zidovudine monotherapy, while Simpson et al.[7] concluded that ZDV/ddC combination therapy costs from $US12 000 to $US20 000 per life year saved. In other fields of medicine, all the interventions reviewed by Schulman et al.[6] cost in excess of $US21 000 per life year saved, except smoking cessation counselling and early ZDV therapy if continuous benefit were derived. Using any of these examples of commonly accepted interventions as benchmarks, our results predict that combination 3TC/ZDV therapy will be relatively cost effective in use. In the base case, an ICER of £6276 was predicted and does not exceed £10 000 under any single sensitivity analysis. Interestingly, the results were not materially affected by an alternative, higher cost scenario, which suggests the conclusions may be generalisable to other settings.

The question of early versus deferred treatment is yet to be answered conclusively. The need for further long term clinical trials comparing the 2 strategies has recently been highlighted.[25] However, this is a question with obvious economic as well as clinical implications. Assuming that there is no difference between early and late treatment in terms of continuous clinical efficacy, the model provides some support for an early intervention strategy, with commencement of combination therapy as the CD4 cell count falls below 500 cells/mm^3.

In economic evaluations, costs are conventionally split into three headings: direct, indirect and intangible.[26] We have taken a public sector finance perspective, since appropriate allocation of public funding to HIV/AIDS care is a particular area of government concern. This resulted in the exclusion of a significant portion of the cost burden – the indirect costs to society of the lost productivity of people living with HIV, who are largely of normal working age. Had the study taken a societal perspective, these costs would need to have been measured and taken into account, and the resulting ICER values would have been more favourable to combination therapy.

We conclude that combination therapy with 3TC/ZDV can be expected to provide a cost-effective intervention in the management of HIV infection in patients with a CD4 cell count of less than 500 cells/mm^3.

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