The cost-effectiveness of treatment with lamivudine and zidovudine compared with zidovudine alone: a comparison of Markov model and trial data estimates
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Combination and monotherapy with antiretroviral agents in the treatment of patients with HIV infection.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
Hypothetical patients with the HIV infection whose initial CD4 cell count was greater than 500.

Setting
Community and hospital. The economic analysis was conducted in North Carolina, USA, Greenford, UK and Freiburg, Germany.

Dates to which data relate
Effectiveness and resource data were identified from literature on clinical trials published in 1996. In addition resource data were also collected from the AIDS Cost and Service Utilisation Survey conducted in 1992 and the 1994 Maryland Hospital Discharge Data Set.

Source of effectiveness data
Effectiveness data were taken from published literature and also from assumptions made by the authors.

Modelling
A Markov state transition model with six disease states was used to estimate lifetime health outcomes and costs associated with LMV/ZDV combination therapy and ZDV alone. Each Markov cycle was assumed to last one year and 40 cycles of the model were run. In each one year period patients were assumed to be only able to transfer to the next worse disease state, thus the minimum life expectancy was 5 years.

Outcomes assessed in the review
The review assessed natural transition rates between different health states for people with HIV, and the duration of treatment effects for LMV/ZDV therapy and ZDV monotherapy alone.
Study designs and other criteria for inclusion in the review
Randomised controlled trials comparing ZDV/LMV therapy with ZDV therapy alone were included in the review.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
One study was used to identify natural transition rates. Three studies examining efficacy were included.

Methods of combining primary studies
Not combined.

Investigation of differences between primary studies
Not stated.

Results of the review
For ZDV monotherapy the average period of treatment effect was found to be 6.5 months, compared with at least 18 months in the combination therapy groups. Transition rates were not reported.

Methods used to derive estimates of effectiveness
Probabilities of transition between states were assumed by the authors to be 1/mean duration times.

Estimates of effectiveness and key assumptions
Using the natural transition rates identified in the literature review the authors assumed that the mean duration time spent in each of the Markov states within the model were as follows:

2 years at a cell count of +500;
1.8 years with cell count 350 - 500;
1.8 years for cell count 200 - 349;
1.5 years for 100 - 199 and
1.3 years from <100 until death.

Transitions between health states were assumed to occur in the middle of each one year cycle, except for first year of monotherapy and second year of combination therapy, where transition was assumed to occur at the mid point between end of efficacy and end of year. The authors assumed, based on the efficacy rates reported in the clinical trials, that the duration of treatment effect for ZDV alone would be 6.5 months and for ZDV/LMV therapy 18 months. Patients in
both groups were assumed to revert to natural progression rates at the end of either period.

**Measure of benefits used in the economic analysis**
Life years gained and quality-adjusted life years gained were the benefit measures. A Markov model was used to extrapolate short-term outcome results to the long term. Utilities were based on a study in the literature by Tsevat et al. In this study utilities for HIV patients were estimated using the Quality of Well-being Scale. Utility weights for the different CD4 cell groups were as follows:

- Cell counts +500, 0.72,
- Cell count range 350-500, 0.72;
- Cell count range 200-350, 0.69;
- Cell count range 100-199, 0.66,
- Cell count below 100, 0.63.

**Direct costs**
Direct costs associated with HIV treatment were estimated from a 1992 study which reported charges using data from the AIDS Cost and Service Utilisation Survey. Specifically, charges included those for hospital, community care, physician, laboratory, drugs and long term care. Out of pocket costs to patients were excluded from the analysis. The charge to cost conversion ratio used was 0.8 and inflated to 1995 costs using the Medical Services Consumer Index. The drug costs for ZDV/LMV and ZDV alone therapy could not be extracted from the published survey and these costs were added. The authors assumed that treatment would be continued for a period of three months beyond the assumed duration of treatment effect. Both costs and outcomes were discounted at a rate of 3% per annum.

**Indirect Costs**
Not evaluated.

**Currency**
US dollars ($).

**Sensitivity analysis**
Discount rates were varied between 0% and 5% for both costs and outcomes, duration of treatment effect for LMV/ZDV was varied between 12 months and 24 months and treatment continuation period in the period following the end of treatment effectiveness was similarly varied between 3 months and 1.5 months.

**Estimated benefits used in the economic analysis**
Incremental quality-adjusted life years (QALYs) for the LMV/ZDV group, compared with the ZDV group alone, for each of the CD4 cell stage groups were as follows:

- +500 cells, 0.53 QALYs;
- 350 - 500 cells, 0.56 QALYs;
- 200 - 349 cells, 0.56 QALYs;
- 100 - 199, 0.57 QALYs.
For the population in the trials reported, incremental QALYs gained were 0.56. Benefits were extrapolated for the patient's lifetime.

**Cost results**

Annual costs when in each CD4 stage state were estimated as follows:

- +500 cells, $3,249;
- 350 - 500 cells, $4,954;
- 200 - 349 cells, $4,954;
- 100 - 199 cells, $11,405
- and <100 cells, $31,841.

The incremental lifetime costs for the LMV/ZDV group compared with the ZDV group alone were $7,320 (+500 cells), $8,970 (350-500 cells), $9,130 (200-349 cells), and $15,315 (100-199 cells). In the trial populations these incremental costs were $10,095.

**Synthesis of costs and benefits**

In the base case scenario incremental costs per life year gained in each of the CD4 cell groups were as follows:

- +500 cells, $10,063;
- 350 - 500 cells, $11,634;
- 200 - 350 cells, $11,235;
- 100 - 199 cells, $17,879.

Similarly, incremental costs per quality adjusted life year gained in each of the CD4 cell groups were as follows:

- $13,821; $15,981; $16,195; $27,045.

Varying the discount rates for costs and benefits to 0% or 5%, incremental costs per life year gained were $10,011 and $10,238 for the 500+ cell group and for the 100 - 199 cell group were $18,155 and $17,704. When the discount rates were set at 0% and 5% of incremental costs per quality-adjusted life year gained were $13,904 and $13,953 for the 500+ cell group respectively and $27,507 and $26,749 for the 100 - 199 cell group. The authors concluded that sensitivity analysis did not produce a large impact on the results of the analysis.

**Authors' conclusions**

The authors concluded that the model demonstrated that earlier intervention with combination therapy was preferable to later intervention, as the incremental cost-effectiveness ratios were lower. Furthermore, these costs are low compared with those for other interventions within the United States. In comparison with cost data collected within clinical trials, costs are higher in the Markov model, but this is because not all costs were collected within the trial comparison. Costs within the Markov model, however, may have been overestimated as the level of hospital care may have reduced since 1992, the costs of drug therapy were overestimated and the trial population from which estimates of efficacy were derived may not be representative of the typical patient in the 100 - 199 cell count group.

**CRD COMMENTARY - Selection of comparators**

A justification for the use of the comparator ZDV alone was given, as this is a recognised therapy for the treatment of HIV infection.
Validity of estimate of measure of benefit
The estimate of benefit was taken from published papers referring to two surrogate marker trials used in the approval of LMV and other studies with longer follow up. It is not clear how these papers were identified.

Validity of estimate of costs
The estimates of costs used in the Markov model were based on a previously published 1992 survey of HIV charges and service utilisation. As noted by the authors, this survey may now provide an over estimate of current costs due to changes in the length of hospital stay required by patients. Only direct costs were included in the analysis and the inclusion of estimates of costs to others in society, such as patients and caregivers, would also have been helpful.

Other issues
It is difficult to generalise the results of this analysis to other countries and settings because of the cost and resource information obtained. Further empirical studies and a longer follow up period are required to provide corroboration for the assumptions that the authors make in their state transition Markov model.

Implications of the study
Comparisons of long-term costs and benefits of treatment for HIV/AIDS require further empirical investigation. The model should attempt to include some estimates of indirect costs to patients and also the costs of informal caregiving which may be significant for patients with HIV.

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None stated.

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